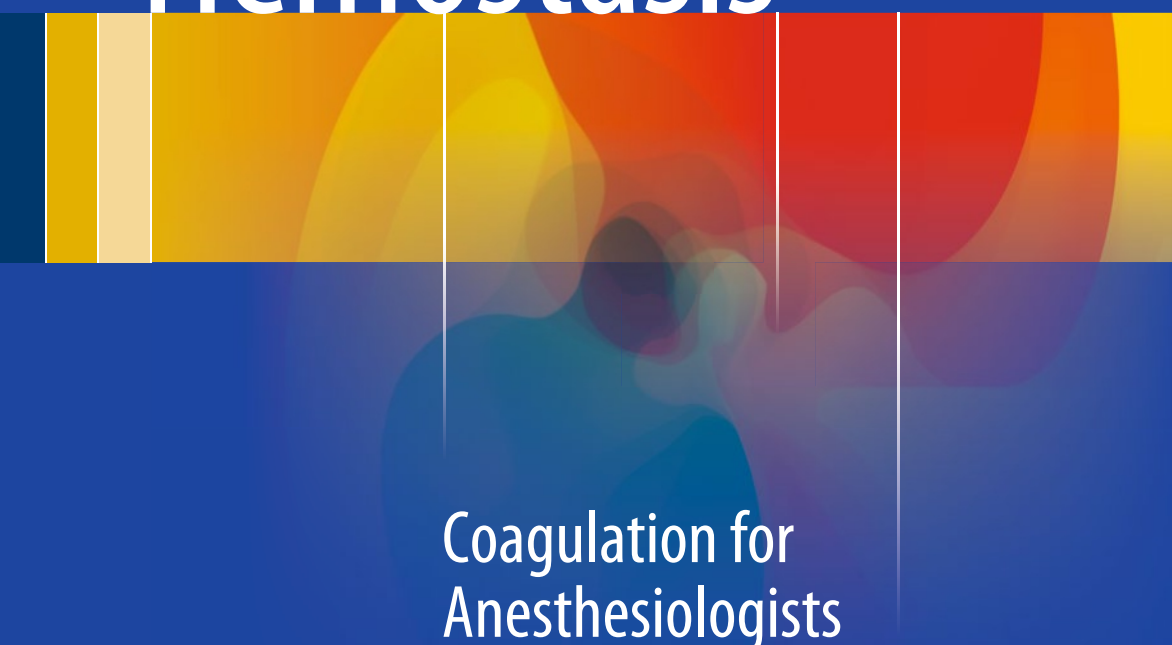
Carlo Enrique Marcucci
Patrick Schoettker *Editors*

Perioperative Hemostasis



Coagulation for Anesthesiologists

Springer

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To Carine, Ella, Catherine, Sophie and Zoé, our girls

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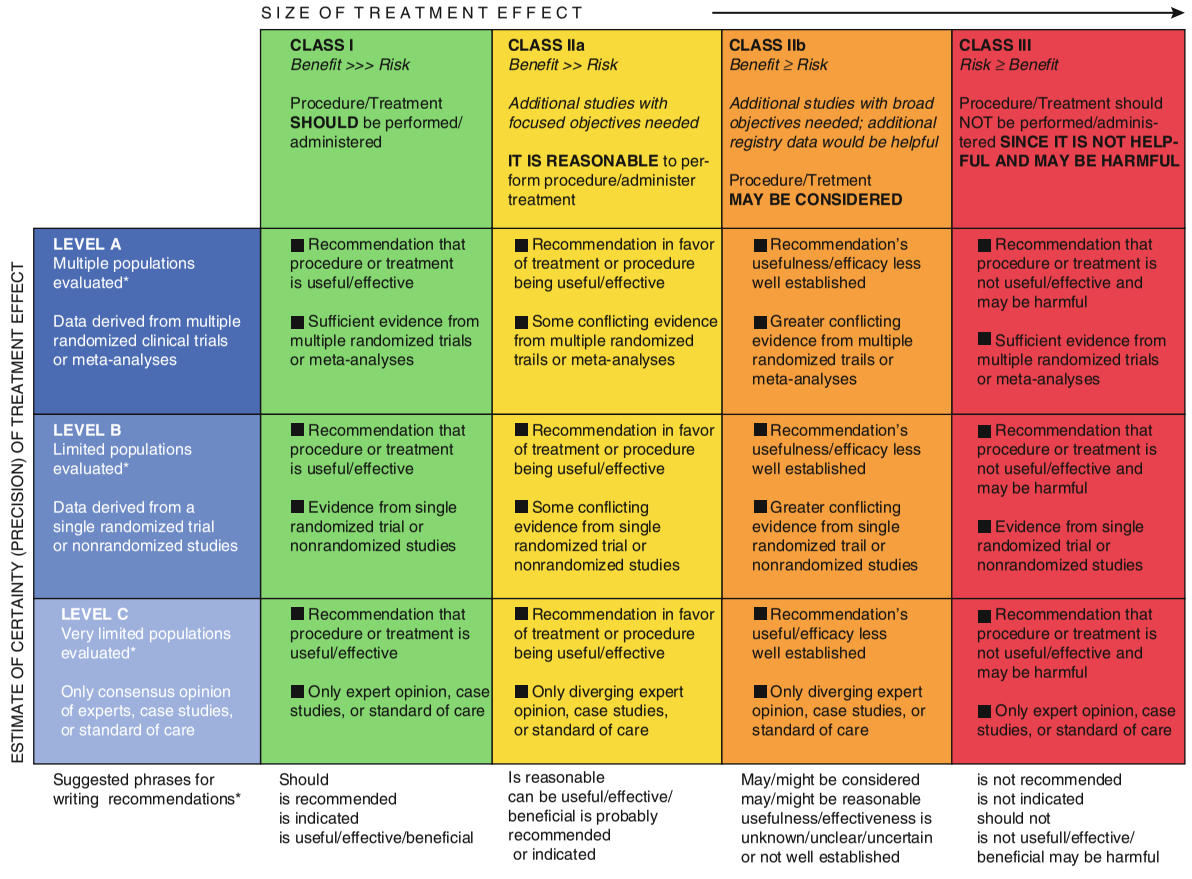

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Abbreviations

%CIn	percent of clotting inhibition
AA	arachidonic acid
Ab	antibodies
ACCP	American College of Chest Physicians
ACoTS	acute coagulopathy of trauma shock
ACP	American College of Physicians
ACS	acute coronary syndrome
ACT	activated clotting time
ADP	adenosine diphosphate
ALI	acute lung injury
AP	antiplatelet
APC	agonist platelet count
APC	activated protein C
aPTT	activated partial thromboplastin time
ARU	aspirin reactions units
ASA	American Society of Anesthesiologists
ASA	acetylsalicylic acid
ASRA	American Society of Regional Anesthesia and Pain Medicine
AT	antithrombin
AT III	antithrombin III
ATC	acute traumatic coagulopathy
ATE	arterial thromboembolism
ATP	adenosine triphosphate
AU	aggregation units
AUC	area under the curve
AVK	anti-vitamin K anticoagulants
AvWD	acquired von Willebrand disease
AvWS	acquired von Willebrand syndrome
BD	base deficit
BMS	bare-metal stents
BNP	brain natriuretic peptide
BPC	baseline platelet count
BT	bleeding time
C4bBP	C4b-binding protein

CA5	clot amplitude at 5 min
CABG	coronary artery bypass graft
cAMP	cyclic adenosine monophosphate
CATS	continuous autotransfusion system
CBC	complete blood count
CERA	continuous erythropoiesis receptor activators
CFT	clot formation time
CHF	chronic heart failure
CLD	chronic liver disease
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
COX-1	cyclooxygenase-1
CPB	cardiopulmonary bypass
CPM	continuous passive motion
CrCl	creatinine clearance
CRF	chronic renal failure
CRP	C-reactive protein
CT	coagulation time
CT	closure time
DATS	discontinuous autotransfusion system
DCR	damage control resuscitation
DCS	damage control surgery
DDAVP	deamino-D-arginine vasopressin
DES	drug-eluting stents
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
EAC	endogenous acute coagulopathy
ECA	endothelial cell activation
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ECS	elastic compressive stockings
ECT	ecarin clotting time assay
EIAs	enzyme immunoassays
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPCR	endothelial protein C receptor
EPI	epinephrine
EPO	erythropoietin
ESA	erythropoiesis-stimulating agents
ESA	European Society of Anaesthesiology
ET	essential thrombocythemia
ETP	endogenous thrombin potential
FBN	fibrinogen
FEIBA	factor eight inhibitor bypassing agent
FFP	fresh frozen plasma

FI	factor I
FNHTR	febrile nonhemolytic transfusion reactions
FVIII	factor VIII
FX	factor X
FXa	activated factor X
FXIII	factor XIII
GP	glycoprotein
GPIb	glycoprotein Ib
HA	human albumin
HAES/HES	hydroxyethyl starch
HAV	hepatitis A virus
HCR	hemostatic control resuscitation
HEA	Hypotensive epidural anesthesia
HELLP syndrome	hemolysis, elevated liver enzymes, and low platelets syndrome
HEV	hepatitis E virus
HF	hyperfibrinolysis
HHS	hypertonic–hyperoncotic solutions
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMWK	high-molecular-weight kininogen
HNA	human neutrophil antigen
HR	hemostatic resuscitation
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
i-CFC	isolated coagulation factor concentrate
ICH	intracerebral hemorrhage
ICU	intensive care unit
IL-6	interleukin 6
INR	international normalized ratio
IPC	intermittent pneumatic compression
ISS	injury severity score
ISTH	International Society on Thrombosis and Haemostasis
ITP	immune thrombocytopenia
ITP	idiopathic thombocytopenic purpura
JW	Jehovah's Witness
LMWH	low-molecular-weight heparin
LPR	low on-treatment platelet reactivity
MA	maximum amplitude
MB	methylene blue
MCF	maximum clot firmness
MI	myocardial infarction
MPS	myeloproliferative syndrome
MTP	massive transfusion protocol

MUF	modified ultrafiltration
MW	molecular weight
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Clinical Excellence
NOAC	novel oral anticoagulant
NS	normal saline
NSAID	nonsteroidal anti-inflammatory drug
NT	N-terminal
OAC	oral anticoagulant
ONTraC	Ontario Nurse Transfusion Coordinators
P	pasteurization
PAI	plasminogen activator inhibitor
PAI-1	plasminogen activator inhibitor 1
PAI-2	plasminogen activator inhibitor 2
PAR4	protease-activated receptor 4
PAS	platelet additive solution
PAU	platelet aggregation units
PBM	patient blood management
PC	platelet count
PC	platelet concentrate
PCC	prothrombin complex concentrate
PCT	photochemically treated
PE	pulmonary embolism
PF4	platelet factor 4
PFA	platelet function analyzer
PGE_1	prostaglandin E1
PK	prekallikrein
PLT	platelets
POC	point of care
PPH	postpartum hemorrhage
PRBC	packed red blood cells
PRU	P2Y12 reaction units
PT	prothrombin time
PV	polycythemia vera
RBC	red blood cell
r-CFC	recombinant coagulation factor concentrate
RCT	randomized control trial
rFVIIa	recombinant activated factor VII
RIPA	ristocetin-induced platelet aggregation
RL	Ringer's lactate
ROTEM	rotational thromboelastometry
RPFA	rapid platelet function assay
rTPA	recombinant tissue plasminogen activator
SCA	Society of Cardiovascular Anesthesiologists
SD	solvent detergent

SIGN	Scottish Intercollegiate Guideline Network
SOPs	standard operating procedures
SSNRI	selective serotonin norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
ST	stent thrombosis
STS	Society of Thoracic Surgeons
TACO	transfusion-associated circulatory overload
TAFI	thrombin-activatable fibrinolysis inhibitor
TAT	thrombin-antithrombin complex
TBI	traumatic brain injury
TEG	thromboelastography
TEM	thromboelastometry
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
THA	total hip arthroplasty
TIC	trauma-induced coagulopathy
TKA	total knee arthroplasty
TM	thrombomodulin
tPA	tissue plasminogen activator
t-PA	tissue-type plasminogen activator
TRALI	transfusion-related acute lung injury
TRAP	thrombin receptor activating peptide
TRIM	transfusion-related immunomodulation
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
TXA	tranexamic acid
TXA2	thromboxane A2
U	units
UFH	unfractionated heparin
u-PA	urokinase-type plasminogen activator
VH or T	vapor and/or heat
VHA	viscoelastic hemostatic assay
VKA	vitamin K antagonist
VTE	venous thromboembolism
vWD	von Willebrand disease
vWF	von Willebrand factor
vWS	von Willebrand syndrome
WHO	World Health Organization
α2-PI	α2-plasmin inhibitor

Contents

Part I

Pre-operative Hemostasis

The Cell-Based Coagulation Model

1

Christoph Sucker and Rainer B. Zotz

1.1 Introduction

The term "hemostasis" summarizes a variety of physiological processes that lead to a cessation of bleeding in case of vascular injury. Hemostasis keeps blood within damaged blood vessels and is therefore a life-saving mechanism. Furthermore, adequate hemostasis is a prerequisite for effective wound healing following injury.

The process of hemostasis is complex. In the initial phase, constriction of injured blood vessels leads to a reduction of blood flow. Then a plug forms, consisting of adhering and aggregating platelets and fibrin; this leads to a complete control of blood loss and allows for the repair of the vascular and tissue defect.

Since antiquity, physicians have been developing and extending theories to explain the process of coagulation. Some of the most important steps on this journey were the description of fibrin as the main content of blood clots, by Johannes Mueller (1801–1858); the description of its precursor, fibrinogen, by Rudolf Virchow (1821–1902); and its isolation by Prosper Sylvain Denis (1799–1863). Alexander Schmidt (1831–1894) and Rudolf Virchow were the first to suggest that the formation of fibrin from fibrinogen is an enzymatic process. Alexander Schmidt termed the fibrinogen-converting enzyme "thrombin" and its precursor "prothrombin" (Schmidt 1872, 1892). In 1890, calcium was found to be essential for coagulation

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(Arthus and Pagès 1890). Platelets were discovered in 1865 and described further in the following years (Brewer 2006).

Paul Morawitz (1879–1936) published his classic theory of plasmatic hemostasis just over 100 years ago. According to his model, prothrombin is converted to thrombin by tissue-derived thrombokinase; thrombin then converts fibrinogen to fibrin – the most important step of coagulation (Morawitz 1905). This first concept of hemostasis was modified and extended over the following years. In particular, more coagulation factors were discovered, allowing for the development of more detailed concepts of the hemostatic process (Wright 1962; Douglas 1999). This resulted in the publication of the "Cascade Model" by MacFarlane and the "Waterfall Sequence Model" of plasmatic hemostasis by Davie and Ratnoff (MacFarlane 1964; Davie and Ratnoff 1964).

In the following sections, we illustrate the process of *primary hemostasis*, defined as all aspects of platelet adhesion and platelet aggregation, and *secondary hemostasis*, defined as the process of fibrin formation and fibrin stabilization. In the final section, we briefly review the most important antithrombotic mechanisms: the *fibrinolytic system*, *protein C/S system*, and *antithrombin*.

1.2 Primary Hemostasis

The term "primary hemostasis" encompasses all aspects of platelet adhesion and aggregation. Apart from platelets, components of the vessel wall – subendothelial matrix components in particular – and von Willebrand factor (vWF) are involved in this process (Riddel et al. 2007). The whole process is depicted in Fig. 1.1.

A healthy endothelium provides a physiological barrier, preventing initiation of hemostasis by subendothelial matrix components, and has specific antithrombotic properties, e.g., the secretion of antithrombotic agents such as nitric oxide and prostaglandins. In the case of vascular injury, a transient local vasoconstriction slows down the blood flow and reduces extravascular blood loss. Hemostasis is initiated when the rupture of this physiological barrier exposes the subendothelium to the blood. VWF is a large multimeric glycoprotein which plays a crucial role in the initial adhesion of platelets, particularly in vascular regions with high shear rates. When subendothelial collagen is exposed to blood due to a vascular injury, vWF quickly binds to it, leading to conformational changes of its binding areas for platelets. This allows platelets to bind to vWF, mediated by their vWF receptors, the glycoprotein (GP) Ib/V/IX complex. This process leads to an approximation of platelets to the endothelial lesion and an initial adhesion. The adhesion is then further stabilized by direct interaction of platelet receptors with subendothelial matrix components, such as contact of platelet collagen receptors GP Ia/IIa and VI with subendothelial collagen. Platelet adhesion to the injured vessel wall and the release of a variety of inductors lead to platelet activation, and through several processes a shape change occurs. The shape change increases the surfaces of the reactive platelets by conversion from a discoid to a globular shape. The excretion of the content of the platelets' α- and δ-granules leads to the release of a variety of components (e.g.,

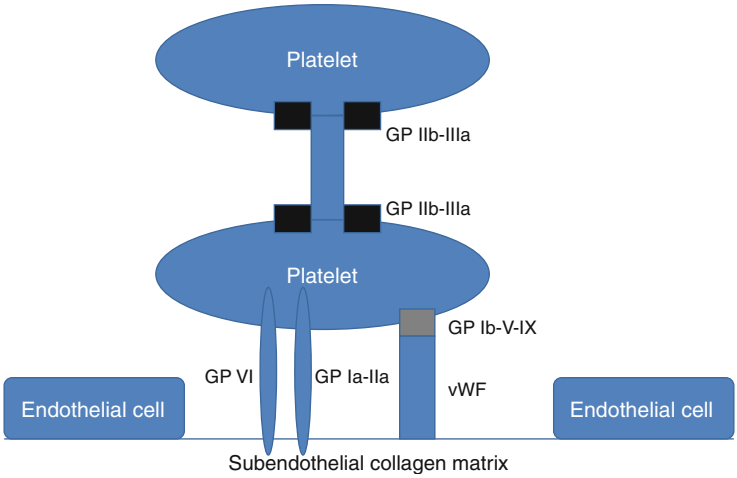


Fig. 1.1 Schematic view of platelet adhesion and aggregation. Following endothelial injury, platelets adhere to collagen by interaction of the receptor glycoprotein (GP) Ib/V/IX with von Willebrand factor which is bound to collagen. This adhesion is stabilized by direct interaction of platelet collagen receptors GP Ia/IIa and GP VI with collagen. Following activation of the aggregation receptors GP IIb/IIIa, platelets aggregate, mediated by von Willebrand factor or fibrinogen

coagulation factors, calcium, ADP) and modulators of hemostasis, such as thromboxane A2 (TXA2) and platelet-activating factor, both of which are potent platelet activators and promote vasoconstriction. Upon activation, platelets also exhibit a more thrombogenic surface by exposing a negatively charged phospholipid layer, providing the catalytic surface for the binding of coagulation factors and, thus, the process of fibrin formation and stabilization (see Chap. 2).

Furthermore, externalization, clustering, and activation of receptors on the platelets' surface occur, allowing for a complex and intense interaction of platelets with matrix proteins and other platelets. In this process, platelets aggregate by cross-linking the highly expressed GP IIb/IIIa aggregation receptors on the platelet surfaces via vWF or fibrinogen.

As a result of primary hemostasis, a primary platelet plug forms on the injured endothelium, mainly consisting of platelets and vWF. This platelet clot is further modified and stabilized by cross-linking of fibrin.

1.3 Secondary Hemostasis: Fibrin Formation and Stabilization

In addition to primary hemostasis as the process of platelet adhesion and aggregation, fibrin formation and stabilization is crucial. The secondary hemostasis process involves multiple enzymatic steps, resulting in the conversion of fibrinogen to fibrin by thrombin and the cross-linking of fibrin by activated coagulation factor XIII. The main proteins needed for plasmatic hemostasis and the process of fibrin generation

Table 1.1 Characteristics of coagulation factors (factor XII is not regarded as an essential coagulation factor according to the current hemostasis model and is, therefore, not shown in the table)

Coagulation factor		Function	Molecular weight (mg/l)	Plasma half-life (h)
I	Fibrinogen	Substrate	3,000	90
II	Prothrombin	Serine protease	100	65
V	Proaccelerin	Cofactor	10	15
VII	Proconvertin	Serine protease	0.5	5
VIII	Antihemophilic factor	Cofactor	0.1	10
IX	Christmas factor	Serine protease	5	25
X	Stuart-Prower factor	Serine protease	10	40
XI	Plasma thromboplastin antecedent	Serine protease	5	45
XIII	Fibrin-stabilizing factor	Transglutaminase	30	200

and stabilization are summarized in Table 1.1. These "coagulation factors" include enzymes of the serine protease family and cofactors that have no enzymatic activity of their own but enhance the reactions of the coagulation enzymes. Some factors, such as tissue factor (formerly factor III) and calcium (formerly factor IV) are no longer regarded as coagulation factors today. Unless activated coagulation factors have an individual name, such as thrombin (factor IIa), they are labeled with the number of the factor and the suffix "a."

In Morawitz's first model of plasmatic hemostasis, prothrombin converted to thrombin in the presence of tissue-derived thromboplastin and calcium, and thrombin then converted fibrinogen to fibrin (Morawitz 1905). In subsequent years, more coagulation factors were detected and characterized, which led to an extension and adaptation of the Morawitz model. However, despite the description of ever more components of hemostasis, the complete interaction of these coagulation factors and the way in which they convert prothrombin to thrombin remained unclear for decades (Riddel et al. 2007). In 1964, two groups of researchers independently reported a model of hemostasis in which the activation of one coagulation factor resulted in the activation of another in a cascade or waterfall sequence, finally resulting in the generation of thrombin. The "Cascade Model" was published by MacFarlane in *Nature* (MacFarlane 1964), shortly followed by an independent publication of the "Waterfall Model," reported in *Science* by Davie and Ratnoff (Davie and Ratnoff 1964). In these closely related models, each coagulation factor was activated by another in cascade sequences, resulting in thrombin generation from prothrombin and conversion of fibrinogen to fibrin. Both models described two different ways in which thrombin formation was induced: firstly there was the intrinsic pathway, for which all the required components were regarded as being present in the blood, and secondly there was the extrinsic pathway, which required an initiation by extravascular, subendothelially localized, and membrane-bound tissue factor (TF) which is identical to the "thromboplastin" reported by Morawitz in 1905. Both models concluded with a final common pathway in which factor X was activated by either the intrinsic or extrinsic pathway, leading to the conversion

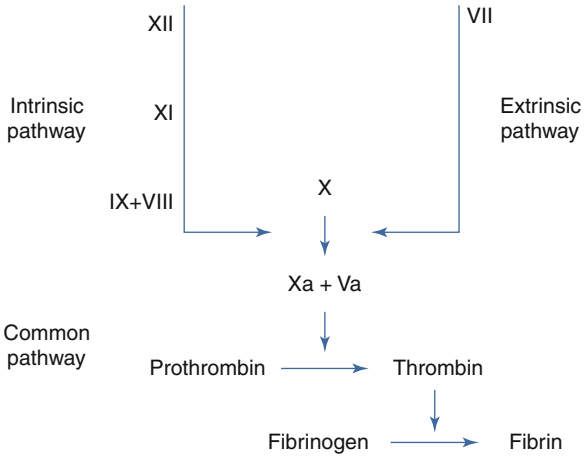


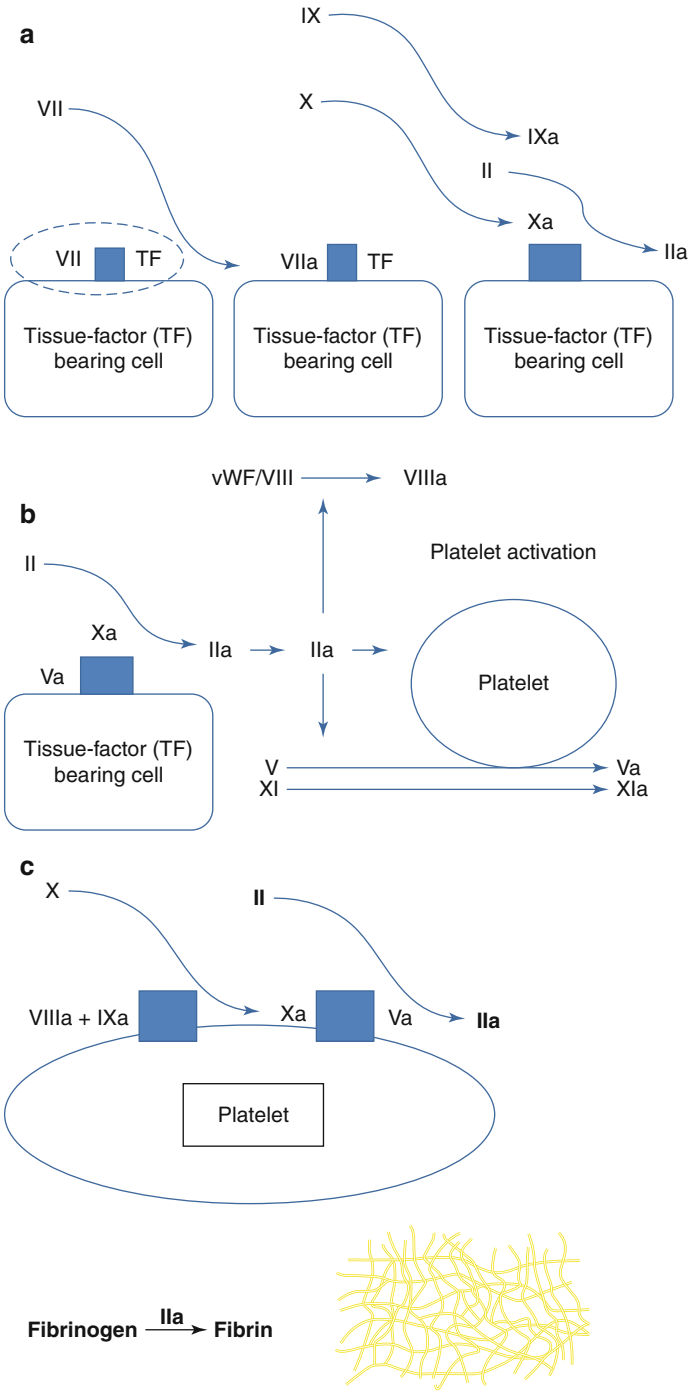
Fig. 1.2 Cascade or Waterfall Model of hemostasis: hemostasis is initiated via activation of the intrinsic or extrinsic pathway of coagulation. In a common final pathway, activated factor X (Xa) together with its cofactor, factor Va, induces thrombin generation from prothrombin, resulting in the conversion of fibrinogen to fibrin

of prothrombin to thrombin and, consequently, to the formation of fibrin from fibrinogen. This classic Cascade or Waterfall Model of plasmatic hemostasis is depicted in Fig. 1.2.

1.3.1 The Current Concept: The Cell-Based Model of Hemostasis

The cascade-type model of hemostasis remained accepted for a long time. However, certain observations led to criticism of this model as it became clear that it was not able to describe the real hemostatic process in vivo. Critical failings in the earlier coagulation models led to further research and the development of a cell-based model of hemostasis by Monroe and Hoffman in 2001. Today this model is widely accepted and regarded as the best description of the process of hemostasis (Hoffman and Monroe 2001; Roberts et al. 2006; Monroe and Hofman 2006).

The cell-based coagulation model distinguishes three distinct overlapping phases of the hemostatic process. According to this concept, *initiation* of coagulation occurs when blood is exposed to TF, expressed on TF-bearing cells. TF then binds to factor VII which leads to activation of factor VII to factor VIIa. If the stimulus is strong enough, further coagulation factors are activated, which results in the formation of small amounts of thrombin generated by the enzymatic cleavage of prothrombin (Fig. 1.3a). The small amounts of thrombin formed in this step, however, are not sufficient for the conversion of fibrinogen to fibrin and for the stabilization of the fibrin clot by means of coagulation factor XIII. In the second phase of the coagulation process, the *amplification*, thrombin activates platelets which then present their thrombogenic surface of negatively charged phospholipids. Here, the coagulation process is catalyzed and thus intensified (Fig. 1.3b). Thrombin activates further coagulation factors, which bind to the activated platelet surfaces and massively increase the thrombin generation in the *propagation* phase of the coagulation process (Fig. 1.3c). The "thrombin burst" generated by these mechanisms leads to


a
IX
X
VII
IXa
II
Xa
IIa
VII
TF
VIIa
TF
Tissue-factor (TF) bearing cell
Tissue-factor (TF) bearing cell
Tissue-factor (TF) bearing cell
b
vWF/VIII
VIIIa
Platelet activation
II
Xa
IIa
IIa
Va
Platelet
Tissue-factor (TF) bearing cell
V
XI
Va
XIa
c
X
II
VIIIa + IXa
Xa
Va
IIa
Platelet
Fibrinogen
IIa
Fibrin

an extensive stimulation of hemostasis and is sufficient to convert fibrinogen to fibrin and to activate factor XIII to XIIIa, which cross-links the fibrin fibers and stabilizes the fibrin clot. In contrast to the previous models, the most recent findings suggest that coagulation factor XII is not needed for the formation of fibrin and not relevant for normal hemostasis.

1.4 Antithrombotic Mechanisms

As a complement to the mechanisms of blood coagulation, antithrombotic mechanisms are required to restrict the process of coagulation, thus preventing thrombotic events. Among these antithrombotic mechanisms, the most important are the *fibrinolytic system* or *fibrinolysis*, *protein C/S system*, and *antithrombin*. Defects in these mechanisms lead to an impaired function of the antithrombotic mechanism and predispose for thrombotic events (Esmon 2006).

1.4.1 Fibrinolytic System

The fibrinolytic system allows for the lysis of a fibrin clot (fibrinolysis). The main fibrinolytic enzyme, plasmin, is derived from its precursor plasminogen upon activation by tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA), which is mainly present in the urine. Plasmin itself cleaves fibrin, producing fibrin degradation products. The fibrinolytic system is strictly regulated. The most important inhibitors are plasminogen activator inhibitor (PAI), which inactivates the plasminogen activators t-PA and u-PA; plasmin inhibitor (previously termed α_2-antiplasmin), which inactivates plasmin; and thrombin-activatable fibrinolysis inhibitor (TAFI), which inhibits the action of plasmin on the fibrin clot. The process of fibrinolysis is depicted in Fig. 1.4. Notably, fibrinolytic capacity differs significantly among different tissues, with high activities in the genitourinary tract and the oral mucosa. This tissue-dependent variability of fibrinolytic capacity provides an explanation of the bleeding pattern in patients with pathologically enhanced fibrinolysis (hyperfibrinolysis).

Fig. 1.3 (**a**) Initiation phase of the cell-based model of hemostasis: the complex of tissue factor (*TF*) and factor VII activates factor VII to factor VIIa. The complex of TF and factor VIIa activates factors IX and X, resulting in the generation of thrombin (IIa) by means of the complex of factor Xa and its cofactor, factor Va (activated by factor Xa). (**b**) Amplification phase of the cell-based model of hemostasis: thrombin activates platelets, which then present a thrombogenic surface. On this catalytic surface, other coagulation factors such as V and XI are activated, and factor VIII is released by its carrier, von Willebrand factor. Factor XIa activates factor IX. Activated platelets bind factors Va, VIIIa, and IXa on their surface. (**c**) Propagation phase of the cell-based model of hemostasis: factor VIIIa/IXa complex activates factor X on the catalytic platelet surfaces, and factors Xa/Va activate prothrombin (factor II), resulting in a massive generation of thrombin (factor IIa) – a "thrombin burst." This burst is able to convert fibrinogen to fibrin and, in addition, to activate factor XIII to XIIIa, which cross-links the fibrin fibers and stabilizes the fibrin clot

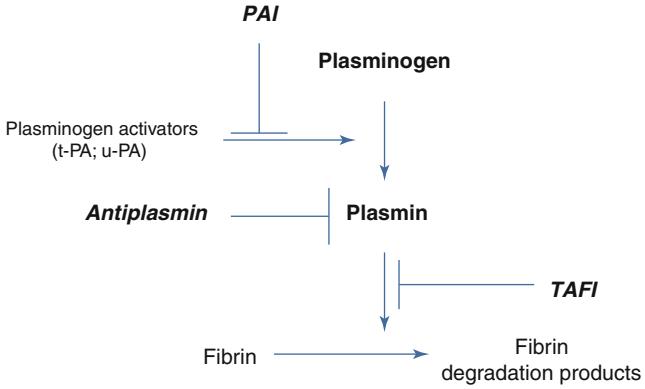


Fig. 1.4 Fibrinolytic system. Plasminogen is converted to plasmin by plasminogen activators, mainly tissue-type plasminogen activator (*t-PA*) or urokinase-type plasminogen activator (*u-PA*). Plasmin cleaves fibrin to fibrin degradation products. The system is strictly regulated by inhibitors such as antiplasmin, plasminogen activator inhibitor (*PAI*), and thrombin-activatable fibrinolysis inhibitor (*TAFI*)

1.4.2 Protein C/S System

The protein C/S system is the main system to terminate an activated clotting process (Esmon 2006). When large quantities of thrombin are generated in the process of plasmatic hemostasis, binding of thrombin to its endothelial receptor thrombomodulin (TM), supported by additional binding of the endothelial protein C receptor (EPCR), initiates the breakdown of plasmatic hemostasis. The complex of thrombin and TM activates protein C. Together with its cofactor, protein S, activated protein C (aPC) cleaves the activated coagulation factors Va and VIIIa, which leads to a breakdown of thrombin formation and, thus, to a cessation of fibrin formation. Deficiencies of protein C and protein S as well as a frequent mutation in the factor V gene that prevents its cleavage by activated protein C, called factor V Leiden, are important inherited risk factors predisposing to thrombotic events. These thrombotic risk factors impair the physiological inactivation of the hemostatic process by aPC, leading to a prolonged and increased thrombin formation and thus an elevated thrombotic risk.

1.4.3 Antithrombin

Antithrombin is an important protein required to localize the coagulation process to the site of vascular injury. In the absence of functional active antithrombin, thrombin and other activated clotting factors would be carried away with the bloodstream and induce clot formation in areas distant from the injured vessel wall. Antithrombin inactivates circulating thrombin by forming enzymatically inactive thrombin-antithrombin complexes. In addition, other activated clotting factors are also

inactivated by antithrombin. Antithrombin deficiency leads to thrombinemia and the presence of activated clotting factors in the blood, potentially inducing blood coagulation regardless of blood vessel injury and thus leading to thrombotic events.

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Laboratory Testing of Hemostasis

2

Fanny Bonhomme and Pierre Fontana

2.1 Introduction

Hemostasis laboratories can carry out large numbers of assays either to obtain accurate and comprehensive diagnoses of hemostatic abnormalities or to monitor antithrombotic treatment. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) are the most prescribed routine tests.

The evaluation of a patient's history, symptoms and clinical signs are essential to assess their bleeding tendency and to determine which laboratory test to use. Moreover, in order to interpret laboratory test results, it is important to understand how the assays are performed and to be aware of their limitations.

A normal range (reference range) is defined as the interval into which 95 % of the values of a reference population fall; thus, 2.5 % of values are inferior to the lower limit, and 2.5 % are superior to the upper limit (Fig. 2.1). Applied to hemostatic testing, this means, for example, that 2.5 % of healthy individuals have a prolonged aPTT (longer than the upper limit).

2.2 Importance of Sample Collection, Processing, and Storage

Pre-analytical variables strongly influence hemostasis test results, and particular attention should be paid to blood collection, sample transportation, and storage. The accuracy of hemostasis tests depends on the sample quality (Lippi et al. 2012).

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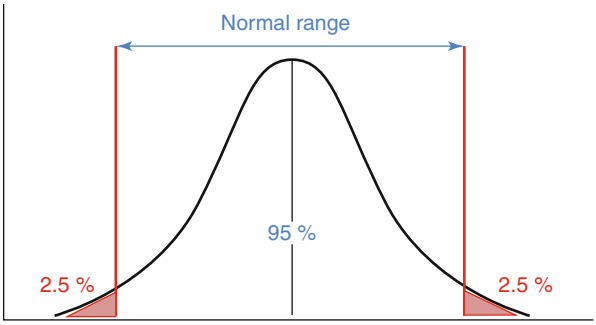


Fig. 2.1 Normal range definition. When values of the reference population are normally distributed, the reference range is defined as the interval containing 95 % of the values

Blood collection must be as thorough as possible in order to obtain reliable results: samples should be obtained from a peripheral vein using an atraumatic puncture, away from any intravenous perfusion line. Tubes containing 3.2 % (0.109 M) sodium citrate are recommended as other anticoagulants may yield invalid results. These tubes must be carefully filled to predetermined levels in order to respect the blood-to-anticoagulant ratio and then gently inverted five times to mix them together. The first few milliliters of blood collected after the puncture should be discarded.

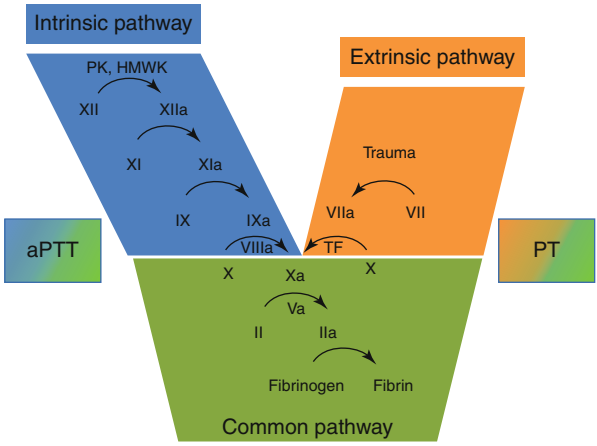
2.3 Coagulation Testing

2.3.1 Coagulation Cascade

The cell-based coagulation model focuses on the successive steps of thrombin generation. These are initiation, propagation, and a burst of thrombin generation that occurs in the close vicinity of cell membranes (i.e., platelets) that provide the phospholipids required for the coagulation reaction (see Chap. 1). Depending on how coagulation is initiated, the classic coagulation cascade describes two somewhat artificial activation pathways that lead to fibrin formation: the intrinsic and extrinsic pathways (Fig. 2.2). The two pathways link up to form a common pathway. This model relates closely to the in vitro coagulation assays usually performed to evaluate the coagulation potency of plasma: aPTT explores the intrinsic pathway, whereas PT explores the extrinsic pathway (Hoffman and Monroe 2005).

2.3.2 Activated Partial Thromboplastin Time (aPTT)

Activated partial thromboplastin time is a clotting assay that measures the intrinsic pathway and is dependent on the concentrations of contact-phase factors (high-molecular-weight-kininogen (HMWK), prekallikrein (PK), factor XII), intrinsic factors VIII, IX, and XI, and on the common pathway factors (II, V, X, and fibrinogen).



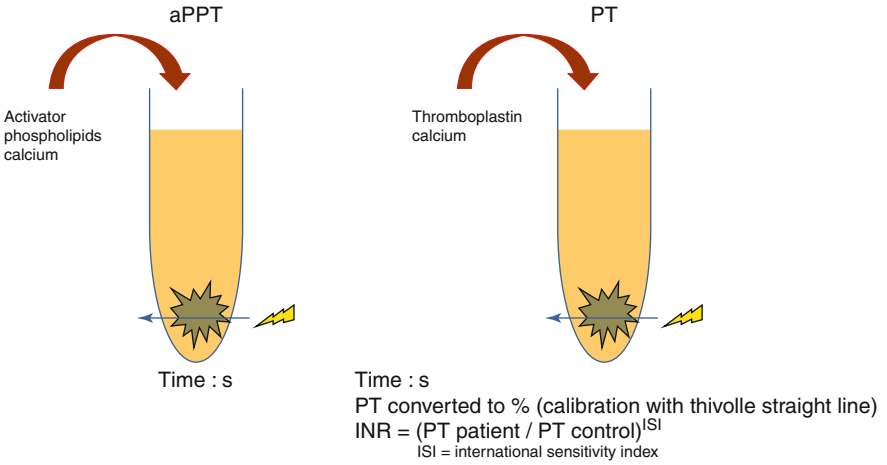


Fig. 2.2 Coagulation cascade model

Fig. 2.3 aPTT and PT principles. aPTT is the time it takes to form a clot after adjunction of calcium and a surface-activating agent into plasma. PT is the time it takes to form a clot after adjunction of calcium and thromboplastin into plasma

After blood centrifugation, calcium and a surface-activating agent are added to plasma. The time it takes to form a clot, expressed in seconds, is aPTT (Fig. 2.3). The normal range is specific to each laboratory and depends on the reagents and device used for the coagulation assay. Generally, aPTT is used as a screening test for a deficiency of more than 50 % in factors VIII, IX, and XI, depending on the reagents used – it is less useful for the detection of deficiencies of common factors. The sensitivity of the test depends on the activators used. The causes of shortened (Lippi et al. 2010) or prolonged aPTT (Olson 1999) are listed in Table 2.1.

Table 2.1 Causes of aPTT abnormalities

Shortened aPTT	
Traumatic/difficult blood puncture	
Pre-analytical problem: handling, storage	
Physical activity	
Obesity	
Pregnancy, postpartum	
Estrogen treatment	
Neoplasia	
Postoperative period	
Venous thromboembolic disease	
Asthma, respiratory failure	
Diabetes	
Hyperthyroidism	
Isolated prolonged aPTT	
Anticoagulant treatment (unfractionated heparin)	Increased hemorrhagic risk
Factor VIII, IX, and XI deficiencies	
Inhibitors of intrinsic pathway factors VIII, IX, and XI	
Factor XII, PK, HMWK deficiencies	No increased hemorrhagic risk
Pre-analytic errors	
Newborns, young infants	
Circulating lupus anticoagulant	Thrombotic risk
Prolonged aPTT and prolonged PT	
Common factor deficiencies (I, II, V, X) or factor inhibitors	Possible increased hemorrhagic risk
Vitamin K deficiency, malabsorption, VKA treatment	
Liver disease	
Some direct thrombin inhibitors	Increased hemorrhagic risk
Disseminated intravascular coagulation	
Dilutional coagulopathy	
Hemorrhage	
Pre-analytic errors	No increased hemorrhagic risk

2.3.3 Prothrombin Time (PT)

Prothrombin time, or Quick time, measures the extrinsic pathway. It assesses the function of factor VII and of the common factors II, V, and X, and fibrinogen. PT is the time it takes for a clot to form after having added calcium and thromboplastin to the plasma. Expressed in seconds, PT is very short in normal individuals (12–13 s). In some countries, PT is expressed as a percentage of the PT of control plasma. For monitoring the treatment of vitamin K antagonist (VKA), PT is standardized according to the characteristics of the thromboplastin and calibrators used and is expressed as an international normalized ratio (INR).

An isolated prolonged PT may rarely reflect an inherited factor VII deficiency (1 in 500,000 of the general population). More commonly it reflects a moderate deficiency in vitamin K-dependent factors.

Prolonged PT, associated with prolonged aPTT, can be due to (Kamal et al. 2007):

- Deficiencies in factors II, V, and X or fibrinogen
- Presence of factor inhibitors

- VKA treatment
- Direct thrombin inhibitor
- Vitamin K deficiency, malabsorption
- Liver disease
- Disseminated intravascular coagulation
- Dilutional coagulopathy
- Hemorrhage

2.3.4 Fibrinogen

Fibrinogen is the most abundant clotting protein in plasma (2–4 g/l). Fibrinogen abnormalities can be either qualitative (dysfibrinogenemia) or quantitative (total lack, afibrinogenemia, or partial deficiency, hypofibrinogenemia).

Fibrinogen measurement is usually performed using a functional qualitative method (von Clauss chronometric assay); when a high concentration of thrombin is added to diluted plasma, the clotting time is proportional to the level of clottable fibrinogen. Fibrinogen activity levels can also be estimated using a prothrombin time-based kinetic assay, which is a rapid, inexpensive, automated assay, although less specific of fibrinogen activity.

Immunoassays for fibrinogen antigen quantification are also available, but are not used for screening tests. These immunological assays measure the protein concentration rather than the functional activity of fibrinogen.

Fibrinogen measurement is indicated in cases of apparent bleeding symptoms or in cases of suspicion of disseminated intravascular coagulation, hepatic insufficiency, or hyperfibrinolysis (Table 2.2).

2.3.5 Specialized Testing

A combination of tests for PT and aPTT is usually the first step of a coagulation assessment. Then, according to the results, further assays may be performed (Sié and Steib 2006).

2.3.5.1 Mixing Studies

A mixing study mixes patient plasma with control plasma. It is able to distinguish between a prolonged clotting time due to a factor deficiency and one due to an

Table 2.2 Causes of abnormal fibrinogen levels

Reduced fibrinogen levels	Increased fibrinogen levels
Disseminated intravascular coagulation	Age
Dilutional coagulopathy	Pregnancy, oral contraception, postmenopausal
Liver disease with decreased synthesis	Inflammatory syndrome
Inherited deficiencies	Malignancy
Thrombolytic therapy	
High doses of corticosteroids	

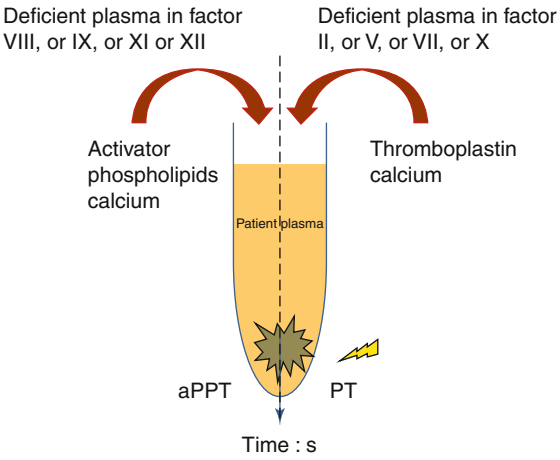


Fig. 2.4 Factor assays principles. Specific factor assays are based on the ability of the patient's diluted plasma to change the clotting times of specific factor-deficient plasmas, measured by aPTT or PT

inhibitor. The control plasma contains the coagulation factors that could be deficient in patient plasma. When the mixture corrects the clotting time, it is indicative of one or more factor deficiencies. When the mixture fails to correct the clotting time, it is indicative of an inhibitor (specific factor inhibitor or lupus anticoagulant).

2.3.5.2 Clotting Factor Assays

Except for the measurement of factor XIII, specific factor assays are based on the ability of patient's diluted plasma to change the clotting time of specific factor-deficient plasmas, measured by PT (for factors II, V, VII, and X) or by aPTT (for factors VIII, IX, XI, and XII). Clotting time is therefore directly proportional to the activity of the factor tested (Fig. 2.4). The result is usually expressed as a percentage of factor activity in control plasma but can also be expressed in IU/dl; one unit of activity being present in 1 ml of normal plasma with 100 % activity, 100 % corresponds to 100 IU/dl. The measurement of factor activity is an essential step in determining the etiology of a prolonged PT or aPTT.

2.3.5.3 Thrombin Time

Thrombin time is the clotting time of plasma in the presence of exogenous thrombin, expressed in seconds. This test looks solely at the conversion of fibrinogen to fibrin. Thrombin time is prolonged in cases of inherited or acquired dysfibrinogenemias or hypo-/afibrinogenemias or in the presence of thrombin inhibitors (heparin, hirudin, dabigatran, elevated levels of fibrin degradation products, some paraproteins, or thrombin antibodies).

2.3.5.4 The Reptilase Test

This test is equivalent to the thrombin time test, but is not sensitive to heparin. It measures the conversion of fibrinogen to fibrin by a thrombin-like enzyme (reptilase). Reptilase is not inhibited by heparin, hirudin, antithrombin antibodies, or antifibrinolytics. The test is used to exclude the presence of dysfibrinogenemia in cases with a prolonged aPTT.

2.3.5.5 D-Dimer Assay

D-dimers are specific breakdown fragments of cross-linked fibrin; they are not produced when non-cross-linked fibrin or fibrinogen are degraded. Increased D-dimer levels reflect the formation of fibrin and subsequent in vivo lysis. There are several methods of measuring D-dimers.

D-dimer levels are elevated in case of thromboembolism (pulmonary embolism, venous thrombosis, arterial thrombosis), malignancy, pregnancy, sepsis, cirrhosis, disseminated intravascular coagulation, and in the postoperative period.

D-dimer levels are widely used to rule out a venous thromboembolic event since a normal result has a high negative predictive value (95–98 %).

2.3.5.6 Thrombin Generation Test

The thrombin generation test measures the quantity of thrombin produced in response to a calibrated stimulus. It is performed on plasma, with or without platelets. The amount of thrombin reflects the overall functioning of the hemostatic system (activators and inhibitors), without assessing fibrinolysis. The main parameters of the thrombogram are (Dieri et al. 2012; Hemker et al. 2006):

- Lag time (= clotting time)
- Peak (= maximal concentration of thrombin)
- Time to peak
- Area under the curve (endogenous thrombin potential = total amount of thrombin)

The thrombin generation test has numerous drawbacks – including the lack of a standardized procedure – which restrict its use mainly to research programs.

2.3.5.7 Thrombophilia Testing

Laboratory testing can help understand recurrent thromboembolic venous or arterial diseases, due to inherited or acquired abnormalities of hemostasis. Thrombophilia can be linked to:

- Anticoagulant protein deficiency: antithrombin, protein C, protein S
- Genetic mutation of factor V (including the Leiden mutation), responsible for activated protein C resistance
- Genetic mutation of factor II (mutation G20210A)
- Presence of antiphospholipid antibodies (anticardiolipin, anti-β2GPI, lupus anticoagulant)

Both functional and antigenic assays are available for antithrombin, protein C, and protein S.

2.4 Primary Hemostasis Testing

Primary hemostasis involves the vessel wall, endothelial cells, platelets, and some serine proteins (von Willebrand factor (vWF), thrombin, and fibrinogen).

Many assays are available for platelet function testing; however, no laboratory test can explore vessel walls or endothelial cells. Platelet function assays are time-consuming, difficult, and very sensitive to pre-analytical variables (drugs, food,

platelet count, temperature, pH, fibrinogen level, quality of sample, storage, transport).

2.4.1 Platelet Count

Platelet count is measured using an automated counter, on blood drawn in EDTA-anticoagulated samples. In cases of thrombocytopenia (<150 G/l), platelet clumps have to be considered; if clumps are identified, platelet count should be assessed on blood collected in citrate-anticoagulated tubes.

The normal platelet count range for adults is 150–400 G/l. Platelet count, of course, does not evaluate their qualitative performance.

2.4.2 Bleeding Time

Bleeding time is supposed to provide an overall picture of primary hemostasis in vivo. It is determined mainly using the Ivy method (normal Ivy incision bleeding time <10 min). The Duke method (earlobe incision) is no longer used. Bleeding time is prolonged in cases of severe thrombocytopenia (platelets <50 G/l), thrombopathy, deep hypofibrinogenemia, afibrinogenemia, dysfibrinogenemia, von Willebrand disease (vWD), severe anemia (hematocrit <30 %), or treatment interfering with platelet function. However, a normal bleeding time does not exclude platelet dysfunction or vWD. The bleeding time procedure is delicate, requiring experienced operators, which partly explains why this method has fallen out of use.

2.4.3 Platelet Function Analyzer (PFA-100® and PFA-200®, Siemens)

The platelet function analyzer is a Food and Drug Administration-approved device used to evaluate acquired or congenital platelet dysfunction and, most importantly, to screen for vWD. This device measures the time (closure time) required for platelets to plug an aperture in a membrane after platelet activation by collagen and epinephrine or by collagen and adenosine diphosphate. This closure time is sometimes referred as the "in vitro bleeding time" and is performed using whole blood (Harrison 2005). Closure time is prolonged in cases of anemia or thrombocytopenia or following the intake of drugs that alter platelet function by inducing acquired thrombopathy.

2.4.4 Light Transmission Platelet Aggregometry

Platelet aggregation assays are indicated for the investigation of inherited or acquired qualitative platelet disorders (Dawood et al. 2012).

These tests are useful in patients suspected with disease of primary hemostasis (purpura, cutaneo-mucous bleeding) with a normal platelet count. After centrifugation, the platelet-rich plasma is incubated with various aggregation activators. Activators commonly used for exploring the different activation pathways of platelets are arachidonic acid, ADP, collagen, TRAP (thrombin receptor agonist peptide), epinephrine, and ristocetin. The modification of light transmission due to platelet aggregation induced by the agonist is then studied. Platelet secretion may also be studied after platelet activation with several agonists. Light transmission platelet aggregometry is usually performed in qualified laboratories.

2.4.5 Diagnosis of von Willebrand Disease

vWD is the most frequent inherited bleeding disorder. The diagnosis is based on bleeding symptoms associated with qualitative or quantitative defects of vWF. The patient's bleeding history, in particular, the family history, is of most importance for the diagnosis of vWD. A panel of assays are available (Favaloro 2009):

- vWF antigen measures the amount of vWF; plasma vWF levels vary with blood group; O blood group patients usually have lower vWF levels (up to 40 %) than individuals of other blood groups.
- Factor VIII coagulant activity measures the functional activity of factor VIII.
- vWF ristocetin cofactor activity and vWF collagen-binding activity measure the functional activity of vWF.

  Further assays are necessary for the diagnosis of subtypes:
- Factor VIII binding assay measures the affinity of vWF for factor VIII (useful in type 2 N vW disease).
- vWF multimer analysis shows how the vWF monomer is multimerized (joined into chains).
- Ristocetin-induced platelet agglutination measures the sensitivity of vWF to ristocetin (useful in type 2B vW disease).

2.5 Monitoring of Antithrombotic Treatment

Several tests are routinely available for assessing the action of anticoagulants such as heparins or vitamin K antagonist. New direct oral anticoagulants (specific inhibitors of thrombin or factor Xa) cannot be monitored using standard coagulation assays and require specific tests. If necessary with regard to antiplatelet therapy, a number of specialized assays are available to assess platelet inhibition, but their utility in clinical and routine practice remains to be determined.

2.5.1 Heparin Monitoring

Since the pharmacodynamic profile of unfractionated heparin (UFH) is poorly predictable, monitoring its anticoagulant effect is essential. The pharmacodynamic

profile of low molecular weight heparins (LMWH) is more predictable, and monitoring should be considered only in selected cases (e.g., mild renal insufficiency or extremely high or low body weight).

2.5.1.1 Unfractionated Heparin (UFH)

aPTT is widely used for monitoring UFH. The target time range is two or three times longer than the basal aPTT value. It must be stressed that the aPTT clotting assay depends on several coagulation factors. Thus, in some instances, aPTT can under- or overestimate the degree of anticoagulation conferred by UFH. This may occur in the case of an important inflammatory syndrome with a very short basal aPTT or in cases of factor deficiency or lupus anticoagulant with longer basal aPTT, for example. In such situations, the use of a specific chromogenic assay that measures the activity of factor Xa provides a more reliable assessment of the anticoagulant effect. Anti-Xa activity measurement requires calibration: a standard curve is constructed using different plasma samples with different concentrations of heparin. After adding known quantities of factor Xa, any residual Xa activity is inversely proportional to the concentration of heparin in the sample. The result can be reported either in international units of heparin per ml (IU/ml) or in anti-Xa units per ml (anti-Xa U/ml).

2.5.1.2 Low Molecular Weight Heparin (LMWH)

LMWHs have a poor antithrombin effect and do not usually affect aPTT. The anti-Xa assay is thus required for monitoring with specific calibrators. Anti-Xa levels are usually measured 3–5 h after a dose of LMWH, when its concentration in the blood is expected to be at its highest level (peak level). Residual anti-Xa tests may also be carried out when accumulation is suspected (e.g., in renal failure).

2.5.2 Fondaparinux and Danaparoid Monitoring

Fondaparinux is a synthetic direct Xa-inhibitor that does not usually require monitoring. In some cases, anti-Xa measurement may be prescribed when there are concerns that fondaparinux may be accumulating. A fondaparinux standard curve is required for reporting fondaparinux levels when using an anti-Xa assay.

Danaparoid is a heparinoid containing heparan sulfate, dermatan sulfate, and chondroitin sulfate. Its activity should be monitored using an anti-Xa assay with danaparoid calibrators.

2.5.3 Vitamin K Antagonist Treatment

See Sect. 2.3.3.

2.5.4 Novel Direct Oral Anticoagulants (NOACs)

Direct oral inhibitors of thrombin (dabigatran) or of factor Xa (rivaroxaban, apixaban) cannot be monitored using simple standardized laboratory assays. At pharmacological doses, these drugs may interfere on different ways with aPTT and PT (depending of the reagents), but aPTT and PT are poorly correlated with NOAC blood concentrations. It should be noted that the standard INR refers to VKA treatment and cannot evaluate the effectiveness of NOACs: the therapeutic ranges of INR used to monitor VKA do not apply to NOACs.

Specific assays for the measurement of NOAC plasma concentrations are available in specialized laboratories and should be ordered in case of hemorrhagic events or emergent surgeries (Sié et al. 2011; Pernod et al. 2013).

2.6 Standard Tests and Predicting Perioperative Bleeding Risk

The goal of preoperative screening for congenital or acquired hemostatic disorders is to prevent perioperative hemorrhagic complications by using appropriate medical and surgical management. When prescribing hemostatic tests prior to invasive procedures, the objective should be to identify those patients with an increased risk of perioperative bleeding. Unfortunately, the standard tests (PT, aPTT, platelet count) have very low positive predictive values for bleeding risk in the general population (Chee et al. 2008; Segal et al. 2005).

The percentage of abnormal test results depends on the indication (systematic testing or clinically indicated), on the reference values, and on the types of patients (Kitchens 2005):

- In selected patients (hemostasis assessment clinically indicated), the percentage of abnormalities may be up to 40 %.
- In patients not selected on the basis of history and clinical examination, standard hemostatic testing revealed 0.5–16.0 % abnormalities.

The performance of systematically prescribed standard hemostatic tests in predicting the bleeding risk during surgery or other invasive procedure is very poor since normal results do not preclude the possibility of hemostatic disease or perioperative hemorrhage.

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Viscoelastic Tests of Hemostasis

3

Catherine Heim and Patrick Schoettker

3.1 Introduction

Traditional plasma-based coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), have proved their utility in detecting abnormalities in the clotting factor cascade. However, these tests evaluate only the initiation of the clotting process and correspond to artificially created segments of hemostasis. They are therefore of limited value in the assessment of the in vivo clotting process. Further, long turnaround times make them poorly suited to the management of acute perioperative bleeding.

In a setting of massive bleeding, the absence of real-time assessment of a patients' capacity for coagulation and his evolving requirements for blood products can be a major issue, leading to empirical treatment and the potential for inappropriate administration of blood products.

The need for a rapid, comprehensive, physiological assessment of the entire process of coagulation, as well as the patient's overall hemostatic capacity, has led to the development of 'global hemostasis assays'; these include viscoelastic tests which allow for a rapid bedside analysis of the patient's in vivo hemostatic condition.

3.2 Viscoelastic Tests

Viscoelastic tests measure the continuous process of clotting in whole blood and its effects on changes in viscosity, elasticity and stability, thus providing global information on the dynamics of a clot's development, its stabilization and ultimately its dissolution (Nair et al. 2010). To date, these tests are the only ones available allowing for a rapid identification of hyperfibrinolysis, a common pattern in massive

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bleeding, especially following major trauma. Today, commercially available viscoelastic tests can be carried out at the bedside and provide the first results within 5 min. There is growing evidence that they may identify early coagulation deficits and thereby facilitate timely goal-directed blood component therapy. Although there is a lack of standardization and evidence-based guidelines for interpretation, these tests are in widespread use in complex surgery and perioperative trauma care. They have also been shown to be valid predictors of transfusion needs (Davenport et al. 2011; Kashuk et al. 2012), to limit the use of blood component therapy and, ultimately, to lead to improved patient outcomes in cardiac surgery, liver transplantation and massive trauma (Ak et al. 2009; Brohi 2009; Johansson 2009; Westbrook et al. 2009; Afshari et al. 2011; Holcomb et al. 2012; Kashuk et al. 2012; Johansson et al. 2013; Tapia et al. 2013). Further, economic analyses have indicated that bleeding management guided by the viscoelastic tests currently available can result in cost savings (Spalding et al. 2007; Gorlinger et al. 2011).

3.3 Technology

Thromboelastography was developed by Dr. Hellmut Hartert in 1948 to describe the viscoelastic changes seen in a sample by using fibrin polymerization (Hartert 1948). Recent innovations adding computer technology have improved its utility for clinical and perioperative assessment and the management of clotting disorders.

There are currently two types of viscoelastometric point-of-care apparatus available on the market: a thromboelastography (TEG) device, the TEG® Hemostasis Analyzer (Haemonetics Corp., Braintree, MA, USA), and a rotational thromboelastometry device, the ROTEM® (Tem International GmbH, Munich, Germany), which evolved from TEG technology. The TEG system has been available for many years in the United States, whereas the US Food and Drug Administration only approved the ROTEM system for clinical use in 2010 (www.fda.gov).

These point-of-care devices are used to assess viscoelastic changes in clotting whole blood under low-shear conditions after the addition of a specific coagulation activator. TEG® and ROTEM® measure the dynamic interaction of coagulation factors, inhibitors and the cellular components of blood during the phases of clotting and subsequent lysis (Solomon et al. 2012; Romlin et al. 2013) (Fig. 3.1). The test procedures are based on a motion sensor which detects clot formation in whole blood in a sample cup. Hartert's original experiment (Hartert 1948) used a metal pin suspended by a torsion wire and immersed in the non-anticoagulated whole blood in a metal sample cup. In TEG®, it is the sample cup that rotates around an immersed fixed pin; in ROTEM®, it is the immersed pin which rotates in a fixed sample cup. Modifications in the rotation as clotting progresses are recorded electronically and expressed both numerically and graphically. TEG® and ROTEM® are static measurement techniques that do not take into account flow-related influences on coagulation capacity. The basic principle of both devices involves the incubation of around 300 µl of citrated whole blood in a cylindrical plastic sample cup which is heated to 37 °C. Adding $CaCl_2$ leads to the recalcification necessary for clot initiation. Then, as the cup and the pin begin to oscillate relative to each other, the sample is activated with a test-specific reagent (Table 3.1). With the start of thrombin generation,

Picture 3.1 TEG® and ROTEM® device

Table 3.1 Technical characteristics of TEG® and ROTEM®

Characteristics	TEG® 5000	ROTEM® delta
Pipetting	Manual	Automated
Measuring technique	Shear elasticity of a coagulation sample by motion of the cup	Shear elasticity of a coagulation sample by motion of the pin
Pin motion	Fixed	Moving
Angle of rotation/oscillation time	4°45′/5 s	4°75′/6 s
Detection system	Pin transduction	Impedance of rotation
Type of detection	Electronic	Optical
Signal transducer	Electrical-mechanical transducer	Optical 4 CCD chips
Measuring channels	2	4
Temperature control (°C)	20–40	30–40
Temperature regulation	Heated cup	Heated metal block
Cup interior and material	Smooth cryolite	Rigid polymethylmethacrylate
Sample volume	360 µl	300 µl
Total reaction volume	360–380 µl	320–340 µl
Operable to height above sea level	3,048 m (10,000 ft)	2,000 m (6,560 ft)

platelets are activated, expressing glycoprotein (GP) IIb/IIIa receptors, and fibrin is formed and subsequently polymerized. The interactions between the GP IIb/IIIa receptors and the polymerized fibrin increase the sample's viscoelasticity which in turn increases the torque between the sample cup and the pin. The suspended pin is connected to a detector system, either a torsion wire (TEG®) or an optical detector via the reflection of light onto a small mirror (ROTEM®). As the sample clotting process progresses, fibrin strands form between the cup and the pin, further impeding rotational movements. These changes are also detected, either mechanically or

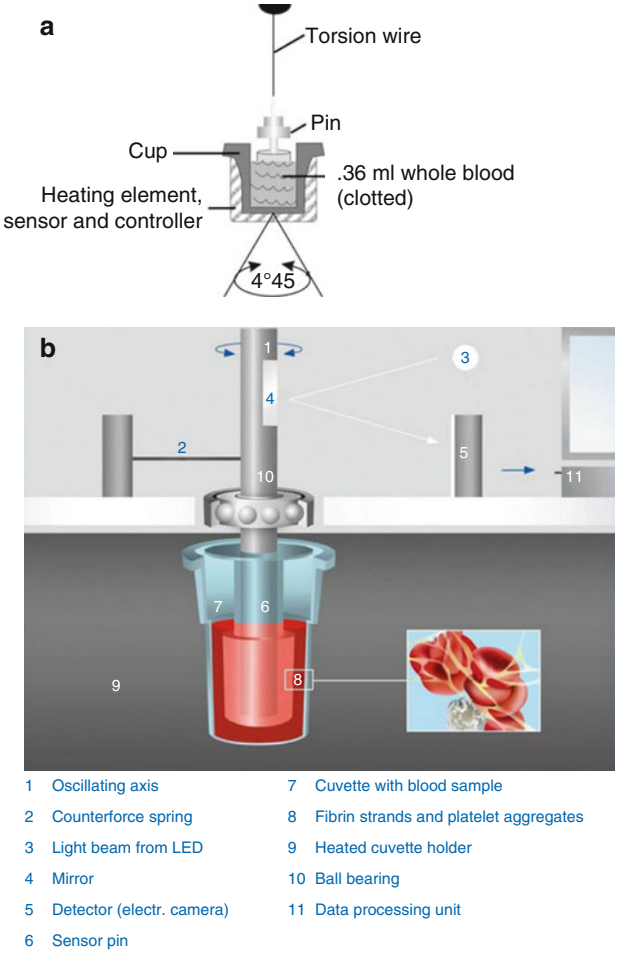

Fig. 3.1 (**a**) Technology for TEG® 5000 (Adapted from www.haemonetics.com). (**b**) Technology for ROTEM® (Adapted from www.rotem.de)

optically, then transmitted electronically and transformed into numerical and graphical read-outs (Figs. 3.1a, b). When no clotting takes place in a ROTEM® assay, for example, the pin's movement is not obstructed, whereas if a clot does form, it attaches to the pin and cup surfaces, impairing pin movement. An amplitude of 0 mm means unobstructed oscillation (no clot), whilst an amplitude of 100 mm can be regarded as total firmness—the pin is completely blocked by the clot.

3.4 Tests and Agents

Whilst TEG® originally used non-anticoagulated whole blood, today this method is essentially only used in research settings. For clinical use, both systems now employ citrated whole blood which is recalcified to initiate coagulation. This allows longer sample storage: in the case of ROTEM®, up to 120 min (Theusinger et al. 2010b). It must be noted that blood sampling using sodium citrate tubes dilutes the blood

samples by approximately 10 %. In addition, citrate may affect platelet GP IIb/IIIa receptors and therefore influence thromboelastographic measurements (Camenzind et al. 2000; Zambruni et al. 2004).

To initiate the sample clotting process in a standardized way, the use of an activator is recommended. Originally, TEG® used celite as a contact activator, but this has been replaced by kaolin (kaoTEG), kaolin + tissue factor (RapidTEG), kaolin + heparinase or abciximab. There are multiple liquid reagents available for ROTEM®, such as ellagic acid and phospholipids (INTEM), tissue factor (EXTEM) and lyophilized heparinase, aprotinin or cytochalasin D as standard activators (Table 3.2). A single-use reagent exists for all ROTEM® tests, thus allowing easier test comparisons, with good correlations to the classic reagents (Rahe-Meyer et al. 2009).

Tissue factor activation enables the clot to reach its maximum amplitude within 10 min. TEG® offers a rapid variant for emergency settings: the rapid (R)-TEG®. R-TEG® differs from standard TEG® via an addition of tissue factor which enhances (RapidTEG) clotting speed; this produces a visualization of the initial clotting phase within seconds and is therefore increasingly used. However, the information on coagulation and clot formation it provides is very limited due to a significant shortening of the reaction time (*R* value), and this could potentially lead to loss of valuable information about this period of clotting. Platelets and fibrinogen are essential components of a clot.

Running several tests in parallel allows a comparative analysis. Comparison of EXTEM and FIBTEM is suited to distinguishing hypofibrinogenaemia from thrombocytopenia. Antifibrinolytic agents (aprotinin) are used to detect fibrinolysis by comparing APTEM to EXTEM. The presence of a heparin effect can be detected by comparing HEPTEM with INTEM (ROTEM®), by using the kaolin clotting time test with or without addition of heparinase (TEG®), respectively. The independent contributions of fibrinogen and platelets can be analysed by adding platelet inhibitors such as abciximab in TEG® or cytochalasin D in ROTEM®.

Table 3.2 Activators for different tests in TEG® and ROTEM®

Activator		Test		
TEG®	ROTEM®	TEG®	ROTEM®	Interpretation
Kaolin	Ellagic acid/ phospholipid	Kaolin	INTEM	Contact activation Similar information to aPTT
Kaolin + tissue factor	Tissue factor	Rapid TEG	EXTEM	Similar information to ACT (R-TEG) and PT (ROTEM)
Kaolin + heparinase	Lyophilized heparinase	Heparinase	HEPTEM	Detection of heparin effect
	Aprotinin		APTEM	Detection of fibrinolysis
Abciximab	Cytochalasin D	TEG functional	FIBTEM	Analysis of fibrinogen component of clot
	Ecarin		ECATEM	Detection of presence of direct thrombin inhibitors

The determination of activated clotting time (ACT) is another piece of information that existing test methods can provide through the incorporation of tissue factor and kaolin into a TEG® sample cup.

Viscoelastic tests may also be helpful in screening for hypercoagulable states. TEG® and ROTEM® analyses of patients with a history of thromboembolic complications showed shorter *R* values and accelerated clot propagation when compared to healthy reference subjects. An increased maximal amplitude (MA) may be a useful indicator of the risk of postoperative thromboembolic events. However, further studies are needed to determine the clinical value of viscoelastic tests for screening for thromboembolic complications (Wilson et al. 2001; McCrath et al. 2005).

3.5 Parameters Measured by TEG® and ROTEM® (Fig. 3.2)

The main goal of TEG® and ROTEM® is the determination of viscoelasticity as expressed by clot amplitude and clot firmness. The dynamic evolution of clot formation over timescale allows a clinical understanding of clot formation. The two systems are a closely related, but due to technical differences, their results are not completely interchangeable. The different materials of the surfaces of the pin and cup exert their forces on procoagulant activity to different extents. Data from older studies using TEG® with metal cups and native whole blood cannot be compared directly with more recent studies using plastic cups and recalcified whole blood (Ganter and Hofer 2008). Reference values are also different between plasma and native or recalcified citrated blood. Nevertheless, the most significant reason for different clot formation variables is the use of different activators at various

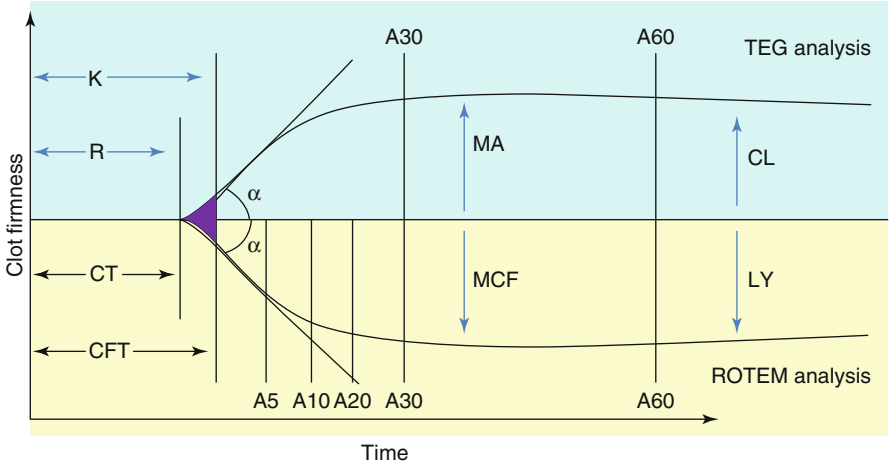

Fig. 3.2 TEG® and ROTEM ® output demonstrating clot initiation, propagation, stabilization and lysis. TEG® parameters: *R* reaction time, *K* kinetics, *α* alpha angle, *MA* maximum amplitude, *CL* clot lysis, *A* amplitude at set time in min (30 and 60). ROTEM® parameters: *CT* clotting time, *CFT* clot formation time, *α* alpha angle, *MCF* maximum clot firmness, *A* amplitude at set time in min (5, 10, 20 and 30), *LY* clot lysis

concentrations. Clinical reference values differ between the two systems and must be interpreted accordingly. Reference values for TEG® are based on unspecified surgical patient samples of limited size (Haemoscope Corporation 2007), whilst those established for ROTEM® were determined in a multicenter study of patients and healthy volunteers (Lang et al. 2005).

There are also differences in nomenclature between the devices and other minor details exist (Table 3.3 and Fig. 3.2).

3.5.1 TEG®-Derived Parameters

R 'Reaction time' (seconds). Time from the start of the test to initial fibrin formation; corresponding to a clot amplitude of 2 mm. This represents the enzymatic portion of the coagulation process.
Simplified: R represents coagulation factors.

K 'Kinetics' (seconds). Time necessary to achieve a given clot strength of an amplitude of 20 mm.
Simplified: *K* represents thrombin.

α Alpha angle. The slope between *R* and *K*. Corresponds to the speed of fibrin build-up and cross-linking/clot strengthening. Dependent on fibrinogen levels.
Simplified: α represents the speed of clot formation.

Table 3.3 Summary of the variables measured

Variable	TEG®	ROTEM®	Process	Correlation to conventional tests
Time from start to 2 mm above baseline	Reaction time R	Clotting time CT	Interval between the start of the test and appearance of the first clot. Initiation of thrombin generation and clot polymerization. Expression of coagulation factor activity	PT, INR, ACT (for R-TEG)
Time from start of clotting to amplitude of 20 mm	*K*	Clot formation time (CFT)	Rate of clot formation, fibrin polymerization and cross-linking with platelet interaction	aPTT, fibrinogen concentration
Alpha angle α	α (slope between *R* and *K*)	α (angle of tangent at 2 mm amplitude)	Rate of clot formation, fibrin polymerization and cross-linking with platelet interaction	Fibrinogen concentration, platelet count
Maximum strength	Maximum amplitude (MA)	Maximum clot firmness (MCF)	Stabilization of clot by platelets and factor XIII	Platelet count
Clot lysis at specific time (min)	CL30, CL60	LY30, LY45, LY60	Degree of fibrinolysis after a given amount of time	

MA Maximum amplitude (millimetres). Represents the ultimate strength of the fibrin clot and therefore the interaction of fibrin, platelets and factor XIII. It is related to the maximum dynamic properties of fibrin and platelet bonding via GP IIb/IIIa. It is affected by changes in fibrinogen, platelet count, function and aggregation.
Simplified: MA represents platelet function, fibrinogen and factor XIII.

A30 Amplitude reached at 30 min after *R*-time.

CL30 Percentage of decrease in clot amplitude at 30 min after MA. Expresses the degree and speed of fibrinolysis as the relationship between amplitude at 30 min and MA

3.5.2 ROTEM®-Derived Parameters

CT Clotting time. Time from the start of measurement to the initiation of clotting.
Simplified: depends on thrombin formation.

CFT Clot formation time. Time from the initiation of clotting to the achievement of clot firmness at 20 mm. Represents the initial rate of fibrin polymerization.
Simplified: depends on fibrin polymerization, platelets and FXIII (acting as clot stabilizer).

α angle Indicates the speed at which a solid clot forms.
Simplified: depending on platelet function and to lesser extent to fibrinogen and coagulation factors.

MCF Maximum clot firmness and viscoelastic strength.
Simplified: clot strength depends mainly on polymerized fibrin, platelets and FXIII.

A10 Amplitude 10 min after CT. Early indicator of achievable MCF.

ML Maximum lysis. Indicates the decrease of clot firmness after MCF. An ML >15 % is a diagnostic for a premature breakdown of the clot (hyperfibrinolysis).

3.6 Differences Between TEG® and ROTEM®

TEG® and ROTEM® basically provide similar informations on the kinetics and strengths of clot formation and have been shown to produce comparable results when samples were activated with the same exogenous activator (Zambruni et al. 2004). However, differences in operating characteristics when different activators are used render their results non-interchangeable (Nielsen et al. 2005; Nielsen 2007; Venema et al. 2010). The use of different nomenclature for identical parameters also makes comparison difficult.

Depending on the activator used, clotting speed can vary significantly. INTEM-activated plasma (ROTEM®), for example, generates a time to clot initiation three times faster than kaolin-activated plasma, as used in TEG® (Nielsen 2007).

Further, viscoelastic test results are also dependent on the concentration of activator in the sample as this particularly affects clot initiation and propagation by influencing thrombin generation (Nielsen et al. 2005). Differences in the composition of the plastic polymer sample cups, which could generate greater surface charges, could potentially contribute an additional source of differences in results (Roche et al. 2006). It has been demonstrated that the plastic tube in which citrated blood is collected may provide additional inference in the activation of coagulation (Roche et al. 2006). However, it seems unlikely that these would affect clinical decision making (Nielsen 2007), and relative trends within one method are still expected to be comparable.

These specificities explain part of the differences in the reference ranges shown in Table 3.4. The manufacturer of TEG® recommends that each institution should determine its own normal values.

Another difference is the speed of result acquisition, with ROTEM® having a faster turnaround time (5–10 min) than TEG® (15–20 min). The main reason for this is that ellagic acid (ROTEM®) activates coagulation faster than kaolin (TEG®).

The two methods have been the subjects of numerous claims about their equivalency or superiority, but neither has actually been proven superior. One study comparing the diagnostic performances of TEG® and ROTEM® in the detection of dilutional coagulopathy, thrombocytopenia, hyperfibrinolysis and the presence of heparin suggested that ROTEM® not only readily distinguishes all the types of coagulopathy cited but also provides faster diagnosis; TEG®, however, failed to distinguish dilutional coagulopathy from thrombocytopenia (Larsen et al. 2011). On the other hand,

Table 3.4 Reference ranges for TEG® (from 'User manual TEG® 5000 Thromboelastograph Hemostasis System') and EXTEM (ROTEM®) (Lang et al. 2005)

Sample type	*R* (min)	*K* (min)	Angle (degree)	MA (mm)	*G* (kd/sc)	Sample size[a]
Celite/kaolin	4–8	0–4	47–74	54–72	6.0–13.2	132
Sodium citrate celite/kaolin	2–8	1–3	55–78	51–69	4.6–10.9	98
Native	12–26	3–13	14–46	42–63	3.2–7.1	132
Sodium citrate native	9–27	2–9	22–58	44–64	3.6–8.5	132
Tissue factor	1–3	1–3	57–78	55–75	6.0–13.0	178
Sodium citrate plus TF	0–2	0–5	52–82	46–72	2.7–12.5	41
Tissue factor kaolin	17–38	30–118	66–82	54–72	5.3–12.4	86
Citrated tissue factor kaolin	22–44	34–138	64–80	52–71	5.0–11.6	89
Tissue factor plus functional fibrinogen	–	–	–	9–29	0–2.0	72
Citrated tissue factor plus functional fibrinogen	–	–	–	10–25	0.5–1.7	72

Test	Normal range (median)
CT (s)	42–74 (55)
CFT (s)	46–148 (95)
A10 (mm)	43–65 (53)
MCF (mm)	49–71 (60)
ML (%)	0–18 (4)

[a]Sample sizes range from 41 to 78 depending on the participating hospitals

ROTEM® has a lower sensitivity to the effect of aspirin on platelets and is, unlike TEG®, unable to detect the effect of low molecular weight heparin (LMWH). TEG® has the advantage of offering a specific test of platelet function, the TEG® Platelet Mapping™ assay. This test analyses platelet function by measuring clot strength and maximum amplitude, reflecting maximum platelet function and detecting reduction in platelet function, represented as percentage of inhibition (see Chap. 4).

Whilst the ROTEM® FIBTEM assay has been validated as an accurate estimate of the fibrinogen contribution to clot strength independent of platelets, the TEG® Functional Fibrinogen assay requires further validation (Solomon et al. 2012). Neither test is a suitable substitute for the traditional plasma-based determination of fibrinogen levels using the Clauss method. Furthermore, the correlation between FIBTEM MCF and the plasmatic concentration of fibrinogen worsens after exogenous fibrinogen administration (Solomon et al. 2011).

Based on these differences, caution is warranted when interpreting comparative data generated by TEG® and ROTEM®. TEG®-based treatment algorithms should not be used thoughtlessly for ROTEM®-based sample analysis and vice versa. Therefore, whilst these two devices can, under similar circumstances, generate similar data, their processes, involving different activator agents, are not equivalent and must be well understood.

3.7 Examples of Interpretation and Special Conditions

The assessments made by TEG® and ROTEM® are illustrated graphically along the horizontal time axis (left to right). The shapes of these representations are often as useful as the results of individual values. The types of activators used need to be taken into account when interpreting reference ranges (Figs. 3.3 and 3.4).

Examples from ROTEM traces with permission from (www.rotem.de)

3.7.1 Normal Patient: Fig. 3.5a

3.7.2 Platelet Deficiency: Fig. 3.5b

3.7.3 Fibrinogen Deficiency: Fig. 3.5c

An abnormal clot formation is indicated by a prolonged clot formation time (CFT) and/or a reduced maximum clot firmness (MCF). The CFT is thereby influenced more strongly by a clot polymerization disorder than the MCF. A prolonged CFT associated with a normal MCF primarily indicates a polymerization disorder, whereas a reduced MCF associated with a normal CFT indicates a deficiency of the clotting substrate such as fibrinogen and/or platelets.

Normal
R; K; MA; Angle = Normal

Anticoagulants/hemophilia
Factor Deficiency
R; K = Prolonged;
MA; Angle = Decreased

Platelet Blockers
Thrombocytopenia/
Thrombocytopathy
R ~ Normal; K = Prolonged;
MA = Decreased

Fibrinolysis (UK, SK, or t-PA)
Presence of t-PA
R ~ Normal;
MA = Continuous decrease
LY30 > 7.5 %; WBCLI30 < 97.5 %;
Ly60 > 15.0 %; WBCLI60 < 85 %

Hypercoagulation
R; K = Decreased;
MA; Angle = Increased

D.I.C
Stage 1
Hypercoagulable state with
secondary fibrinolisis

Stage 2
Hypocoagulable state

Fig. 3.3 TEG output in various clinical situations (From 'User manual TEG® 5000 Thromboelastograph Hemostasis System')

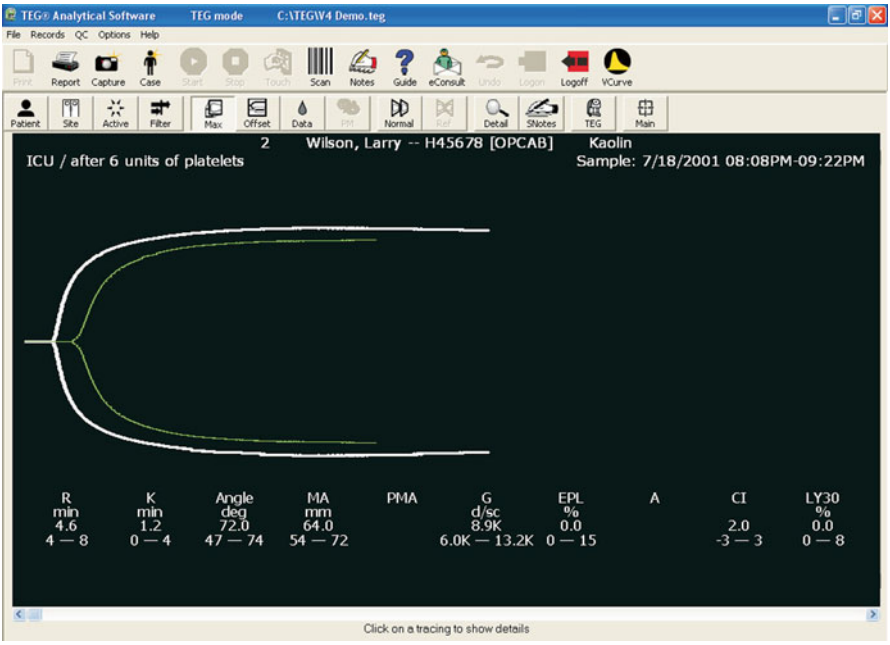

Fig. 3.4 Example of a TEG trace before and after treatment

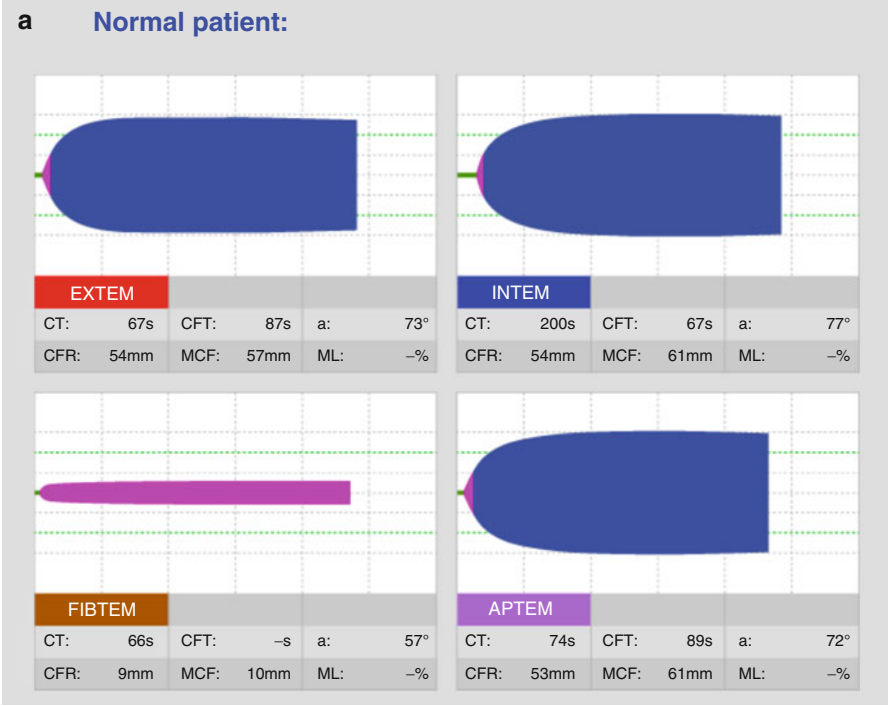

Fig. 3.5a With permission from www.rotem.de

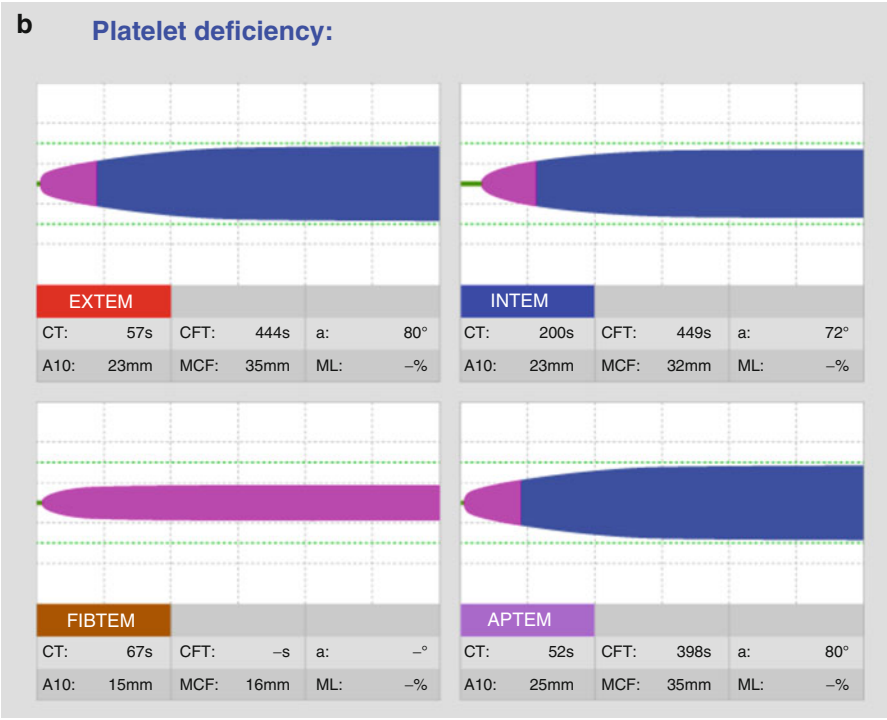

Fig. 3.5b With permission from www.rotem.de

3.7.4 Hyperfibrinolysis: Fig. 3.5d

Fibrinolysis is detected by the lysis of the clot. This is defined as an ML value >15 % or by the discovery of better clot formation in APTEM than in EXTEM. This is expressed as an overall shorter CFT and a greater MCF in APTEM than in EXTEM. In patients with massive bleeding, several algorithms use the shortening of the CT value in APTEM in comparison to EXTEM, as a trigger for the administration of an antifibrinolytic drug. Both TEG® and ROTEM® have been shown to give reliable values for diagnosing and monitoring hyperfibrinolysis and for guiding antifibrinolytic therapy in severely bleeding patients (Levrat et al. 2008; Hunt 1996). An assessment of fibrinolysis is based on the measurement of the kinetics of clot destruction expressed as LY30/ML, measuring the decrease of MA/MCF after its peak value. Additionally, ROTEM® provides a specific test, the APTEM, which allows the comparison of clotting with (APTEM) and without (EXTEM) the addition of an antifibrinolytic agent. In trauma patients, this test has been shown to provide a specificity of 100 % and a high sensitivity of 75–100 % (Levrat et al. 2008).

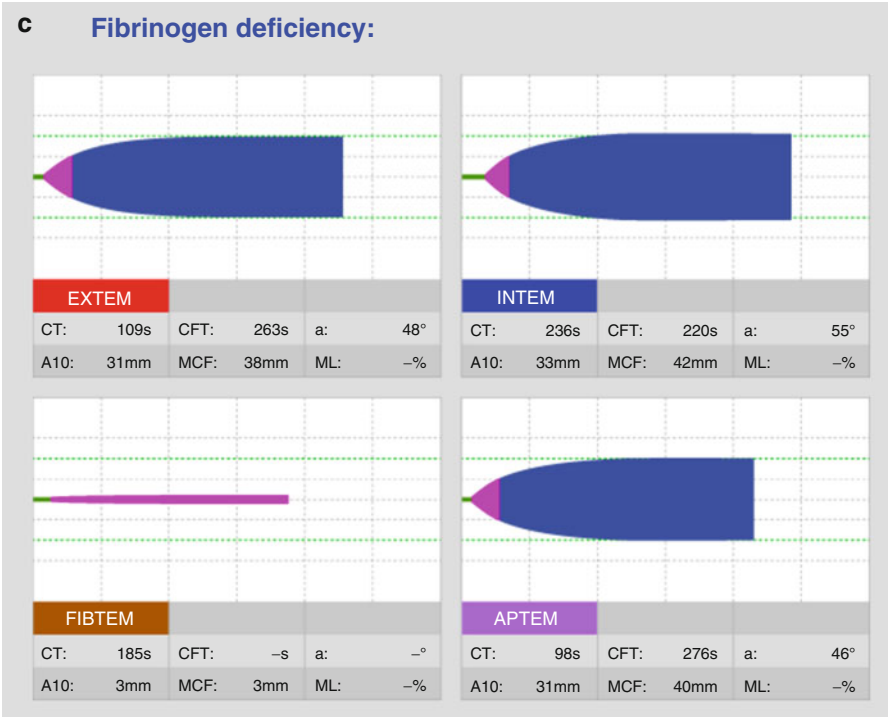

Fig. 3.5c (With permission from www.rotem.de)

3.7.5 Heparin Influence: Fig. 3.5e

Prolonged clotting time indicates that the activation of coagulation is perturbed. Factor deficiency, or inactivation due to the presence of heparin, for example, needs to be considered. Heparin reversal after cardiac surgery is traditionally guided by measuring ACT, despite evidence that correlation to plasmatic heparin concentration is poor. TEG® and ROTEM® may provide useful information about residual heparin effects after protamine reversal by comparing R or CT in whole blood with and without the addition of heparinase (Ak et al. 2009) (Sect. 3.7.5).

3.7.6 Influence of Specific Coagulation Factors

R and CT are prolonged in cases of inherited or acquired coagulation factor deficiencies. Normalization of these, after the administration of fresh frozen plasma, fibrinogen concentrate or prothrombin complex concentrates, is an indicator of the normalization of coagulation factor activity.

Correction of coagulation factor deficiencies will further increase clot strength and can be seen in enhanced MA (TEG®) and MCF (ROTEM®). However, persistent low MA or MCF, despite the substitution of coagulation factors, is mainly due

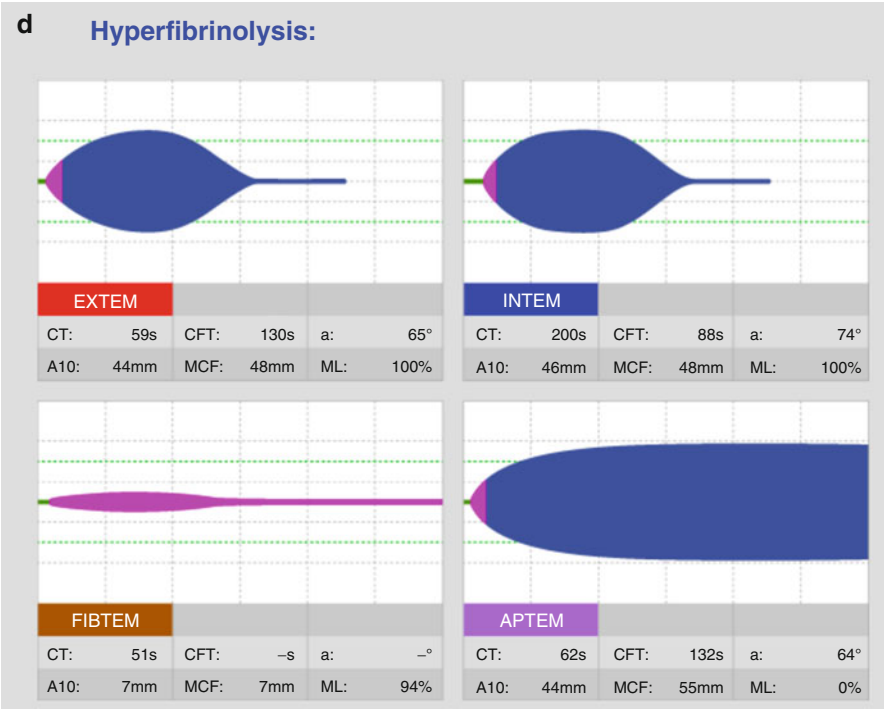

Fig. 3.5d With permission from www.rotem.de

to a lack of either fibrinogen or platelets. Typically, R or CT will be normalized whilst MA or MCF remains below reference values, producing a narrowed trace.

The distinction as to whether a lowered MA or MCF is due to fibrinogen or platelet deficiency can be made by adding platelet inhibitors, as in the functional fibrinogen test (TEG®) or the FIBTEM (ROTEM®), thus showing fibrinogen's contribution to clot firmness (Sect. 3.7.3).

ROTEM® and TEG® are both sensitive to the administration of rFVIIa, generally demonstrating a dose-dependent decrease of R or CT, with a concomitant increase of MA or MCF. This response, however, is best seen in cases of inherited coagulopathies and less in patients with acquired coagulation deficiencies (Sorensen and Ingerslev 2005). According to the concept that an optimal response to rFVIIa treatment necessitates the presence of sufficient clotting components, the use of TEG® or ROTEM® may be helpful in optimizing coagulation profiles before the administration of rFVIIa. The value of these devices for monitoring the efficacy of this therapy is less clear.

FXIII contributes to the conversion of fibrin monomers into fibrin polymers and therefore to clot firmness. Low levels of FXIII have been identified using ROTEM® and expressed as a low MCF, increased clot formation time and fibrinolysis (Jambor et al. 2009); substitution resulted in increased clot strength and reduced CFT (Theusinger et al. 2010a). TEG® and ROTEM® may therefore be used to help guide FXIII substitution therapy.

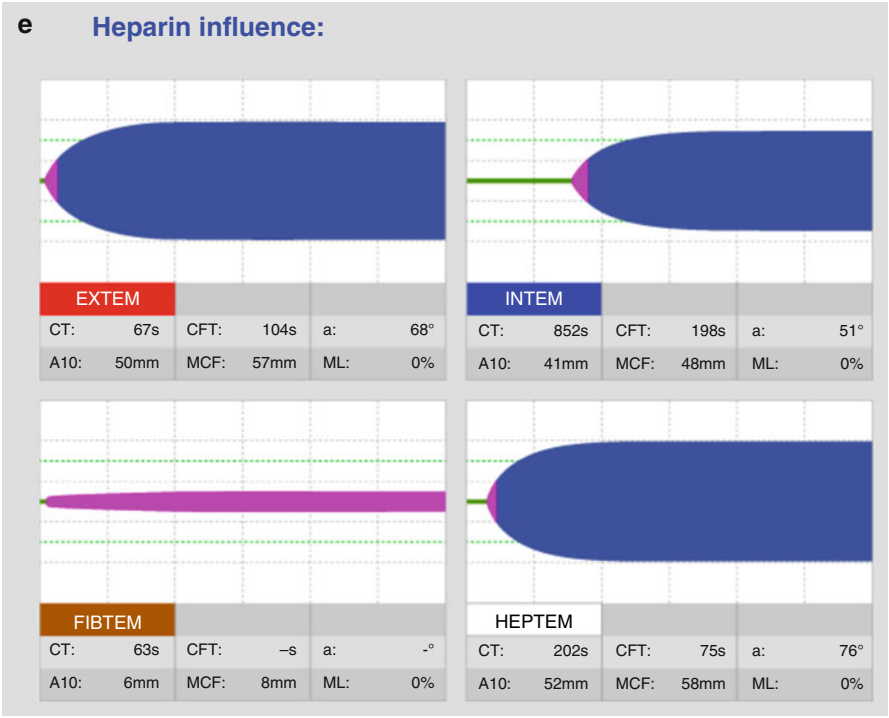

Fig. 3.5e With permission from www.rotem.de

3.8 Downsides and Caveats

Several issues are as yet unresolved with regard to the standardization of methodology and the interpretation of currently available viscoelastic tests. To date, neither TEG® nor ROTEM® has been validated for clinical use. Standardization of interpretation and evidence-based treatment algorithms are lacking and subject to intense research. Further, significant inter-laboratory variability has been revealed (with coefficients of variation exceeding 10 %) and needs to be addressed (Kitchen et al. 2010; Chitlur et al. 2011). Regular external quality controls and proficiency testing should be mandatory. Personnel using these devices need to be adequately trained to avoid manipulation errors (Ganter and Hofer 2008).

Due to the fact that it is a mechanical device, with its pin in free suspension, TEG® is easily affected by external vibrations or shocks and thus needs to be performed in a vibration-proof environment. This may indeed be a difficult requirement for a point-of-care device in an emergency setting. The automated pipette, touch screen and intuitive software of ROTEM®, on the other hand, are seen by many as particularly user friendly.

TEG® and ROTEM® analyses are commonly used as point-of-care coagulation tests in emergency and operation rooms as well as in intensive care settings.

However, in some centres, these tests are performed in specialized, centralized laboratories, thus allowing dedicated, qualified personnel to perform these moderately complex coagulation assays under the appropriate quality control guidelines. A rapid transport system to the laboratory, combined with a dedicated computer network to provide an online display of the results at the point-of-care, makes laboratory-conducted thromboelastography and thromboelastometry comparable with bedside testing regarding turnaround times and results (Wallin et al. 2008).

Conclusion

TEG® and ROTEM® technology allows a real-time assessment of the viscoelastic properties of clot formation and lysis in whole blood. Running several samples in parallel, using a variety of activators and inhibitors, allows detailed separate analysis of clot initiation, propagation, stabilization and dissolution. The influence of various components can be distinguished. Many newer diagnosis and treatment algorithms for bleeding patients include the use of TEG® or ROTEM®. However, despite evidence that such algorithms reduce blood product use and improve clinical outcomes, further studies are warranted in order to determine a clinical correlation with their results and to allow for the development of evidence-based treatment guidelines.

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Point-of-Care Platelet Function Tests

4

Gabriele Casso, Fabio Lanzi, and Carlo E. Marcucci

4.1 Introduction

Platelets are small, discoid, anucleate blood cells produced by cytoplasmic fragmentation of megakaryocytes (George 2000). In the adult, 1×10^{12} inactive blood platelets are continuously flowing over 1,000 m^2 of vascular surface with minimal adhesion or aggregation (Versteeg et al. 2013). Platelets play a key role in primary hemostasis. Their main function, when activated, is to stop hemorrhage after tissue trauma and vascular injury. However, platelets are also important contributors to pathological thrombotic disorders (e.g., acute coronary syndromes, ischemic stroke, peripheral occlusive arterial disease) (Davi and Patrono 2007; Jennings 2009) and an increasing number of patients require long-term antiplatelet therapy.

Platelet activation by the principal agonists during primary hemostasis and the site of action of antiplatelet drugs are described in Fig. 4.1.

Even though inherited or acquired platelet dysfunction can influence bleeding during surgery, evidence for the usefulness of perioperative platelet function analysis is still controversial (Kehrel and Brodde 2013).

The European Society of Anaesthesiology (ESA) recently published guidelines on the management of severe perioperative bleeding (Kozek-Langenecker et al. 2013). Recommendations about perioperative platelet function analysis are weak. Preoperative platelet function testing is only suggested in relation to a positive bleeding anamnesis. In cases with a suspicion of decreased platelet function caused by medical conditions or by antiplatelet therapy, platelet function assessment can be used preoperatively.

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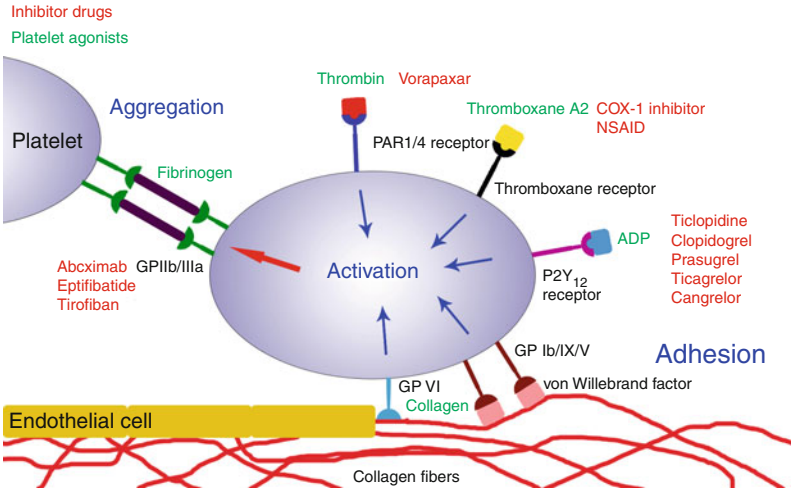

Fig. 4.1 Platelet agonists involved in platelet activation and site of action of antiplatelet drugs

In 2012, the Society of Thoracic Surgeons (STS) published updated guidelines on the use of antiplatelet drugs in patients having cardiac and noncardiac surgery (Ferraris et al. 2012). Its experts recommended that for patients on dual antiplatelet therapy it is reasonable to use objective tests, rather than arbitrarily defined delays, to decide on the timing of surgery (Class IIa, level of evidence B). Preoperative platelet function assessment may be useful to identify patients—those with high residual platelet reactivity despite antiplatelet drugs—who can undergo surgery without an increased risk of bleeding (Class IIb, level of evidence B). Finally, point-of-care testing of perioperative platelet function may be useful in limiting blood transfusions (Class IIb, level of evidence B).

4.2 Point-of-Care Platelet Devices

Various methods for platelet function analysis exist today (Harrison 2005; Michelson 2009; Pakala and Waksman 2011; Kehrel and Brodde 2013). Most of them must be performed in a laboratory setting on centrifuged platelet-rich plasma: light transmission aggregometry, for example, originally described by Born in 1962 (Born 1962), is still considered the "gold standard." These laboratory tests are time-consuming and require training and laboratory skills.

Recently, several whole blood point-of-care tests have been developed which can be performed in a near-patient setting, for example, in operating theaters or intensive care units (Enriquez and Shore-Lesserson 2009). The potential advantages of these tests are simplified workflows (no transport of samples to laboratory), rapid turnaround times, and targeted management of coagulation disorders.

As yet, a "perfect," standardized, and widely accepted point-of-care platelet function assay that can be used in acute perioperative settings does not exist (Sambu and Curzen 2011). All the techniques available have their strengths and weaknesses; therefore, it is important to understand the potential indications and limitations of these different devices.

In this chapter, we will present the working mechanisms, normal values, interpretation, clinical use, limitations, and pitfalls of the five point-of-care platelet function analyzers most widely used in perioperative care today. Unless stated otherwise, the normal ranges described are those provided by the manufacturers. It is noteworthy that some manufacturers advise the establishment of local normal ranges.

The principle behind all of these devices is the same: platelets are activated using selective receptor agonists—epinephrine, adenosine diphosphate (ADP), collagen, arachidonic acid (AA), prostaglandin E1 (PGE_1), thrombin, or thrombin receptor-activating peptide (TRAP). After activation, maximum platelet function is measured using different methods: one is based on shear stress (Platelet Function Analyzer (PFA)-100/200®), three on platelet aggregation (Plateletworks®, VerifyNow®, Multiplate®), and one on platelet contribution to clot strength (TEG Platelet Mapping®). The presence of an antiplatelet drug will reduce platelet activation by the specific agonist; however, activation by the other agonists remains possible (e.g., clopidogrel will only suppress activation by ADP). The failure of antiplatelet therapy, whether labeled as low treatment response, drug resistance, or high on-treatment platelet reactivity, can easily be determined using these tests when a specific agonist can still activate platelets despite treatment using the corresponding receptor blocker. This finding is associated with an increased risk of thromboembolic complications, such as thrombosis of a coronary stent. Low on-treatment platelet reactivity, on the other hand, is diagnosed when a very high degree of inhibition is found and is associated with an increased risk of bleeding complications.

GP IIb/IIIa inhibitors do not interfere with platelet activation but interfere with aggregation by inhibiting the platelet-fibrinogen interaction. The presence of these drugs will thus reduce aggregometry measurements regardless of the activator used.

Finally, in global platelet dysfunction, not related to antiplatelet drugs, all of the agonists fail to sufficiently activate patients' platelets.

4.2.1 Platelet Function Analyzer (PFA)-100/200®

4.2.1.1 Working Mechanism (Fig. 4.2)

The PFA-100/200® system (Siemens Healthcare Diagnostics, Deerfield, IL, USA) simulates platelet adhesion, activation, and aggregation (primary hemostasis) under high shear flow conditions in disposable cartridges. This can be defined as a kind of in vitro bleeding time. Small amounts (0.8 ml) of citrated whole blood are aspirated at high shear rates (5,000–6,000/s) through a small capillary toward a platelet-activating membrane with a microscopic aperture (147 μm). The cartridge

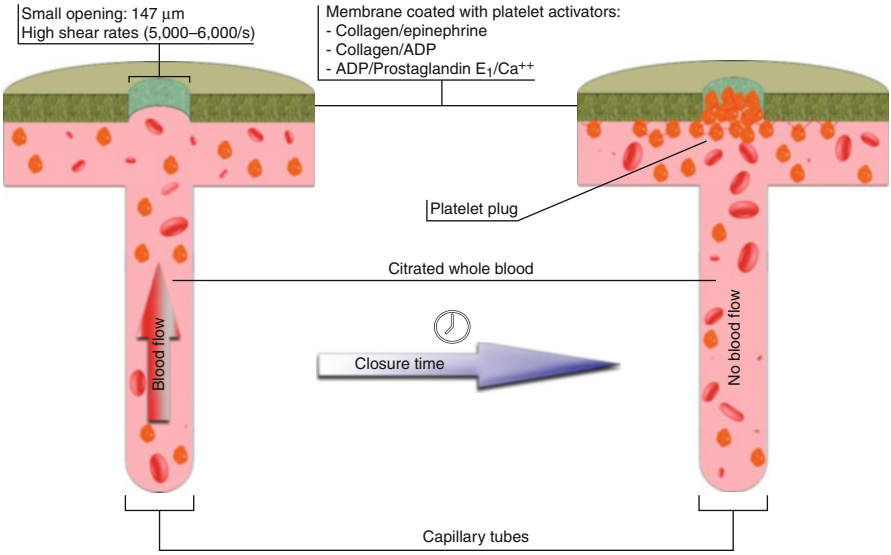

Fig. 4.2 Working mechanism of the PFA 100/200® system

membranes are coated with collagen and either epinephrine (COL/EPI) or adenosine diphosphate (COL/ADP). A new cartridge (Innovance® PFA P2Y) using a membrane coated with ADP, prostaglandin E1, and calcium has recently become available; it is supposed to be more sensitive to P2Y12 inhibitors. The activators, in association with the high shear rates, induce platelet activation and aggregation leading to a gradual occlusion of the small aperture by a growing platelet plug. Time to complete occlusion of the membrane orifice, inducing cessation of blood flow, is termed closure time (CT) and expressed in seconds (s). Platelet function is inversely correlated to CT. The test is completed in 5–8 min (maximum CT 300 s) and must be performed within 4 h of blood sample collection.

4.2.1.2 Normal Values and Interpretation

The normal values for PFA-100/200® are presented in Table 4.1.

A prolonged CT for both the COL/EPI and COL/ADP tests is indicative for anemia (hematocrit >0.28), thrombocytopenia (platelet count $<100 \times 10^9$/l), von Willebrand disease (vWD), or an inherited/acquired platelet dysfunction (e.g., GP IIb/IIIa inhibitors) (Madan et al. 2001, 2002)).

In the case of a prolonged CT for COL/EPI, but a normal COL/ADP test, platelet dysfunction has most likely been induced by acetylsalicylic acid (ASA). An Innovance® PFA P2Y CT of more than 106 s implies drug-induced inhibition of the P2Y12 receptor (e.g., clopidogrel).

If the Innovance® PFA P2Y CT is less than 106 s in a patient treated with a P2Y12 receptor-blocking agent, low treatment response is likely.

Table 4.1 Normal values for the PFA-100/200® assays

Assay	CT
COL/EPI	≤180 s
COL/ADP	≤110 s
INNOVANCE®PFA P2Y	≤106 s

CT closure time, *s* seconds

4.2.1.3 Clinical Use in Perioperative Care

PFA® is a simple and rapid global platelet function screening assay. In a recent meta-analysis, the pooled, weighted sensitivity and specificity for the tests used to detect a primary hemostasis disorder were 82.5 and 66.9 % for the COL/EPI and 88.7 and 85.5 % for the COL/ADP (Karger et al. 2007). The PFA® system has been used to identify platelet function disorders before surgery (Cammerer et al. 2003; Koscielny et al. 2004). In patients with a positive bleeding history, it demonstrates a high sensitivity and specificity for preoperative platelet dysfunction (Koscielny et al. 2004). In cardiac surgery, there are conflicting results about its capacity to predict postoperative bleeding. Some studies seem positive (Cammerer et al. 2003; Sucker et al. 2011), others negative (Wahba et al. 1998; Forestier et al. 2002; Fattorutto et al. 2003). In orthopedic surgery, preoperative prolongation of the PFA-100® test was correlated with increased postoperative drain output (Ng et al. 2009). In neurosurgery, preoperative screening with the PFA® system increased the administration of desmopressin, without reducing perioperative bleeding or transfusions (Karger et al. 2012).

4.2.1.4 Limitations and Pitfalls

CT increases progressively with decreases in hematocrit (<0.28 %) and if the platelet count falls below 100×10^9/l. CT is highly dependent on von Willebrand factor (vWF) levels (inverse correlation). This test is not sensitive for all platelet function disorders (e.g., gives a false negative in patients with storage pool disease or mild type I vWD) (Favaloro 2001). There is little data on the validity of the new Innovance® P2Y assay (Linnemann et al. 2010; Edwards et al. 2012; Tsantes et al. 2012; Scavone et al. 2014).

Advantages and disadvantages of the (PFA)-100/200® are presented in Table 4.2.

4.2.2 Plateletworks®

4.2.2.1 Working Mechanism

Plateletworks® (Helena Laboratories, Beaumont, TX, USA) is based on platelet aggregation in a fresh whole blood sample. When activated by agonists, platelets form aggregates resulting in a reduction in the number of plasmatic free platelets. The Plateletworks® methodology is simple, and the test is quick to perform (less than 5 min). The two-step method first involves using an impedance cell counter (e.g., ICHOR® or IICHOR II® from Helena Laboratories, Beaumont, TX, USA) to measure the baseline platelet count (BPC) in an EDTA anticoagulated whole blood

Table 4.2 Drug sensitivity, advantages, and disadvantages of the (PFA)-100/200® system

Assessment of drug effect	+	−
Aspirin P2Y12 inhibitors	Rapid, automated, and easy test Can be used by non-skilled personnel Whole blood, no requirements for sample preparation Low sample volume (pediatric use) High shear condition rates (physiological condition)	Requires pipetting Dependent on hematocrit and platelet count Depends on vWF levels

sample (1 ml). The second step is to repeat the platelet count on another citrated sample that has been exposed to a known platelet agonist (collagen, ADP, or AA). The agonist will stimulate functional platelets to aggregate into clumps. These aggregates exceed the threshold limitations for platelet size and the cell counter no longer counts them as platelets. The difference in the platelet count between the baseline and agonist platelet count (APC) in the stimulated samples provides a direct measurement of platelet aggregation.

4.2.2.2 Normal Values and Result Interpretation

The percentage of platelet aggregation is defined as $[(BPC-APC)/BPC] \times 100$. The percentage of platelet inhibition can be defined as $(APC/BPC) \times 100$.

Thrombocytopenic samples (until platelet count $>27 \times 10^9$/l) may be tested using the Plateletworks® assay. Finally, the cell counting system provides a complete blood count (CBC).

Normal ranges for the various activators are presented in Table 4.3.

Combining the results of the different tests allows for the detection of and differentiation between various causes of platelet dysfunction (Table 4.4).

4.2.2.3 Clinical Use in Perioperative Care

The Plateletworks® assay has been used to monitor reversal of preoperative clopidogrel and nonsteroidal anti-inflammatory drug (NSAID) inhibition in elective surgery patients (Craft et al. 2005). In cardiac surgery, preoperative platelet inhibition measured using the Plateletworks® collagen test was associated with increased postoperative blood loss (Ostrowsky et al. 2004). A recent study also found a significant correlation between reduced Plateletworks® ADP-induced platelet aggregation and postoperative blood loss in patients treated with clopidogrel undergoing coronary artery bypass grafting (CABG) (Dalen et al. 2012).

Table 4.3 Reference ranges for the Plateletworks® assays

Assay	Reference range
AA	60–100 % aggregation
ADP	86–100 % aggregation
Collagen	70–100 % aggregation

AA arachidonic acid, *ADP* adenosine diphosphate

Table 4.4 Interpretation of test results for the Plateletworks® assays

AA (aggregation)	ADP (aggregation)	Collagen (aggregation)	Interpretation
Normal 60–100%	Normal 86–100%	Normal 70–100%	Normal platelet function, no significant effects of antiplatelet drugs
Abnormal <60%	Normal 86–100%	Abnormal <70 %	Aspirin (COX-1 inhibition)
Normal 60–100%	Abnormal <86%	Abnormal <70%	P2Y12 inhibitor or GP IIb/IIIa inhibitor
Abnormal <60%	Abnormal <86%	Abnormal <70%	P2Y12 inhibitor or GP IIb/IIIa inhibitor with aspirin
Normal 60–100%	Normal 86–100%	Abnormal <70%	Fibrinolysis or adhesion defect

AA arachidonic acid, *ADP* adenosine diphosphate, *COX-1* cyclooxygenase-1

4.2.2.4 Limitations and Pitfalls

The agonist tube should be tested within 10 min of the collection of the blood sample in order to avoid overestimation of platelet inhibition as a result of spontaneous platelet disaggregation (van Werkum et al. 2010). Advantages and disadvantages of the Plateletworks® assay are presented in Table 4.5.

4.2.3 VerifyNow®

4.2.3.1 Working Mechanism (Fig. 4.3)

VerifyNow® (Accumetrics, San Diego, CA, USA) is based on the former Ultegra Rapid Platelet Function Assay (RPFA). The RPFA was introduced in 1998, primarily for monitoring GP IIb/IIIa antagonist activity (Smith et al. 1999). The device is easy to use and provides a result rapidly, using about 2 ml of citrated whole blood. It is a fully automated point-of-care test that requires no pipetting. The tube containing the

Table 4.5 Drug sensitivity, advantages, and disadvantages of the Plateletworks® system

Assessment of drug effect	+	−
Aspirin P2Y12 inhibitors GP IIb/IIIa inhibitors	Rapid and easy test Whole blood, no requirements for sample preparation Provides CBC and platelet count Low sample volume (1ml) Can be used in thrombocytopenic patients	Analysis time dependent (sample must be examined within 10 min of collection) Few clinical studies

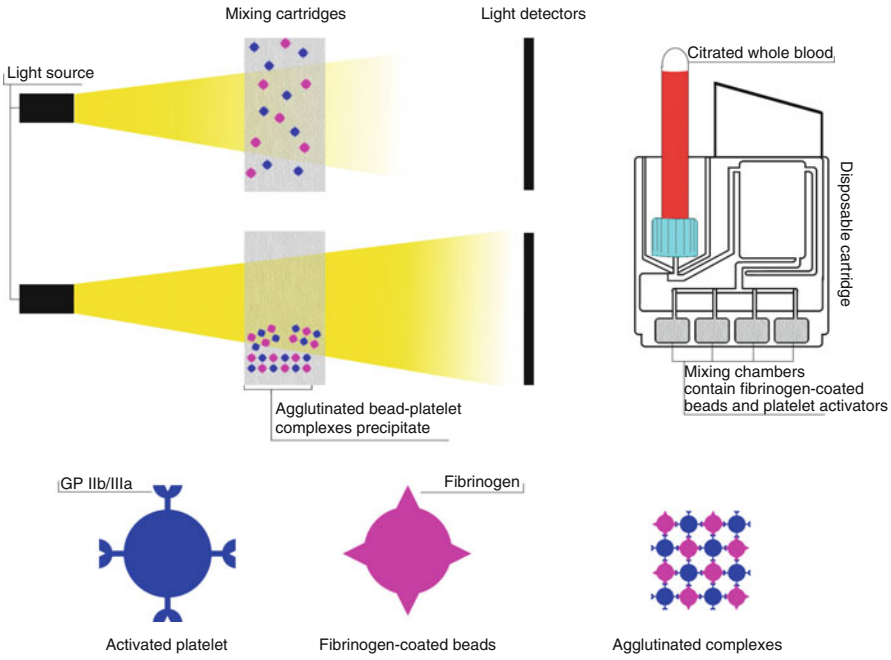

Fig. 4.3 Working mechanism of the VerifyNow® system

blood sample is directly inserted onto a special disposable cartridge. The cartridges' mixing chambers contain fibrinogen-coated polystyrene beads and platelet activators: 4 μM of TRAP in the VerifyNow IIb/IIIa test®, 1 mM of AA in the VerifyNow Aspirin test®, and 20 μM ADP + 22 nM PGE_1 in the VerifyNow PRU test®.

Table 4.6 Baseline values and expected ranges after abciximab and eptifibatide treatment for the VerifyNow IIb/IIIa ® assay

Drug	Baseline prior to drug administration	≥80 % inhibition	≥95 % inhibition
abciximab	125–330 PAU	0–44 PAU	0–13 PAU
eptifibatide	136–288 PAU	0–31 PAU	0–10 PAU

PAU platelet aggregation units

Stimulated platelets will activate GP IIb/IIIa receptors on their surface, which will bind to the fibrinogen, agglutinating the beads. Agglutinated bead-platelet complexes will precipitate and the solution will become more transparent. The device continuously measures light transmittance through the mixing chamber and directly correlates this to the proportion of platelet activation. Direct pharmacological blockade of the GP IIb/IIIa receptors or indirect suppression of their expression by AA or ADP inhibitor drugs diminishes platelet aggregation and therefore light transmittance. The VerifyNow IIb/IIIa test® must be run within 15 min of drawing the blood sample. The VerifyNow PRU test® and the VerifyNow Aspirin test® require sample incubation times of 10 and 30 min, respectively.

4.2.3.2 Normal Values and Result Interpretation

4.2.3.2.1 VerifyNow IIb/IIIa Test®

This test measures GP IIb/IIIa receptor blockade in patients treated with abciximab or eptifibatide. The GP IIb/IIIa test also detects platelet inhibition by tirofiban, but no normal range or cutoff values are available for this drug; results for these patients should therefore be interpreted with care.

In patients treated with abciximab, blood samples are collected in citrated tubes. Heparinized tubes must be used in patients treated with eptifibatide.

TRAP-mediated expression of GP IIb/IIIa receptors involved in platelet aggregation is expressed in platelet aggregation units (PAU). Expected values are in the range of 0–330 PAU.

Baseline and expected values are represented in Table 4.6.

4.2.3.2.2 VerifyNow Aspirin Test®

This test uses AA as its activator, which the platelets' cyclooxygenase-1 (COX-1) enzyme metabolizes to thromboxane-A_2. The test measures platelet response to ASA, the COX-1 inhibitor. Thromboxane A_2-mediated expression of GP IIb/IIIa receptors involved in platelet aggregation is expressed in aspirin reactions units (ARU). Expected values are in the range of 350–700 ARU. The cutoff for aspirin's therapeutic effect is 550 ARU. More than 550 ARU in patients treated with aspirin is indicative for aspirin resistance.

4.2.3.2.3 VerifyNow PRU Test®

This test measures platelet response to P2Y12 inhibitors (e.g., clopidogrel, prasugrel, ticlopidine, and ticagrelor).

The amount of ADP-mediated aggregation specific to the platelet P2Y12 receptor is expressed in P2Y12 reaction units (PRU). The reference range is 194–418. Values below 194 PRU are evidence of a P2Y12 inhibitor effect. For patients treated with P2Y12 inhibitors, values above 208 PRU are considered high on-treatment platelet reactivity with an increased risk of thrombotic events (e.g., stent thrombosis). Conversely, values below 82 PRU are considered low on-treatment platelet reactivity (LPR) with an increased risk of bleeding events (Tantry et al. 2013).

A percentage inhibition index (%inh) can be derived by using a second channel with TRAP as the agonist. TRAP activates platelets through the thrombin receptor, independently of the presence of P2Y12 inhibitors. The channel will thus provide a baseline value (BASE) for platelet function. The inhibition index can be calculated as [(PRU/BASE) × 100] and seems to be less dependent on the hematocrit than PRU measurements (Voisin et al. 2011).

4.2.3.3 Clinical Use in Perioperative Care

VerifyNow® has been extensively studied in invasive cardiologic procedures to monitor P2Y12 drug-induced blockade. Recently, two large randomized controlled trials in percutaneous coronary artery revascularization showed no benefit in using VerifyNow® for the clinical management of antiplatelet drugs (Price et al. 2011; Collet et al. 2012). Only a few studies have been conducted in the perioperative setting. In a recent retrospective study of trauma patients chronically treated with clopidogrel, low PRU values predicted higher platelet transfusion needs (Short et al. 2013). In cardiac surgery, a significant correlation was found between preoperative platelet inhibition measured by VerifyNow PRU® and blood loss or transfusion requirements (Alstrom et al. 2009).

4.2.3.4 Limitations and Pitfalls

Patients who have been treated with GP IIb/IIIa inhibitor drugs should not be tested using the VerifyNow Aspirin® or the VerifyNow PRU® tests until platelet function has totally recovered. This occurs approximately 14 days after discontinuation of abciximab and up to 48 h after eptifibatide and tirofiban.

Patients with thrombocytopenia (platelet counts $<100 \times 10^9$/l) or with congenital platelet disorders (e.g., vWD) have not been studied using the VerifyNow® system. Advantages and disadvantages of the VerifyNow® assay are presented in Table 4.7.

4.2.4 Multiple Electrode Aggregometry Analyzer (Multiplate®)

4.2.4.1 Working Mechanism (Fig. 4.4)

The Multiplate® analyzer (Roche Diagnostics, Rotkreuz, Switzerland) is a whole blood platelet function assay based on electrical impedance aggregometry (Toth et al. 2006). The impedance aggregometry method was developed by Cardinal and Flower and has been used since 1979 (Cardinal and Flower 1979a, b). Impedance aggregometry is based on the principle that platelets are non-thrombogenic in their resting state but change shape and expose receptors on their surface when activated,

Table 4.7 Drug sensitivity, advantages, and disadvantages of the VerifyNow® system

Assessment of drug effect	+	–
Aspirin P2Y12 inhibitors GP IIb/IIIa inhibitors	Rapid and simple test (real point-of-care) Can be used by non-skilled personnel Does not require pipetting No sample preparation required	Long incubation time for VerifyNow Aspirin test® Cannot be used to detect congenital platelet disorders Influence of thrombocytopenia is unknown

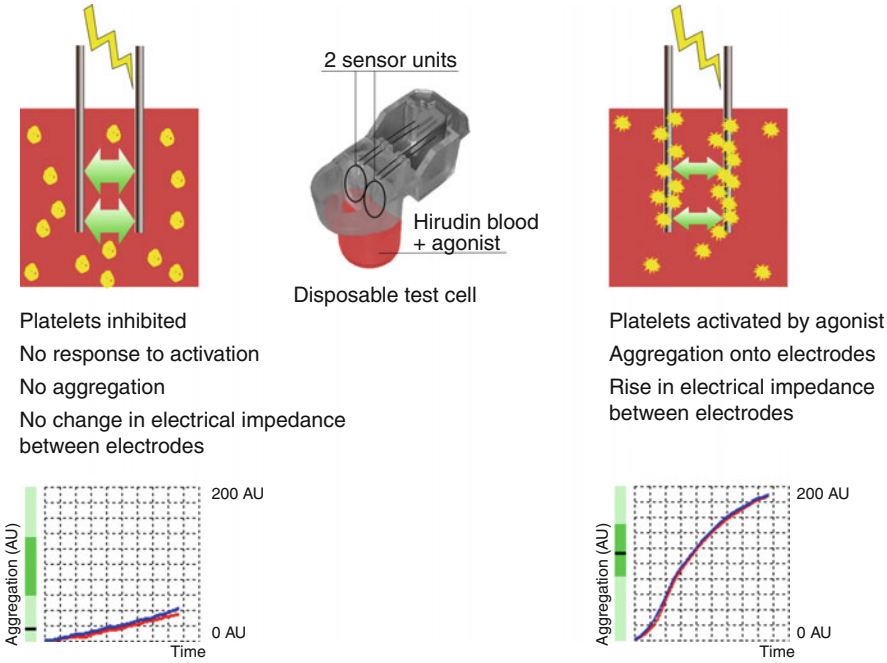

Fig. 4.4 Working mechanism of impedance aggregometry Multiplate®. *AU* aggregation units

thus allowing them to adhere to vascular injuries and artificial surfaces. The Multiplate® analyzer provides a disposable test cell containing two independent sensor units, each consisting of two, fine, highly conductive electrodes. A small quantity (300 µl) of hirudin-anticoagulated whole blood is pipetted in the test cell, mixed with 300 µl of saline using a stirring magnetic bar, and incubated at 37 °C for 3 min. A specific platelet activator is then added to the solution. Activated platelets

Table 4.8 Reference ranges for the Multiplate® assay

Assay	AUC reference ranges
ASPI test	71–115 U
ADP test	57–113 U
TRAP test	94–156 U
COL test	46–116 U
RISTO test	90–201 U

AUC area under the curve, *U* aggregation unit

adhere to and aggregate on the sensor electrodes; this leads to an increase in the impedance measured between them. The impedance is recorded over a 6-min period and displayed graphically. Both sensor units in each test cell measure the rise in impedance independently. As an internal quality assessment, the two measurements must coincide for the test to be valid.

The Multiplate® analyzer is equipped with five channels for the simultaneous measurement of different samples and/or agonists. A wide array of different platelet agonists is available to permit a differentiated diagnosis of acquired and inherited platelet dysfunction:

ASPI test: cyclooxygenase-dependent aggregation (stimulation by 0.5 mM of AA) sensitive to ASA, NSAIDs, and other inhibitors of platelet COX-1.

ADP test: ADP-induced platelet activation (stimulation by 6.5 μM ADP) sensitive to clopidogrel, prasugrel, ticagrelor, and other P2Y12 receptor antagonists.

TRAP test: platelet stimulation via the thrombin receptor (using 32 μM of thrombin receptor-activating peptide), sensitive to GP IIb/IIIa receptor antagonists (e.g., abciximab, eptifibatide, and tirofiban).

COL test: collagen-induced aggregation (using 3.2 μg of collagen).

RISTO test: vWF- and GP Ib-dependent aggregation (using 0.77 mg/ml ristocetin).

4.2.4.2 Normal Values and Result Interpretation

Three parameters that represent the increase in impedance are calculated: area under the aggregation curve (AUC), aggregation, and velocity. AUC is the parameter most used since it depends on both the curve's height and slope. It is expressed in units (U) or sometimes as AU*min (for conversion, 10 AU*min equals 1U). Aggregation is the maximum height of the curve and is expressed in arbitrary aggregation units (AU). Finally, velocity represents the slope of the curve and is expressed in AU/min. Reference ranges for AUC are presented in Table 4.8.

Less than 40 U in the ASPI test indicates adequate inhibition of COX-1 by aspirin (Al-Azzam et al. 2012); less than 30 U is considered strong inhibition (von Pape et al. 2007).

For patients using P2Y12 receptor blockers, a recent expert consensus defined an ADP test of more than 46 U as high on-treatment platelet reactivity, which is associated with increased ischemic risk. ADP test results of less than 19 U are defined as low on-treatment platelet reactivity, which is associated with an increased bleeding risk (Tantry et al. 2013).

Table 4.9 Drug sensitivity, advantages, and disadvantages of the Multiplate® system

Assessment of drug effect	+	−
Aspirin P2Y12 inhibitors GP IIb/IIIa inhibitors	Rapid (< 10 min), easy test Whole blood, no requirements for sample preparation Low sample volume (0.3 ml/test) Multiple agonists available allowing a wide range of different acquired and inherited platelet dysfunction detection	Requires pipetting Sensitive to thrombocytopenia

4.2.4.3 Clinical Use in Perioperative Care

In a trauma setting, a recent study found a correlation between decreased ADP and TRAP test values on admission to the emergency room and increased mortality (Solomon et al. 2011). In cardiac surgery, preoperative platelet dysfunction measured using the Multiplate® was associated with increased platelet transfusion requirements and/or increased postoperative bleeding (Rahe-Meyer et al. 2009; Solomon et al. 2010; Ranucci et al. 2011). For patients on P2Y12 inhibitory drugs, a preoperative ADP test value of less than 31 U was correlated with increased postoperative bleeding and platelet transfusion requirements (Ranucci et al. 2011).

Multiplate® technology allowed assessment of cardiopulmonary bypass-induced platelet dysfunction and of enhanced platelet function following desmopressin administration (Velik-Salchner et al. 2009; Weber et al. 2010, 2012; Steinlechner et al. 2011). It was also possible to assess platelet transfusion requirements after cardiac surgery using the ADP test (Rahe-Meyer et al. 2009).

4.2.4.4 Limitations and Pitfalls

In the Multiplate®, signal reaction requires a tight attachment of the platelets to the sensor's surface. The system seems, therefore, more dependent on physiological calcium levels than other tests (e.g., PFA100/200®, VerifyNow®). Citrated blood sampling tubes affect the free calcium concentration in blood, so hirudin coated tubes are preferred. Samples should be analyzed within the period of 3 h after blood collection. The Multiplate® system is sensitive to thrombocytopenia and the blood samples used must have platelet counts of at least 150×10^9/l for the ASPI test, at least 100×10^9/l for the ADP and COL tests, and at least 50×10^9/l for the TRAP test (Stissing et al. 2011). Advantages and disadvantages of the VerifyNow® assay are presented in Table 4.9.

4.2.5 Thromboelastography Platelet Mapping®

4.2.5.1 Working Mechanism

Thromboelastography (TEG) provides assessment of the viscoelastic properties of a blood clot in vitro. This technique is extensively described in Chap. 3. The TEG Platelet Mapping® system (Haemoscope Corporation, Niles, IL, USA) is a recent modification of the standard TEG technique designed to specifically asses platelet contribution to clot strength (Craft et al. 2004). Platelet Mapping® determines the reduction in maximum amplitude (MA) of the TEG assay due to antiplatelet therapy. Three different sample analyses must be performed. Baseline thrombin-induced clot strength is measured by adding kaolin to whole blood. Kaolin initiates the intrinsic pathway, which leads to thrombin generation. Thrombin is a highly potent platelet activator that mediates maximal expression of GP IIb/IIIa receptors, cleaves fibrinogen into fibrin, and activates factor XIII for fibrin cross-linking. The MA of this clot is named $MA_{thrombin}$ and represents the maximum capacity of the platelets. In a second assay, activator F (reptilase and factor XIIIa) is added to heparinized blood. Reptilase is an enzyme that cleaves fibrinogen to fibrin monomers without activating platelets or other coagulation factors. Factor XIIIa covalently binds the monomers to produce a stable fibrin clot. Maximal tensile strength of this fibrin clot is named MA_{fibrin} and represents a zero platelet contribution. In the third assay, heparinized blood is stimulated by activator F and either 1 mmol/l of AA (Platelet Mapping AA assay) or 2 μmol of adenosine diphosphate (Platelet Mapping ADP assay). The MA of these platelet-fibrin clots is named MA_{AA} or MA_{ADP}, respectively.

4.2.5.2 Normal Values and Result Interpretation

The results of Platelet Mapping® are reported as percent inhibition and percent aggregation. The percentage of platelet aggregation is calculated as % platelet aggregation = $[(MA_{AA\ or\ ADP} - MA_{fibrin})/(MA_{thrombin} - MA_{fibrin})] \times 100$. The percentage of inhibition induced by antiplatelet drugs is calculated as % platelet inhibition = $100 - [(MA_{AA\ or\ ADP} - MA_{fibrin})/(MA_{thrombin} - MA_{fibrin})] \times 100$ (Fig. 4.5). Getting the MA value from the TEG assays may take 30–40 min after the onset of the tests. In order to get platelet function results sooner, an additional parameter called percent of clotting inhibition (%CIn) has recently been proposed (Hobson et al. 2007). It compares the areas under the curve of the ADP or AA assays and thrombin-stimulated assays at 15 min (AUC15).

There is little data available on the normal values for MA. In 43 healthy patients, MA for thrombin, fibrin, AA and ADP assays were $MA_{thrombin}$, 60.9 ± 4.5 mm; MA_{fibrin}, 7.5 ± 2.7 mm; MA_{AA}, 64.6 ± 2.7 mm; and MA_{ADP}, 51.1 ± 8.1 mm (Table 4.10) (Bochsen et al. 2007).

While on treatment, aspirin resistance is defined as more than 50 % aggregation or less than 50 % inhibition in the Platelet Mapping® AA assay (Tantry et al. 2005).

P2Y12 inhibitory drug resistance is defined as more than 50 % aggregation or less than 50 % inhibition in the Platelet Mapping® ADP assay.

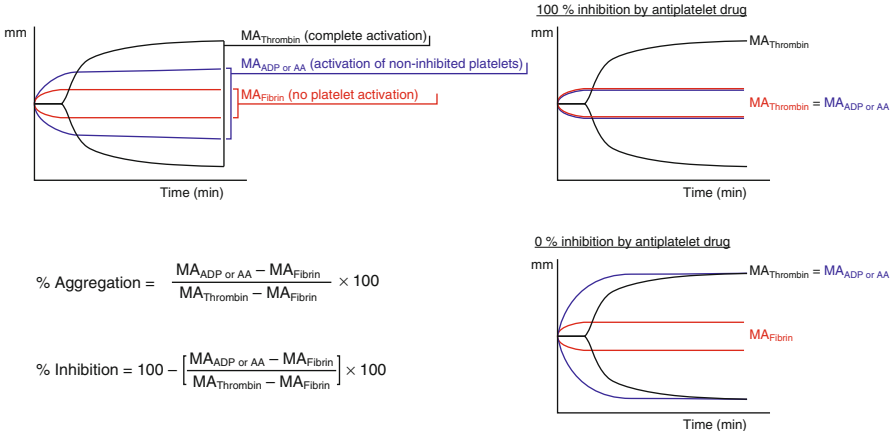

Fig. 4.5 Calculation of TEG Platelet Mapping® results. *MA* maximum amplitude of the TEG assay expressed in millimeter (mm)

Table 4.10 Normal values for healthy subjects not on antiplatelet therapy for the Platelet Mapping® assay (Bochsen et al. 2007)

Assay	Normal values (mm)
$MA_{thrombin}$	60.9 (±4.5)
MA_{fibrin}	7.5 (±2.7)
MA_{AA}	64.6 (±2.7)
MA_{ADP}	51.1 (±8.1)

In literature on interventional cardiology, several definitions for high on-treatment platelet reactivity while on P2Y12 inhibitory therapy are proposed: ≥70 % platelet aggregation (Bliden et al. 2007), MA_{ADP} >47 mm (Gurbel et al. 2010), or MA_{ADP} >50 mm for high reactivity, MA_{ADP} 35–50 mm for intermediate reactivity, and MA_{ADP} <35 mm for low reactivity (Mahla et al. 2012).

A more recent expert consensus on the definition of on-treatment platelet reactivity to ADP associated with ischemia and bleeding determined the following cutoffs: high on-treatment platelet reactivity, MA_{ADP} >47 mm, associated with increased ischemic risk; and low on-treatment platelet reactivity, MA_{ADP} <31 mm, associated with increased bleeding risk (Tantry et al. 2013).

4.2.5.3 Clinical Use in Perioperative Care

In trauma or urgent general surgery, Platelet Mapping® can be used preoperatively to detect residual platelet inhibition by ASA or clopidogrel (Collyer et al. 2009). Clopidogrel-induced platelet dysfunction, measured by Platelet Mapping®, was associated with increased postoperative bleeding in cardiac surgery in patients on dual antiplatelet therapy (Preisman et al. 2010). In off-pump CABG, a high percentage of inhibition by clopidogrel (% inhibition ≥70 %) predicts increased blood loss and transfusion requirements (Kwak et al. 2010). Timing surgery after clopidogrel cessation by using platelet function monitoring shortens the preoperative waiting

Table 4.11 Drug sensitivity, advantages, and disadvantages of the TEG Platelet Mapping® system

Assessment of drug effect	+	−
Aspirin P2Y12 inhibitors GP IIb/IIIa inhibitors	Whole blood Low sample volume Additional information about clot's viscoelastic properties, and coagulation pathway	Use of 3 different channels for measurements (2 TEG devices) Requires pipetting

period in comparison to applying arbitrary delays and results in blood loss comparable to clopidogrel-naive patients undergoing the same type of surgery (Mahla et al. 2012).

4.2.5.4 Limitations and Pitfalls

TEG Platelet Mapping® is technically more demanding than other point-of-care platelet function tests. It requires repeated pipetting for sample preparation. The Platelet Mapping® assay requires three measurement channels, employing two TEG machines for one patient. Advantages and disadvantages of the TEG Platelet Mapping® assay are presented in Table 4.11.

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Hemostasis Assessment and Evaluation

5

Christoph Sucker and Rainer B. Zotz

5.1 Assessment of Plasmatic Hemostasis

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the most frequently used assays for the routine assessment of plasmatic hemostasis. These widely available assays are employed to detect coagulation factor deficiencies, particularly those predisposing to perioperative bleeding. With regard to the classic cascade or waterfall model of plasmatic hemostasis, PT detects factor deficiencies localized in the extrinsic coagulation pathway and the final common pathway, whereas aPTT is sensitive to defects in the intrinsic coagulation pathway and the common pathway. Another assay, thrombin time (TT), detects an insufficient conversion of fibrinogen to fibrin upon stimulation by thrombin. This assay is used to diagnose an absence, deficiency, or dysfunction of fibrinogen but also factors inhibiting or disturbing the action of thrombin on fibrinogen, such as heparin or thrombin inhibitors. The effect of different coagulation defects on these screening assays is reflected by the cascade or waterfall model of hemostasis (see Sect. 1.3).

The causes of prolonged PT and aPTT, whether or not they predispose to bleeding, are summarized in Table 5.1. Notably, combinations of different defects of plasmatic hemostasis may not only yield abnormal results in one test but may influence all screening assays. Since all the assays mentioned above are based on the measurement of plasma turbidity for the detection of fibrin production, turbid patient plasma, such as in severe hyperlipidemia, may interfere with them significantly.

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Table 5.1 Routine coagulation assays distinguishing defects related or not related to bleeding

PT	aPTT	TT	Defect related to bleeding	Defect not related to bleeding
Normal	Normal	Normal	Factor XIII deficiency Von Willebrand disease (mild)	–
Prolonged	Normal	Normal	Factor VII deficiency Vitamin K antagonist/ deficiency Liver disease	–
Normal	Prolonged	Normal	Factor VIII deficiency (hemophilia A) Factor IX deficiency (hemophilia B) Factor XI deficiency Von Willebrand disease Acquired hemophilia	Lupus anticoagulant Factor XII deficiency HMWK deficiency (Pre)kallikrein deficiency
Prolonged	Prolonged	Normal	Factor II deficiency Factor V deficiency Factor X deficiency Combined deficiencies	?
Normal/ prolonged	Prolonged	Prolonged	Treatment with heparin, hirudin, argatroban	–
Normal/ prolonged	Normal prolonged	Prolonged	Afibrinogenemia Hypofibrinogenemia Hemorrhagic dysfibrinogenemia Heparin-like defects Inhibitors of fibrin polymerization Treatment with heparin, hirudin, argatroban	Thrombotic dysfibrinogenemia

Bleeding with normal screening assay and platelet count results can be caused by mild von Willebrand disease, factor XIII deficiency, platelet defects or medication, low molecular weight heparin (LMWH), hypothermia, acidosis, and hypocalcemia. Low platelet counts with normal screening assays are found in cases of pseudothrombocytopenia, idiopathic thrombocytopenic purpura (ITP), and hereditary platelet disorders (e.g., Bernard–Soulier syndrome, gray platelet syndrome). Low platelet counts with prolonged aPTT/PT are found in cases of disseminated intravascular coagulation (DIC), hemodilution, and liver disease

The screening assays for plasmatic hemostasis exhibit considerable weaknesses: depending on which assay is used, sensitivity may not be sufficient when trying to diagnose mild defects of plasmatic hemostasis, even in cases where they are associated with bleeding. The assays detect fibrin formation but are not sensitive to the subsequent process of fibrin cross-linking or stabilization, and therefore they cannot find deficiencies of coagulation factor XIII (fibrin stabilizing factor). To detect factor XIII deficiency, its activity has to be determined separately. Furthermore, these screening assays may be prolonged not only in cases of defects predisposing to bleeding but also in cases with irrelevant defects. In particular, aPTT may be prolonged in case of factor XII deficiency, in high molecular weight kininogen deficiency, in (pre)kallikrein deficiency, or in the presence of lupus anticoagulant; none of these defects predisposes to bleeding and they may be regarded as irrelevant in a surgical context.

5.2 Assessment of Primary Hemostasis

Defects of primary hemostasis include quantitative and functional platelet disorders and von Willebrand disease (vWD).

Decreased platelet counts are easily detectable by means of the blood cell count, routinely performed prior to surgery. Notably, pseudothrombocytopenia caused by EDTA-induced agglutination of platelets is not a rare phenomenon, but it can wrongly suggest an increased risk for bleeding. Since the platelet count in the patient is normal, pseudothrombocytopenia is actually a laboratory phenomenon without relation to bleeding. It can easily be diagnosed by determining the platelet count in a medium other than EDTA, such as citrated blood, or in commercially available collection tubes specifically made for platelet counts. A normal platelet count in either of these media, in combination with a low platelet count in EDTA blood, rules out relevant thrombocytopenia and proves irrelevant pseudothrombocytopenia.

In contrast to thrombocytopenia, platelet dysfunction is more difficult to detect because the required assays are neither generally available nor routinely performed. Congenital abnormalities of platelet function disorder are associated with a heightened risk of bleeding. Typically, patients with a platelet function disorder suffer from mucocutaneous bleeding of varying severity and bleed excessively after surgery or trauma. The laboratory assessment appropriate for the evaluation of a suspected inherited platelet function disorder should be based on a two-step diagnostic strategy: the first step, based on screening tests, helps to build a diagnostic hypothesis, which should then be tested by a second step, based on the use of more specific tests (Podda et al. 2012).

Light transmission aggregometry is the classic assay for the detection of platelet dysfunction. Platelets are stimulated with various agonists (collagen, epinephrine, adenosine diphosphate (ADP), ristocetin, arachidonic acid) that induce platelet aggregation in normal platelets. Upon platelet stimulation by the agonist, this method determines their physiological aggregation response as light transmission increases through platelet-rich plasma. By contrast, platelet-rich plasma will remain

turbid when platelets do not aggregate normally upon stimulation. Aggregometry requires specialized skills and considerable time for sample preparation prior to examination (Shah and Ma 2007). A variant of this method – impedance aggregometry – does not depend on turbidity but measures changes in electrical resistance over time. Impedance aggregometry is easier to perform and uses whole blood rather than platelet-rich plasma.

In recent years, another device, namely, the platelet function analyzer (PFA-100), has gained an important role in the diagnosis of defects in primary hemostasis. The PFA-100 measures the time taken to close an aperture in a collagen-coated net membrane containing a platelet agonist (epinephrine or ADP) when blood passes through it under high-shear stress conditions. Defects of primary hemostasis (particularly thrombocytopenia, platelet function disorders, and vWD) will reduce clot formation on the artificial collagen matrix, prolonging the closure time. This method is highly sensitive for the detection of severe platelet-related defects, as well as vWD. Congenital platelet disorders prolong PFA-100 closure times in a manner proportional to their severity. However, PFA-100 is less sensitive to milder disorders such as storage pool disease, primary secretion defects, and Hermansky–Pudlak syndrome; false-negative results are also possible (Hayward et al. 2006).

Further classification of detected platelet defects is challenging and requires specialized methods, such as flow cytometry for quantification of platelet receptors and activation and electron microscopy. These methods are only available in a few specialized laboratories that focus on the diagnostic assessment of rare platelet disorders and do not play an important role in a surgical context.

Apart from platelet pathologies, vWD is another disorder affecting primary hemostasis. The underlying absence, reduction, or dysfunction of the plasmatic protein, von Willebrand factor (vWF), may not be detected by the classic screening assays of plasmatic hemostasis, PT, and aPTT. aPTT is only prolonged in approximately one third of vWD patients. Relevant vWD may be detected by a prolongation of the closure times in the platelet function analyzer, which has a high diagnostic sensitivity for it. However, when the PFA-100 records prolonged closure times (CT), it is necessary to distinguish a platelet disorder from vWD. Specific assays for the diagnosis of this hemostatic defect include the determination of vWF antigen levels (vWF:Ag) and vWF activity, mostly performed by determining the so-called ristocetin cofactor (vWF:RCo) or collagen binding activity (vWF:CB). Further differentiation of subtypes of vWD requires specialized assays such as multimeric analysis, factor VIII binding assay, and ristocetin-induced platelet aggregation (RIPA). These assays are only performed in specialized laboratories and in most cases are not immediately available.

Bleeding time is no longer thought to be a valid screening test, preoperatively or otherwise, and has been largely replaced by PFA-100. Bleeding time results are poorly reproducible and exhibit low sensitivity and specificity. In the absence of a clinical history of bleeding disorder, bleeding time is not a useful predictor of the risk of hemorrhage associated with surgical procedures. Furthermore, a normal bleeding time does not exclude the possibility of excessive hemorrhage associated with invasive procedures (Shah and Ma 2007; Peterson et al. 1998).

5.3 Preoperative Detection of Hemostatic Defects

In a normal setting, preoperative diagnostic assessment includes a platelet count and measurement of PT and aPTT for the detection of potential defects associated with bleeding. Using these assays, thrombocytopenia and most coagulation factor deficiencies associated with bleeding will be identified. However, platelet function defects, most cases of vWD and factor XIII deficiency, will remain undetected. Since platelet dysfunction – mainly secondary to underlying disease or intake of drugs – and vWD are by far the most common disorders associated with bleeding, the usual preoperative diagnostic assessment does not at all exclude the presence of clinically relevant hemostatic defects. However, there is increasing evidence that a defect can be ruled out with greater accuracy if standard coagulation assays are combined with a standardized questionnaire addressing the presence of potential hemostatic defects (Table 5.2).

Table 5.2 Patient history for the preoperative exclusion of hemostatic defects associated with bleeding

Patient history	Important aspects
Bleeding symptoms	*Provoked bleeding*: previous bleeding related to surgery, dentistry, or trauma *Spontaneous bleeding*: epistaxis, hematoma, gingival bleeding, heavy menstrual bleeding, joint and muscle bleeding
Diseases/conditions potentially associated with bleeding disorders	Hepatic disease Renal disease Hematological disorders Myelodysplastic disorder Myeloproliferative disorder Paraproteinemia Cardiopulmonary bypass Extracorporeal membrane oxygenation
Medication associated with bleeding disorders	Platelet inhibitors Aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole GpIIb/IIIa receptor inhibitors Analgesics/antiphlogistics (ibuprofen, diclofenac, etc.) Cilostazol Selective serotonin reuptake inhibitors (SSRI) Beta-lactam antibiotics Herbal medicine (e.g., ginkgo, garlic, ginger, ginseng) Oral anticoagulants Cumarines, dabigatran, rivaroxaban, apixaban Parenteral anticoagulants Heparins, fondaparinux, hirudin, argatroban
Family history	Increased bleeding tendency or defined hemostatic defects in relatives

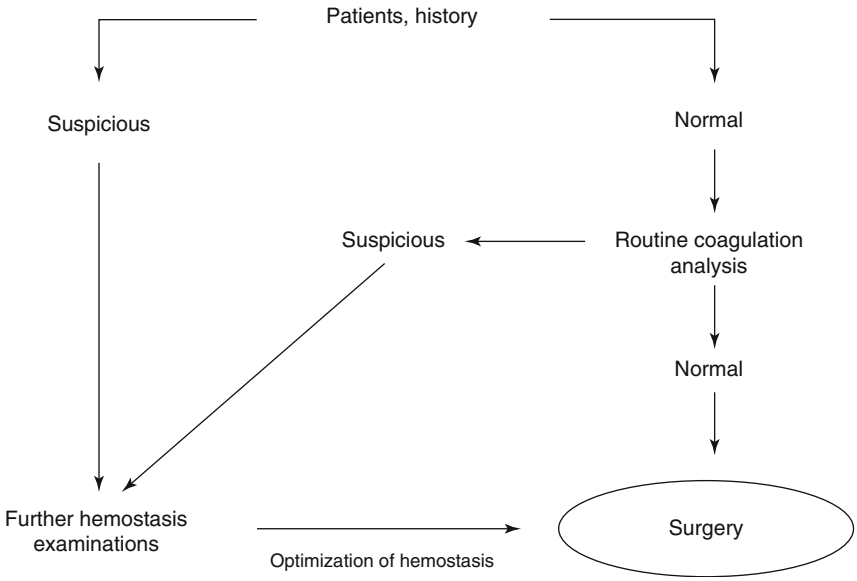

Fig. 5.1 Proposed approach to preoperative assessment of hemostatic defects

An adequate standardized questionnaire of a patient's history and the usual screening assays can be used to rule out a relevant hemostatic defect. In particular, the combined analysis of a patient's history and the laboratory assays has a high negative predictive value for the exclusion of defects associated with bleeding. By contrast, a positive patient history is associated with the presence of a relevant hemostatic defect in approximately 40 % of patients (Koscielny et al. 2004). Any hint of a hemostatic defect should lead to postponement of elective surgery to allow for further examination and preoperative optimization of hemostasis prior to surgery. A feasible and practical approach is shown in Fig. 5.1. Further analyses in case of normal screening results (PT, aPTT, TT, platelet count) may include platelet functions assays, vWF activity, and factor XIII activity.

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Congenital Bleeding Disorders

6

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6.1 Introduction

Congenital bleeding disorders are found in all the world's racial groups. They can affect the plasmatic coagulation cascade, as well as platelet function, with different patterns of inheritance (sex-linked recessive, autosomal recessive, and autosomal dominant). Taken all together, they affect roughly 1 in 200 people. Hemophilia A and B are inherited in a sex-linked recessive way, and together with the more frequent von Willebrand disease, they constitute the largest group of inherited plasmatic bleeding disorders (Table 6.1).

In order to avoid catastrophic outcomes, the identification of a congenital bleeding disorder is crucial for the optimization of hemostasis in a perioperative setting. Useful diagnostic tools include the global tests of coagulation – as first-choice laboratory tests – prothrombin time (PT/INR) and activated partial thromboplastin time (aPTT). There are also platelet function screening tests, such as the thrombocyte global test PFA-100 for initial hemostasis or whole blood impedance aggregometry. Figure 6.1 gives an overview of the diagnostic efficacy of these tests.

In general, treatment of hereditary deficiencies of coagulation proteins consists of an appropriate replacement therapy under the supervision of an experienced hemostaseologist. Dosing and frequency of substitution are dependent on the clinical problem, risk of bleeding, and pharmacokinetics of the factor concentrates used. Elimination half-lives and target levels required for an adequate hemostatic effect under physiological conditions are shown in Table 6.2.

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Table 6.1 Prevalence of various bleeding disorders in the general population

Factor deficiency	Frequency
Fibrinogen	1:1 m
Factor II	1:2 m
Factor V	1:1 m
Factor V and factor VIII	1:1 m
Factor VII	1:0.5 m
Factor VIII	1:10,000
Factor IX	1:50,000
Factor X	1:1 m
Factor XI	1:1 m
Factor XIII	1:2 m
Von Willebrand type 3	1:250,000–1 m
Von Willebrand type 1 or 2	1:200

m million

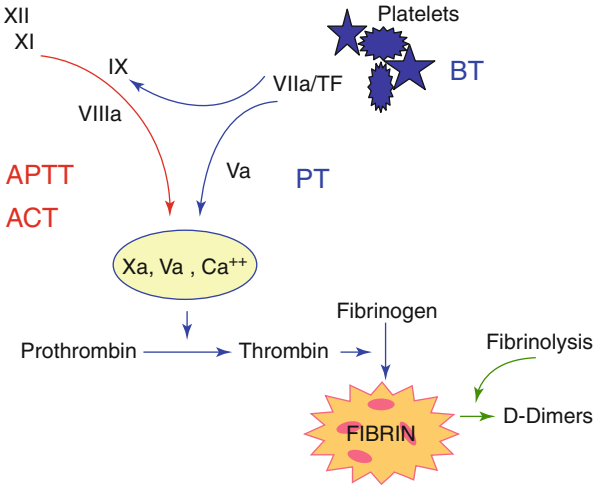

Fig. 6.1 Classic overview of the coagulation cascade with positioning and diagnostic efficacy of the global coagulation tests, distinguishing the extrinsic system (*blue arrow*), the intrinsic system (*red arrow*), and the common pathway (*PT* prothrombin time, *APTT* activated partial thromboplastin time, *ACT* activated clotting time, *BT* bleeding time)

Table 6.2 Elimination half-life (t ½) of various coagulation factors and their minimum concentrations required in plasma for an adequate hemostatic effect under physiological conditions

Factor	Name	t ½ (h)	Hemostatic level	Preoperative target level
I	Fibrinogen	90	0.5–1 g/l	>1 g/l
II	Prothrombin	70	20–40 %	>50 %
V		24	15–20 %	>20 %
VII		6	15 %	>50 %
VIII		12	5–10 %	>50–100 %
IX		24	5–10 %	>50–100 %
X		40	15–20 %	>50 %
XI		60	15–20 %	>20 %
XII		52	<1 %	
XIII		72	2–5 %	>50–100 %
vWF		12	40 %	>50–100

6.2 Autosomal Dominant Disorders

6.2.1 Von Willebrand Disease

Von Willebrand disease (vWD) is a hemorrhagic disorder caused by a deficiency of von Willebrand factor (vWF) measured either as an activity or a protein. VWF consists of multimeric protein units that are heterogeneous in size. As a rule, larger vWF multimers show a higher hemostatic efficacy than smaller ones. Von Willebrand multimers are produced in endothelial cells and megakaryocytes; they are stored in the Weibel-Palade bodies of endothelial cells, in the alpha granules of platelets, and in subendothelial connective tissue. VWF has two key functions: on one hand, by binding to the GP Ib/V/IX complex on the platelet surface VWF mediates platelet adhesion to subendothelial collagen at sites with high shear stress, and on the other hand, VWF is the carrier protein for circulating factor VIII preventing its rapid proteolysis. VWD is the most frequent congenital bleeding disorder, with an estimated prevalence of 1:200–300 in the general population. There are three types of vWD, with several subtypes showing different clinical presentations (Table 6.3).

The clinical presentation of vWD is mostly mucocutaneous bleeding, such as easy bruising, epistaxis, bleeding after tooth extraction or other surgical interventions, and menorrhagia.

Laboratory assays for the diagnosis of vWD are either quantitative or qualitative. Quantitative immunoassays measure the amount of vWF present in plasma expressed as von Willebrand antigen (vWF:Ag). The qualitative or functional assays measure the activity of vWF. Qualitative assays can measure the vWF collagen-binding activity (vWF:CB) or the vWF ristocetin cofactor activity (vWF:RCo). Ristocetin is an antibiotic that causes platelet agglutination, but only in the presence of large vWF multimers.

The diagnosis of vWD can be made easily in patients with vWF activity below 35 %. However, many patients with a bleeding history present borderline vWF activity between 35 and 60 %. Patients belonging to this group may be difficult to diagnose, since they can overlap with a low variant of normal persons with blood group O, who physiologically have vWF activity at the lower limit of the normal

Table 6.3 Classification of von Willebrand disease (vWD)

Type vWD	Description
1	Partial quantitative deficiency of vWF
2	Qualitative deficiency of vWF
2A	Decreased platelet-dependent vWF function with lack of large multimers
2B	Increased affinity of vWF to GPIb and loss of large and medium multimers
2M	Decreased platelet-dependent vWF function with normal multimeric analysis
2N	Decreased vWF affinity for FVIII
3	Complete deficiency of vWF

vWF von Willebrand factor, *GPIb* glycoprotein Ib, *FVIII* factor VIII

Table 6.4 Comparative laboratory findings in types of von Willebrand disease

Type vWD	vWF:Ag	vWF:RCo	vWF:RCo/vWF:Ag	Large vWF multimers
1	↓	↓	>0.6	Normal
2				
2A	↓	↓↓	<0.7	↓
2B	↓	↓↓	<0.7	↓↓
2M	↓	↓↓	<0.7	Normal
2N	→ or ↓	→ or ↓	>0.6	Normal
3	↓↓↓	↓↓↓	–	↓↓↓

range, without clinical bleeding. Therefore, an adequate personal and family bleeding history and an adequate laboratory workup, including platelet function testing, are required in such cases.

6.2.1.1 Von Willebrand Disease Type 1

VWD type 1 presents a partial quantitative deficiency of vWF with both reduced vWF antigen and vWF activity. It includes about 75 % of all patients with vWD. The symptoms are easy bruising, epistaxis, gum bleeding, menorrhagia, bleeding after dental procedures, postsurgical bleeding, or postpartum hemorrhage.

Laboratory Findings

Whereas PT/INR is normal, aPTT can be slightly increased in more severe forms of vWD type 1, with low FVIII levels. VWF antigen and vWF activity are decreased in parallel (Table 6.4).

6.2.1.2 Von Willebrand Disease Type 2

VWD type 2 presents with qualitative defects of the vWF multimers. According to their specific defects, they are subdivided into type 2A, 2B, 2M, and 2N.

6.2.1.2.1 Von Willebrand Disease Type 2A

Type 2A is the most common of type 2 VWD. It presents a lack of large vWF multimers, which leads to impaired platelet adhesion.

Laboratory Findings

PT, aPTT, and FVIII levels show the same patterns as in vWD type 1. VWF:Ag is typically normal or slightly low, while vWF activity is clearly lower, which leads to a ratio vWF:RCo/vWF:Ag below 0.7. Analysis of multimers reveals a lack of large vWF multimers (Table 6.4).

6.2.1.2.2 Von Willebrand Disease Type 2B

In contrast to type 2A, type 2B shows an increased affinity and binding of vWF to the von Willebrand receptor (GPIb/V/IX) on platelets as a result of a "gain-of-function" mutation. This leads to a faster clearance of both von Willebrand multimers (especially large- and medium-sized molecules) as well as platelets. Hence, patients with this subtype often present with mild thrombocytopenia, which can be

aggravated under surgery, during pregnancy, or during substitution with vWF concentrates.

Laboratory Findings
Laboratory assessment of PT/INR, aPTT, FVIII, vWF activity, and antigen is similar to vWD type 2A. Additionally, there is a typical multimeric pattern with a lack of large- and middle-sized multimers. Typically, using ristocetin in lower than normal concentrations causes these patients' platelets to aggregate. This finding distinguishes type 2B from 2A (Table 6.4).

6.2.1.2.3 Von Willebrand Disease Type 2M
In type 2M, vWF shows a reduced capacity to bind to the von Willebrand receptor (GPIb/V/IX) on platelets, but in contrast to type 2A and 2B, normal (ultra) large vWF multimers are present.

Laboratory Findings
VWF:Ag is normal, FVIII is normal or only slightly low, vWF activity is low, and large vWF multimers are normal (Table 6.4).

6.2.1.2.4 Von Willebrand Disease Type 2N (vWF Normandy)
In this subtype, von Willebrand multimer interaction with platelets is maintained, but the capacity to bind FVIII is decreased or even absent. This results in a faster elimination of FVIII since its normal elimination half-life is only 2 h, instead of 12 h for vWF. Clinically, this entity cannot be distinguished from mild hemophilia A.

Laboratory Findings
Findings are normal or prolonged aPTT, reduced FVIII activity, and normal or only slightly decreased vWF antigen and activity (Table 6.4). Differentiating type 2N from hemophilia A is only possible by measuring the FVIII binding capacity of vWF (low in vWD 2N, normal in hemophilia A).

6.2.1.3 Von Willebrand Disease Type 3
Type 3 vWD is a rare defect presenting with undetectable or very low (<5 %) levels of both vWF antigen and activity. The prevalence in the general population is estimated to be one to three per million people.

The clinical phenotype of type 3 is a pronounced predisposition for mucocutaneous bleeding, such as easy bruising, epistaxis, menorrhagia in women, and bleeding after tooth extraction or other surgical interventions. Muscle and joint bleeding similar to severe hemophilia A or B can also occur, since very low levels of vWF lead to artificially low levels of FVIII.

Laboratory Findings
Findings are normal PT/INR, prolonged aPTT due to the low FVIII levels, very low or undetectable levels of vWF antigen and activity, and absence of the whole spectrum of vWF multimers in the multimeric analysis (Table 6.4).

Treatment of vWD

The mainstay for the treatment of vWD in situations of acute bleeding is substitution with a concentrate containing vWF (Haemate®, Wilate®, Wilfact®). Dosing is usually weight adjusted. Elimination half-life of substituted vWF is 14–17 h; thus, in most cases once or twice daily substitution is appropriate. Fresh frozen plasma (FFP) is an insufficient source of vWF and should not be used for this purpose. Cryoprecipitate preparations contain high concentrations of vWF, but are no longer used because they are not pathogen inactivated.

Depending on the severity of the deficiency and the extent of the trauma, desmopressin (DDAVP) (Octostim®, Minirin®) can be used as an alternative means to increase endogenous vWF and FVIII levels by stimulating the release of vWF from the endothelium. Desmopressin is given intravenously as a short infusion over 30 min (0.3 μcg/kg body weight). Alternatively, it can be given subcutaneously, repeating once or twice every 24 h. If active mucocutaneous bleeding is present, treatment should include an antifibrinolytic agent (e.g., tranexamic acid 10 mg/kg bw IV) because desmopressin also stimulates endogenous fibrinolysis by release of tissue plasminogen activator. Intranasal application of desmopressin might be an option for self-treatment in case of bleeding, but due to its variable bioavailability, it is not preferred in the perioperative setting. Desmopressin should be used cautiously in vWD type 2B because it shows low efficacy and might aggravate thrombocytopenia: infusion time can be prolonged to 60 min. Desmopressin has no effect in type 3 patients.

VWD type 3 is treated by substitution with a vWF/FVIII concentrate. The FVIII component is essential in achieving adequate hemostasis at the beginning of the treatment. High purity vWF concentrates with very low levels of FVIII, such as Wilfact®, must initially be given together with an FVIII concentrate because it takes hours for the endogenous FVIII level to rise after substitution with pure vWF.

Secondary prophylaxis with a vWF concentrate (10–20 IU/kg bw, two to three times a week) is standard care in type 3 patients with recurrent bleeding complications.

6.2.2 Fibrinogen Deficiency

Congenital fibrinogen deficiency is a rare bleeding disorder with a prevalence of one in one million people. Afibrinogenemia and hypofibrinogenemia are quantitative disorders describing a lack of or reduced fibrinogen, respectively. Fibrinogen is a soluble protein that is abundant in plasma. It is involved in the final step of the coagulation cascade: it forms the fibrin clot after enzymatic proteolysis by thrombin. Fibrinogen's mean half-life is about 90 h, and the hemostatic level needed under physiological conditions is 1.0–1.5 g/l. There is suggestive evidence that higher levels are needed for a hemostatic effect (1.5–2.0 g/l) in conditions such as trauma coagulopathy or postpartum hemorrhage.

Complete absence of fibrinogen causes a clinical phenotype with pronounced bleeding complications, and the majority of those affected show bleeding episodes from birth, with umbilical bleeding, and later with gastrointestinal and urogenital

hemorrhages. Patients with hypofibrinogenemia on the other hand do not bleed spontaneously, but often show postoperative bleeding complications.

In addition to the quantitative fibrinogen disorders, dysfibrinogenemia, a qualitative fibrinogen defect, has also been described. About 50 % of these patients are asymptomatic, a quarter shows bleeding tendency, and about 20 % interestingly present with thrombophilia. The exact pathophysiological mechanism of this higher risk for thrombosis is not clear. Several mechanisms are postulated. One possible explanation is that an impaired binding of thrombin to fibrinogen causes higher circulating levels of thrombin, which in turn activate platelets and lead to a procoagulant state. Another possible explanation is a disturbance in fibrinolysis due to defects of the fibrinogen molecule.

Laboratory Findings

Afibrinogenemia is characterized by prolonged aPTT, PT, and thrombin clotting times. No detectable fibrinogen can be found. Hypofibrinogenemia has mostly normal global tests and variably decreased levels of functional fibrinogen. Dysfibrinogenemia has decreased functional fibrinogen, but normal protein values in the immunological assays.

Treatment of Fibrinogen Deficiency

Normally, most patients with hypofibrinogenemia or dysfibrinogenemia do not need prophylactic treatment, and substitution should be given only when necessary. In case of invasive procedures or surgery, fibrinogen levels should be corrected to normal by substitution with a fibrinogen concentrate. Caution is needed in cases of dysfibrinogenemia because overdosing can cause thrombotic complications.

Patients with afibrinogenemia should receive regular secondary prophylaxis of substitution with a fibrinogen concentrate once every 1 or 2 weeks. Traditionally, the minimal level of fibrinogen required to prevent spontaneous bleeding had been placed at 1.0–1.5 g/l. There is increasing suggestive evidence from observations of coagulopathy in trauma that this level should be corrected to 1.5–2.0 g/l, depending on the situation.

In cases with menorrhagia, antifibrinolytic treatment and/or hormonal treatment may prove useful.

FFP is not a good source for fibrinogen, but it could be used in cases of a lack of concentrates or when additional natural coagulation proteins and enzymes are needed.

6.3 Sex-Linked Recessive Disorders

6.3.1 Hemophilia A (Factor VIII Deficiency)

Hemophilia A is a deficiency in FVIII and is the most common type of hemophilia. FVIII is a complex plasma protein that is mostly synthesized in the hepatocytes and circulates in a non-covalent complex with vWF. The prevalence of hemophilia A

Table 6.5 Severity of hemophilia A or B

Level	Percentage of factor VIII or IX activity in plasma (%)	International units per milliliter of whole blood (IU)
Normal	50–150	0.5–1.5
Mild hemophilia	6–40	0.06–0.4
Moderate hemophilia	1–5	0.01–0.05
Severe hemophilia	<1	<0.01

varies in different countries: it ranges from 0.7 to 1.3 in 10,000 people. FIX deficiencies, or hemophilia B, are rarer, with a prevalence of 1 in 50,000 people.

Factor VIII or IX levels in hemophilia are found to be below 50 % and are classified in three severity groups (severe, moderate, and mild). Classification is based on the factor concentration, reflecting the clinical phenotype (Table 6.5). Mild hemophilia often only first presents as a bleeding episode after trauma or surgery. Severe hemophilia often presents as a bleeding tendency when a child starts to walk or sometimes days after birth. The severity of bleeding correlates very well with the factor level measured. Spontaneous muscle and joint bleeding (specially the ankles, knees, and elbows) is typical for the severe form of hemophilia. A tentative explanation for joint bleeding in hemophilia is the fact that soft tissues in the joints express very low levels of tissue factor, a protein which is crucial in the initiation of the coagulation cascade.

Laboratory Findings

Hemophilia A has normal PT/INR, prolonged aPTT, reduced FVIII activity in the specific assay, and normal bleeding time.

Treatment of Hemophilia A

Substitution with the missing protein is the modern mainstay of hemophilia A treatment. Primary or secondary prophylaxis with regular substitution, two to four times a week, is a common mode of application. Prophylaxis begins in the first year of life and continues throughout adulthood. Regular prophylaxis has been shown to protect from chronic joint arthropathy and acute bleeding. In case of invasive procedures, surgery, or trauma, a more intensive substitution scheme is chosen. Table 6.6 gives dosing and target levels of FVIII. About 15–30 % of severe hemophiliacs develop acquired alloantibodies against FVIII after repeated substitution with FVIII concentrates. Special treatment protocols based on immunotolerance induction or immunosuppression are then needed for eradication of the inhibitor.

6.3.2 Hemophilia B (Factor IX Deficiency)

Hemophilia B, the hereditary FIX deficiency, is the second most common form of hemophilia. FIX is a vitamin K-dependent serine protease synthesized in the liver. It is activated by FVIIa or FXIa and in its activated form catalyzes the conversion of factor X to Xa.

Table 6.6 Indicated dosing of factor VIII concentrates in case of bleeding

Type of hemorrhage	Desired level (IU/dl)	Duration (days)
Joint	40–60	1–2
Superficial muscle	40–60	2–3
Iliopsoas and deep muscle or substantial blood loss		
Initial	80–100	1–2
Maintenance	30–60	3–5
Central nervous system		
Initial	80–100	1–7
Maintenance	50	8–21
Throat and neck		
Initial	80–100	1–7
Maintenance	50	8–14
Gastrointestinal		
Initial	80–100	1–6
Maintenance	50	7–14
Renal	50	3–5
Deep laceration	50	5–7
Major surgery		
Preop	80–100	1–3
Postop	60–80	1–3
	40–60	4–6
	30–50	7–14
Minor surgery		
Preop	50–80	
Postop	30–80	1–5

Adapted from the World Federation of Hemophilia guidelines

The prevalence of congenital FIX deficiency varies in different regions of the world, with 1.2–2.7 per 100,000 people. The clinical phenotype of hemophilia B does not differ from that of hemophilia A. Bleeding appears very early in life and mostly affects joints or muscles. Classification according to severity is the same as for hemophilia A.

Laboratory Findings

Hemophilia B has normal PT/INR, prolonged aPTT, reduced FIX activity in the specific assay, and normal bleeding time.

Treatment of Hemophilia B

Substitution with FIX concentrates in episodes of bleeding or suspected bleeding is the mainstay of treatment for hemophilia B (Table 6.7). In severe forms, primary or secondary prophylaxis with substitution is recommended two to three times a week. Because FIX has a longer half-life than FVIII, it can be given at longer intervals. After repeated substitution with concentrates, about 3–5 % of severe hemophilia B patients develop acquired alloantibodies against FIX. Special treatment protocols based on immunotolerance induction or immunosuppression are then needed to eradicate the inhibitor.

Table 6.7 Indicated dosing of factor IX concentrates in case of bleeding

Type of hemorrhage	Desired level (IU/dl)	Duration (days)
Joint	40–60	1–2
Superficial muscle	40–60	2–3
Iliopsoas and deep muscle or substantial blood loss		
Initial	60–80	1–2
Maintenance	30–60	3–5
Central nervous system		
Initial	60–80	1–7
Maintenance	30	8–21
Throat and neck		
Initial	60–80	1–7
Maintenance	30	8–14
Gastrointestinal		
Initial	60–80	1–6
Maintenance	50	7–14
Renal	40	3–5
Deep laceration	40	5–7
Major surgery		
Preop	60–80	1–3
Postop	40–60	1–3
	30–50	4–6
	20–40	7–14
Minor surgery		
Preop	50–80	
Postop	30–80	1–5

Adapted from guidelines of the World Federation of Hemophilia

6.4 Autosomal Recessive Bleeding Disorders

6.4.1 Factor II (Prothrombin) Deficiency

Prothrombin is a vitamin K-dependent factor, synthesized in the liver and activated through factor Xa. The active form of prothrombin is thrombin. Thrombin plays a pivotal role, converting fibrinogen to fibrin, simultaneously activating platelets as well as the natural coagulation inhibitor, protein C. It is therefore a crucial element in the regulation of the coagulation system.

Hereditary prothrombin deficiency is a rare disorder with a prevalence of about one in two million people, and it is inherited in an autosomal recessive manner. Two different phenotypes can be distinguished: type 1 presenting as hypoprothrombinemia and type 2 as dysprothrombinemia. The former shows lower antigen and activity levels, whereas the latter may reach normal levels of prothrombin antigen, but is dysfunctional. Depending on the severity of the deficiency, the affected patients may show spontaneous bleeding or suffer provoked hemorrhages. In general, slight bleeding episodes such as epistaxis, gum bleeding, or menorrhagia predominate.

About 40 % of the normal FII level is necessary for adequate hemostatic function, although the factor level does not always correlate with the bleeding tendency.

Laboratory Findings
Factor II deficiency exhibits prolonged aPTT and PT/INR, normal bleeding time, and reduced FII levels in the specific assay.

Treatment
Treatment consists of on demand substitution with FII concentrates. These are available in the form of four-factor prothrombin complex concentrates (4fPCC, Prothromplex®, Beriplex®, Octaplex®), containing FIX, FX, and FVII in addition to FII. If these are not available, FFP can also be used as a source of FII, if appropriately dosed (10 ml/kg BW).

6.4.2 Factor V Deficiency

The incidence of FV deficiency is estimated at one in one million people and is phenotypically almost exclusively inherited as a type 1 deficiency (activity and antigen are lower in parallel). FV is a protein synthesized in the liver and acts as a cofactor in the prothrombinase complex. This complex activates prothrombin into thrombin. About 80 % FV circulates in plasma, and 20 % is stored in the alpha granules of platelets. The origin of the FV found in the platelets is not yet well understood. It is known that megakaryocytes are able to acquire FV by endocytosis, as well as synthesize FV. The required level of the protein in plasma for an adequate hemostatic effect is about 40 %. Only some of the affected patients with a heterozygous mutation show a clinically increased bleeding tendency with epistaxis, menorrhagia, or mucosal bleeding. Bleeding complications occur mostly as provoked events after surgery or invasive diagnostic procedures. The homozygous form presents with spontaneous bleeding and an increased tendency of hematoma, as well as joint and muscle bleeding.

The severity of the bleeding does not correlate well with the plasma protein level.

Laboratory Findings
Factor V deficiency exhibits prolonged PT/INR and aPTT, normal bleeding time, and decreased FV activity in the specific assay.

Treatment
Treatment consists in substituting FV on demand. As there is no FV concentrate available, FFP is the only source. FV is an unstable protein even under proper storage conditions. Retention values of FFP after thawing give no more than 60 % of FV activity with respect to the original material before deep freezing. Alternatively, recombinant activated factor VII (rFVIIa, NovoSeven®) could be used off-label for hemostasis.

6.4.3 Combined Deficiency of Factors V and VIII

The incidence of this defect is about one in two million people. The genetic defect which causes this combined factor deficiency affects the transport system between

the endoplasmic reticulum and the Golgi apparatus of factor-producing cells. Postsurgical and mucosal bleeding are the most common clinical presentations; spontaneous muscle and joint bleeding is not usual.

Laboratory Findings
PT and aPTT are prolonged. Isolated reduction in factor V and VIII activities is found in the specific assay.

Treatment
Depending on the severity of the deficit, FVIII concentrates and FFP can be used. In mild bleeding, antifibrinolytics may also be an alternative.

6.4.4 Factor VII Deficiency

The congenital FVII deficiency is the most frequent of the rare bleeding disorders (30 %). The prevalence of its severe form (FVII <2 %) is estimated to be about 1 in 500,000 people. The clinical phenotype presents a wide spectrum of bleeding from mucosal to intracranial hemorrhages. The minimum FVII level required for an adequate hemostatic effect is 10–15 %.

Laboratory Findings
Factor VII deficiency exhibits prolonged PT/INR, normal aPTT, and low FVII activity levels in the specific assays.

Treatment
Factor VII concentrates can be used for substitution in cases of bleeding (high purity FVII, recombinant FVIIa, or 4fPCC). Preferably nonactivated forms of concentrates should be used. In heterozygous deficiencies, no substitution is normally required even in case of surgery, since levels of FVII in these cases range from 20 to 50 %. Caution is required in cases of potential vitamin K deficiency, where FVII can soon reach inappropriately low levels. Although its elimination half-life of 5 h is short, a less frequent substitution scheme turns out to be adequate even in case of surgery.

In severe cases, especially in children, prophylactic substitution can be given three times a week.

6.4.5 Combined Deficiency of the Vitamin K-Dependent Clotting Factors

In this combined deficiency, the defect is situated in the enzyme responsible for the gamma-glutamyl carboxylation of the coagulation factors. Vitamin K acts as cofactor for gamma-glutamyl carboxylase. Carboxylation takes place in the liver and enables specific proteins to bind calcium. This step is essential for the coagulation enzymes to anchor on the coagulation-active phospholipids of platelets and cell membranes. Affected patients not only have low levels of procoagulant factors II,

VII, IX, and X but also of the natural coagulation inhibitors, proteins C and S. Clinically, this bleeding disorder manifests itself early in life, with umbilical cord bleeding and central nervous system hemorrhages.

Laboratory Findings
This combined deficiency exhibits prolonged PT/INR and aPTT and low levels of FII, FVII, FIX, FX, and proteins C and S.

Treatment
Treatment consists in on demand substitution of the missing coagulation proteins using a concentrate. Four-factor PCC products are used for this purpose (Prothromplex®, Beriplex®, Octaplex®). High doses of vitamin K in adults (1 × 10–15 mg daily) orally or intravenously might also lead to a partial increase of the factor levels and prevent major bleeding. If not otherwise possible, fresh frozen plasma (FFP) can be used as a source of FII, FVII, FIX, and FX. Depending on the severity of the clinical phenotype, a secondary chronic prophylaxis with high-dose vitamin K or four-factor PCC might be considered.

6.4.6 Factor X Deficiency

Congenital FX deficiency affects one in one million people. FX is synthesized in the liver and is physiologically activated by the complex tissue factor/FVIIa or FIXa/FVIIIa, so that thrombin can subsequently be generated. FX deficiency is ranked among the most severe of the rare coagulation defects. We can differentiate type 1 with low antigen and activity levels and type 2 with an almost normal antigen level, but lower antigen activity.

Bleeding complications begin early in life, with umbilical cord and central nervous system bleeding. Other common presentations are muscle and joint bleeding, bleeding in the gastrointestinal tract, and menorrhagia.

Laboratory Findings
Prolonged PT/INR and aPTT and low factor X activity.

Treatment
Treatment consists in FX substitution using a concentrate. There are no high-purity FX concentrates available. Four-factor PCC products are used for this purpose (Prothromplex®, Beriplex®, Octaplex®). Alternatively, a combined FIX/FX product can be used (Factor IX/X Behring®). If these are not available, FFP can be used as a source of FX. Treatment can be combined with antifibrinolytics.

6.4.7 Factor XI Deficiency

Factor XI is a serine protease synthesized in the liver. In plasma, it forms a complex with high molecular weight kininogen, which protects it from degradation while in

circulation. Thrombin activates FXI. The activated FXIa further catalyzes the activation of FIX.

The majority of people affected by FXI deficiency have a low but detectable FXI level. The severity of bleeding, however, does not correlate with the factor levels measured. Bleeding manifests itself as mucosal or surgical bleeding. Joint or muscle bleeding is not common at all. FXI deficiency is the second most common bleeding disorder in women after vWD.

Laboratory Findings

FXI deficiency exhibits prolonged aPTT, normal PT/INR, and low FXI levels in the specific assays.

Treatment

Treatment consists of substitution with FXI concentrate (Hemoleven®). Dosing should be calculated cautiously, because overdosing or even correction to high normal levels can cause thrombotic complications. FFP may be used as an alternative source for FXI. Treatment may be combined with antifibrinolytics.

6.4.8 Factor XII Deficiency

Congenital deficiency of FXII is not associated with bleeding, so that it is not considered a hemorrhagic disorder. On the contrary, there is suggestive evidence that it might cause a tendency to thrombosis, since FXII is involved in the activation of the complement pathway and of fibrinolysis.

Laboratory Findings

Factor XII deficiency exhibits normal PT/INR, prolonged aPTT, and reduced levels of FXII activity in the specific assays.

Treatment

There is currently no recognized indication for FXII substitution.

6.4.9 Factor XIII Deficiency

FXIII is an additional factor in the coagulation cascade; present as a proenzyme in plasma, it is activated by calcium and thrombin. Activated FXIIIa, a transglutaminase, catalyzes the cross-linking between the fibrin monomers and turns them into fibrin; it also protects fibrin clots from fibrinolysis by incorporating antiplasmin and other factors into the structure.

Congenital FXIII deficiency in its severe form (FXIII activity <5 %) is rare and manifests as a severe bleeding disorder. Furthermore, it is the hereditary bleeding disorder with the highest incidence of central nervous system hemorrhages (30 %): affected patients show hematomas, muscle bleeding, and delayed postsurgical hemorrhages. The occurrence of umbilical cord bleeding is 80 %.

At FXIII activity levels below 60 %, there is suggestive evidence of correlation with intra- and postoperative bleeding. Bleeding in these patients can be prevented after correction of the deficiency with substitution of FXIII.

Laboratory Findings
FXIII deficiency exhibits normal PT/INR and activated aPTT and low levels of FXIII activity and antigen in the specific assays.

Treatment
Treatment consists of FXIII substitution on demand using a FXIII concentrate (Fibrogammin®). A single dose of 1,250 IE is usually sufficient for a long-lasting effect since the protein's elimination half-life is long (72 h). In severe cases, regular secondary prophylaxis may be required every 4–6 weeks.

6.4.10 Glanzmann's Thrombasthenia

Glanzmann's thrombasthenia is an inherited platelet disorder caused by a congenital deficiency of the fibrinogen receptor on the platelet surface (GP IIb/IIIa). It has a prevalence of one in one million in the general population. Although each component of this integrin is genetically coded by a different chromosomal locus, lack of expression of one component, either IIb or IIIa, causes deficiency of the whole receptor on the platelet surface. GP IIb/IIIa is essential for the last step of platelet aggregation and formation of the platelet thrombus using fibrinogen as a ligand. Lack of GP IIb/IIIa mostly causes mucocutaneous bleeding (usually provoked) and less often muscle or joint bleeding. Three levels of severity have been described: type 1 with <5 % of GP IIb/IIIa, type 2 with 10–20 % of GP IIb/IIIa, and type 3 with normal but nonfunctional GP IIb/IIIa.

Laboratory Findings
Glanzmann's thrombasthenia exhibits normal PT/INR and aPTT, but prolonged BT. In platelet aggregation assays, it shows a specific pattern in the responsiveness of platelets to various agonists. Using flow cytometry, it shows a loss or severe reduction of GP IIb/IIIa density on platelets.

Treatment
The most efficient treatment for this disorder is transfusion of normal platelets. However, this may cause rare transfusion-associated adverse events, such as the generation of iso- or alloantibodies against GP IIb/IIIa. Although the risk of alloimmunization has clearly been reduced since the introduction of leukocyte filtration and single-donor thrombocytapheresis in transfusion medicine, platelet transfusions should be avoided if possible. Very often, surgery cannot be performed on these patients without platelet transfusion. In such cases, human leukocyte antigen-compatible products should be chosen, and the number of transfusions should be kept to a minimum perioperatively. Antifibrinolytics combined with rFVIIa (NovoSeven®) are successfully used in mild or moderate bleeding. Desmopressin might also help in case of mild bleeding.

6.4.11 Bernard-Soulier Disease

Bernard-Soulier disease (BSD) is an inherited platelet disorder caused by a congenital deficiency of the vWF receptor on the platelet surface (GP Ib/V/IX). Prevalence in the general population is less than one in one million. Although each component of this integrin is genetically coded by different chromosomal loci, lack of expression of either component Ib or IX causes total deficiency of the receptor on the platelet surface. GP Ib/V/IX is essential for the first steps of platelet adhesion and aggregation using vWF as a ligand to bind to other platelets or to endothelial cells. Additionally, lack of GP Ib/IX causes loss of symmetry of the platelet membrane leading to large platelets and mild thrombocytopenia. The clinical picture involves mucocutaneous bleeding (usually provoked), menorrhagia, and less often muscle or joint bleeding.

Laboratory Findings

BSD exhibits normal PT/INR, normal aPTT, prolonged BT, and thrombocytopenia with large platelet volume (MPV >10 fl). Platelet aggregation assays show a specific pattern in the responsiveness of platelets to various agonists. Using flow cytometry, it shows loss or severe reduction of GP Ib/IX density on platelets.

Treatment

The most efficient treatment of BSD is transfusion of normal platelets. However, this might cause rare transfusion-associated adverse events, such as iso- or alloantibodies against GPIb/IX. Although the risk of alloimmunization has clearly been reduced since the introduction of leukocyte filtration and single-donor thrombocytapheresis in transfusion medicine, platelet transfusions should be avoided if possible. Very often surgery cannot be performed on these patients without platelet transfusion. In such cases, human leukocyte antigen-compatible products should be chosen, and the number of transfusions should be kept to a minimum perioperatively. Antifibrinolytics, along with rFVIIa (NovoSeven®), are successfully used in mild or moderate bleeding. Desmopressin might also help in case of mild bleeding.

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Acquired Hemostatic Disorders

7

Stefano Barelli, Sabine Blum, and Anne Angelillo-Scherrer

7.1 Introduction

Hemostatic disorders may be inherited or acquired. Acquired hemostatic disorders comprise thrombocytopenia and platelet dysfunction, coagulation factor deficiencies, excessive anticoagulation, and hemorrhagic complications due antiplatelet drugs, anticoagulation, and thrombolysis. Blood disorders associated with myeloproliferative neoplasms and disseminated intravascular coagulation (DIC) can cause both bleeding and thrombosis. Heparin-induced thrombocytopenia (HIT), antiphospholipid antibody syndrome, and thrombotic microangiopathies are conditions that cause thrombocytopenia, but they are more frequently responsible for thrombosis than for bleeding (Fig. 7.1). The present chapter focuses on acquired disorders (congenital coagulopathies are presented in Chap. 6). Antiplatelet and anticoagulant drug complications are presented in Chap. 8.

7.2 Thrombocytopenia

7.2.1 Acquired Thrombocytopenia

Acquired thrombocytopenia is the most common cause of thrombocytopenia. In the absence of a platelet function disorder, spontaneous bleeding may occur when the platelet count is <10–20 G/L of blood. Thrombocytopenia may result from decreased platelet production in cases of bone marrow infiltration by neoplastic cells, acute alcohol toxicity, infections, and vitamin B12 or folate deprivation. It may also be drug induced. Thrombocytopenia can be isolated or part of a more general process such as bone marrow failure, acute leukemia, DIC, chronic liver disease, or

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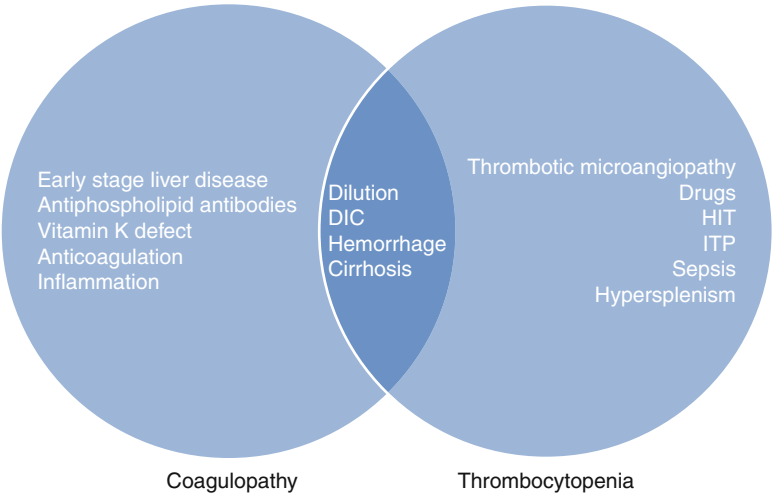

Fig. 7.1 The critically ill patient. *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *ITP* immune thrombocytopenia

thrombotic microangiopathy. The causes of thrombocytopenia can be classified by taking into account the clinical setting, such as outpatient versus inpatient (Table 7.1).

HIV infection often results in thrombocytopenia, and immune thrombocytopenia (ITP) occurs in about 40 % of HIV-infected patients and 2.6 % of hepatitis C patients. Thrombocytopenia is a common feature of sepsis, where it probably results from a combination of impaired platelet production and platelet consumption.

Primary ITP is an autoimmune disorder and the most common cause of isolated thrombocytopenia. Thrombocytopenia is caused by autoantibodies, directed against platelet antigens, which increase the clearance of circulating platelets and decrease platelet production by bone marrow megakaryocytes. Bleeding symptoms such as intracranial hemorrhage are uncommon except in severe ITP. First-line therapy is usually given when platelet counts are <30–50 G/L; it consists of glucocorticoid therapy at 1 mg/kg/day and/or intravenous immunoglobulins at 2 g/kg for 2–5 days (Provan et al. 2010). Tranexamic acid – an antifibrinolytic drug – may be administered together with a platelet transfusion, particularly when bleeding occurs at the mucosal level. Splenectomy, rituximab, and thrombopoietin receptor agonists are second-line therapies.

Drug-induced thrombocytopenia is common and may be caused by marrow suppression as well as immune or nonimmune thrombocytopenia. A list of potentially offending drugs can be found on http://www.ouhsc.edu/platelets/ditp.html. In immune-mediated drug-induced thrombocytopenia, platelet counts recover promptly after treatment interruption, usually 5–10 days after the withdrawal of the drug (Stasi 2012). The correct diagnosis is a challenge when the substance causing the thrombocytopenia is not a drug but is in a beverage, food, or herbal remedy (Stasi 2012). Glucocorticoid therapy 1 mg/kg/day is administered when platelets are <10 G/L and if bleeding is not severe. In case of severe bleeding, treatment

Table 7.1 Causes of thrombocytopenia with regard to the clinical setting

Outpatients
ITP
Drug-induced thrombocytopenia
Infections (HIV, hepatitis C, CMV, other recent viral infections, Helicobacter pylori)
Hypersplenism
Autoimmune disorders
Hematological malignancies
Bone marrow failure
Chemotherapy-induced thrombocytopenia
Chronic DIC
Inherited thrombocytopenia
Common variable immunodeficiency
Inpatients
Inpatients in ICU or with multisystemic illness
Infections
Drug-induced thrombocytopenia
Acute or chronic DIC
Liver disease
HIT
Bone marrow disorders, including hematological malignancies
TTP/HUS
Macrophage activation syndrome
Chemotherapy-induced thrombocytopenia
Dilutional thrombocytopenia
Posttransfusion purpura
Inpatients with cardiac disease
HIT
Cardiopulmonary bypass
Intra-aortic balloon pump/ECMO
GPIIb/IIIa inhibitors
Other drug-induced thrombocytopenia
Dilutional thrombocytopenia
Patients in the emergency department
ITP
Drug-induced thrombocytopenia
Alcohol toxicity
Bone marrow disorders
DIC
Liver disease
Chemotherapy-induced thrombocytopenia
TTP/HUS
Pregnancy/postpartum patients
Gestational thrombocytopenia
ITP
HELLP syndrome
Preeclampsia
Abruptio placentae
TTP/HUS

Adapted from Aird and Mark (2002), Stasi (2012)
ITP immune thrombocytopenia, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *TTP/HUS* thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, *ECMO* extracorporeal membrane oxygenation, *HELLP syndrome* hemolysis, elevated liver enzymes, and low platelets

combines platelet transfusion with intravenous immunoglobulins and high-dose glucocorticoids. Patients often suffer from petechial hemorrhages and urinary or gastrointestinal tract bleeding. Intracranial bleeding is rare.

GPIIb/IIIa inhibitors are antiplatelet agents that may also induce thrombocytopenia (see Chap. 8). HIT is detailed below (Sect. 7.2.2). Emergency surgery in the context of thrombocytopenia can be performed if a platelet transfusion is provided immediately before surgery. If necessary, additional platelet concentrates can be administered during and after surgery. When appropriate, specifically if the surgical procedure involves mucosae, the treatment can be completed with tranexamic acid.

7.2.2 Heparin-Induced Thrombocytopenia

HIT is a "clinical-pathological syndrome" occurring during heparin therapy. HIT is caused by IgG antibodies that bind platelet receptors and recognize PF4-heparin complexes. Because the IgG antibodies activate platelets and induce platelet clearance, they are responsible for a decrease in platelets and a prothrombotic state during heparin therapy. Previous exposure to unfractionated heparin (UFH) and, less frequently, to low-molecular-weight heparin (LMWH) is necessary for the initiation of the process.

Few patients with suspected HIT have true HIT. The diagnosis requires a clear clinical picture and laboratory confirmation of platelet-activating antibodies. Even if anti-PF4-heparin antibodies are easily detectable using enzyme immunoassays (EIAs), only a minority of these antibodies are truly platelet activating, respecting an "iceberg model"; these platelet-activating properties are best detected by activation or aggregation assays.

The following steps are recommended to avoid overdiagnosing HIT (Warkentin 2011):

- *Assessment of pretest probability with the 4Ts scoring system*: the score is a simple clinical tool to help decide whether further investigation and a change of anticoagulation is appropriate (Table 7.2).
- *Laboratory testing*: this should be ordered only if the 4Ts score is intermediate or high. EIAs are widely available and highly sensitive, but not sufficiently specific for platelet-activating antibodies. All positive EIA results need to be confirmed by activating or aggregation assays (serotonin-release assay or heparin-induced platelet activation test).

One mainstay of HIT treatment is the discontinuation of all forms of heparin treatment and the administration of an alternative anticoagulant. Anti-vitamin K anticoagulants (AVK) are contraindicated as an initial treatment due to their transient procoagulant properties (reduction of protein C level). Half of those individuals identified as having HIT concomitantly face the risk of a thrombosis; therefore, an ultrasound screening of the lower limbs is recommended. The risk of thrombosis remains elevated for at least 30 days after heparin therapy and as long as the platelet count has not returned to the normal range.

Table 7.2 4T pretest HIT scoring system

4Ts	2 points	1 point	0 points
Thrombocytopenia	PC fall >50 % and platelet nadir $\geq 20 \times 10^9$/l	PC fall 30–50 % or platelet nadir $10–19 \times 10^9$/l	PC fall <30 % and platelet nadir $<10 \times 10^9$/l
Timing of platelet count fall	Clear onset between days 5–10 or PC fall ≤1 day (prior heparin exposure within 30 days)	Consistent with 5–10 days fall but not clear (e.g., missing PC); onset after day 10; or fall ≤1 day (prior heparin exposure 30 –100 days ago)	PC fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute ischemic reaction post intravenous UFH bolus	Progressive or recurrent thrombosis: non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proved)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Adapted from Lo et al. (2006)
Pretest score 6–8 = high probability, 4–5 = intermediate probability, 0–3 = low probability
PC platelet count, *UFH* unfractionated heparin

- There are two alternative classes of anticoagulants for HIT treatment:
  (1) Antithrombin-dependent activated factor X (Xa) inhibitors, such as sodium danaparoid. Anticoagulant activity can be easily monitored by anti-Xa activity measurement. Their long half-life is a disadvantage in perioperative contexts.
  (2) Direct thrombin inhibitors, such as argatroban, have a short half-life. Monitoring can be performed by measuring activated partial thromboplastin time and specific antithrombin (IIa) activity.

Before hematological referral, the following aspects should be assessed (Warkentin 2011):

1. The overall likelihood of HIT.
2. The indication for therapeutic anticoagulation.
3. The renal/hepatic function.
4. The type of surgical procedure planned.

Further reading on HIT management can be found in (Selleng et al. 2007) and in the Clinical Practice Guideline on the management of HIT on www.hematology.org/practice/guidelines.

7.3 Acquired Platelet Dysfunction

Whereas inherited platelet dysfunction is rare, acquired platelet dysfunction is common. Platelet function may be affected by drugs, such as antiplatelet drugs or antidepressants, or by systemic disorders like uremia, liver failure, and myelodysplastic or myeloproliferative disorders.

In case of bleeding, platelet transfusion may be required. Desmopressin is a vasopressin analog that favors release of von Willebrand factor (vWF) from tissue stores (mainly endothelial cells) and may be used in acquired platelet disorders such as uremia. Desmopressin is administered at the dose of 0.3 μg/kg, intravenously in 50 mL of saline over 30 min or subcutaneously (Mannucci and Tripodi 2012). Recombinant activated factor VII (rFVIIa) may be used in the context of hemorrhagic complications (Franchini et al. 2008).

7.4 Acquired Multifactorial Deficiencies

Acquired multifactorial deficiencies are common and may result from vitamin K deficiency, liver disease, or DIC.

7.4.1 Vitamin K Deficiency

A lack of vitamin K impairs posttranslation γ-carboxylation of vitamin K-dependent proteins: factors II, VII, IX, and X, as well as proteins C, S, and Z. Vitamin K deficiency is frequent in neonates, to whom it should be provided systematically to prevent bleeding. In adults, vitamin K deficiency is mainly due to malabsorption as well as vitamin K metabolism impairment by VKA, antibiotics, or rodenticides.

7.4.2 Chronic Liver Disease

The hemostatic process is a complex interplay between the endothelium, platelets, coagulation factors, and the fibrinolytic system. It is balanced by prohemostatic and antihemostatic drivers; however, in chronic liver disease (CLD), this balance is altered (Fig. 7.2) (Lisman and Leebeek 2007). Most procoagulant factors decrease in parallel to the anticoagulant factors (Tripodi and Mannucci 2011). Thrombin – the pivotal factor of coagulation – is synthesized in amounts comparable to healthy subjects, but its generation is reduced by thrombocytopenia. In CLD, prohemostatic factors that are not exclusively synthesized by the liver have unusually high levels (vWF, which restores platelet adhesion to endothelium, and factor VIII, which drives thrombin generation). Tissue plasminogen activator levels are increased due to enhanced release by activated endothelium and/or by decreased hepatic clearance.

In CLD, simple defects are the result of complex pathological processes (Lisman and Leebeek 2007; Roberts et al. 2010):

- Thrombocytopenia: reduced megakaryopoiesis (reduced thrombopoietin, coinfection, alcohol abuse, folate deficiency, and medication), splenic sequestration, viral infections, primary biliary cirrhosis, or DIC
- Defective platelet function: acquired storage pool defect, defective transmembrane signal transduction, decreased levels of functional platelet receptors, or reduced hematocrit, and dyslipidemia

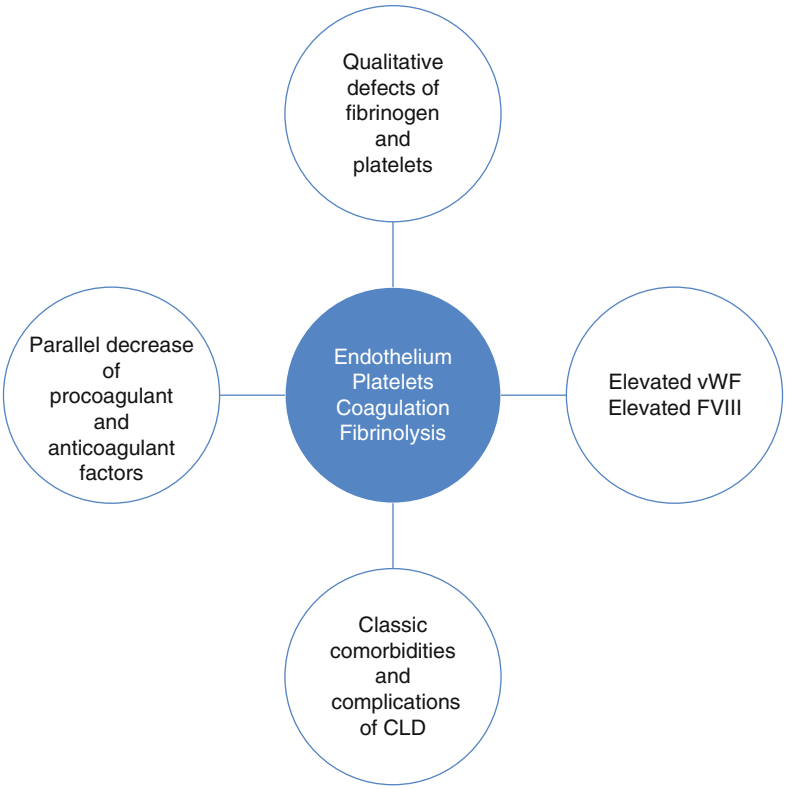

Fig. 7.2 Hemostasis in chronic liver disease (*CLD*). *vWF* von Willebrand factor, *FVIII* factor VIII

- Low or defective coagulation factors: reduced hepatic synthesis function, vitamin K deficiency, DIC, dysfunctional circulating fibrinogen, and altered fibrin polymerization due to excessive sialic acid content

In CLD, the laboratory pattern sometimes resembles the DIC pattern, but DIC should always be suspected in the presence of a trigger (e.g., sepsis) with evolving hemostatic abnormalities (consumption of factors and platelets).

7.4.2.1 Management

The correction of a coagulopathy in a non-bleeding patient is not required (Roberts et al. 2010; Gines et al. 2012). Conservative measures such as vitamin K substitution are recommended for the optimization of hemostasis in CLD. Predicting bleeding complications in CLD patients is challenging. The clinician should base her/his evaluation on three indicators:

1. Patient

   The majority of hemorrhages are due to the rupture of portosystemic varices (Lisman and Leebeek 2007). Bacterial infections, vitamin K deficiency (low dietary intake, loss of intestinal bacterial flora after antibiotherapy, intra-/extrahepatic cholestasis), and renal failure increase the tendency to bleed.

2. Laboratory values

   Current routine coagulation tests offer only limited help in the proper evaluation of the state of hemostatic balance in CLD (Tripodi and Mannucci 2011). For example, a prolonged prothrombin time (PT) does not necessarily indicate that the CLD patient is naturally anticoagulated, and a borderline PT could underestimate the risk of bleeding. Emerging global coagulation tests better reflect the interplay of all the factors involved in hemostasis (thrombin generation tests, thromboelastography) (Roberts et al. 2010).

3. Type of bleeding or surgery

   Acute variceal bleeding is mainly the consequence of anatomical changes and depends on the Child-Pugh score and endoscopic features. It is best treated with fluid resuscitation, pharmacological treatment, and endoscopy. For elective surgical procedures (paracentesis, central venous catheter insertion, or liver biopsy), the potential need for transfusion must anticipated. Transfusions should target a hemoglobin level of >70–80 g/l and platelet counts >50 G/L. Prophylactic transfusion of fresh frozen plasma (FFP) is associated with a risk of volume overload, infection, and transfusion-related acute lung injury (TRALI). This makes the use of prothrombin complex concentrates (PCC) more appropriate. There is no advantage to using recombinant FVIIa (Bosch et al. 2008).

7.4.3 Disseminated Intravascular Coagulation

DIC is a generalized coagulation process secondary to increased thrombin generation and fibrin deposition. Microvascular thrombi lead to organ dysfunction. Consumption of platelets and coagulation factors lead to bleeding (Levi and Ten Cate 1999; Levi et al. 2002). DIC is a systemic process without a specific anatomical localization. Due to its bad prognosis, DIC is also known as the acronym for "Death Is Coming." Interleukin-6 and tumor necrosis factor-α play pivotal roles in thrombin generation.

DIC can develop acutely or remain chronic. Acute DIC occurs in patients with sepsis, after surgery, trauma, or an incompatible blood transfusion, as an obstetrical complication, or as a complication of acute promyelocytic leukemia. Chronic DIC is more common in solid malignancies but can also be observed in large aortic aneurysms.

The principal triggers of DIC are listed below and can be memorized with the acronym "LAST HOME":

- Liver failure
- Angiopathy (macro and micro)
- Sepsis/severe inflammation
- Trauma (head trauma, fat embolism, tissue destruction)
- HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets syndrome)
- Obstetric events (amniotic fluid embolism, *abruptio placentae*)

- Malignancies (myeloproliferative neoplasms, solid tumors)
- Exogenous materials (drugs, transfusion products, toxins, prosthetic materials)

DIC is probably the main mechanism underlying thrombocytopenia in intensive care units. Independent of the severity and the cause of illness, DIC is a marker for severe homeostatic disturbance and predicts a fatal outcome (Vanderschueren et al. 2000).

7.4.3.1 Diagnosis

DIC is not a disease in itself, but a syndrome (Levi et al. 2002). Several clinical conditions mimic the hemostatic pattern of DIC. Overall, DIC should be suspected when a patient presents with:

- An underlying medical or surgical condition compatible with DIC
- Multiple organ failure
- Bleeding and/or thrombotic diathesis
- Thrombocytopenia associated with multiple coagulation factor deficiencies and hyperfibrinolysis (low fibrinogen, high D-Dimers, fibrin degradation products, and fibrin monomer levels).

We recommend using the scoring system of the International Society on Thrombosis and Haemostasis (ISTH) to easily identify overt DIC (Taylor et al. 2001) (Table 7.3).

7.4.3.2 Management

Treatment options should target the cause of DIC and aim to improve the patient's condition rather than the laboratory values (Levi et al. 2009; Thachil and Toh 2012; Wada et al. 2013).

Transfusion of blood components is indicated ONLY during active bleeding or in periprocedural situations. Target blood component levels are:

- Platelets >50 G/L in case of active bleeding and >20 G/L in patients with a high risk of bleeding. Platelet concentrates can be administered.
- PT or aPTT <1.5 times the upper limit of the normal range. FFP should be privileged. PCC may be considered in actively bleeding patients if FFP transfusion is impossible.
- Fibrinogen >1.5 g/l. The administration of fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with fibrinogen levels persistently <1.5 g/l despite FFP replacement.

Table 7.3 Diagnosis of disseminated intravascular coagulation (DIC)

	0	1	2
PLT [G/L]	>100	<100	<50
FBN [g/l]	>1	<1	
D-dimers [µg/l]	<200	200–3,200	>3,200
PT [%]	>55	55–40	<40

Adapted from Taylor et al. (2001)
A score >5 indicates overt DIC. An underlying disorder known to be associated with DIC is mandatory for the use of this score
PLT platelet, *FBN* fibrinogen, *PT* prothrombin time

When using anticoagulant drugs, LMWH is preferable to UFH; however, it is worth noting that there is no direct evidence of the effects of anticoagulants on DIC.

- Therapeutic doses of UFH or LMWH can be considered in cases of DIC with a predominance of thrombosis.
- Prophylactic anticoagulation with UFH or LMWH is recommended in critically ill, non-bleeding patients to prevent venous thromboembolism (VTE).

Antifibrinolytic agents (e.g., tranexamic acid) may be beneficial in several DIC processes because DIC leads to hyperfibrinolysis. These processes include:

- Trauma if bleeding persists despite FFP transfusion
- Massive postpartum hemorrhage

7.4.3.3 Conclusion

Critically ill patients are at risk of developing DIC, and thus this diagnosis should be assessed as early as possible.

Platelet count and simple coagulation tests (PT, fibrinogen level, or D-dimers) are of great value in identifying overt DIC and following its process.

7.5 Acquired Coagulation Factor Deficiencies

Inhibitors are autologous antibodies to coagulation factors that can develop in different clinical circumstances, such as acquired hemophilia A in the peripartum or in the context of lymphoproliferative neoplasms (alloantibodies only develop in the context of factor substitution for hemophilia A or B). In theory, it is possible to develop an inhibitor to any given coagulation factor; however, inhibitors to FVIII and vWF (see Sect. 7.6) are the most frequent. Patients with acquired FVIII deficiency (also called "acquired hemophilia A") present a broad spectrum of clinical signs ranging from superficial bruising to life-threatening bleeding. The incidence of acquired FVIII deficiency is 1.4/million/year (Collins 2012). The main treatment consists in treating the underlying clinical problem, if it can be clearly identified, for example, as a lymphoproliferative syndrome. If this is not possible, in most of the cases, the hematologist will initiate an immunosuppressive treatment with corticosteroids, monoclonal anti-CD20 antibodies (rituximab), or cyclophosphamide, or a combination of those therapies. However, no treatment will correct the targeted coagulation factor immediately. Should a surgical procedure be necessary, adequate hemostasis must be reached using a treatment that bypasses the targeted coagulation factor. Invasive procedures should thus be avoided when possible. One drug used to overcome the inhibitors of coagulation factors is rFVIIa (NovoSeven®). It bypasses factors VIII and IX and directly activates factor X, which then activates prothrombin to thrombin. Another possible bypassing agent is factor VIII inhibitor bypassing activity (FEIBA®). Both agents seem to have about the same effect on hemostasis (Baudo et al. 2012). Standardized laboratory assays cannot monitor responses to either of these agents. The performances of thrombelastography and thrombin generation, as well as the interpretation of aPTT graphs, are promising indicators, but are not yet standardized (Pivalizza and Escobar 2008). If neither hemostatic agent succeeds in stopping the hemorrhagic process, one option for rapid inhibitor

eradication is immunoadsorption. This technique is neither a standard procedure nor is it available in most hospitals. Most surgical experience has come from hemophilia patients with inhibitors, but bleeding patterns can differ significantly compared to patients with acquired hemophilia and the same aPTT or antibody levels.

The recommended prophylaxis for surgery in patients with FVIII inhibitors is 90–150 μg/kg of rFVIIa every 2–6 h, with increasing time intervals after the first or second postoperative day. Alternatively, a continuous infusion of 50 μg/kg/h can be administered (Huth-Kuhne et al. 2009; Baudo et al. 2010), but it must be noted that no trials have compared continuous and bolus treatment or different dosages. Following major surgery, the alternative treatment is FEIBA® with a recommended loading dose of 100 IU/kg followed by 200 IU/kg every 8 h for 3 days and then a tapering of the daily dose to 150–100 IU/kg for 9–17 days (Tjonnfjord 2004).

Acquired FV inhibitors are rare, with fewer than 200 cases described in the literature. The resulting tendency to bleed can vary and is not necessarily associated with residual plasma levels (Franchini and Lippi 2011). Both PT and aPTT are prolonged. Most cases have been provoked by exposition to bovine thrombin products, which are used in surgery for localized hemostasis, but the condition can occur in other circumstances (malignancies, autoimmune diseases, etc.). In case of clinical bleeding, platelet transfusion and FFP are the treatments of choice – effective in about 70–80 % of cases (Ang et al. 2009) – as platelets protect FV from circulating inhibitors. Some published cases have described the successful use of rFVIIa (Jeimy et al. 2008; Lebrun et al. 2008; William 2008); others describe plasmapheresis and immunoadsorption as effective (Tribl et al. 1995; Fu et al. 1996). High-dose intravenous immunoglobulins also seem to rapidly increase FV levels (Buclin et al. 1992; de Raucourt et al. 2003).

Acquired FXIII inhibitors have been described. They can occur in patients using large doses of antibiotics or other drugs, suffering from autoimmune diseases or monoclonal gammopathies, or even spontaneously (Otis et al. 1974; Milner et al. 1977; Ahmad et al. 1996; Luo et al. 2010). As with all acquired factor deficiencies due to inhibitors, eradication of the inhibitor would be the ideal treatment for FXIII inhibitors. In case of bleeding or emergency surgery, treatment options are limited as FXIII is the last factor in the coagulation cascade stabilizing the fibrin clot. Replacement therapy with FFP has been tried, but has not been reliably successful. FXIII concentrate (Fibrogammin®) can increase FXIII levels with doses between 50 and 150 IU/kg (Luo and Zhang 2011), but there have been reports of unsuccessful results (Miesbach 2005). In one case with severe hemorrhages, rFVIIa and tranexamic acid were provided in addition to FXIII concentrate (Boehlen et al. 2013). Immunoglobulin infusions take several days to become effective; the same is true for rituximab treatment, which takes even longer.

7.6 Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AvWS) is a rare disorder, but probably more frequent than we might expect. It is normally associated to an underlying disorder, such as lymphoproliferative or myeloproliferative neoplasms, other malignancies,

Table 7.4 Treatment of acquired von Willebrand syndrome

First choice in AvWS	Second choice in AvWS
Intravenous immunoglobulins 2 g/kg on 2 days (not if monoclonal IgM) with expected effect after 12–72 h	Desmopressin
Haemate P® 30 IU/kg before and 20–30 IU/kg 2 h into surgery, postoperative 20–30 IU/kg 3×/day for 5 days	Plasma exchange (3–4 l/day)
Antifibrinolytic drugs if a site with high fibrinolytic activity	rFVIIa 90 µg/kg

Refs. Federici et al. (2000), Maddox et al. (2005), Tiede et al. (2011)
AvWS acquired von Willebrand syndrome, *rFVIIa* recombinant activated factor VII

aortic stenosis (also when part of the Heyde syndrome), or, more rarely, autoimmune diseases. In these conditions vWF is eliminated more rapidly, either due to autoantibodies or to absorption on the surface of platelets or malignant cells. Infused vWF and FVIII concentrates will also rapidly be eliminated, if the underlying condition has not been treated. The same holds true when desmopressin is administered to increase endogenous vWF and FVIII. Table 7.4 summarizes treatment option for AvWS. Anecdotal reports mention the efficacy of plasma exchanges with 3–4 l/day of FFP for several days (Bovill et al. 1986; Silberstein et al. 1987; Federici et al. 2000; Maddox et al. 2005). This method can be useful, but it is not feasible for emergency procedures. It is recommended that emergency patients receive immunoglobulins intravenously (2 g/kg, if possible divided into 2 doses, infused 24 h apart). However, this treatment is ineffective in patients with AvWS in a monoclonal IgM setting (Federici et al. 2000). Factor improvement occurs 12–72 h after treatment and can last from days to weeks (Tiede et al. 2011). In cases showing no factor correction or cases of emergency surgery, 30–100 IU/kg of Haemate P® can be infused before surgery and 20–30 IU/kg two hours into surgery. In the postoperative setting, 20–30 IU/kg of Haemate P® 3 times daily for 5 days seems to be an adequate treatment (Maddox et al. 2005; Tiede et al. 2011). If the response to Haemate P® is diminishing, a further dose of 1 g/kg of immunoglobulins can be given intravenously. rFVIIa is another possibility to control bleeding, administered at the usual dosage of 90 µg/kg. However, there is currently only a limited experience of this treatment. Antifibrinolytic drugs, such as tranexamic acid, can be used in surgery on sites with a high fibrinolytic activity, such as the gastrointestinal tract or the oral cavity, but they are contraindicated in patients with macrohematuria.

During surgery, normal factor levels should be aimed for; in the postoperative setting, plasma levels of at least 50 % seem to be sufficient (Frank et al. 2002).

7.7 Coagulation Impairment Secondary to Drug Therapy

7.7.1 Opioid Abuse

In cases of chronic opioid abuse, morphological and rheological platelet changes can occur. An accumulation of free fatty acids can induce these changes (Zvetkova et al. 2010).

7.7.2 Antiplatelet Drugs and Anticoagulants

See Chap. 8

7.7.3 Antidepressant Drugs

Selective serotonin reuptake inhibitors (SSRIs) are known to have an influence on platelet function. In combination with oral anticoagulation therapy such as warfarin, the bleeding risk is even higher (Cochran et al. 2011). This holds true only for SSRIs and serotonin and norepinephrine reuptake inhibitors (SSNRIs). Other antidepressants do not increase the risk of bleeding when given concomitantly with warfarin, and the classic tricyclic antidepressants do not seem to alter platelet function.

SSRIs are known to alter platelet aggregation (Sarma and Horne 2006) and increase the risk of gastrointestinal bleeding (Dalton et al. 2003). Platelet aggregation is altered by different mechanisms, such as the inhibition of the serotonin transporters (Abdelmalik et al. 2008) and the depletion of serotonin inside the platelets (Dalton et al. 2003), but also by decreasing platelet count (Ataoglu and Canan 2009). Before elective surgery, it would be suitable to discontinue the use of these drugs to allow normal platelet function. In emergency surgery platelet concentrates should be given only in case of bleeding, as not every patient under SSRIs will show a tendency to bleed.

7.7.4 Thrombolytic Drugs

Thrombolysis is performed by intravenous or intra-arterial administration of plasminogen activators, such as recombinant tissue plasminogen activator (rTPA), in order to induce blood vessel recanalization. Cerebral hemorrhage is the most severe complication of thrombolysis.

Recommendations for the prevention of complications due to thrombolysis are (Trouillas and von Kummer 2006):

- Respect the guidelines regarding the contraindications to thrombolysis.
- Do not prescribe LMWH during the 24 h following thrombolysis.
- Avoid UFH immediately after thrombolysis.
- Analysis of hemostasis should be performed before and 2 h after the start of thrombolysis with a blood count and determination of the levels of fibrinogen and fibrinogen degradation products or D-dimers.

7.8 Malignancies

A recent retrospective analysis has shown an “unacceptably” high risk of thrombotic events in patients with malignancies (Moore et al. 2011). Venous events include deep vein thrombosis (DVT), pulmonary embolism (PE), and visceral/

splanchnic and cerebral vein thrombosis. Some patients may also present superficial vein thrombosis. Venous malignancy per se is a risk factor for DVT (Prandoni et al. 2005). About 10 % of patients with idiopathic DVT have an underlying malignancy. Arterial events comprise stroke, myocardial infarction, and arterial embolism.

The activation of coagulation in patients with a malignancy is caused by the acute-phase reaction, anticancer treatments, and prothrombotic properties of tumor cells. The latter induce tissue factor, protease-activating factor X, plasminogen activator inhibitors which lead to impaired fibrinolysis and cytokines targeting the endothelium, leukocytes, and platelets. The whole process is influenced by the stage of the disease, invasive procedures (e.g., central venous catheter), and the patient's profile (inherent thrombophilia).

7.8.1 Diagnosis

Indicators of a possible undiscovered malignant process in a patient with DVT are:

- No apparent classic risk factors for DVT
- Recurrent DVT
- Bilateral involvement
- A high level of D-dimers (>4,000 mg/l) at presentation
- DVT in a patient younger than 60 years old

The stage of malignancy influences the thrombotic pattern: arterial embolism can be seen in ongoing chemotherapy or in the presence of a nonbacterial endocarditis; DIC can be found in metastatic disease.

7.8.2 Management

For patients with cancer, the initiation of antithrombotic prophylaxis is particularly recommended in:

- Metastatic disease
- Surgical procedure
- Placement of a central venous catheter
- Inflammatory and/or infectious conditions

UFH and particularly LMWH are the cornerstones of DVT prophylaxis. Oral anticoagulation by VKA is difficult to manage because of pharmacokinetic concerns (poor nutrition, co-medication, or liver dysfunction), hemorrhagic concerns (thrombocytopenia secondary to chemotherapy, to radiotherapy, or to medullar spread of cancer), or surgical concerns (long half-life imposing reversal by factor concentrates in case of emergency).

7.8.3 Conclusions for Clinical Practice

These conclusions are based on guidelines of the American College of Chest Physicians http://www.chestnet.org/accp/guidelines.

For patients with a high risk of VTE who are undergoing abdominal or pelvic surgery for cancer, but who do not otherwise exhibit a high risk for major bleeding complications, extended pharmacological prophylaxis with LMWH is recommended (4 weeks).

In patients with DVT of the leg and/or a PE and active cancer, treatment with LMWH is recommended over VKA therapy. In patients with DVT and cancer who are not treated with LMWH, VKA is suggested over dabigatran or rivaroxaban as a long-term therapy.

In patients with acute DVT and/or PE and a contraindication to anticoagulation (hemorrhage, surgery, or thrombocytopenia), the use of an inferior vena cava filter is recommended (see also Chap. 8). A conventional course of anticoagulant therapy should be considered as soon as the risk of bleeding resolves.

In cancer patients who have upper extremity DVT that is associated with a central venous catheter, 3 months of anticoagulation treatment is recommended if the catheter is removed. If the catheter is not removed, anticoagulation treatment should be continued as long as the central venous catheter remains.

7.9 Monoclonal Gammopathies

7.9.1 Mechanism

Monoclonal gammopathies interfere with coagulation through several mechanisms:

- Shear wall stress due to increased blood viscosity.
- Fibrin polymerization with the loss of a harmonious clot structure.
- Autoantibody-like behavior of monoclonal proteins on coagulation factors (thrombin, FVIII, and vWF) with enhanced clearance (e.g., acquired von Willebrand syndrome).
- Absorption of coagulation factors (mostly FX) by subendothelial paraprotein deposits in AL amyloidosis. It is usually associated with a prolonged aPTT (this condition requires a hematologist's expertise).
- Heparin-like activity of certain monoclonal proteins.

7.9.2 Diagnosis

Paraprotein interference with hemostasis can be suspected in the following situations:

- History of lymphoproliferative disorders or plasma cell dyscrasia (chronic lymphocytic leukemia, Waldenström disease, MGUS, multiple myeloma)
- Bleeding complications with normal classic coagulation tests
- New onset mildly prolonged aPTT
- Abnormal primary hemostasis tests such as PFA-100.
- Poor response to Desmopressin
- Etiologic diagnosis of AvWS
- Monoclonal gammopathy

- Essential thrombocytosis
- Severe aortic stenosis (Heyde syndrome triad)

7.10 BCR/ABL-Negative Myeloproliferative Neoplasms

BCR/ABL-negative myeloproliferative syndromes (MPS) can be associated with either hemorrhagic complications or, more often, thrombotic complications, or worse, both.

7.10.1 Thrombotic Complications

Polycythemia vera (PV) and essential thrombocythemia (ET) are two types of MPS that are associated with up to 50 % of thrombotic events (Elliott and Tefferi 2005), with arterial thrombotic events being more common than venous events (Fenaux et al. 1990; De Stefano et al. 2008). The most common events among patients with PV and ET are ischemic strokes (De Stefano et al. 2008). The prevalence of splanchnic and cerebral vein thrombosis is unusually high in patients with MPS, and such events might be the presenting feature of the disease, even before diagnosis (Reikvam and Tiu 2012). Thrombotic risk is higher due to elevated hematocrit with hyperviscosity, thrombocytosis, and leukocytosis (Wolanskyj et al. 2006). Janus kinase 2 (JAK2) mutations can also add to the thrombotic risk through increased red cell adhesiveness (Buss et al. 1985) and altered platelet signaling (Falanga et al. 2007). Patients with MPS are treated with aspirin and/or cytoreduction, according to their risk level.

7.10.2 Hemorrhagic Complications

Most patients with hemorrhagic complications suffer from ET associated with a high platelet count or are patients with secondary bleeding due to anticoagulation for thrombotic risk (De Stefano et al. 2008; Tartaglia et al. 1986). Bleeding in patients with thrombocytosis is normally due to AvWS and occurs when platelets rise over 1000 G/L, in association with the loss of large multimers due to the binding of vWF to platelets (Michiels et al. 2001). Dysfunctional platelets can be a further problem (Elliott and Tefferi 2005; Landolfi et al. 1995).

7.10.3 Treatment

Both thrombotic and hemorrhagic complications can be treated by cytoreduction, such as hydroxyurea treatment, with effect on all blood lineages. A high hematocrit alone can be treated with phlebotomy; a high platelet count alone can be lowered with anagrelide. Another option for lowering peripheral blood cell counts is interferon. Normally, patients with MPS take aspirin on a regular basis. If possible, peripheral blood cell counts should be within normal ranges before surgical

procedures. In emergency, surgery platelet count should be at least $<100 \times 10^9$/l to reduce the risk of bleeding. With regard to thrombotic complications, patients at high risk should receive an appropriate antithrombotic prophylaxis with, for example, LMWH.

7.11 Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome is an acquired autoimmune tendency to thrombosis that is diagnosed when antiphospholipid antibodies are present, together with a history of thrombosis and/or complications during pregnancy. Treatment comprises antithrombotic drugs. In the perioperative setting, the management of antiphospholipid antibody syndrome requires input from a hematologist.

One category of antiphospholipid antibodies, called "lupus anticoagulant," can interfere with in vitro coagulation tests such as PT, aPTT, and ACT. It is important to be aware of the impact of this interference on patient monitoring in the perioperative setting, particularly if a cardiopulmonary bypass must be performed. Interference can be circumvented by using a Hepcon® test or by measuring the heparin concentration by anti-Xa activity tests (Jervis et al. 2009).

7.12 Thrombotic Microangiopathies

Thrombotic microangiopathies are characterized by direct antiglobulin test-negative hemolytic anemia, thrombocytopenia, petechial hemorrhages, fever, and/or renal and neurological complications. Diagnosis of thrombotic microangiopathies may prove difficult, and the input of a hematologist is required to best define perioperative management.

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Antiplatelet Therapy and Anticoagulation

8

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8.1 Antiplatelet agents

8.1.1 Introduction

Perioperative management of antiplatelet (AP) drugs is a major challenge. Dual AP therapy (aspirin plus clopidogrel, prasugrel, or ticagrelor) is the key to preventing myocardial infarction (MI) after acute coronary syndrome (ACS) or stent thrombosis (ST) following the implant of bare-metal (BMS) or drug-eluting stents (DES). In this population, platelet inhibition in the perioperative period is particularly important because of the increased platelet activity associated with the postoperative acute inflammatory response. Unfortunately, AP drugs also increase the risk of surgical bleeding. The key question is whether the risk of thrombosis when AP agents are withdrawn is higher than the risk of hemorrhage when they are maintained. Current recommendations are based on the results of highly reliable cardiologic trials (level of evidence A) and on large observational or prospective studies collected in surgery and anesthesiology (level of evidence B). Taken together, these data can be considered as adequate for defining the safest possible strategy.

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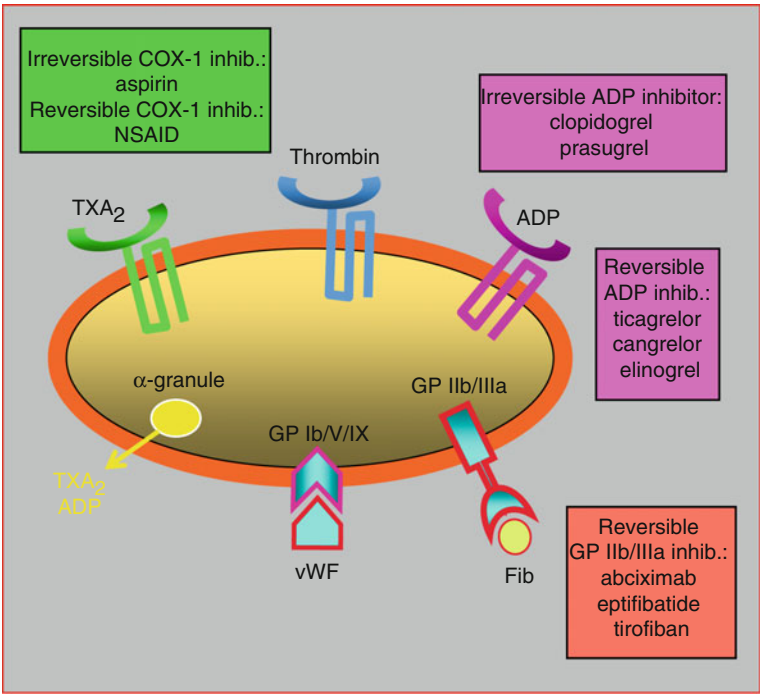

Fig. 8.1 Classification of the different AP agents. Blockers of von Willebrand factor/adhesion molecules and thrombin receptor blockers are under investigation (Adapted with permission from www.pac4.ch). *ADP* adenosine diphosphate, *cAMP* cyclic adenosine monophosphate, *COX-1* cyclooxygenase-1, *Fib* fibrinogen, *inhib* inhibitor, *NSAID* nonsteroidal anti-inflammatory drug, *TXA_2* thromboxane A_2, *vWF* von Willebrand factor

8.1.2 Antiplatelet Therapy

The different AP agents are classified according to the type of receptor they inhibit on the platelet (Fig. 8.1). Their pharmacology is described in Tables 8.1 and 8.2. At doses of 50–160 mg/day, aspirin completely inhibits the cyclooxygenase-1 (COX-1) enzyme which converts arachidonic acid to thromboxane A2 (TXA_2), the ligand for the homonymous platelet receptor. However, 6–10 % of the population shows a low response to aspirin treatment, resulting in insufficient platelet inhibition. In some patients, this is due to insufficient inhibition of the COX-1 enzyme by aspirin. Yet in others, due to a predominance of alternative activation pathways (e.g., ADP, thrombin), the platelet function remains normal in spite of sufficient COX-1 inhibition. Competitive interaction with nonsteroidal anti-inflammatory drugs (NSAIDs) may also reduce aspirin efficiency (Patrono and Rocca 2010).

Clopidogrel (Plavix™, Iscover™) is a prodrug which is oxidized into an active metabolite in a two-step process by hepatic cytochromes. This metabolite irreversibly blocks the adenosine diphosphate (ADP) receptor (P2Y12) and reduces platelet activity by 50–60 % (Hall and Mazer 2011). Clopidogrel's efficiency may be

Table 8.1 Activity and route of administration of antiplatelet drugs

	Receptor	Link with receptor	Biotransformation	Route
Aspirin	COX-1 (TXA_2)	Irreversible	None	Oral
Clopidogrel	ADP $P2Y_{12}$	Irreversible	P450 (liver, 2-steps)	Oral
Prasugrel	ADP $P2Y_{12}$	Irreversible	P450 (liver)	Oral
Ticagrelor	ADP $P2Y_{12}$	Reversible	None	Oral
Abciximab	GP IIb/IIIa	Irreversible	None	Intravenous
Tirofiban	GP IIb/IIIa	Reversible	None	Intravenous
Eptifibatide	GP IIb/IIIa	Reversible	None	Intravenous

Adapted with permission from www.pac4.ch

Table 8.2 Pharmacokinetics of antiplatelet drugs

	Loading dose	Maintenance dose	Time-to-peak effect	Half-life
Aspirin	160–325 mg	50–160 mg/day	<1 h	<1 h[a]
Clopidogrel	300–600 mg	75 mg/day (150 mg/day)	3 (600)–6 h (300 mg)	7.5 h (metab <1 h)[a]
Prasugrel	60 mg	10 mg/day	1 h	3.7 h (metabolite)[a]
Ticagrelor	180 mg	2×90 mg/day	2 h	7–10 h
Abciximab	0.25 mg/kg	0.125 mcg/kg/min	2 h	23 h
Tirofiban	0.4 mcg/kg/min	0.1 mcg/kg/min	15 min	2.0 h
Eptifibatide	180 mcg/kg	2.0 mcg/kg/min	10 min	2.5 h

Adapted with permission from www.pac4.ch
Perf continuous perfusion, *Iv* intravenous, *Metab* metabolite
[a]The pharmacological half-life does not correspond to the clinical effect for irreversibly blocking agents because termination of clinical activity relies on platelet renewal (10 %/day)

lowered because of competition for the same cytochromes by midazolam, fluoxetine, some lipophilic statins (particularly atorvastatin), and some proton pump inhibitors (particularly omeprazole). Although the evidence for an increase in cardiovascular complications is modest, it is safer to avoid the administration of atorvastatin, omeprazole, and clopidogrel simultaneously (Bates et al. 2011). There are no major differences in terms of bleeding between aspirin and clopidogrel monotherapy. After cessation of aspirin or clopidogrel, bleeding time and global platelet activity return to baseline levels in 5 days (Bhatt et al. 2006).

Up to 30 % of patients respond poorly to clopidogrel. One reason is polymorphism in the genes that code the hepatic enzymes involved in the synthesis of the active metabolite. Patients with abnormal alleles are 1.6–3.5 times more likely to experience cardiovascular complications and stent thrombosis when treated with clopidogrel (Mega et al. 2010). Patients who maintain a residual platelet activity after a loading dose of clopidogrel are four to six times more likely to suffer infarction and stent thrombosis than normal responders (Aradi et al. 2010) (Fig. 8.2).

Compared to clopidogrel, prasugrel (Effient™) is faster acting, is more potent, and has a much lower rate of low responders. It is more efficient in diabetics and patients with ST-elevation MI and is twice as efficient in preventing stent

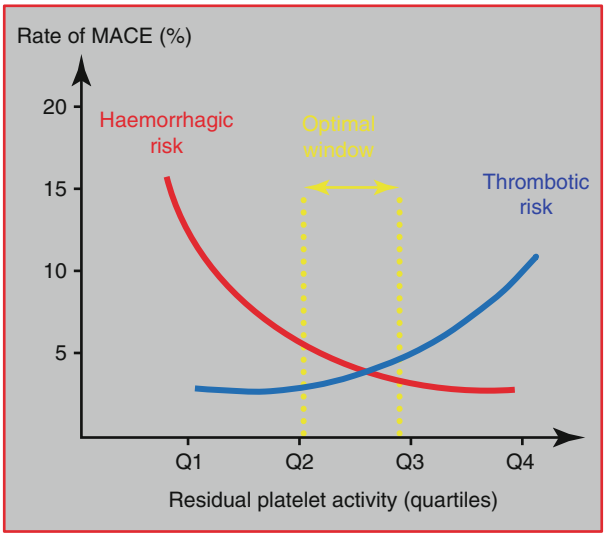

Fig. 8.2 Rate of major adverse cardiac events (MACE, *in blue*) after percutaneous coronary intervention and stenting according to the residual platelet activity after a loading dose of aspirin and clopidogrel. Since adverse events cluster in the highest quartile (Q4), there is a larger benefit to decrease platelet activity from Q4 to 50 % than from 50 % to Q1. The curve for hemorrhagic risk (*in red*) is mirrorlike and varies in the opposite direction. These two curves determine an optimal window with the best combination of minimal risk of bleeding and maximal platelet inhibition (Adapted with permission from Price (2009))

thrombosis. However, it does increase the risk of spontaneous hemorrhage 1.5 times and of surgical bleeding up to four times (Wiviott et al. 2007). Considering its potency, prasugrel cessation 7 days before surgery is recommended.

Ticagrelor (Brilinta™, Brilique™, Possia™) is a powerful and reversible ADP receptor blocker. One hour after a loading dose, 80 % of platelet activity is inhibited and after cessation, it takes 3 days for platelet function to recover (Gurbel et al. 2009). Ticagrelor is more efficient than clopidogrel in preventing stent thrombosis, yet does not increase the hemorrhagic risk (Wallentin et al. 2009). Because some patients produce a long-acting metabolite, it is recommended to stop ticagrelor 5 days before an operation.

Cangrelor is an intravenous fast onset and offset drug, which will be useful for preoperative substitution of long-acting agents. It abolishes platelet aggregation but allows a complete recovery of platelet activity within 1–3 h of stopping the perfusion (Angiolillo et al. 2012).

Dual AP therapy is essential after ACS or stent implantation because vascular lesions and stents behave like unstable plaques if they are not fully covered by a cellular layer. It takes 6 weeks for the frame of a BMS to become covered by smooth muscle cells and 3 months to be protected by a normal endothelium. DES have a slower endothelialization rate: 20 % at 3 months and 60 % at 1 year (Joner et al. 2006). Thus, the minimal duration of dual AP therapy following implantation is 6

Table 8.3 Recommended duration of antiplatelet therapy

Aspirin (75–325 mg/day): lifelong therapy, without interruption	
Dual therapy: aspirin plus clopidogrel (75–150 mg/day) or prasugrel (10 mg/day) or ticagrelor (90 mg 2×/day)	
Simple angioplasty without stenting	4–6 weeks
PCI and bare-metal stents	Min 6 weeks, optimally 6–12 months
Myocardial infarction	Minimum 6 months
Acute coronary syndrome (unstable)	12 months
PCI and drug-eluting stents (first generation)	Minimum 12 months
PCI and drug-eluting stents (second to third generation):	6–12 months
High-risk situations	>12 months, occasionally lifelong

Adapted with permission from www.pac4.ch
PCI percutaneous coronary intervention

weeks for BMS and 12 months for DES (Table 8.3) (Task Force on Myocardial Revascularization of the European Society of, the European Association for Cardio-Thoracic et al. 2010). These periods can be prolonged beyond 1 year for high-risk stents (DES implanted in dominant, ostial, or bifurcated positions) and high-risk patients (previous ST, diabetes, cardiac or renal failure). Late DES thrombosis is a rare (0.6 %/year) but catastrophic event with a mortality of 9–45 % since it leads to the acute interruption of flow in a previously normal vessel (Dangas et al. 2011). New-generation DES have a faster rate of endothelialization and a lower incidence of ST; depending on the type of stent, the duration of dual AP therapy is 6–12 months.

8.1.3 Withdrawal of AP Agents

Cessation of AP therapy is associated with an increased mortality and ischemic risk: the shorter the duration, the higher the complication rate. Aspirin withdrawal is associated with an increased risk of cardio- and cerebrovascular complications (Biondi-Zoccai et al. 2006). Cases of acute DES thrombosis following aspirin withdrawal have been reported more than 3 years after stent implantation (Artang and Dieter 2007; Fujimoto et al. 2009). Thrombotic events peak 7 days after interruption, whatever the duration of treatment (Eisenberg et al. 2009). Therefore, aspirin should be a lifelong therapy, never interrupted (Task Force on Myocardial Revascularization of the European Society of, the European Association for Cardio-Thoracic et al. 2010). Stopping clopidogrel is the most significant independent predictor for ST (Gaglia and Waksman 2011). During the first 6 months of therapy, the average delay between clopidogrel cessation and ST is 9 days (Schulz et al. 2009). Although the usefulness of prolonging dual therapy beyond 1 year remains unsettled, there is clear clinical evidence that its cessation during that first year is exceedingly dangerous (Valgimigli et al. 2012).

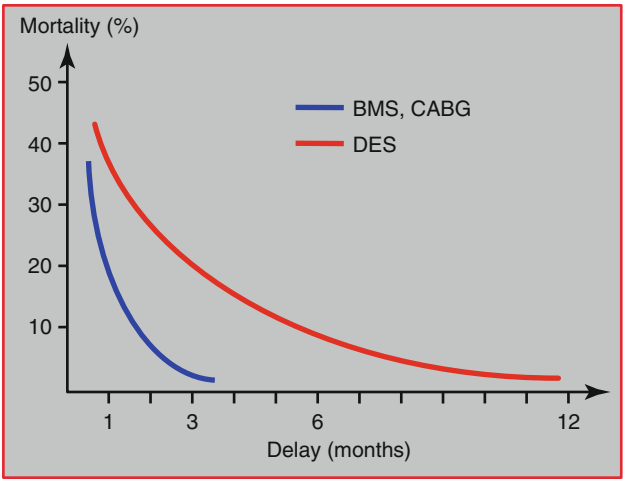

Fig. 8.3 Schematic illustration of the relationship between mortality for noncardiac surgery and time since revascularization in case of perioperative interruption of dual antiplatelet therapy. During the first 6 weeks after coronary artery bypass graft surgery (*CABG*), bare-metal stents (*BMS*), or drug-eluting stents (*DES*), mortality is around 30 %. After BMS and CABG, it takes 3 months for postoperative mortality to reach the level of patients with no active coronary artery disease, whereas after DES the plateau of the curve is reached only after 12 months

The interruption of AP drugs is more hazardous in the perioperative period because of the ensuing increased platelet stimulation and the acute systemic inflammatory reaction. Interruption is the major independent factor predicting cardiac complications after noncardiac surgery (Barash and Akhtar 2010). Stopping dual AP therapy to allow major surgery during the first 3 months after angioplasty and stenting (BMS or DES) leads to an average cardiac mortality of 30–50 %, whereas it is ≤5 % when the treatment is maintained perioperatively (Sharma et al. 2004; Schouten et al. 2007; Nuttall et al. 2008; Rabbitts et al. 2008). Mortality is inversely related to the delay between revascularization and surgery (Fig. 8.3).

The recommended delays between revascularization and noncardiac surgery are as follows:

- Angioplasty without stenting: 2–4 weeks (vital surgery only).
- BMS and coronary artery bypass graft (CABG): 6 weeks for vital surgery and 3 months for elective surgery.
- DES: >12 months for elective surgery; vital surgery could be performed within 2–12 months under full AP therapy.

8.1.4 Hemorrhagic Risk Linked to AP Agents

The body of evidence shows that aspirin or clopidogrel taken alone increase average blood loss by 20 % during noncardiac surgery (Chassot et al. 2007). Some operations can show a significant increase in postoperative hemorrhage, such as

tonsillectomy or transurethral prostatectomy. Life-threatening hemorrhage has only been reported in intracranial neurosurgery. A meta-analysis including 474 studies comparing surgical bleeding across all kinds of surgery reports no difference in mortality and complication rates between patients who took aspirin and those who did not (Burger et al. 2005).

With aspirin and clopidogrel dual therapy, the relative risk of bleeding increases by up to 50 %, as observed in orthopedic, vascular, abdominal, thoracic, urological, and endoscopic surgery (Moore and Power 2004; Albaladejo et al. 2011; Chernoguz et al. 2011; Taylor et al. 2011). Although hemostasis is difficult and tedious, particularly because of the increased oozing from bones and raw tissues, surgical mortality and long-term morbidity are not increased. In series comparing general surgery with and without dual AP therapy, the transfusion rate is inconsistently affected (relative increase: 4, 12, 16, and 17 %) (Wilson et al. 2003; Schouten et al. 2007; Rabbitts et al. 2008; Chernoguz et al. 2011). Aspirin and clopidogrel do not appear to cause an increase in surgical complications, except for surgery in a closed space (intracranial neurosurgery, surgery of the spinal canal or the posterior ocular chamber) or surgery associated with massive hemorrhage and difficult hemostasis. In these cases, clopidogrel, prasugrel, and ticagrelor should be interrupted or substituted by a short-acting agent (Chassot et al. 2007; Eberli et al. 2010). In cardiac surgery, the situation is more critical due to the full heparinization during heart-lung bypass: blood loss and reoperation for bleeding control are more than doubled; the transfusion rate is increased up to four times; however, mortality remains unchanged (Task Force on Myocardial Revascularization of the European Society of, the European Association for Cardio-Thoracic et al. 2010).

8.1.5 Recommendations and Guidelines

Current recommendations are based on the safest possible management of the dangers of discontinuing AP agents prematurely (Douketis et al. 2008; American Society of Anesthesiologists Task Force on Neuraxial et al. 2009; Task Force on Myocardial Revascularization of the European Society of, the European Association for Cardio-Thoracic et al. 2010; Korte et al. 2011). They are illustrated as an algorithm in Fig. 8.4 and are summarized in Table 8.4.

- Aspirin for primary prevention can be interrupted 5 days before surgery, except in high-risk cases, such as diabetics.
- Aspirin or clopidogrel monotherapy for secondary prevention after a stroke, ACS, MI, or coronary revascularization should be maintained throughout the perioperative period, whatever the duration of treatment.
- Aspirin plus dipyridamole dual therapy after stroke should be maintained throughout the perioperative period.
- Aspirin plus clopidogrel/prasugrel/ticagrelor dual therapy in patients with a low cardiovascular risk: maintain continuous treatment with aspirin; stop clopidogrel 5 days, prasugrel 7 days, and ticagrelor 5 days before surgery; restart

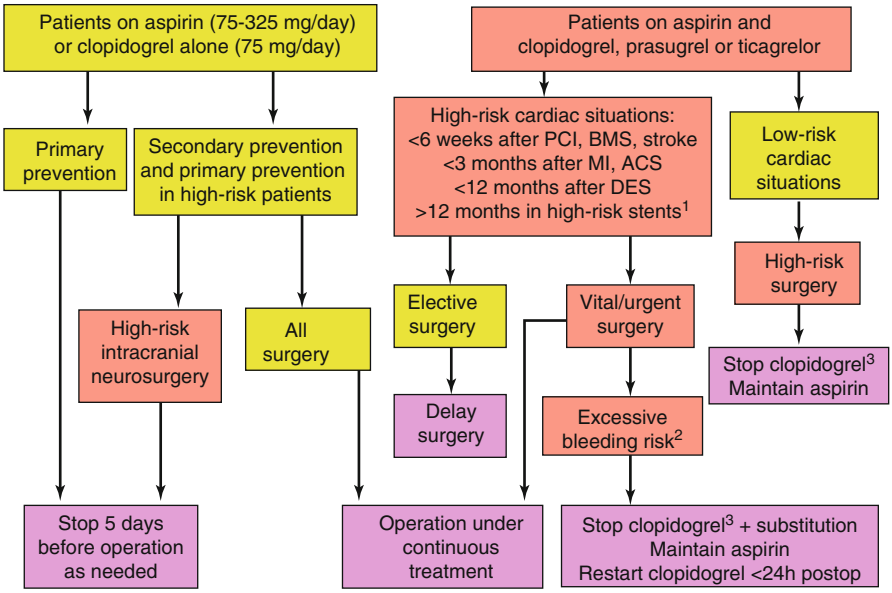

Fig. 8.4 Algorithm for the preoperative management of patients under antiplatelet therapy. Low-risk conditions are depicted in *yellow*, high-risk conditions in *red*, and decisions in *magenta*. *1* High-risk stents: multiple stents, long stent, proximal location (left main), and bifurcation lesions; patients with previous stent thrombosis; stent in unique patent vessel. *2* Excessive risk of bleeding: invasive surgery associated with severe bleeding and difficult hemostasis, or bleeding in closed spaces (intracranial neurosurgery, intramedullary canal surgery, posterior eye chamber ophthalmic surgery). *3* The same recommendations apply to prasugrel and ticagrelor. In all cases, restart AP within 24 h postoperative. *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft surgery (Adapted with permission from www.pac4.ch and form Eberli et al. (2010))

clopidogrel/prasugrel/ticagrelor within 24 h after surgery, preferably with a loading dose (if hemorrhagic risk is low).

- Aspirin plus clopidogrel/prasugrel/ticagrelor dual therapy in patients with high cardiovascular risk: delay elective surgery for 3 months after a stroke, BMS, or CABG, 6 months after acute coronary syndrome or infarction, and 12 months after DES. Beyond these delays: maintain aspirin; if clopidogrel/prasugrel/ticagrelor is still prescribed, discuss with the cardiologist and the surgeon whether to stop or maintain. Delay vital or semi-urgent surgery for at least 6 weeks if possible; maintain both aspirin and dual therapy.

During the first 6 weeks after ACS or revascularization, the operative risk is exceedingly high – even higher than without coronary revascularization. The full benefit of revascularization only manifests itself 3 months after BMS or CABG and 12 months after DES, when mortality returns to the level of noncoronary patients. All elective operations should therefore be postponed beyond these delays. Only vital surgery should be performed on patients still on dual AP therapy; unless the

Table 8.4 Recommended preoperative management of patients under antiplatelet therapy according to the hemorrhagic risk of surgery

	Low-risk patient >3 months after PCI, BMS, CABG or CVA >6 months after ACS or MI >12 months after regular DES	*Intermediate risk* 6–12 weeks after PCI, BMS, CABG, or CVA 3–6 months after MI or ACS >12 months after high-risk DES	*High-risk patient* <6 weeks after PCI, BMS, CABG, ACS, CVA <3 months MI or ACS <6 months after MI or ACS with complications <12 months after DES
Low hemorrhagic risk Transfusion not required Peripheral and wall surgery, minor ENT and orthopedics, endoscopy without biopsy/resection, eye anterior chamber, dentistry	Maintain aspirin or clopidogrel	Proceed with elective surgery: maintain aspirin Maintain clopidogrel, prasugrel, or ticagrelor if prescribed	Postpone elective surgery Proceed with vital/urgent surgery: maintain aspirin and clopidogrel, prasugrel, or ticagrelor without interruption
Intermediate risk Transfusion may be required Visceral and vascular surgery, major ENT and orthopedics, urology, endoscopy with biopsy/resection	Maintain aspirin or clopidogrel	Postpone elective surgery according to risk balance Proceed with vital surgery: maintain aspirin, maintain clopidogrel, prasugrel, or ticagrelor if prescribed	Postpone elective surgery Proceed with vital surgery: maintain aspirin and clopidogrel, prasugrel, or ticagrelor without interruption
High hemorrhagic risk Transfusion required Cardiac surgery, surgery with massive bleeding Surgery in closed space (intracranial, intramedullary canal, posterior eye chamber)	Stop aspirin or clopidogrel if necessary (5 days preoperatively) Restart <24 h postoperatively	Postpone elective surgery Proceed with vital/urgent surgery: maintain aspirin Stop clopidogrel (5 days), prasugrel (7 days), or ticagrelor (3–5 days) if prescribed, restart <24 h postoperatively	Postpone elective surgery Proceed with vital/urgent surgery: maintain aspirin Stop clopidogrel (5 days), prasugrel (7 days), ticagrelor (3–5 days). Substitution with tirofiban or eptifibatide (3–4 days perfusion)

Adapted with permission from Chassot et al. (2010) and from www.pac4.ch
ACS acute coronary syndrome, *BMS* bare-metal stents, *CABG* coronary artery bypass graft, *CVA* cerebrovascular accident, *DES* drug-eluting stent, *ENT* ear, nose and throat surgery, *MI* myocardial infarction, *PCI* percutaneous coronary intervention

hemorrhagic risk is excessive, dual AP therapy should not be interrupted before surgery. Heparin and LMWHs have no AP activity and are not adequate substitutes for long-acting AP drugs since stent thrombosis is a platelet-mediated phenomenon. A bridge using a 3-day continuous perfusion of a short-acting anti-GP IIb/IIIa agent, such as eptifibatide or tirofiban, is the only effective substitute for clopidogrel or

prasugrel, when aspirin is maintained (Savonitto et al. 2010). The perfusion can be stopped 6–8 h before surgery. After the operation, AP therapy should be resumed within the first 24 h.

8.1.6 Intraoperative Management

Intrathecal and epidural anesthesia are strictly contraindicated in case of dual AP therapy, although they are allowed in patients taking aspirin only, up to 325 mg/day (Gogarten et al. 2010). Although they undoubtedly improve patient comfort, their impact on cardiovascular outcomes is negligible. With a five- to tenfold increase in MI, the risk linked to AP withdrawal is obviously much higher than the benefit expected from neuraxial blockade. Stopping AP drugs in order to perform an intrathecal or epidural anesthesia is therefore clearly unjustified.

Aspirin, clopidogrel, and prasugrel are irreversible blockers. Since they have no antidotes, platelet renewal (10 %/day) is the only way for platelet aggregation to return to normal. As soon as 50 % of platelets have been renewed, blood hemostasis functions normally. Therefore, 5–7 days without AP therapy are required to prevent excessive surgical bleeding. It is commonly accepted that a substance's plasma level is negligible after 3 half-lives. Therefore, 24 h after the last intake of clopidogrel (half-life: 7.5 h) and 12 h after the last dose of prasugrel (half-life: 3.7 h), there is no residual AP activity in the plasma. Although the patient's native platelets are still inhibited, the platelets transfused after these delays will function adequately.

After cessation of the reversible AP drug ticagrelor, platelet function recovers more rapidly compared to clopidogrel, since it is not dependent on platelet renewal. Yet, 48 h after interruption of either drug, platelets still show the same degree in inhibition. Only 3 days after cessation, ticagrelor shows a lower degree of inhibition than clopidogrel (Gurbel et al. 2009).

As a reversible drug, ticagrelor will be redistributed from circulating platelet receptors to the receptors of transfused platelets. Platelet transfusion my therefore not be efficient to reverse the AP effect in emergency situations.

Postoperative stent thrombosis – usually manifested as an acute ST-elevation MI leading to cardiogenic shock – is an extreme emergency. It must be treated within 3 h by PCI and angioplasty and has a survival rate of only 65 % (Berger et al. 2001).

8.2 Anticoagulants

8.2.1 Introduction

Anticoagulant therapy is an integral part of perioperative management. The mechanisms of action of currently used anticoagulant drugs are described in Fig. 8.5, and their effects on coagulation are listed in Table 8.5.

Patients can be prescribed prophylactic doses of anticoagulants to prevent venous thromboembolism. They can receive therapeutic doses of anticoagulants to treat or

prevent recurrence of a venous thromboembolism or to prevent stroke or systemic arterial embolism in a context of atrial fibrillation, heart failure, or after the placement of prosthetic heart valves.

During the preoperative phase, the indications for anticoagulation therapy have to be confirmed in order to determine, on one hand, the thrombotic risk in case of interruption and, on the other hand, the risk of bleeding when continuing anticoagulation (Kearon et al. 2012).

Following this investigation, a detailed protocol comprising the pre-, peri-, and postoperative phases can be established. The urgency of the surgical procedure must also be taken into account when setting up of the protocol.

In this section, we will review existing anticoagulants and propose strategies for their use in a perioperative context.

8.2.2 Heparins and Fondaparinux

8.2.2.1 Introduction

Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) are polysaccharides that bind to antithrombin (AT) and potentiate its inhibitory effect on thrombin (FIIa) and activated factor X (FXa) (Fig. 8.5). This effect varies according to the type of heparin molecule used:

- UFH predominantly potentiates anti-IIa activity.
- LMWHs predominantly potentiate anti-Xa activity.

Fondaparinux is a synthetic pentasaccharide that selectively binds and activates AT. It is too short a molecule to enable bridging between AT and thrombin; thus, it selectively potentiates the anti-Xa activation of AT without effecting thrombin; see Fig. 8.5 (Garcia et al. 2012).

8.2.2.2 Monitoring

The anticoagulant response to UFH varies between patients; it is therefore standard practice to monitor UFH and adjust the dose based on the results of coagulation tests. When administered at therapeutic doses, the anticoagulant effect of UFH is usually monitored using the activated partial thromboplastin time (aPTT). Activated clotting time (ACT) allows monitoring of the higher UFH doses given in the context of PCI or cardiac surgery. A therapeutic aPTT range of 1.5–2.5 times the control time is widely accepted (Basu et al. 1972; Garcia et al. 2012). UFH levels can also be monitored using anti-Xa assays. “Heparin resistance” is a term used when patients require unusually high doses of heparin to achieve a therapeutic aPTT (Green et al. 1994; Levine et al. 1994; Anand et al. 1997; Garcia et al. 2012). Several mechanisms explain heparin resistance: AT deficiency (Olson et al. 1998), increased UFH clearance (Hirsh et al. 1976; Green et al. 1994), high levels of heparin-binding proteins (Whitfield et al. 1983; Brey 1992), and elevated levels of FVIII (Edson et al. 1967; Levine et al. 1994) and/or fibrinogen (Edson et al. 1967).

Monitoring LMWH and fondaparinux is unnecessary, except in the contexts of obesity, renal failure, or pregnancy (Garcia et al. 2012). LMWH and

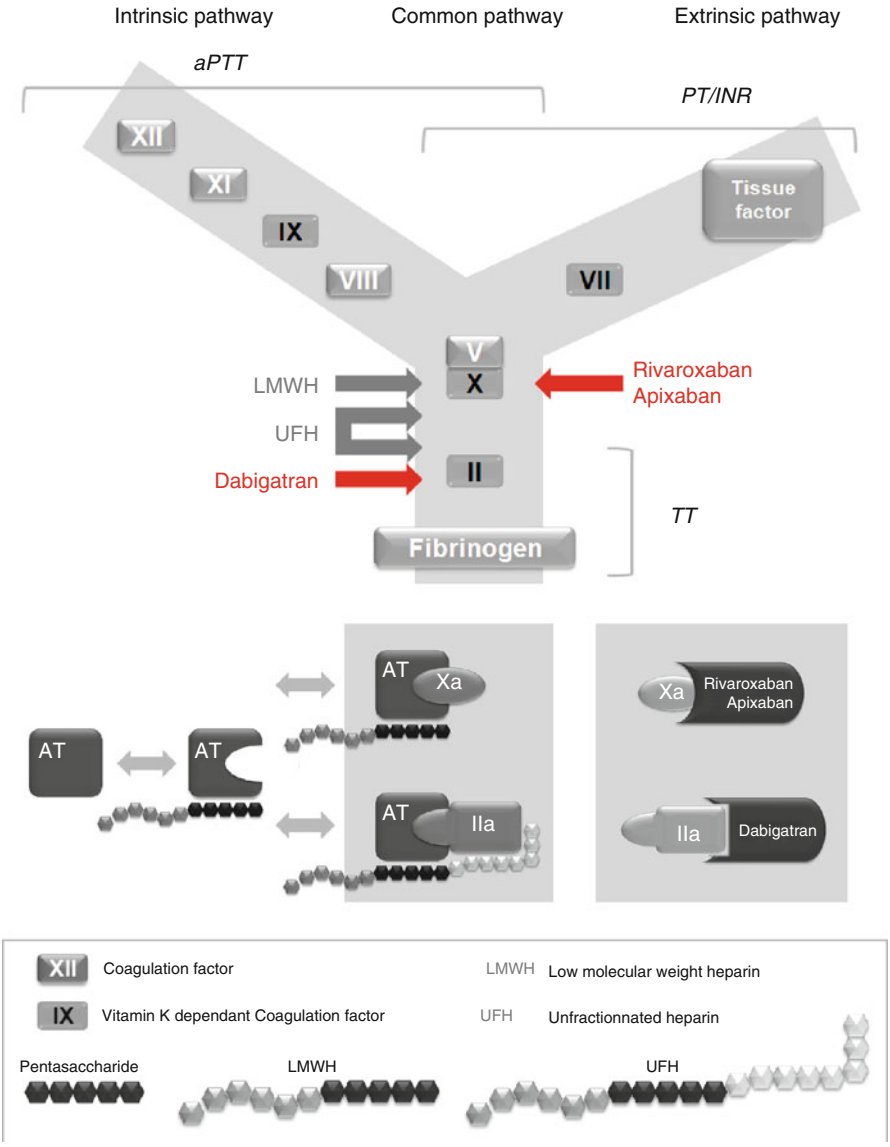
Intrinsic pathway
Common pathway
Extrinsic pathway
aPTT
PT/INR
XII
XI
IX
VIII
VII
Tissue factor
V
X
II
LMWH
UFH
Dabigatran
Rivaroxaban
Apixaban
TT
Fibrinogen
AT
Xa
IIa
Rivaroxaban
Apixaban
Dabigatran
Coagulation factor
Vitamin K dependant Coagulation factor
LMWH Low molecular weight heparin
UFH Unfractionnated heparin
Pentasaccharide
LMWH
UFH

Fig. 8.5 Anticoagulants and their targets (anticoagulation in the context of heparin-induced thrombocytopenia is presented in Chap. 7). Vitamin K antagonists produce their anticoagulant effect by interfering with the γ-carboxylation of the vitamin K-dependent factors II, VII, IX, and X (*in black*). Unfractionated heparin (*UFH*) is an indirect anticoagulant that binds to antithrombin (*AT*), enhancing its ability to inhibit activated factor X (FXa), thrombin (FIIa), and other coagulation factors. Low-molecular-weight heparins (*LMWH*) derived from UFH by chemical or enzymatic depolymerization and fondaparinux is a synthetic analog of the AT-binding pentasaccharide found in UFH and LMWH. Fondaparinux, too short to enable bridging between AT and thrombin, selectively potentiates the anti-FXa activity of AT. Similarly LMWHs only have a marginal impact on thrombin. Dabigatran is a direct, selective inhibitor of thrombin, hence independent of AT activity. Rivaroxaban and apixaban are direct, highly selective, factor Xa inhibitors. Clot-based assays comprise the prothrombin time (*PT*), the activated partial thromboplastin time (*aPTT*), and the thrombin time (*TT*). *PT* is used to assess the extrinsic and common pathways of coagulation. Clotting is initiated by recalcifying citrated plasma in the presence of thromboplastin (a mixture of tissue factor and phospholipids). In order to promote standardization of the PT, the World Health Organization (WHO) developed an international reference thromboplastin and recommends that the PT ratio be expressed as the *International Normalized Ratio* or *INR* to evaluate the effect of anti-vitamin K anticoagulants. *aPTT* is used to assess the integrity of the intrinsic coagulation pathway (prekallikrein, high-molecular-weight kininogen, factors XII, XI, IX, VIII) and final common pathway (factors II, V, X, and fibrinogen). It is performed by recalcifying citrated plasma in the presence of a thromboplastic material that does not have tissue factor activity (hence the term partial thromboplastin) and a negatively charged substance (i.e., celite, kaolin, or silica). *TT* measures the final step of the clotting pathway, the conversion of fibrinogen to fibrin. The test is performed by recalcifying citrated plasma in the presence of dilute bovine or human thrombin (Adapted with permission from EHM Swiss Medical Publishers Ltd. Gavillet and Angelillo-Scherrer (2012))

Table 8.5 Effects of anticoagulants on coagulation tests

Anticoagulant	Target	aPTT	PT	INR	TT	Fibrinogen	D-dimers	Anti-Xa	Anti-IIa
Vitamin K antagonists	II, VII, IX, X, protein C and S	↑	↑	↑	↑	↔	↔	↔	↔
Unfractionated heparin	IIa and Xa (AT-dependent)	↑	↔	↔	↑	↔	↔	↑	↑
Low-molecular-weight heparin	Mainly Xa (AT-dependent)	↔	↔	↔	↑	↔	↔	↑	↔
Dabigatran	IIa[a]	↑	↑	↑	↑	↔	↔	↔	↑
Rivaroxaban	Xa[a]	↑	↑	↑	↔	↔	↔	↑	↔
Apixaban	Xa[a]	↑	↑	↑	↔	↔	↔	↑	↔

Refs. Barrett et al. (2010), Pengo et al. (2011), Ageno et al. (2012), Asmis et al. (2012), Garcia et al. (2012), Samama et al. (2012)

AT antithrombin, coagulation factors are indicated by roman numbers, the "a" suffix stands for "activated"

[a]Free and bound form

fondaparinux monitoring is done by measuring the peak anti-Xa level reached 3–5 h after the subcutaneous injection of the anticoagulant. The anticoagulation is considered to be well adapted if the peak anti-Xa level is within the target range. In the context of renal failure, it is useful to measure the trough level in order to verify that the LMWH level is low enough to perform surgery without an augmented risk of bleeding. To lower the risk of prosthetic valve thrombosis in pregnant women receiving LMWH, the trough and peak anti-Xa levels can be measured to guide dose adjustments. In this context, the trough can be more useful than the peak anti-Xa level for determining an adequate baseline anticoagulant effect.

8.2.2.3 Reversal

Protamine sulfate is a basic protein that was originally extracted from salmon testicles. It displaces AT and neutralizes heparin by forming a complex with it, and it has a partial antagonist effect on LMWH. In the absence of heparin, protamine sulfate shows an anticoagulant effect. It is routinely used after cardiopulmonary bypass, but rarely for bleeding resulting from heparin administration. The administration of protamine sulfate can be associated with hemodynamic changes ranging from mild systemic hypotension to severe pulmonary hypertension with hemodynamic collapse. Several mechanisms can contribute to these effects: direct protamine-induced histamine release, anaphylactic reactions (IgE mediated), and anaphylactoid reactions (IgG mediated). The immune-mediated reactions can be based on anti-protamine antibodies or on anti-heparin-protamine complex antibodies. It is generally recommended to slowly administer protamine through a peripheral venous line, since central venous administration could exacerbate the adverse reactions. Three elements need to be specified in order to calculate a correct dosage:

1. Route of heparin administration (subcutaneous half-life > intravenous half-life)
2. Type of heparin (half-life of LMWH > half-life of UFH)
3. Delay between heparin administration and protamine sulfate administration

Dosage is also based on the fact that 1 mg of protamine sulfate inactivates 100 IU of heparin or 100 IU anti-Xa of LMWH.

When the clinical setting requires the neutralization of LMWH's anticoagulant effect, the following approach is proposed (Garcia et al. 2012):

- If LMWH was administered within 8 h, protamine sulfate must be given at a dose of 1 mg per 100 IU of anti-Xa activity up to a maximum single dose of 50 mg (1 mg enoxaparin equals approximately 100 IU anti-Xa).
- A second dose of 0.5 mg protamine sulfate per 100 IU anti-Xa should be provided if bleeding persists.
- Smaller doses of protamine sulfate can be administered if the time since LMWH administration is longer than 8 h.

It is important to accurately calculate the necessary protamine dose since it has an intrinsic anticoagulant effect, which may lead to increased bleeding in case of an overdose. Fondaparinux does not bind to protamine sulfate. If uncontrollable bleeding occurs with fondaparinux, recombinant activated FVII may be effective (Bijsterveld et al. 2002).

8.2.3 Vitamin K Antagonists

Vitamin K antagonists (VKA) are classic oral anticoagulation drugs that generate the same effect as a vitamin K deficiency. They include phenprocoumon, warfarin, and acenocoumarol. In elective perioperative settings, these drugs are replaced by UFH, LMWH, or fondaparinux, as these periods are associated with a thromboembolic risk of 0–2 % if VKA are interrupted (Mourelo et al. 2008) and a bleeding risk of 2–25 % if VKA are continued during surgery (Jaffer et al. 2010). There are several ways to reverse the anti-vitamin K effect. For elective surgery, the patient can simply stop taking VKA with overlapping treatment of LMWH. If surgery is more urgent, but not immediate, the patient can receive a vitamin K supplement, for example, 10 mg/day of intravenous vitamin K1. Finally, for same-day urgent surgery, prothrombin complex concentrates (PCC) can be administered. For a 70 kg patient with an estimated plasma volume of 2,500 ml, the substitution dose is calculated as follows:

$$\left[\left(\text{PT aimed\%} - \text{PT measured\%}\right)/100\right] \times 2{,}500$$

If the patient's weight is significantly different, the plasma volume can be estimated according to the following formula:

$$\text{Weight}\left(\text{kg}\right) \times 40 = \text{plasma volume}\left(\text{ml}\right)$$

For a durable reversible effect, vitamin K1 is associated with PCC. The duration of vitamin K1 administration depends on the VKA half-life.

8.2.4 Novel Oral Anticoagulants

8.2.4.1 Introduction

Novel oral anticoagulants (NOACs) specifically target either thrombin or FXa (Fig. 8.5). They have a rapid onset of action, few drug interactions, and predictable pharmacokinetics and pharmacodynamics, making routine coagulation monitoring unnecessary. However, there are situations in which assessment of the anticoagulant effect of OACs is important: these include hemorrhage or thrombosis occurring under anticoagulation, emergency surgery, polypharmacy, overdose, renal or liver failure, compliance monitoring, and extreme bodyweights. Moreover, NOACs affect routine coagulation tests (Table 8.5).

Management protocols of NOACs prior to elective surgery exist, but clinical experience is currently insufficient to provide solid guidelines on the management of emergencies including major bleeding in patients receiving NOACs. No specific antidotes are available at present.

8.2.4.2 Pharmacology Review

Dabigatran is a selective, competitive, reversible, direct thrombin inhibitor. It is not absorbed by the intestine and therefore given as an absorbable prodrug, dabigatran etexilate (Pradaxa™) (Ageno et al. 2012). Its oral bioavailability is low

(approximately 6 %) (Stangier et al. 2007). Absorption of dabigatran etexilate is influenced by gastric pH; to optimize intestinal absorption, capsules contain tartaric acid (Connolly et al. 2009). The prodrug is converted into the active compound by plasma esterases. Peak plasma concentration is reached 1–2 h after intake. In healthy volunteers, the terminal half-life is ~9 h following a single dose and 12–17 h after repeated dosing (Stangier et al. 2007; Ageno et al. 2012). A steady-state level is reached in 2–3 days (Ageno et al. 2012). One-third of the circulating drug is bound to plasma proteins, and the drug is mainly cleared by the kidneys. Consequently, it is not recommended to administer the drug to patients with a creatinine clearance <30 ml/min. Similarly, the drug should not be prescribed to patients with severe liver failure and should be avoided in pregnant or lactating women.

Rivaroxaban (Xarelto™) specifically and competitively binds to the active site of FXa and prevents its interaction with prothrombin. Its bioavailability is high (80–100 %). Peak plasma concentrations are reached after 2–4 h after intake, and the terminal half-life is between 5 and 13 h (Kubitza et al. 2005; Weitz 2010; Ageno et al. 2012). Plasma protein binding is high (92–95 %). One-third of the drug is secreted unchanged by the kidneys, and two-thirds undergo hepatic metabolization into inactive metabolites by cytochrome P450 CYP3A4. Rivaroxaban is also a substrate of the transporter protein P-glycoprotein. Therefore, competition with other drugs for either CYP3A4 or P-glycoprotein could lead to clinically significant drug interactions. The drug should not be prescribed to patients with creatinine clearance <30 ml/min (Patel et al. 2011), to patients with severe liver dysfunction, or to pregnant or lactating women.

Apixaban (Eliquis™) is a selective, reversible, direct FXa inhibitor. This active drug has a mean bioavailability of 52 %. Plasma concentration peaks 3–4 h after intake and elimination half-life is 9–14 h (Kubitza et al. 2005; Weitz 2010; Ageno et al. 2012). Plasma protein binding is high (about 87 %). Apixaban is eliminated by oxidative metabolism and renal (27 %) and intestinal routes (Zhang et al. 2009). Similarly to rivaroxaban, any drug interfering with either CYP3A4 or P-glycoprotein could lead to a clinically significant drug interaction. Apixaban should not be prescribed to patients with severe renal (creatinine clearance <15 ml/min) or hepatic failure. It should be avoided in pregnant or lactating women.

8.2.4.3 Reversal Prior to Elective Surgery

The reversal strategy for dabigatran should take into account renal function. Creatinine needs to be checked – and the creatinine clearance calculated – several days before elective surgery. The interruption protocol for dabigatran further takes into account bleeding risk and type of surgery (Table 8.6). Thrombin time should be measured 6–12 h before surgery in patients at high risk of bleeding or if major surgery is planned (van Ryn et al. 2010). A normal result would exclude any residual anticoagulant effect of dabigatran. If the thrombin time is prolonged, specific tests should be performed to assess dabigatran concentration (Stangier et al. 2007). Hemodialysis might be considered in patients with severe renal impairment and persistently elevated dabigatran plasma concentrations (van Ryn et al. 2010).

For the direct FXa inhibitors, considering their short half-life, cessation of medication may be sufficient to reverse the anticoagulant effect. However, we suggest

Table 8.6 Reversal of novel anticoagulants prior to elective surgery

	Rivaroxaban/apixaban	Dabigatran
Invasive procedures	*High thromboembolic risk*	*High thromboembolic risk*
	Consider bridging with UFH/LMWH	Consider bridging with UFH/LMWH
	Start with parenteral anticoagulation	Start with parenteral anticoagulation
	12–24 h after the last dose of rivaroxaban/apixaban	12–24 h after the last dose of dabigatran
	Low thromboembolic risk or high bleeding risk[a]	*Standard bleeding risk*[b]
	CrCl ≥50 ml/min: last dose of rivaroxaban ≥24 h before the procedure	CrCL ≥80 ml/min: stop dabigatran 24 h before the procedure
	CrCl <50 ml/min: stop rivaroxaban at least 24–48 h before the procedure	CrCL 50–79 ml/min: stop dabigatran 1–2 days before the procedure
		CrCL 30–49 ml/min: stop dabigatran 2–3 days before the procedure
		High bleeding risk/major surgery[b]
		CrCL ≥80 ml/min: stop dabigatran 2 days before the procedure
		CrCL 50–79 ml/min: stop dabigatran 2–3 days before the procedure
		CrCL 30–49 ml/min: stop dabigatran 4 days before the procedure
Dental procedures	Most dental procedures can be performed without interrupting anticoagulation. However, the decision needs to be personalized for each patient	

Be aware of drug-drug interactions that could influence the elimination of anticoagulants
UFH unfractionated heparin, *LMWH* low-molecular-weight heparin, *CrCl* creatinine clearance
[a]From Ref. Pengo et al. (2011), Ageno et al. (2012)
[b]From Ref. Stangier et al. (2007), Gavillet and Angelillo-Scherrer (2012)

checking renal function and slightly modify the reversal protocol in case of renal failure (Table 8.6). Reversal can be monitored by measuring anti-FXa activity (specific assays) (Barrett et al. 2010; Samama et al. 2012).

8.2.4.4 Reversal in an Emergency

There is no evidence-based strategy for emergency reversal of NOACs (Pengo et al. 2011; Ageno et al. 2012). In case of major bleeding, general measures comprise the following: the discontinuation of the NOAC; the initiation of appropriate clinical support, including mechanical compression and local as well as surgical hemostasis; blood product transfusion; volume substitution; inotropic drugs; and maintenance of adequate diuresis (Table 8.7). Transfusion of platelet concentrates might be proposed if thrombocytopenia is present or in case antiplatelet drugs have been administered. If the initial support described above is insufficient, PCCs, recombinant FVIIa, or FEIBA™ (factor eight inhibitor bypass activity) might be infused empirically in cases of life-threatening bleeding or emergency surgery (Table 8.7). The decision to administrate these products should be based upon the clinical

Table 8.7 Reversal of novel anticoagulants in emergency

Bleeding severity	Recommendations
Low	Delay the next dose of NOAC or stop the treatment
Moderate	Appropriate treatment of symptoms
	Mechanical compression
	Surgical hemostasis
	Volume substitution, inotropic drugs, maintenance of an adequate diuresis
	Blood product transfusion
Severe or failure of symptomatic treatments	1. Prothrombin complex concentrates (PCCs) 25–50 IU/kg IV
	2. Factor Eight Inhibitor Bypassing Activity (FEIBA™) 30–50 IU/kg IV
	3. Recombinant activated factor VII (NovoSeven™)
	4. Overdose: activated charcoal to reduce absorption (ingestion <8 h before)
	5. Consider hemodialysis for dabigatran
	6. Consider plasmapheresis for rivaroxaban or apixaban

Refs. Pharma (2009), Eerenberg et al. (2011), Pengo et al. (2011), Ageno et al. (2012), Warkentin et al. (2012)
Nota bene: The efficacy of the abovementioned treatments is not evidence based

situation and not on laboratory tests. It is important to realize that these products are highly prothrombotic and that their administration might be complicated by thrombotic events. Their use should therefore be limited to life-threatening situations. For dabigatran, reversal can be monitored by measuring the thrombin time (see Sect. 8.2.4.3). However, because this test is highly sensitive to dabigatran, an assessment of its concentration by specific tests would be more accurate (Stangier et al. 2007). For anti-Xa drugs, reversal can be monitored by measuring anti-Xa activity (Barrett et al. 2010; Samama et al. 2012). Hemodialysis could complete the reversal strategy for dabigatran (Warkentin et al. 2012).

8.2.5 Vena Cava Filters

The use of inferior vena cava filter is recommended in patients with acute proximal deep vein thrombosis and/or pulmonary embolism who have a contraindication to anticoagulants, i.e., an unacceptable risk of bleeding (Garcia et al. 2012). If the contraindication to anticoagulation is temporary (e.g., during active bleeding), it is possible to insert a temporary retrievable filter and remove it when anticoagulation treatment can be safely restarted. However, it is worth noting that most retrievable filters are not removed (Mismetti et al. 2007; Dabbagh et al. 2010; Jaff et al. 2011; Garcia et al. 2012). Furthermore, retrievable filters that do not get removed might display a higher complication rate than permanent filters (Mismetti et al. 2007, p 223; Dabbagh et al. 2010, p 493; Nicholson et al. 2010, p 1827).

Insertion of an inferior vena cava filter does not eliminate the risk of pulmonary embolism and does increase the risk of deep vein thrombosis. Consequently, it is suggested that patients who have an inferior vena cava filter inserted should receive a conventional course of anticoagulants when the contraindication to anticoagulation is withdrawn (Garcia et al. 2012). Venous thrombosis at the site of filter insertion occurs in about 10 % of patients (Streiff 2000).

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Intravenous Fluids and Coagulation

9

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9.1 Introduction

In hemorrhagic shock, intravascular hypovolemia is one of the key factors contributing to insufficient oxygen delivery and subsequent tissue hypoxemia. Thus, in order to restore tissue perfusion, restoration of intravascular volume is one of the main aims of shock therapy. Both crystalloid and colloid solutions are frequently used. Compared to colloids, higher volumes of crystalloids are required to exert an equal intravascular volume effect (Jacob et al. 2012). It is noteworthy that large quantities of crystalloids have significant side effects, such as tissue edema, diminished blood viscosity, and hemostatic alterations. Colloids provide larger increases in intravascular volume, resulting in faster hemodynamic stabilization. However, artificial colloids can also cause adverse effects such as anaphylactic reactions, impairment of renal function, and alteration of hemostasis, which is potentially associated with an increased tendency to bleed (Choi et al. 1999).

Controversy regarding the optimal choice and composition of resuscitation fluids is ongoing. Randomized controlled trials (RCTs) have failed to prove that resuscitation with colloid solutions provides survival benefits compared to fluid therapy with crystalloids (Perel and Roberts 2012). The use of colloids is associated with an increased mortality compared to crystalloids in patients with severe sepsis and in trauma patients (Perner et al. 2012). This finding could be related to the negative effects of colloids on blood coagulation and platelet function

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Table 9.1 Mechanisms potentially related to the effects of fluid therapy on hemostasis

Direct effects of hemodilution on
(a) Coagulation factor activity
(b) Inhibitors of the coagulation system
(c) Platelet count
Reduction of coagulation factors
(a) Factor VIII
(b) von Willebrand factor
Diminished fibrin polymerization
(a) Reduction in clot strength
(b) Increased fibrinolysis
Direct effects on platelet function
(a) Coating
(b) Intracellular signal transduction
Changes in blood viscosity

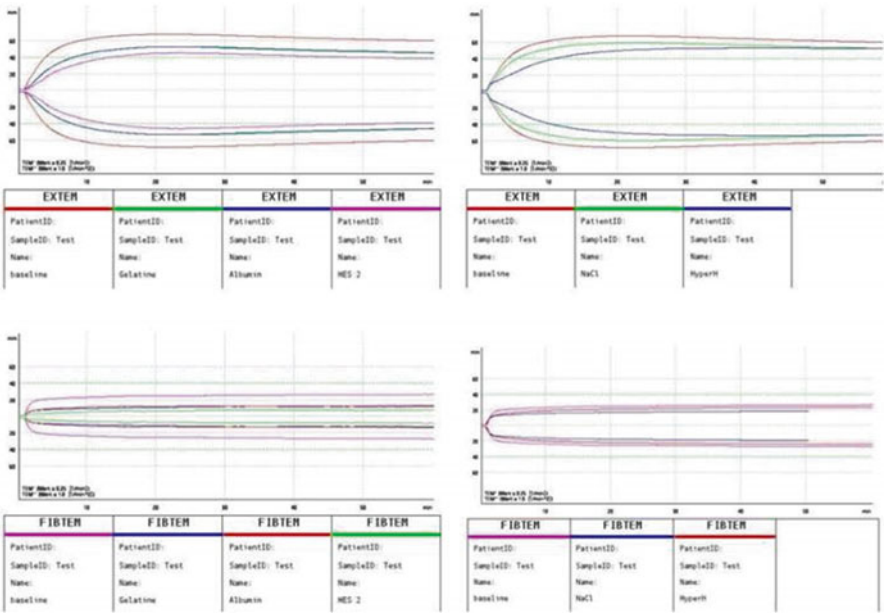

Fig. 9.1 ROTEM® results from an in vitro model of 33 % hemodilution. Two ROTEM® tests were performed: an extrinsically activated test using tissue factor (*EXTEM*) and an extrinsically activated test without platelet component (*FIBTEM*). The most pronounced reduction in maximum clot firmness (MCF) was observed with 6 % HES 130/0.4. Dilution of whole blood with 5 % human albumin and 4 % gelatin produced similar reductions in MCF. Normal saline induced only moderate changes in MCF

(Schierhout and Roberts 1998). There is a paucity of evidence that one colloid is superior to another with regard to survival (Bunn and Trivedi 2012).

Infusion of large amounts of fluid results in nonspecific dilution of coagulation factors, coagulation inhibitors, and platelets (Table 9.1). In addition, the administration of artificial colloids leads to specific alterations of coagulation factors. Acquired von Willebrand syndrome and low FVIII activity can be observed, impairing both

primary and secondary hemostasis (Kozek-Langenecker 2009). Viscoelastic tests such as thromboelastometry (ROTEM®) or thrombelastography (TEG®) have shown that clot strength (i.e., clot quality) is reduced following dilution with artificial colloids both in vitro and in vivo (Fig. 9.1) (Jones et al. 2003; Mittermayr et al. 2007; Fenger-Eriksen et al. 2009). This effect is due to the inhibition of fibrin polymerization (Fries et al. 2002; Fenger-Eriksen et al. 2009). Scanning electron microscopy revealed impairment of the reticular network of fibrin strands following dilution of blood samples with artificial colloids (Fig. 9.2) (Mardel et al. 1998; Fries et al. 2005; Sorensen and Fries 2012). Platelet dysfunction has also been reported after infusion of artificial colloids (Gamsjager et al. 2002; Deusch et al. 2004).

9.2 Crystalloid Solutions

Crystalloid fluids are widely used for volume resuscitation. These solutions are safe and well tolerated at low volumes, but their intravascular volume expansion effect is low. Within minutes, 80 % or more of the infused volume can cross the capillary

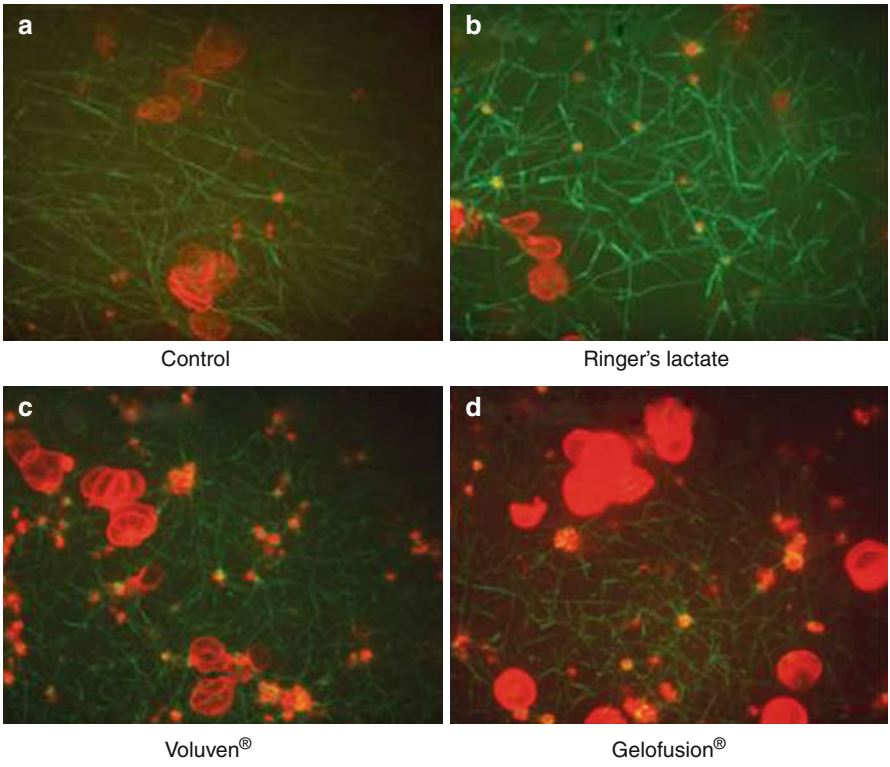

Fig. 9.2 In vitro effects on clotting of 50 % dilution of whole blood with different fluids: (**a**) no dilution (whole blood), (**b**) Ringer's lactate, (**c**) 6 % HES 130/0.4, and (**d**) 4 % gelatin. 6 % HES 130/0.4 disturbed the fibrin meshwork more than Ringer's lactate or gelatin (With permission from Sorensen and Fries (2012))

membrane from the intravascular compartment into the interstitial space (McIlroy and Kharasch 2003). Therefore, large amounts of crystalloids are often necessary to provide a sufficient increase in intravascular volume, introducing a significant risk of soft tissue edema.

Normal saline (NS) is a solution with 0.9 % of sodium chloride, with an osmolality of 308 mOsm/l. It contains 154 mmol/l of sodium and 154 mmol/l of chloride. It can therefore be considered neither physiological nor balanced, yet NS is frequently used as a plasma substitute. In contrast, balanced electrolyte solutions are isotonic and have electrolyte compositions close to that of plasma (Guidet et al. 2010).

9.2.1 Effect on Coagulation Factors and Thrombin Generation

In vivo and in vitro studies have suggested a hypercoagulable state following moderate hemodilution with crystalloids (Ruttmann 2002; Ruttmann et al. 1996, 2001, 2006; Petroianu et al. 2000; Ng et al. 2002). Other investigators refute such a prohemostatic effect and suggest that these findings are an in vitro phenomenon only (Innerhofer et al. 2002).

High-volume crystalloid replacement therapy results in dilution not only of prohemostatic coagulation factors but also of coagulation system inhibitors, such as antithrombin III (AT III) and proteins S and C (Ruttmann et al. 1996). A variety of positive feedback loops in the clotting mechanism are regulated by AT III; therefore, a small change in its concentration may have a profound effect on the initiation and amplification of the clotting process – potentially much greater than that suggested by the change in absolute concentration (Jesty 1986). Indeed, *Dunbar and Chandler* measured thrombin generation in plasma diluted to 40 % of normal, which resulted in an increase in thrombin generation. Dilution in excess of 40 %, however, caused a decline in thrombin generation. Thus, when all plasma proteins decrease at the same time, including inhibitory factors such as AT III, thrombin generation initially increases (Dunbar and Chandler 2009).

9.2.2 Viscoelastic Findings

Ng et al. studied the effect of hemodilution with NS in patients undergoing major hepatobiliary surgery. Seven milliliter per kilogram of blood were withdrawn and simultaneously replaced with 14 ml/kg of NS. They observed decreases in *r*-time and in *k*-time indicating hypercoagulability (Ng et al. 2002). Ruttmann et al. reported comparable results in patients scheduled for vascular surgery. Randomly allocated patients received either 1,000 ml Ringer's lactate (RL) or 500 ml 6 % hydroxyethyl starch (HES) 200/0.5. In the crystalloid group, TEG measurements revealed a faster onset of coagulation, an increased rate of clot formation, and an increase in clot strength. The observed shortening of *r*- and *k*-times suggests an

imbalance between activated procoagulants and a reduction in anticoagulants, particularly AT III (Ruttmann et al. 2006).

9.3 Balanced Fluids

When using large quantities of crystalloid solutions, such as NS, development of dilutional hyperchloremic acidosis has been described (Rehm and Finsterer 2003). It is well known that acidosis impairs coagulation, particularly platelet function and thrombin generation (Kermode et al. 1999; Meng et al. 2003). Therefore, it has been speculated that balanced solutions may potentially avoid or minimize these effects. However, there is poor evidence that high volumes of NS have a clinically relevant, negative impact on coagulation, bleeding tendency, or the need for allogeneic blood transfusion (Gamsjager et al. 2002).

9.3.1 Effects on Coagulation Factors and Thrombin Generation

Brummel-Ziedins et al. measured thrombin production in a dilution model using different fluids. Fifty percent dilution with NS rapidly decreased thrombin generation, whereas RL dilution was associated with a constant thrombin generation level. The authors suggested that this might be explained by RL's higher Ca^{++} content (Brummel-Ziedins et al. 2006).

9.3.2 Clinical Studies

In vivo studies comparing both fluids reported only minor differences between balanced and non-balanced solutions. Waters et al. compared RL with NS in major aortic surgery. Only minor, nonsignificant differences in blood loss, in favor of RL, were observed. There were no differences in transfusion of red blood cells (RBCs) or fresh frozen plasma (FFP) (Waters et al. 2001).

Studies comparing colloids in NS with balanced electrolyte solutions have not reported relevant differences in blood loss. For example, Casutt et al. revealed that HES 130/0.4 in a balanced solvent had similar effects on hemostasis (Casutt et al. 2010). Kulla et al. investigated patients undergoing abdominal surgery. No significant differences in coagulation parameters and blood loss were observed between balanced and unbalanced HES solutions (Kulla et al. 2008). Schaden et al. recently compared two different HES preparations containing tetrastarch in balanced solution, or NS, in healthy volunteers. Blood was subjected to a blood gas analysis, an assessment of platelet function by multiple electrode aggregometry, and thromboelastometry. After infusion of either 20 ml/kg HES in balanced solution or in NS, there was no significant change in calcium concentration, and only a minor impact on platelet aggregation and clot formation as assessed by ROTEM® (Schaden et al. 2012).

9.4 Colloid Solutions

9.4.1 Albumin

Albumin is the major serum protein synthesized in the liver. It contributes to 80 % of plasma colloid oncotic pressure. The molecular weight (MW) is approximately 66–69 kDa. Intravenous human albumin (HA) is derived from pooled human plasma, which introduces a theoretical risk of pathogen transmission.

HA is available for intravenous infusion either as an iso-oncotic 4–5 % solution or as a hyperoncotic 20–25 % solution. It is dissolved in isotonic saline. The volume efficacy of 4–5 % HA is low. In contrast, the high oncotic load of 25 % HA increases intravascular volume by approximately five times the volume administered (Hauser et al. 1980). The serum half-life is about 16–18 h (Scatchard et al. 1944).

The cost of HA is higher than that of colloids or crystalloids, which may limit its use for routine volume replacement. For patients with hypovolemic shock, there is no evidence that HA reduces mortality when compared with less expensive alternatives such as crystalloids (Roberts et al. 2011). A large double-blind RCT failed to demonstrate that 4 % HA confers a clear benefit over NS in critically ill patients (Finfer et al. 2004). In a subgroup of patients with severe brain trauma, higher mortality was observed among patients receiving 4 % HA, compared with those receiving NS (Myburgh et al. 2007).

9.4.1.1 Effects on Coagulation Factors and Thrombin Generation

Compared to artificial colloids, the effect of HA on coagulation factor and fibrinogen concentration is minor (Lucas et al. 1982; Denis et al. 1987; Myburgh et al. 2007). However, similarly to synthetic colloids, the oncotic pressure of HA can cause an efflux of plasma proteins to the interstitial fluid space which might affect coagulation (Lucas et al. 1982; Denis et al. 1987). An animal study revealed that, compared with crystalloid resuscitation, HA-supplemented fluid therapy significantly reduced fibrinogen and factor VIII concentration and increased prothrombin time (PT) (Johnson et al. 1979).

Kheirabadi et al. compared 5 % HA with 6 % HES 670/0.7 (Hextend™) and 6 % dextran 70 in a 40 % hemodilution model in rabbits. Thrombin generation assays revealed a shortened lag time in the HA group. Total thrombin generation and maximum thrombin concentration were unchanged in HA-diluted samples but decreased significantly following dilution with synthetic colloids. Total blood loss was lowest in the HA group (Kheirabadi et al. 2008).

9.4.1.2 Viscoelastic Findings

TEG analyses from the *Kheirabadi* study revealed a shortened *r*-time in the albumin group. Maximum clot strength was significantly reduced in all three groups but again decreased less in the HA group (Kheirabadi et al. 2008). Coats et al. studied in vitro dilution of whole blood to 40 % using different resuscitation fluids. A Sonoclot™ device was used to measure the clots' viscoelastic properties. Of all the investigated colloids, 3.5 % urea cross-linked gelatin (Haemaccel®) had the fewest

effects on dynamic clot formation, followed by HA. The latter reduced activated clotting time by 2 % and exhibited a 47 % reduction in clot rate (rate of fibrin formation) (Coats et al. 2006).

Our own group recently compared NS with 5 % HA, 4 % gelatin, and 6 % HES 130/0.4 in an in vitro dilution model investigating ROTEM® variables. Compared to undiluted whole blood, 33 % in vitro hemodilution with 5 % HA reduced maximum clot firmness in the extrinsically activated EXTEM test, and a more pronounced reduction was observed in the fibrin polymerization test (FIBTEM). Our in vitro study confirmed the observation that 5 % HA has less effect on ROTEM® test results than other colloids (Schlimp et al. 2013).

9.4.1.3 Effects on Platelets

Evans et al. investigated the effects of different fluids on platelet aggregation and agglutination in orthopedic patients. HA significantly reduced aggregation in response to collagen. In contrast, a small but significant increase in agglutination was also observed in the albumin group (Evans et al. 2003).

9.4.1.4 Clinical Studies

Niemi et al. studied the effect of 4 % HA and 6 % HES 120/0.7 in patients undergoing total hip arthroplasty. Postoperatively, Von Willebrand factor (vWF) was higher in the HA group, but no differences were observed in blood loss (Niemi et al. 2005). The same group investigated the effect of postoperative administration of different colloids on hemostasis in 45 patients following cardiac surgery. The most pronounced impairment of coagulation was found after administration of 6 % HES 200/0.5. HA appeared to have the least effect on hemostatic variables, including ROTEM® parameters (Niemi et al. 2006) (Table 9.2).

One study has reported hemostatic alterations following HA administration. Johnson et al. found impaired coagulation in trauma patients after administering HA as a supplement to massive transfusion. During the first 5 postoperative days, patients receiving HA required more RBC units (7.1 vs. 3.8) and more FFP (455 ml vs. 317 ml). The authors suggested that HA may exert antihemostatic and platelet-lowering effects, with a risk of increased blood loss after surgery or trauma (Johnson and Criddle 2004).

9.4.2 Dextran

Dextrans are mixtures of polydisperse polysaccharides of various sizes and MWs. They are produced by the dextransucrase enzyme during growth of *Leuconostoc* bacteria in media containing sucrose. Between 50 and 70 % of dextran molecules are excreted unchanged via urine. Dextranase completely metabolizes the remaining dextran molecules to CO_2 and H_2O. Dextrans have MWs ranging from 40 to 70 kDa and are dissolved in NS. Dextran 70 is usually available as a 6 % solution, while dextran 40 is usually a 10 % solution. Due to its higher concentration, dextran 40 is a more potent volume expander than dextran 70, exerting higher colloid oncotic pressure. However, the volume expansion effect of dextran 40 is short lived

Table 9.2 Effects of different fluids on hemostatic variables

	Crystalloids	Albumin	Dextrane	Gelatin	Heta/penta starch	Tetrastarch	HS/ HHS
Levels of vWF and F VIII	↔	↔	↓↓↓	↓	↓↓	↓	↔
Thrombin generation	↑	↔		↓	↓		↔
Viscoelastic coagulation tests							
r+*k*-time CT, CFT	↑	↓	↓↓↓		↓	↓	↓↓
Maximum clot firmness	↓	↓	↓↓↓	↓↓	↓↓↓	↓↓↓	↓
Platelet function	↔	↔	↓↓↓	↓	↓↓	↓	↓↓

CT coagulation time, *CFT* clot formation time, *k-time* clotting time, *r-time* reaction time, *vWF* von Willebrand factor, *HS*/*HSS* hypertonic saline/hyperoncotic-hypertonic solutions

due to the fact that it is eliminated by the kidneys more quickly than other colloids (de Jonge and Levi 2001).

In most European countries, dextrans have disappeared from the market due to potentially life-threatening side effects such as severe anaphylactic reactions, acute renal failure, and bleeding diatheses.

9.4.2.1 Effects on Coagulation Factors and Thrombin Generation

Both dextran 40 and dextran 70 produce dose-related hemostatic defects additional to the effects of hemodilution. Dextran 70 appears to cause a significantly greater impairment of coagulation than dextran 40 (Batlle et al. 1985; de Jonge and Levi 2001).

Dextran's inhibitory effects on coagulation have been attributed to reductions in the activity or plasma levels of factors V, VII and VIII, and vWF (Batlle et al. 1985). Furthermore, increased fibrinolysis has been reported following dextran infusion. It has been suggested that increased plasma concentrations of tissue plasminogen activator (t-PA) and decreased levels of its most important antagonist, plasminogen activator inhibitor 1 (PAI-1), are responsible for these findings (Eriksson and Saldeen 1995).

9.4.2.2 Viscoelastic Findings

TEG measurements indicate that dextrans bind to fibrinogen and interfere with fibrin cross-linking, reducing clot elasticity or clot strength. Fifty percent dilution of blood with 10 % dextran 40 completely inhibited clot formation in TEG analysis (Mortier et al. 1997).

9.4.2.3 Effects on Platelets

Dextran's effect on platelet function is multifactorial; they relate to reductions in platelet adhesion and aggregation and vWF inhibition (Batlle et al. 1985). Dextran molecules are understood to exert a coating effect on cellular elements of the blood,

including platelets. Prolonged bleeding times, observed after dextran infusion, are in part related to diminished platelet function (Alexander et al. 1975).

9.4.2.4 Clinical Studies

Dextrans have been used for the prevention of postoperative venous thrombosis and pulmonary embolism (Clagett et al. 1995; de Jonge and Levi 2001). In order to minimize the risk of bleeding, dextran infusion should be restricted to patients with normal hemostasis. An upper limit of 20 ml/kg/day should not be exceeded. Patients with renal insufficiency face an increased risk of bleeding because of dextran's prolonged intravascular half-life and the likelihood of uremic platelet dysfunction (de Jonge and Levi 2001).

9.4.3 Gelatin

Gelatins are polydisperse polypeptides with an MW of approximately 35 kDa, manufactured by degradation of bovine collagen (de Jonge et al. 1998). Two different formulations of gelatin are available: 4 % succinylated gelatin (Gelofusine®) and 3.5 % polygeline (Haemaccel®; degraded gelatin polypeptides cross-linked by urea). Due to their small MW, up to 50 % of gelatins are cleared within 4–6 h after administration, and complete plasma clearance is achieved within 3 days. Gelatins have the advantage of an unlimited daily dose. However, of all the artificial colloids, gelatins carry the highest risk of anaphylactic reaction (Laxenaire and Mertes 2001), and like other artificial colloids, they affect the coagulation system and platelet function (Van der Linden and Schmartz 1992).

9.4.3.1 Effect on Coagulation Factors and Thrombin Generation

Infusion of 1 l of gelatin-based solution in healthy volunteers decreases thrombin generation, as assessed by the measurement of thrombin–antithrombin complexes and prothrombin fragment F1 + 2. Compared with NS, a 1.7-fold increase in bleeding time has been observed at 60 min and a 1.4-fold increase at 120 min (de Jonge et al. 1998).

9.4.3.2 Viscoelastic Studies

Several studies have shown a significant reduction in maximum clot firmness (clot strength) in response to gelatin hemodilution; this is attributed to impaired fibrin polymerization (Egli et al. 1997; Mardel et al. 1998; Fenger-Eriksen et al. 2009; Jin and Yu 2010). The effect is most pronounced when using a fibrin polymerization test (e.g., the FIBTEM test in ROTEM®) (Schlimp et al. 2013).

In vitro experiments have shown that hemodilution with gelatin reduces maximum clot firmness to a greater extent than NS (de Jonge et al. 1998; Mardel et al. 1998). Mardel et al. compared Haemaccel® and Gelofusine® with RL and found significantly lower clot elasticity with both gelatin preparations (26.2 and 22.2 % lower than RL, respectively) (Mardel et al. 1998). One suggested mechanism is that gelatin binds with fibronectin and decreases the plasma concentration of this protein (Engvall et al. 1978; Brodin et al. 1984). Fibronectin contributes to clot stability by forming covalent cross-links with fibrin. Furthermore, it is suggested that gelatin might be

incorporated into the clot as it forms, interfering with fibrin architecture and impairing the clot's strength and stability (Mardel et al. 1998; Kheirabadi et al. 2008).

9.4.3.3 Effects on Platelets

Following infusion, Gelofusine® has been shown to exert a small, transient inhibitory effect on platelet aggregation (Evans et al. 1998). In the same study, Haemaccel® showed more significant inhibition of platelet aggregation through the glycoprotein (GP) IIb/IIIa receptors. Furthermore, gelatin administration decreases plasma levels of vWF. Aggregation studies have also revealed significant impairment of ristocetin-induced platelet aggregation, suggesting additional interference via the GP Ib receptor (Tabuchi et al. 1995). Overall, the prolonged bleeding times observed with gelatin could be a consequence of impaired primary hemostasis (de Jonge et al. 1998).

9.4.3.4 Clinical Studies

It is uncertain whether gelatin infusion increases bleeding tendency. To date, only one study in cardiac surgery patients has reported increased blood loss following gelatin infusion, in comparison with albumin (Tabuchi et al. 1995).

Karoutsos et al. studied 42 ASA I patients undergoing total hip or knee replacement. The effects of moderate intraoperative hemodilution with gelatin, HES, or 5 % HA were assessed using TEG. Findings differed from the abovementioned studies, as they found clear evidence of a state of hypercoagulability in the gelatin group, with significant decreases in *r*- and *k*-time and an increase in alpha angle. There were no significant between-group differences in intraoperative blood loss and RBC transfusion (Karoutsos et al. 1999).

9.4.4 Starches

HES are derived from amylopectin and consist of highly branched polysaccharides, similar to glycogen. HES solutions are available either as iso-oncotic 6 % or hyperoncotic 10 % fluids. The volume effect of a 10 % solution exceeds the infused volume, and it is therefore considered a plasma expander (Westphal et al. 2009). Compared to gelatin and crystalloids, the initial volume expansion of HES is greater and lasts longer (Van der Linden and Ickx 2006).

HES are polydisperse fluids with a wide range of MW. HES solutions can be categorized as high-MW (>400 kDa), medium-MW (200–400 kDa), and low-MW fluids (<200 kDa) (Jungheinrich and Neff 2005).

The most important physicochemical aspect of HES is the degree of substitution, defined as the proportion of hydroxyl groups per glucose molecule replaced by hydroxyethyl subunits. Increased substitution increases the solubility of starch in water and, more importantly, reduces the rate of destruction by serum amylase (Kozek-Langenecker 2005). Highly substituted (hetastarch 0.62–0.75), medium-substituted (pentastrach 0.5), and low-substituted (tetrastarch 0.4) HES preparations are available.

HES substitution is possible at different positions of the glucose molecule, with the C_2 to C_6 ratio describing the ratio of hydroxyethyl group substitutions at these positions. It has been shown that a high C_2 to C_6 ratio reduces degradation of the HES molecule by α-amylase and delays elimination from the bloodstream (Karoutsos et al. 1999). Newer HES preparations have low MW and low substitution of hydroxyethyl subunits, resulting in rapid metabolism and clearance.

The mechanisms of coagulopathy induced by HES infusion are multifactorial: slow degradation of HES enables interaction with platelets, the coagulation cascade, and the fibrin polymerization process (Kozek-Langenecker 2005). Thus, it has been suggested that HES solutions with a prolonged half-life produce more pronounced side effects than those with a short half-life. First- and second-generation HES solutions were associated with adverse effects on renal function, tissue storage, and coagulopathy. Modern, rapidly degradable HES formulations have less of an impact on the coagulation cascade, particularly the factor VIII–vWF complex (Jungheinrich et al. 2004).

9.4.4.1 Effect on Coagulation Factors and Thrombin Generation

Acquired von Willebrand syndrome, together with a decrease in circulating factor VIII of up to 80 %, has been reported in both healthy volunteers and patients receiving HES (Kapiotis et al. 1994; Conroy et al. 1996; Jamnicki et al. 2000; Jones et al. 2003; Jungheinrich et al. 2004; Jungheinrich and Neff 2005; Kozek-Langenecker 2005; Van der Linden and Ickx 2006). Kapiotis et al. compared the effect of 6 % HES 200/0.5 in isotonic saline with 5 % HA using healthy volunteers. The infusion of 500 ml significantly reduced levels of factor VIII:C in the HES group. However, there were no significant differences between the study groups regarding other coagulation and fibrinolytic parameters, such as activated partial thromboplastin time (aPTT), fibrinogen, thrombin–antithrombin complexes, D-dimers, t-PA, and PAI-1 (Kapiotis et al. 1994). Recent studies have suggested that rapidly degradable HES solutions have only minor effects on coagulation. Even high doses of tetrastarch (50–70 ml/kg) did not impair factor VIII activity (Kasper et al. 2003; Neff et al. 2003).

Fenger-Eriksen et al. studied cancer patients following 30 % hemodilution with HES 130/0.4. Fibrinogen, factor II, factor X, and factor XIII decreased significantly below levels typically expected from dilution. Endogenous thrombin potential, however, remained unchanged (Fenger-Eriksen et al. 2009).

9.4.4.2 Viscoelastic Studies

The study by Fenger-Eriksen et al. revealed that 30 % hemodilution with HES 130/0.4 had no significant effect on whole-blood clotting time or maximum velocity of clot formation, compared with baseline observations (Fenger-Eriksen et al. 2009).

However, both in vivo and in vitro studies have reported early, dose-dependent disturbances in fibrin polymerization following HES infusion (Treib et al. 1999; Kozek-Langenecker 2005). This results in a marked decrease in the velocity of clot formation, together with a decrease in the α-angle (Schramko et al. 2010; Schlimp et al. 2013).

More importantly, a pronounced and significant reduction in maximum clot firmness has been observed. In particular, fibrin-based assays, such as FIBTEM, reveal significantly diminished fibrin polymerization following dilution with HES products (Fries et al. 2002, 2005; Schramko et al. 2010; Schlimp et al. 2013). Only minor differences between HES 130/0.4 and HES 200/0.5 have been identified (Jamnicki et al. 1998; Entholzner et al. 2000; Sossdorf et al. 2009; Casutt et al. 2010).

Some studies suggest that HES solutions might also increase clot lysis (Mittermayr et al. 2008). In an in vivo study, Jamniki et al. investigated TEG findings following hemodilution with HES 200/0.5 and HES 130/0.4. Clot lysis after 60 min increased significantly after hemodilution with both fluids (Jamnicki et al. 1998).

9.4.4.3 Effects on Platelets

HES solutions have been shown to reduce the platelet contribution to hemostasis. Several mechanisms have been proposed, such as a decrease in expression and availability of the GP IIb/IIIa receptors (Stogermuller et al. 2000; Deusch et al. 2003; Thaler et al. 2005). Coating of platelets by HES macromolecules, nonspecific modification of cytoplasmic membrane structures, and consequent inhibition of conformational changes to GP IIb/IIIa receptors have all been discussed (Stogermuller et al. 2000). In vitro studies have identified nonspecific binding of HES molecules to platelet surfaces as a potential mechanism of HES-induced platelet inhibition (Deusch et al. 2003). In healthy volunteers, slowly degradable HES significantly prolongs PFA-100 closure times (Stogermuller et al. 2000). In addition to these direct effects, decreased vWF activity may further reduce platelet responsiveness after HES administration (Strauss et al. 2002). However, rapidly degradable HES has only minor effects on platelet function (Franz et al. 2001). Further, HES does not seem to affect intracellular signal transduction of platelets (Gamsjager et al. 2002).

One study randomly assigned 30 patients with cerebrovascular disease to receive daily infusions of up to 1.5 l of 6 % HES 200/0.62, 10 % HES 200/0.5, or 6 % HES 40/0.5. Platelet count significantly decreased in all three groups, but the largest drop was observed in the HES 200/0.62 group. The authors speculate that HES macromolecules attach to platelets and are subsequently phagocytosed (Treib et al. 1996).

9.4.4.4 Clinical Studies

Despite their negative side effects on laboratory and viscoelastic parameters, modern, rapidly degradable HES 130/0.4 solutions have not been shown to increase blood loss. A double-blind RCT of 42 patients with severe blunt trauma compared resuscitation using 6 % HES 130/0.4 versus NS. The HES group required significantly more blood products than patients receiving NS; however, the mean injury severity score was significantly higher in the HES group. The effect of HES on blood loss thus remains unclear (James et al. 2011). Studies in orthopedic and cardiac surgery patients show that 6 % HES 130/0.4 is associated with lower blood loss and transfusion requirements than 6 % HES 200/0.5 (Langeron et al. 2001; Niemi et al. 2005).

Studies comparing 3.5 % urea-linked gelatin and 6 % HES 130/0.4 reported no significant differences in either the number of patients receiving allogeneic blood products or the volume of RBCs, FFP, or platelets administered (Van der Linden et al. 2005; Schramko et al. 2010).

Mittermayr and coworkers investigated 61 orthopedic patients who received 6 % HES 130/0.4, 4 % gelatin, or RL solution. The RL group had the lowest number of patients receiving allogeneic blood products. The highest number of RBCs was transfused to the gelatin group. However, significant differences in baseline hemoglobin levels between the study groups made interpretation of these results difficult (Mittermayr et al. 2007).

9.5 Hypertonic–Hyperoncotic Solutions

In experimental and preclinical studies, rapid infusion of small amounts (4 ml/kg) of hypertonic 7.2–7.5 % saline (HS) solutions have proved to be effective in hypotensive patients, with rapid restoration of cardiovascular function and tissue blood flow (Velasco et al. 1980; Tollofsrud et al. 1998). For the restoration of intravascular volume, the infusion of 4 ml/kg 7.5 % HS was reported to be as effective as an infusion of 2–3 l of crystalloids. Improvement in cardiovascular function has been attributed to the redistribution of body water from the extravascular to the intravascular compartment by the osmotic forces of HS (~2,400 mosm/l) (Smith et al. 1985). However, the vascular volume expansion is relatively transient unless an oncotically effective colloid (e.g., dextran 70 or a starch) is combined with HS to hold the fluid in circulation. These fluids are called hypertonic–hyperoncotic solutions (HHS) (Angle et al. 1998). Numerous animal studies have revealed attenuated inflammation, enhanced organ function, and improved survival rates following hemorrhagic shock and resuscitation with HS/HHS (Smith et al. 1985; Angle et al. 1998).

A recent RCT investigated the effect of out of hospital infusions of HS, HHS, and NS in hypotensive trauma patients. This study was unable to demonstrate a clinically significant survival benefit of HS when it was infused during the early phase of hemorrhagic shock treatment. It is noteworthy that, in the subgroup of patients who received no blood transfusions in the first 24 h, infusions of HS increased mortality (Bulger et al. 2011).

Similar results have been found in patients with severe isolated brain injury. Among patients with severe traumatic brain injury, but not in hypovolemic shock, initial resuscitation with either HS or HHS provided no benefit over NS, in terms of 6-month neurological outcome (Bulger et al. 2010).

9.5.1 Effects on Coagulation Factors and Thrombin Generation

Several different HS preparations, from 1.6 to 29.9 %, with and without the addition of artificial colloids, have been used in experimental and clinical studies (Johnson

and Criddle 2004). However, sound conclusions regarding the influence of HS/HHS are impossible due to the heterogeneity of the fluids.

Coats et al. investigated the in vitro effect of HHS (including dextran) on coagulation. A mild pro-hemostatic effect was observed up to a dilution of 11 %, but anticoagulant properties were evident above this level. At 15 % dilution, coagulation was grossly deranged (Coats and Heron 2004).

Wilder et al. reported that HS has strong anticoagulant and antiplatelet effects. Dilution with HS to a level of only 5 % caused a significant prolongation of PT. In contrast, there was no significant change in PT following 5 % dilution with hypertonic sorbitol or mixtures based on glycine (Wilder et al. 2002).

A 20 % dilution with 3 % saline resulted in a 52 % reduction of thrombin generation and 11 % reduction of fibrin formation. Increasing the dilution to 30 % decreased fibrin formation by 89 % (Brummel-Ziedins et al. 2006).

9.5.2 Viscoelastic Tests

In vitro, 10 % dilution of blood with HHS has been shown to cause significant impairment of fibrin polymerization (Hanke et al. 2011). Haas et al. studied the effect of HHS in vivo in an uncontrolled bleeding model in pigs. Median fibrinogen polymerization was significantly higher among animals receiving HHS, compared with those receiving 4 % gelatin or 6 % HES 130/0.4. Furthermore, median blood loss after liver incision was significantly lower in the HHS group (Haas et al. 2008a).

9.5.3 Effects on Platelets

In one study, platelet activation, as determined by α-granule release, decreased by 40 % following 10 % dilution of whole blood with HHS. Complete cessation of platelet activation was observed after 20 % dilution (Brummel-Ziedins et al. 2006). The authors suggested that platelets shrink and become dysfunctional, diminishing the surface required for propagation of thrombin generation (Brummel-Ziedins et al. 2006).

Wilder et al. reported that platelet function was critically impaired by HS hemodilution at a level of just 5 % (Wilder et al. 2002). Hanke et al. used multiple electrode aggregometry to study platelet function in whole blood following HS and HHS dilution in vitro. With 5 % dilution, both dilutants impaired platelet aggregation (Hanke et al. 2011).

9.6 Restoring Coagulation After Dilution Coagulopathy

All artificial colloids interfere with the process of fibrinogen polymerization, reducing maximum clot firmness in viscoelastic coagulation tests. To overcome this problem, fibrinogen supplementation has proved effective both in vitro and in vivo (Fries et al. 2005; Schramko et al. 2009; Grottke et al. 2010; Schlimp et al. 2013). Using a

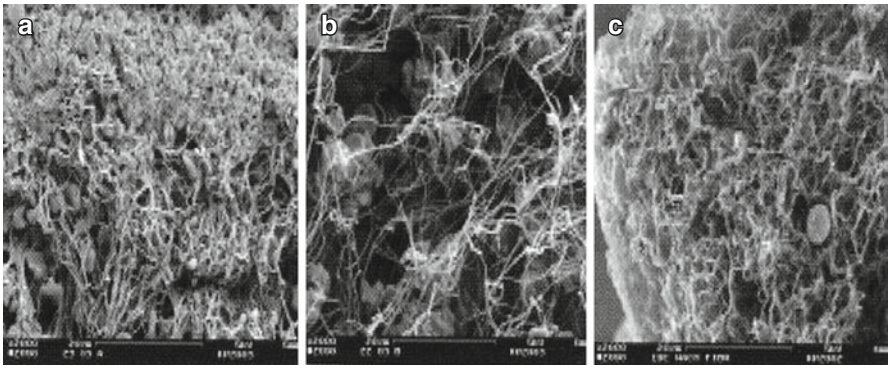

Fig. 9.3 Electron microscopy scans of blood clots formed from (**a**) undiluted whole blood, (**b**) blood diluted 65 % with gelatin, and (**c**) blood diluted 65 % with gelatin and the addition of fibrinogen concentrate (With permission from Fries and Martini (2010))

33 % in vitro dilution model, Schlimp et al. recently showed that fibrinogen concentrate was effective in increasing clot firmness in blood samples diluted with either albumin or gelatin. In samples diluted with HES, however, the effect was poor (Schlimp et al. 2013). Fries et al. reported improved clot firmness following fibrinogen administration in a porcine model of uncontrolled bleeding (Fig. 9.3) (Fries et al. 2005). Grottke et al. replaced 80 % of blood volume with HES 130/0.4, RL, and retransfused erythrocytes. The animals randomly received 70 mg/kg fibrinogen concentrate, 200 mg/kg fibrinogen concentrate, or a placebo before blunt liver injury was induced. Total blood loss was significantly lower, and survival was significantly higher, in both fibrinogen groups as compared to controls. Microscopy revealed no thrombosis in either group (Grottke et al. 2010).

Factor XIII supplementation, together with fibrinogen, partially restores clot formation in blood samples diluted in vitro with different colloids (Niemi et al. 2005). Again, the effect is significantly lower in the HES group compared to albumin and gelatin. The combination of factor XIII and fibrinogen effectively normalized maximum clot firmness in blood samples diluted with either albumin or gelatin. Haas and coworkers further investigated the effect of fibrinogen, factor XIII, and FFP in a 60 % hemodilution model. Fibrinogen together with factor XIII restored crystalloid-induced impairment of clot strength, while FFP only shortened coagulation times (Haas et al. 2008b).

As shown in elective surgery patients, desmopressin has the potential to reverse the colloid-induced decreases in levels of factor VIII and vWF (Conroy et al. 1996). Another potential option for such reversal is the administration of factor VIII/vWF concentrate, but there are no clinical data to support this strategy.

Conclusion

Crystalloids exert only minor effects on coagulation parameters, apart from the effects of hemodilution. Artificial colloids impair coagulation and platelet function to a greater extent than natural colloid albumin. Gelatin and rapidly degradable, short-acting HES seem to have similar effects on blood loss. There is no conclusive evidence that balanced solutions are superior to non-balanced fluids.

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Split Blood Products

10

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10.1 Plasma

10.1.1 Product Description and Selection for Transfusion

Plasma is the acellular fraction of blood, separated from the cellular blood components either by centrifugation of citrated whole blood or donor apheresis, with typical unit volumes averaging from 200 to 300 mL. There are several types of plasma products used for supplementation or replacement of soluble coagulation factors. The most widely recognized plasma component is fresh frozen plasma (FFP), which requires freezing at −18 °C within 6–8 h of collection (AABB 2013a). Plasma frozen within 24 h after phlebotomy (FP24) is similar to FFP in its preparation but differs in that it may be frozen at or below −18 C within 24 h after collection. Frozen plasma products prepared for transfusion requires thawing and warming to between 30 and 37 C. This takes 20–30 min, depending upon the equipment used for thawing and the unit volume. If the prepared plasma is not transfused within the initial 24-h post-thaw period, it can be relabeled as "thawed plasma" for use within 5 days after

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the initial thaw (AABB 2013a; Benjamin and McLaughlin 2012; Eder and Sebok 2007). The utility of thawed plasma is twofold: (1) it provides rapidly available plasma for the management of massive hemorrhage, and (2) it extends available plasma inventory by avoiding wastage of plasma suitable for transfusion (Downes et al. 2001). One rarely used plasma product, available in the USA, is liquid plasma. Unlike the previously described plasma products, liquid plasma has never been frozen; it is separated from a whole blood unit no later than 5 days before its expiration date and has a shelf life of 26 days from the date of the source blood collection (40 days if CPDA-1 is used as the anticoagulant for the parent component) (AABB 2013a; Benjamin and McLaughlin 2012).

Forms of pathogen-reduced plasma are widely available in Europe but until recently have not been available in the USA. Solvent/detergent-treated plasma (S/D plasma) is one of the most frequently used pathogen-reduced plasma products. Pooled plasma composed of a given ABO type undergoes viral inactivation with solvents (i.e., 1 % tri(n-butyl) phosphate) and detergents (i.e., 1 % Triton-X 100), which are subsequently extracted by oil and affinity ligand chromatography for selective binding of prion proteins (PrP^{Sc}). This treatment significantly inactivates lipid-enveloped viruses such as HIV and Hepatitis C as well as cellular pathogens such as bacteria and protozoa. While the pathogen inactivation process is ineffective against non-lipid-enveloped viruses such as hepatitis A (HAV) and parvovirus B19, product specifications identify minimum levels of B19 and hepatitis E virus (HEV) genetic material permissible, as well as minimum levels of neutralizing antibodies directed against HAV and B19 (Benjamin and McLaughlin 2012). This product had not been approved for use in the USA until January 2013, when the FDA approved *Octaplas*® (Octapharma, Austria) for transfusion (FDA 2013; Riedler et al. 2003; Ozier et al. 2011; Sachs et al. 2005; Sinnott et al. 2004).

Methylene blue (MB)-treated plasma is another pathogen-reduced product available in Europe. Methylene blue is an aniline dye which, upon light activation, generates reactive oxygen species that inactivate enveloped and some nonenveloped viruses, with lesser activity directed against protozoa and bacteria (Benjamin and McLaughlin 2012). Unlike S/D plasma, MB plasma is a single donor component.

Plasma contains ABO isoagglutinins, the naturally occurring antibodies directed against ABO antigens, and therefore must be ABO compatible with the recipient's red cells (see Table 10.1); however, cross-matching is not required. Group AB plasma, which lacks antibodies directed against A and B antigens, is compatible with all blood types and is used as emergency release plasma when there is insufficient time for determining the recipient's blood type (Wehrli et al. 2009). The Rh (D) type is not always matched because immunization to Rh (D) antigen has rarely been reported as a result of transfusion of Rh (D)-positive plasma to Rh (D)-negative individuals. Hemolytic reactions as a consequence of infusion of an undetected antibody directed toward recipient RBC antigens are rarely seen, as is alloimmunization to RBC antigens (Ching et al. 1991).

Table 10.1 ABO compatibility of blood components

Recipient blood group	Recipient alloantibodies	ABO-compatible blood components				
		Whole blood	Packed red cells	Plasma	Cryoprecipitate	Platelets
A	Anti-B	A	A or O	A or AB	A or AB (preferred)	A or AB (preferred)
B	Anti-A	B	B or O	B or AB	B or AB (preferred)	B or AB (preferred)
AB	Nil	AB	O, A, B, or AB	AB	AB (preferred)	AB (preferred)
O	Anti-A and anti-B	O	O	A, B, AB, or O	Any	Any

For platelet transfusions given to small pediatric or infant patients, the donor plasma should be ABO compatible with recipient red cells. Note the rare AB group is the universal plasma donor, while the common O group is the universal PRBC donor. ABO compatibility is required for plasma but may be waived in some circumstances for adult patients receiving cryoprecipitate or platelets

10.1.2 Indications

Notable variation exists in published guidelines for plasma transfusion (ASA 2006; Ferraris et al. 2011; Iorio et al. 2008; O'Shaughnessy et al. 2004; Fuller and Bucklin 2010; Roback et al. 2010), although there is agreement on its indication for replacement of coagulation factors in bleeding or surgical patients, particularly those suffering from disseminated intravascular coagulation (DIC) or undergoing massive transfusion. Many guidelines recommend using the international normalized ratio (INR) at or greater than 1.5 as an indication for plasma transfusion (O'Shaughnessy et al. 2004). However, a consensus on laboratory value "triggers" for plasma transfusion has not been reached. For massive hemorrhage, empiric transfusion of plasma in set ratios to RBC units is widely practiced in the USA (Holcomb et al. 2013; Dzik et al. 2011). Retrospective and observational studies on massive transfusion in military and civilian trauma have reported associations between higher plasma/RBC transfusion ratios and improved survival (Holcomb et al. 2013; Borgman et al. 2007; Shaz and Hillyer 2010), although definitive data on optimal use of plasma in this setting has yet to emerge (Holcomb et al. 2013).

Plasma is also indicated as a replacement fluid in therapeutic apheresis for thrombotic thrombocytopenia purpura (TTP) (Szczepiorkowski et al. 2010) and for coagulation factor replacement in patients with congenital deficiencies of single factors (such as FV and FXI), but should not be used for factor replacement in congenital factor deficiencies if factor concentrates are readily available (i.e., FVIII concentrates in hemophilia A patients). Additional indications include rapid warfarin reversal in an actively bleeding patient, although guidelines are emerging preferentially recommending prothrombin complex concentrates as a first-line agent (Ageno et al. 2012; Keeling et al. 2011; Morgenstern et al. 2010; Ansell et al. 2008). Plasma is not appropriate to use as a nutritional supplement or as a source of immunoglobulin and

should not be used as a volume expander when blood volume can safely and adequately be replaced with other agents such as colloids (AABB 2013).

10.1.3 Dose and Therapeutic Effect

In a nonpregnant individual, 1 mL of plasma contains approximately 1 unit of coagulation factor activity. Nonpathogen-reduced plasma products contain slightly less than 1 U/mL clotting factors due to approximately 10 % dilution from anticoagulant solution and naturally occurring variability in factor levels between individual donors (Benjamin and McLaughlin 2012; Eder and Sebok 2007). Administration of a 10–20 mL/kg dose of plasma typically increases circulating coagulation factor levels by 20–30 % (Spector et al. 1966). Standardization of clotting factors in S/D plasma manufacturing allows for more precise dosing; a dose of 12–15 mL/kg should raise most coagulation factors levels by up to 25 %. Plasma doses exceeding 15 mL/kg present increasing risks for volume overload in the recipient unless given in context of ongoing blood loss or therapeutic plasmapheresis (Murad et al. 2010; Popovsky 2004). Standard dosing protocols are appropriate for FFP and FP24, as well as for liquid plasma as these three products are considered essentially hemostatically equivalent for almost all clotting factors except for FV and FVIII—despite slight variations between clotting factors existing between these products (Benjamin and McLaughlin 2012; Eder and Sebok 2007; Downes et al. 2001; Sidhu et al. 2006; Yazer et al. 2008, 2010; Gosselin et al. 2013) (see Table 10.2). The process of solvent detergent treating of plasma also results in a decrease in FV and FVIII (Buchta et al. 2004). While remaining within regulatory requirements, declines in procoagulant levels may be clinically significant and require patient monitoring (Benjamin and McLaughlin 2012; Buchta et al. 2004).

Liquid plasma dosing is the same as that for FFP and FP24. Additional recommendations in the literature are that liquid plasma should be used in conjunction with either thawed FFP or FP24 and limited to a shelf life less than 15 days. A study by Gosselin et al. demonstrated significant drops in the levels of FV, FVIII, vWF, protein S, and endogenous thrombin activity (the thrombin generation potential of the product) at 30 days (Gosselin et al. 2013). Because of the decreased levels of both clotting and antithrombotic factors, liquid plasma is recommended only for massive transfusion support in patients with life-threatening hemorrhage and significant coagulation factor deficiencies (AABB 2013a).

In the USA, earlier forms of S/D plasma retained clotting factor levels close to those in other licensed plasma products, though reductions in protein C, protein S (Flamholz et al. 2000), antiplasmin, and antitrypsin activity were noted (Theusinger et al. 2011; Pock et al. 2007). In the early 2000s, reports of thrombotic adverse events and increased fibrinolysis after the use of S/D plasma prompted withdrawal of the product from the US markets (Flamholz et al. 2000; de Jonge et al. 2002). Currently, the manufacturer of FDA-approved Octaplas® claims to have all coagulation factors within their known references ranges and the same hemostatic activity as FFP (Heger et al. 2006). The only exception is the inhibitor α-2 antiplasmin, which is below the cited reference range. Protein S levels are lower in S/D plasma

Table 10.2 Average values of coagulation factors found in different plasma and cryoprecipitate preparations

Factors	Thawed plasma from FFP (Downes et al. 2001)		Thawed plasma from FP24 (Yazer et al. 2008)		Cryo from FP24 (cryo24) (Yazer et al. 2010)		Liquid plasma (Gosselin et al. 2013)		
Ref. range (U/mL)	Day 1	Day 5	Day 1	Day 5	Standard	Cryo24	Day 1	Day 15	Day 30
Factor V (0.70–1.50)	0.70	0.66	1.40	0.87			1.10	0.77	0.50
Factor VII (0.60–1.60)	0.90	0.72	1.09	0.96			0.97	0.78	1.08
VWF:Ag (340–820)					448.1	505.9	0.73	0.50	0.40
Factor VIII (0.60–1.50)	1.07	0.63	0.60	0.69	2.16	2.52	0.72	0.56	0.50
FX	0.85	0.80					1.10	1.11	1.12
FIX (0.60–1.50)			1.20	1.26			0.86	0.84	0.76
Antithrombin III (0.80–1.20)			0.89	0.92					
Protein C (0.70–1.40)			1.05	0.96			0.88	0.89	0.86
Protein S (0.58–1.28)			0.70	0.52			0.90		0.91
Protein S activity (0.76–1.35 IU/mL)							0.90	0.48	0.22
Fibrinogen (150–350 mg/dL)	225	225	320	318	455.8	575.8	2.92	2.76	2.75

Further details including the variability of these levels can be found in the individual references (Downes et al. 2001; Yazer et al. 2008; Gosselin et al. 2013; Yazer et al. 2010)

as compared with FFP; as such, the use of S/D plasma is not recommended for use in patients with severe protein S deficiency (Theusinger et al. 2011).

MB-treated plasma, however, may have markedly reduced hemostatic (Pock et al. 2007) and antithrombotic (Alvarez-Larran et al. 2004) efficacy; other photochemical pathogen reduction treatments of plasma, such as amotosalen, are also being evaluated and appear more equivalent to FFP (de Alarcon et al. 2005; de Valensart et al. 2009; Mintz et al. 2006a, b).

10.2 Cryoprecipitate and Plasma, Cryoprecipitate Reduced

10.2.1 Product Description and Selection for Transfusion

Cryoprecipitated antihemophilic factor (cryoprecipitate) is the cold-precipitated protein fraction collected by centrifugation from a frozen plasma component thawed at 1–6 °C. A single 10–15 mL cryoprecipitate unit is enriched in high-molecular-weight proteins including vWF, FVIII, fibrinogen, fibronectin, and FXIII (AABB 2013a).

Cryoprecipitate is stored at −18° C or below, and preparation time prior transfusion includes 30 min or more to thaw and pool individual units into one dose. Unlike plasma, cryoprecipitate cannot be stored in a thawed form and causes the longest preparation delay when used as a component of a massive transfusion protocol. Cryoprecipitate administration in adults does not need to be ABO compatible; however, the transfusion of large volumes of ABO-incompatible cryoprecipitate in to any single recipient may cause positive direct antiglobulin test results and, rarely, mild hemolysis (Dzik et al. 2011; Nascimento et al. 2011). Rh compatibility does not need to be considered for pre-transfusion product selection (Downes and Schulman 2011).

The stability of FVIIIC, vWF antigen, and fibrinogen between standard cryoprecipitate and cryoprecipitate made from FP24 plasma has been demonstrated (Yazer et al. 2010). Cryoprecipitates derived from pathogen-inactivated plasma treated with psoralens, however, contain significantly reduced levels of fibrinogen, FVIII, and ADAMTS-13 (an enzyme degrading vWF), although the vWF quantity and quality are well preserved (Cid et al. 2013).

The plasma supernatant remaining after the preparation of cryoprecipitate is termed "plasma, cryoprecipitate reduced" also known as "cryo-poor plasma" or cryosupernatant. Compared with other plasma products, this blood fraction is depleted of vWF, FVIII, FXIII, and fibrinogen. However, many of the remaining clotting factors are found in levels similar to that in FFP or FP24, including factors II, V, VII, IX, X, and XI (AABB 2013a; Benjamin and McLaughlin 2012; Wehrli et al. 2009).

10.2.2 Indications, Dosage, and Therapeutic Effect

Cryoprecipitate was originally developed as a FVIII concentrate for the treatment of hemophilia A, but the availability of safer, purified, or recombinant FVIII concentrates has largely supplanted its use in these patients. The primary indication for cryoprecipitate in modern transfusion practice is as a fibrinogen concentrate (Callum et al. 2009). Cryoprecipitate is the most frequently used fibrinogen concentrate in the USA and is the only one approved for use in the USA for treatment of acquired fibrinogen deficiency such as surgical blood loss, trauma, or postpartum hemorrhage. Pasteurized fibrinogen concentrates are increasingly replacing cryoprecipitate for treatment of both congenital and acquired fibrinogen deficiencies (Franchini and Lippi 2012; Kozek-Langenecker et al. 2013; Wikkelso et al. 2013). In the USA, each unit of cryoprecipitate is expected to contain >80 IU FVIII and >150 mg fibrinogen, with typical adult doses ranging from 6 to 10 pooled units. The following formula is recommended for calculating cryoprecipitate dosage: body weight (in kg) × 0.2 = number of cryoprecipitate units to raise fibrinogen by 50–100 mg/dL (AABB 2013a). Therapeutic recovery of transfused fibrinogen from cryoprecipitate may be reduced by consumption in ongoing hemorrhage or fibrinolysis. A recent retrospective review of plasma fibrinogen increments following cryoprecipitate transfusion in the setting of trauma found a mean increase of 55 mg/dL after an

average transfusion of 8.7 units (±1.7) (Stanworth 2007). Cryoprecipitate remains a second-line therapy for von Willebrand disease and hemophilia A, as well as bleeding secondary to uremia (Hedges et al. 2007). Additionally, the 2013 European Society for Anaesthesia perioperative bleeding guidelines suggest that the use of cryoprecipitate for the treatment of hypofibrinogenemia is indicated if fibrinogen concentrates are not available (Kozek-Langenecker et al. 2013).

The depletion of FVIII, fibrinogen, vWF, and FXIII in cryosupernatant limits its utility and renders it unsuitable as a substitute for other forms of plasma. Cryosupernatant has been used most widely as a replacement fluid during therapeutic apheresis for the treatment of thrombotic thrombocytopenic purpura (AABB 2013a). Both cryosupernatant and cryoprecipitate have potential utility for treating acquired coagulation factor deficiency in Jehovah's Witness (JW) patients. While typically refusing transfusion, the JW community leadership has allowed for individuals to consider accepting "processed" fractions of blood products as a matter of individual conscience (Hughes et al. 2008; Sniecinski et al. 2007).

10.3 Platelet Concentrates

10.3.1 Product Description

Platelets are small (2–3 μm in diameter) anucleate cell fragments which bind to sites of injury, providing the phospholipid surface for coagulation enzymes to assemble and generate thrombin (Hoffman and Monroe 2001). In addition, they contribute key protein and molecular elements for fibrin clot formation as well as exerting a contractile force that draws together the margins of injury. Platelet concentrates are obtained either from whole blood or by collection from donors via apheresis. Platelet concentrates derived from a single 450–500 mL whole blood collection contain greater than 5.5×10^{10} platelets per unit, with a typical adult dose formed by pooling 4–6 concentrates (AABB 2013a). Apheresis platelets contain over 3×10^{11} platelets per unit, and contrary to other platelet concentrates, they have the advantage that they represent only a single donor exposure per transfusion, reducing the risk of transfusion-transmitted infections. While some *in vitro* differences have been observed between platelets derived from the different collection methods (Vasconcelos et al. 2003), these have little clinical consequence, and these products are interchangeable (Slichter 2007; Chambers and Herman 1999).

One notable characteristic of platelet components is their cold intolerance. The exposure of platelet concentrates to temperatures of 4 °C or less results in platelet shape change, functional defects, and increased circulatory clearance rates (Hoffmeister et al. 2003; Rao and Murphy 1982). Platelets also have the shortest shelf life of any transfused product: the time from collection to expiration is 5 days; attempts to extend the approved storage time have failed (Dumont et al. 2010). This is due in part to the relatively short functional life of platelets (7–10 days in the circulation) but also to the risks of bacterial proliferation due to storage at room temperature (Palavecino et al. 2010).

Platelets, whether in the form of platelet concentrate or apheresis platelets, are a plasma-rich product and should, ideally, be ABO compatible with the recipient to avoid the infusion of ABO isoagglutinins. However, inventory shortages often prompt the use of ABO-incompatible platelets; these are typically well tolerated, but hemolytic transfusion reactions have been reported in rare instances (Slichter 2007; Fung et al. 2007; Josephson et al. 2010). The highest risk ABO-incompatible platelet transfusions are those from group O single donor products administered to group A or B recipients, due to the tendency of group O individuals to form high titer anti-A and anti-B antibodies (Chambers and Herman 1999). Lastly, although platelets do not bear RhD antigens, trace red blood cell content in platelet products has driven the practice of transfusing RhD-negative donor platelets to RhD-negative recipients to avoid alloimmunization. Should inventory shortages necessitate transfusion of RhD-positive platelets to RhD-negative recipients—particularly women of child-bearing age or female pediatric patients with child-bearing potential—treatment with anti-RhD immunoglobulin is recommended to avoid RhD alloimmunization (British Committee for Standards in Haematology 2012).

10.3.2 Indication, Dose, and Therapeutic Effect

Platelet transfusion is indicated (1) as prophylaxis against hemorrhage in severely thrombocytopenic patients (most widely defined as $<10 \times 10^9$/L platelets) and (2) for the treatment of bleeding in patients with thrombocytopenia or platelet dysfunction (AABB 2013a; ASA 2006; Slichter 2007; Slichter et al. 2010). Therapeutic platelet transfusion in the context of massive transfusion or DIC should be administered with the aim of keeping the recipient's platelet count at $>50 \times 10^9$/L (British Committee for Standards in Haematology 2012). The transfusion of one unit of platelets typically increases platelet count by $20–40 \times 10^9$/L.

The majority (86 %) of platelets are given to patients with hematologic malignancies; 68 % are given for bleeding prophylaxis and 32 % to treat acute bleeding episodes (McCullough et al. 1988). Other indications include dilutional thrombocytopenia after massive transfusion, qualitative platelet disorders, rare congenital disorders of platelet function such as Glanzmann thrombasthenia, or drug-induced platelet dysfunction. Aspirin-, clopidogrel-, abciximab-, or prasugrel-related platelet dysfunction should respond to platelet transfusion although high circulating plasma levels of eptifibatide or clopidogrel also render transfused platelets dysfunctional (Vilahur et al. 2007). Little data are available for ticagrelor, but due to its reversible binding to the P2Y12 receptor, transfused platelets can be inhibited by redistribution of ticagrelor from native to the transfused platelets.

The current recommended transfusion trigger for prophylaxis in oncology patients is 10×10^9/L (Rebulla et al. 1997). For patients who are bleeding or undergoing invasive procedures the trigger is typically higher (National Institutes of Health Consensus Conference 1987; ASA 2013). While the American Society of Anesthesiologists (2006) proposes a platelet count of 50×10^9/L as a trigger for platelet transfusion prior to an invasive procedure (ASA 2013), a target closer to $>100 \times 10^9$/L is often favored for neurosurgical interventions as historically

bleeding time was shown to steadily increase below this level (Slichter and Harker 1978).

Pathogen-inactivated, photochemically treated (PCT) platelets offer the promise to minimize transfusion-related infection with a broad range recognized and emerging bacteria, viruses, and protozoa (McCullough et al. 2004). Synthetic psoralens intercalate with microbial DNA or RNA and, upon exposure to ultraviolet light, cross-link pyrimidine bases to prevent microbial replication. While equivalent hemostatic efficacy was seen in clinical trials of standard versus PCT platelets (McCullough et al. 2004; Cid et al. 2012), the in vivo recovery of PCT platelets was lower and others dispute their efficacy (Kerkhoffs et al. 2010). PCT platelets are approved for use in Europe, but not in the USA.

Platelets require a supportive milieu derived from the plasma they are stored in; most apheresis units are stored in 100 % plasma with ACD-A anticoagulant. Reduction of plasma volume allows diversion of the plasma for other uses and may reduce the risk of plasma-associated TRALI occurring on transfusion of plasma-containing platelets. The use of platelet additive solutions (PAS) such as InterSol® (Fenwal Inc., Zurich, IL) allows plasma reduction to be tolerated by supplementing electrolytes and buffers. PAS platelets demonstrate in vivo recovery and survival that exceed FDA requirements (van der Meer et al. 2010; Dumont et al. 2013).

Future developments in available platelet products include reconstituted, cryopreserved platelets. The in vivo survival of transfused thawed, resuspended, cryopreserved platelets met FDA criteria (Dumont et al. 2013), and in vivo hemostatic activity appears adequate (Khuri et al. 1999). However, while the relevance to hemostasis is unclear, adequate 24-h in vivo recovery remains a regulatory hurdle.

10.3.3 Whole Blood as a Source of Platelets

While fresh whole blood may be viewed as ideal treatment for trauma resuscitation, there are several logistical and functional limitations. First, it would limit availability of other blood components, and second, if not used when fresh, how long could it be stored and how rapidly do storage lesions develop? The longer whole blood remains in storage, the more platelets and white cells aggregate in the product, increasing the risks of adverse reactions following transfusion. Erythrocytes promote aggregation and activation of platelets within the product, thereby defeating one of the therapeutic benefits of using whole blood. Although some *in vitro* measures support the hemostatic function for whole blood refrigerated for up to 21 days (Pidcoke et al. 2013). Many issues would have to be addressed before whole blood can be licensed by the FDA and readily available for transfusion.

10.4 Complications of Transfusion

Transfusion-related complications originate from immunologic complications or contamination with infectious agents (Eder and Chambers 2007; Kleinman et al. 2003). A comprehensive review of all adverse transfusion reactions is beyond the

scope of this chapter, particularly the infectious complications, but will be reviewed briefly.

10.4.1 Transfusion-Transmitted Infections

All blood components bear the risk of transmitting infectious diseases, despite careful screening of blood donors and (in many countries) universal testing of the blood supply for infectious disease markers. Pooled products such as pooled platelets or cryoprecipitate, which have not undergone pathogen inactivation, present increased risks due to the multiple donor exposures. Existing and emerging infectious agents are of greatest local or regional importance in endemic areas, but international travel increases exposure to pathogens. If all pathogens are not included in existing screening mechanisms in a traveler's native country, travel may increasingly limit suitable blood donors. Rigorous donor screening, serologic testing, and nucleic acid amplification testing have proven extremely effective in reducing the risk of transfusion-transmitted infections in developed nations (Bowden and Sayers 1990), but transfusion-transmitted infection remains a serious concern throughout the developing world.

In 2009, the American Association of Blood Banks Transfusion-Transmitted Diseases Committee made up of volunteer members with expertise in infectious disease convened to publish a supplement to the journal *Transfusion* on the threat to the North American blood supply from emerging infectious diseases (Stramer et al. 2009). They prioritized specific agents into categories: red agents had the highest priority, followed by orange, yellow, and white. For further understanding of the classification system, readers are directed to the reference (Stramer et al. 2009).

Red agents include human variant Creutzfeldt-Jakob disease, dengue viruses, and *Babesia* species. Orange agents include Chikungunya virus, St. Louis encephalitis virus, *Leishmania* species, *Plasmodium* species, and *T. cruzi*. Yellow agents include chronic wasting disease prions, human herpes virus 8, HIV variants, human parvovirus B19, influenza A virus subtype H5N1, simian foamy virus, *Borrelia burgdorferi*, and hepatitis A virus. White agents include hepatitis E and *Anaplasma phagocytophilum* (Stramer et al. 2009).

10.4.2 Bacterial Contamination

Bacterial contamination of blood components can be asymptomatic or induce sepsis with a high mortality. It is especially relevant to platelet products as they are the only component to not undergo refrigerated storage. Incidences approximate 5–30 in 10,000 units of random donor-pooled platelets, 0.5–23 in 10,000 units of apheresis platelets stored at room temperature, 0.25 in 10,000 units of packed RBCs stored at 4 °C, and, rarely, in FFP or cryoprecipitate contaminated during thawing in water baths (Kleinman et al. 2003). Bacterial contamination of platelet products is acknowledged as the most frequent infectious risk from transfusion (Blajchman and Goldman 2001; Brecher and Hay 2005). Along with TRALI and clerical errors

resulting in ABO mismatch, it is considered one of the most common causes of death from transfusion, with mortality rates ranging from 1:20,000 to 1:85,000 donor exposures (Hillyer et al. 2003).

Clinically recognized septic reactions have been reported at a rate of 1 in 2,500 to 1 in 11,400 for whole blood-derived platelet concentrate pools and 1 in 15,400 for apheresis platelets. Symptoms occurred after 17–42 % of contaminated platelet transfusions, with a 17 % mortality rate (Kleinman et al. 2003; Brecher and Hay 2005). The incidence of severe septic episodes has not been clearly established but is probably approximately 200/million platelet units transfused (50 % sensitivity) (Blajchman and Goldman 2001; Walker 1987). Given the 5-day storage life and the persistent risk of platelet shortage, in September 2005, the FDA trialed the use of 7-day apheresis platelets under the surveillance program PASSPORT to determine the safety of extending the storage life. The study was discontinued early after 2 true-positive cultures were detected in 2,571 day 8 platelets (778/million) (Dumont et al. 2010). However, based on risk modeling, overall recipient risk may not have been improved by the reduced inventory caused by withdrawal of 7-day apheresis platelets. From an inventory management standpoint, platelet pools would have replaced them, potentially increasing infection risk and delaying a TRALI risk reduction strategy (Kleinman et al. 2009). Pathogen reduction strategies may further renew enthusiasm for 7-day storage.

10.4.3 Acute Hemolytic Transfusion Reaction

Acute hemolytic transfusion reactions are one of the most serious complications of transfusion and remain as one of the leading causes of transfusion-related mortality worldwide (Eder and Chambers 2007; Vamvakas and Blajchman 2010). These reactions result from RBC lysis or accelerated clearance by the reticuloendothelial system resulting from RBC transfusion into a recipient with preformed antibodies directed against donor erythrocytes. Rarely, plasma-rich blood products have been implicated in hemolytic reactions by passive transfer of antibodies directed against recipient erythrocytes (Fung et al. 2007). Antibodies directed against ABO antigens are the most frequent source of incompatibility (Ching et al. 1991; Josephson et al. 2010), for example, transfusion of O platelets containing anti-A and anti-B. Pre-transfusion plasma reduction and ABO matching easily avoid this complication.

10.4.4 Febrile Nonhemolytic Transfusion Reaction

Febrile nonhemolytic transfusion reactions (FNHTR) represent an essentially benign, albeit unpleasant, transfusion reaction most notable for development of fever, defined as a temperature elevation of >1 °C above pre-transfusion temperature. Patients may also experience chills, rigors, nausea, and vomiting. Occasionally patients will manifest such signs and symptoms in the absence of fever. FNHTRs are caused by pyrogenic cytokines, such as IL-1, Il-6, or TNF-α, which accumulate in blood products during storage. The onset of symptoms usually occurs during

transfusion but may present toward the end of the transfusion process or even within 1–2 h afterward due to the increasing level of cytokine exposure. The diagnosis of FNHTR is one of exclusion, having ruled out other causes of febrile reactions such as hemolytic transfusion reactions, septic reactions, or contributions from comorbidities or medications. Treatment is supportive, including antipyretics such as acetaminophen (Heddle 2007).

10.4.5 Allergic Reactions/Anaphylaxis

Allergic transfusion reactions are one of the most common adverse transfusion reactions, with incidence rates estimated between 1 and 3 % (Vamvakas 2007; Domen and Hoeltge 2003). Clinical presentation varies, but most manifests solely with cutaneous symptoms such as urticaria, pruritus, erythema, and angioedema (Domen and Hoeltge 2003). These minor allergic reactions are thought to be most often mediated by preexisting recipient IgE or IgG targeting plasma protein antigens. Passive transfer of IgE directed against recipient plasma allergens or other environmental allergens has also been observed. Accordingly, allergic reactions occur most frequently with plasma-rich products (including platelets) but may also occur in plasma-deplete products such as red cell units. Antihistamines such as diphenhydramine or famotidine form the cornerstone for treatment of minor allergic transfusion reactions with corticosteroids reserved for more severe reactions.

Rarely, severe allergic reactions may rapidly progress to anaphylactic shock within minutes after symptom onset. These reactions are characterized by bronchospasm, hypotension, nausea and vomiting, chest pain, and tachycardia. IgA-deficient patients who have developed class-specific anti-IgA are at risk; however, this group only represents a fraction of anaphylactic transfusion reactions (AABB 2013a). Causative agents vary widely from anti-haptoglobin antibodies to passive transfer of allergens to which a patient is already sensitized, such as recently ingested foods (i.e., peanuts) (Jacobs et al. 2011). Ultimately, anaphylaxis is an unpredictable and potentially fatal transfusion outcome requiring swift action to prevent an adverse outcome. Severe allergic reactions or anaphylaxis should be managed in a similar fashion to anaphylaxis from other causes, with administration of epinephrine (with or without other vasopressors as needed) and corticosteroids, maintenance of a patent airway, and volume infusion to maintain hemodynamic stability. Testing for associated DIC and postponing procedures requiring further transfusion should also be considered.

10.4.6 Transfusion-Related Acute Lung Injury (TRALI)

10.4.6.1 Pathophysiology

Transfusion of plasma-containing blood products—which include all blood products other than washed cellular blood products—may result in a syndrome of noncardiogenic pulmonary edema and acute respiratory distress. Clinical findings defining TRALI include (1) onset during or within 6 hours of transfusion; (2) severe hypoxemia,

such as less than 90 % oxygen saturation on room air; (3) diffuse bilateral pulmonary infiltrates on chest x-ray; (4) absence of volume overload; and (5) no preexisting acute lung injury (Kleinman et al. 2004). TRALI may also be associated with fever, chills, hypotension, and transient leukopenia. The primary pathophysiologic mechanism is believed to be a reaction between donor anti-leukocyte antibodies and recipient leukocytes, which results in leukocyte activation (Marques et al. 2005), sequestration, and infiltration into the pulmonary capillary bed (Fung and Silliman 2009). Leukocyte activation results in pulmonary microvascular injury and capillary leakage with an influx of proteinaceous fluid into the alveolar space (Bux and Sachs 2007). A "two-hit" hypothesis for the pathogenesis of TRALI holds that the first hit is due to recipient neutrophils primed for activation by virtue of the patient's underlying clinical condition. The second hit involves activation of these neutrophils by anti-leukocyte antibodies or biological response modifiers contained in the transfused product (Silliman 2006). In rare cases, the transfused product may provide both hits (Kelher et al. 2009).

Female donors sensitized to human leukocyte antigens (HLA) by pregnancy are most frequently implicated as the source of blood products which have been linked to TRALI cases (Densmore et al. 1999; Powers et al. 2008; Triulzi et al. 2009). The frequency of anti-HLA antibodies ranges from 1.7 % for never pregnant females to 32.2 % for four or more pregnancies, whereas males and previously transfused donors all showed very low frequency of anti-HLA antibodies (in the range of 1–2 %) (Triulzi et al. 2009; Kakaiya et al. 2010). As a result, many blood collection agencies in the USA and Europe limit or prohibit collection of plasma-rich blood products from female donors (Eder et al. 2010; Funk et al. 2012; Jutzi et al. 2008; Keller-Stanislawski et al. 2010; Lucas et al. 2012; Middelburg et al. 2010; van Stein et al. 2010).

The best available, current TRALI incidence estimate comes from a prospective study surveilling hypoxemia after transfusion of over 450,000 units between 2006 and 2009. Ninety-one TRALI cases were identified with an incidence of 1 in 3,141 in 2006 compared with 1 in 12,346 in 2009 after the introduction of gender-based mitigation strategies (Toy et al. 2012).

10.4.6.2 Diagnosis and Management

The diagnosis of TRALI is clinical and not based on the results of laboratory investigations for the presence of anti-leukocyte antibodies in the donor (Popovsky and Moore 1985; Goldberg and Kor 2012). Although cognate leukocyte antibody-antigen matches are often seen in TRALI cases, their absence does not rule out TRALI (Kopko et al. 2003; Stafford-Smith et al. 2010). Careful patient evaluation of suspected TRALI should involve both the clinical team and the transfusion service and include posttransfusion chest x-rays, measures of oxygenation, and evaluation for volume overload. Once TRALI is suspected, the transfusion must be immediately discontinued and the blood bank informed (Su and Kamel 2007). The details of the transfusion workup are beyond the scope of this chapter. Briefly, following all cases of TRALI and some cases of possible TRALI, the blood bank and the blood collection facility should investigate all donors associated with TRALI or possible TRALI cases for the presence of antihuman leukocyte antigen (HLA) and possibly antihuman neutrophil antigen (HNA) antibodies (Reil et al. 2008). Few laboratories (mostly

in Europe) also perform leukocyte cross-matching as part of the evaluation. The extent of these investigations varies depending upon the availability of donor samples (usually not a problem), the availability of neutrophil antibody testing, and the availability of a recipient sample for HLA antigen typing (Kopko et al. 2001, 2003). A donor with HLA antibodies matching an affected recipient is classified as an implicated donor and is deferred from future plasma apheresis or platelet apheresis donation. If a donor has the highly morbid anti-HNA 3a antibodies, most blood banks will defer the donor from any type of blood donation (Davoren et al. 2003).

The management of the patient with TRALI/possible TRALI is supportive, with oxygen supplementation for the correction of hypoxemia and hemodynamic support for hypovolemia and associated hypotension (Wallis 2007). Most patients who develop TRALI or possible TRALI will require endotracheal intubation and ventilatory support (approximately 70–80 %) (Popovsky and Moore 1985; Vlaar et al. 2010; Gajic et al. 2007a; Wallis 2003). Early reports described a mean duration of ventilatory support of approximately 40 h (Popovsky and Moore 1985), while more recent evidence points to longer period of respiratory support (approximately 3–10 days) (Vlaar et al. 2010; Gajic et al. 2007a). TRALI is not responsive to diuretics, and the role of corticosteroids remains unclear (Peter et al. 2008); the majority of patients recover with supportive care.

10.4.6.3 Prevention

It has been well established that donors implicated in TRALI cases are more likely to be female and multiparous (Toy et al. 2012; Gajic et al. 2007b). While not all studies support the benefit of avoiding female plasma (Welsby et al. 2010), the overwhelming evidence supports the implementation of gender-based policies for reducing TRALI incidence from plasma transfusion. These factors resulted in the implementation of a new TRALI risk mitigation policy during the mid- to late 2000s throughout most of Europe and the USA, in which plasma units were predominantly obtained from male donors, thereby avoiding the transfusion of plasma units from female donors. This policy is feasible for plasma transfusion because the number of plasma units collected from whole blood or apheresis collections meets, or is in excess of, demand. In contrast, this policy is challenging for group AB platelet and plasma components (Reesink et al. 2012), where restriction of units to male donors jeopardizes supply (see Table 10.3). Despite that, in 2013 the AABB announced new TRALI risk mitigation standards requiring high-plasma volume components come from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy to rule out the presence of anti-HLA antibodies, regardless of ABO group. These new standards are to go into effect in 2014 (AABB 2013b).

Some blood centers have implemented a policy of testing selected populations of platelet apheresis donors for anti-HLA antibodies or resuspending apheresis platelets in platelet additive solution (PAS) (Lucas et al. 2012; Reesink et al. 2012; Kleinman et al. 2010) although there are inadequate data to evaluate its effect on the incidence of TRALI following platelet transfusion (Kakaiya et al. 2010; Reesink et al. 2012).

Table 10.3 Following implementation of the American Red Cross TRALI mitigation strategies, the incidence of TRALI cases 2008–2010 fell for all but group AB plasma where female donors still comprise 40 % of the group AB donor pool

Component	Cases (*n*)	TRALI rates per 10^6
A, B, O plasma	9	1.9
AB plasma	12	24.9
RBC	39	2.2
Apheresis platelets	19	8

Adapted from Reesink et al. (2012)

The use of solvent/detergent-treated plasma has also been promoted as a TRALI risk reduction strategy. In contrast to a TRALI incidence from single donor plasma units of 1 in 31,000 units, observational data (Riedler et al. 2003) and hemovigilance data from France between 2007 and 2008 (Ozier et al. 2011) identify a zero incidence of TRALI with this product with undetectable HLA antibodies (Sachs et al. 2005).

While hemovigilance data may be subject to biased reporting, these international data present compelling evidence supporting the global implementation of gender-based TRALI risk reduction strategies, provided inventory or organizational impediments are not restrictive.

10.4.7 Volume Overload

10.4.7.1 Pathophysiology

Transfusion-associated circulatory overload (TACO) will cause transfusion-related respiratory insufficiency and is thought to occur when the rate of transfusion exceeds the recipient's cardiovascular adaption to the additional workload. The rapid infusion of excessive volume can result in dyspnea, hypoxemia, elevated central venous pressure, and pulmonary edema (Eder and Chambers 2007).

TACO is typically reported in elderly patients and small children, due to their relatively small circulating volume but can occur in all age ranges. Compromised cardiac function, positive fluid balance, and rapid blood product administration are additional risk factors for TACO, which appears to occur more frequently in operative or intensive care settings, where large fluid volumes and blood are administered (Li et al. 2011).

While the primary mechanism of TACO centered around fluid overload (Popovsky 2004; Li et al. 2010), this has recently been questioned as the median transfusion volume in patients who develop TACO is only 3 (2–7) units (Li et al. 2011) and a large proportion of reported TACO cases occur after a single blood unit exposure (Popovsky et al. 1996). Similarly, Roubinian et al. reported no statistically significant differences in hourly fluid balance or the number of blood component units transfused in the 24-h interval preceding the TACO or TRALI episode (Roubinian et al. 2012).

TACO is also typically associated with increased systemic blood pressure (Popovsky 2010; Klein and Anstee 2006), which exceeds that expected from the

volume challenge alone, suggesting a possible effect of vasoconstricting substances in the transfused blood product (Donadee et al. 2011). While most likely associated with RBC transfusion, a sudden increase in the systemic vascular resistance has the clear potential to compromise left ventricular function resulting in the elevated left atrial pressures and ultimately hydrostatic pulmonary edema characteristic of TACO.

10.4.7.2 Diagnosis and Management

Distinguishing TRALI from TACO is important but often difficult (Skeate and Eastlund 2007; Popovsky 2009). Generally, TRALI is more likely to be associated with fever, hypotension, and exudative pulmonary infiltrates and less likely to respond to diuresis, whereas TACO is more likely to be associated with volume overload (e.g., positive fluid balance, elevated jugular venous pressure) or poor cardiac function (e.g., history of congestive heart failure, reduced left ventricular ejection fraction, or diastolic dysfunction). Similarly, elevated systolic blood pressures near the time of dyspnea onset, cardiomegaly, and/or increased circulating levels of brain natriuretic peptide (BNP) or N-terminal (NT)-pro-BNP support a diagnosis of TACO rather than TRALI (Popovsky 2009; Zhou et al. 2005; Tobian et al. 2008; Li et al. 2009; Rice et al. 2011; Ely et al. 2001).

Differentiating TRALI from TACO can be a significant challenge, particularly as both may coexist (Popovsky 2009, 2010; Gajic et al. 2006). Related to this, approximately 30 % of ALI/ARDS patients show evidence of left atrial hypertension (Wheeler et al. 2006), increasing the difficulties of differential diagnosis and explaining a degree of diuretic responsiveness associated with TRALI.

While chest x-ray findings of bilateral infiltrates are similar to TRALI, TACO shows symptomatic improvement with diuresis. Patients with suspected TACO should have any ongoing transfusion paused to establish the diagnosis, with diuretics and supportive care given as indicated before attempting further transfusion. Resumption of transfusion should be approached with a slower infusion rate and careful vigilance for recurrent symptoms.

10.4.8 Metabolic Complications and Hypothermia

As all blood products are collected and stored in citrate-based anticoagulants, large volume transfusions may be complicated by hypocalcemia (Eder and Chambers 2007). Citrate binds divalent cations such as calcium and magnesium and is rapidly metabolized by the liver. Whereas citrate is easily cleared during nonurgent transfusions, citrate load during massive transfusion may overwhelm this clearance mechanism (Sihler and Napolitano 2010). In the awake patient, hypocalcemia presents initially with chills, tingling, dizziness, and tetany; continued progression of citrate toxicity can lead to prolonged QT interval, decreased left ventricular function, and cardiac arrhythmias. While hypocalcemia can be managed by slowing the rate of transfusion, in ongoing massive transfusion, and in patients with liver dysfunction or under general anesthesia, calcium replacement therapy should be guided by the patient's ionized calcium concentration.

Hypothermia can lead to multiple systemic derangements, including peripheral vasoconstriction, cardiac dysfunction, acidosis, and coagulopathy (Moffatt 2013). The effects of hypothermia and acidosis on coagulation have been observed both clinically and in vitro. Decreases in core temperature <34 °C and pH <7.1 after massive transfusion are predictive for the development of coagulopathy (Eder and Chambers 2007). The activity of tenase (FVIIa/tissue factor) and prothrombinase (FXa/FVa) complexes is directly dependent on temperature, with both showing a 1.1-fold loss of activity at 33 °C as compared to 37 °C (Meng et al. 2003). Even more dramatically, FVIIa/tissue factor and FXa/FVa show sharp decreases in activity in acidic environments, with activity decreasing by 55 and 70 % at pH 7.0, respectively (Viuff et al. 2008). Blood products transfused in this setting may be less effective, and, similarly, transfusion of chilled blood products especially in large volumes is absolutely contraindicated.

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Coagulation Factor Concentrates

11

Lars M. Asmis

11.1 Introduction

Perioperative management of coagulation involves the use of blood products. Patients have typically been transfused whole blood or derivatives of whole blood, including red blood cell (RBC) concentrates, platelet concentrates (PC), and plasma. Fractionated plasma products, in the form of single and combined coagulation factor concentrates, have been available for decades. Following isolated human coagulation factors, recombinant coagulation factors eventually became a part of standard medical practice. Both isolated and recombinant types of coagulation factor preparations can contain nonactivated or activated coagulation factors. A third group of drugs used to manage perioperative bleeding includes medications that alter either the activity (e.g., tranexamic acid) or the plasma levels (e.g., desmopressin) of coagulation-related proteins. The latter group of drugs will be discussed in Chap. 12.

The transfusion of any blood product requires a thorough risk–benefit evaluation (Dunbar et al. 2012; Hardy 2012; Berseus et al. 2013; Shaw et al. 2013). From the very beginnings of transfusion medicine, it has been known that the use of cell-containing transfusion products, such as RBC concentrates, is associated with potential side effects. Transfusion reactions, due to blood group incompatibility in RBC transfusion, are potentially lethal treatment complications. Due to the way they are produced, platelet concentrates may harbor a significant risk of sepsis. Storage at room temperature is conducive to bacterial growth in these products that may lead to patient harm (Stroncek and Rebulla 2007). Fresh frozen plasma (FFP) was originally considered a "cell-free" product. As a cell-free product containing physiological coagulation factors and inhibitors, it was assumed to be safe. It has

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since been shown that FFP may be contaminated with fragments of cellular origin, termed as microparticles, as well as soluble mediators including antibodies and interleukins (George et al. 1986; Theusinger et al. 2011). These contaminants can potentially lead to adverse effects. A rare but dangerous complication of FFP transfusion is transfusion-related acute lung injury (TRALI) that is associated with increased mortality (Inaba et al. 2010).

The ongoing quest for efficient and safe transfusion products has resulted in the development of isolated coagulation factor concentrates (i-CFC) and recombinant coagulation factor concentrates (r-CFC). This chapter focuses on isolated (single) and combined coagulation factor concentrates. Based on differences in regulation and approval procedures in various countries, there are relevant geographical differences in the availability and use of coagulation factor products. Indications for the various products vary significantly from country to country. Substitution of i-CFC in acquired coagulation factor deficiencies represents on-label use in some countries, while it is off label in others. This chapter discusses the most frequently used coagulation factor concentrates.

11.2 Coagulation Products

11.2.1 Fibrinogen Concentrate

11.2.1.1 Background

Fibrinogen was the first coagulation factor to be discovered. In an open wound, the white aggregates of fibrin strands can be seen with the naked eye. In the nineteenth century, Home coined the term "fibrin," and Virchow postulated that there was a precursor molecule, which he called "fibrinogen." In 1905, fibrinogen was already defined as a coagulation factor I (FI) in a review by Morawitz (1905). Hiippala and colleagues established fibrinogen's key role in perioperative hemostasis and demonstrated that it was the first coagulation factor to reach critical levels in massive bleeding (see "Indications", below) (Hiippala et al. 1995).

11.2.1.2 Description

Fibrinogen, synthesized in the liver, is an abundant plasma protein with concentrations typically ranging between 1.5–4.0 g/l and 6–13 μmol/l. Fibrinogen's molecular weight is approximately 340 kDa. It is a heterodimer with two sets of α, β, and γ chains. The six chains are N covalently linked in the central E domain. Two sets of α, β, and γ chains extend from the E domain to form 2 so-called D domains at their distal ends. Thrombin (FIIa) cleaves activation peptides from the central (E domain) end of the α and β chains, releasing two sets of fibrinopeptides, A and B, thereby exposing polymerization sites. After the release of these fibrinopeptides, the molecules are called fibrin or fibrin monomers. The fibrin monomers aggregate to form soluble fibrin strands that form by the interaction of the D and E domains of neighboring molecules. Initially, the interaction between fibrin monomers is reversible; the

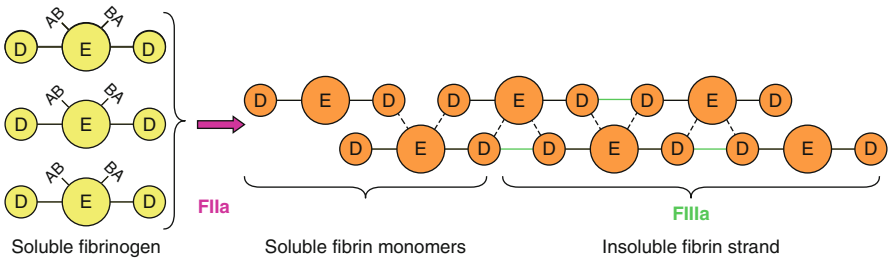

Fig. 11.1 Model of fibrinogen polymerization. Thrombin (*FIIa*)-induced cleavage of the fibrinopeptides A and B from soluble fibrinogen molecules leads to the generation of soluble fibrin monomers that reversibly aggregate into a soluble fibrin monomer gel. Activated factor XIII (*FXIIIa*) can irreversibly stabilize the monomers into an insoluble and stable fibrin strand through covalent cross-linking

resulting fibrin strand can potentially disintegrate again. Only once factor XIII (FXIII) has covalently cross-linked the individual fibrin monomers does the fibrin strand become irreversibly interconnected (Nieuwenhuizen 1995; de Maat and Verschuur 2005; Sorensen et al. 2011b; Levy et al. 2012) (see Fig. 11.1).

The three polypeptide chains (Aα, Bβ, and γ) are encoded by three distinct genes, all residing on chromosome 4. The three genes contain interleukin 6 (IL-6) response elements, which explains why fibrinogen is an acute phase reactant.

Fibrinogen is a glycoprotein that has a plasma half-life of approximately 100 h (Blomback et al. 1966). Liver disease and sepsis increase turnover. In liver cirrhosis, glycosylation may be altered, leading to acquired dysfibrinogenemia, characterized by circulating fibrinogen molecules with reduced biological activity. Degradation of soluble fibrinogen is mediated by "normal protein degradation, the coagulation process, and unknown pathways." Stabilized fibrin (and soluble fibrinogen) degradation occurs by plasmin-induced proteolysis (de Maat and Verschuur 2005).

Fibrinogen has at least four major biological functions: it is a substrate of coagulation; it is a cross-linker in platelet aggregation; it is a coagulation inhibitor as "antithrombin I"; and it is a substrate for interaction with other proteins (Weisel and Litvinov 2013). Most other coagulation factors are serine proteases capable of specifically recognizing target molecules and activating many of them. For example, one activated molecule of factor X (FXa) can activate more than 1,000 prothrombin molecules (FII), while one thrombin molecule can activate more than 1,000 molecules of fibrinogen. Enzymatically active coagulation factors can continue to interact with many other target molecules while fibrinogen, in its role as substrate, will be consumed. One activated molecule of fibrinogen will give rise to one molecule of fibrin in the resulting clot. Fibrinogen's second role is that of the cross-linker in platelet aggregation. Once platelets have been activated "outside in," an "inside-out" activation will occur that leads to an altered structure of the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor on the platelet surface. This structural change permits the interaction of one fibrinogen molecule with several GP IIb/IIIa receptors on several

platelets, leading to the formation of platelet aggregates. The third role involves fibrinogen's ability to bind thrombin (Sorensen et al. 2011b). Finally, there is FXIII, which is reported to covalently link α2-plasmin inhibitor (α2-PI) on to fibrinogen (Richardson et al. 2013). This reaction is important for the stability of the resulting fibrin clot (see below).

11.2.1.3 Indications

11.2.1.3.1 Acquired Fibrinogen Disorders

Hiippala's pioneering work identified the clinical relevance of fibrinogen in massively bleeding patients (Hiippala et al. 1995). He studied 60 massively bleeding patients and measured platelet counts and coagulation factor levels. Based on "critical levels," or thresholds, which he took from a prominent coagulation textbook of the time, he observed that the fibrinogen threshold of 1.0 g/l was reached at 142 % of blood loss. Other parameters he monitored only fell below their respective thresholds considerably later: platelet count at 230 %, FII at 201 %, FV at 229 %, and FVII at 236 %.

Others corroborated the finding that fibrinogen will be the first factor to reach critical levels in massive bleeding (Martini et al. 2005; Fenger-Eriksen et al. 2009c). Acquired hypofibrinogenemia is thus a frequently observed problem in massively bleeding patients. Suggested treatment thresholds lie ≥1.5 g/l (Fenger-Eriksen et al. 2009a). A less frequent problem is acquired dysfibrinogenemia. This may occur in end-stage liver cirrhosis as a consequence of an altered glycosylation of fibrinogen molecules that interferes with the plasma assembly of fibrin monomers. The laboratory hallmark of this disorder is longer thrombin time and a reduced ratio of functional to antigenic fibrinogen tests (<0.7).

11.2.1.3.2 Congenital Disorders of Fibrinogen

Congenital disorders of fibrinogen are registered indications for fibrinogen substitution in many countries. There are various such disorders, including afibrinogenemia (no measurable protein), hypofibrinogenemia (<1.5 g/l), and dysfibrinogenemia. Afibrinogenemia and dysfibrinogenemia are orphan diseases with frequencies of approximately 1:1,000,000 (Peyvandi et al. 2012a). Experienced physicians should manage prophylaxis and treatment of acute bleeding in these patients as these diseases can also manifest a thrombotic phenotype depending on the molecular pathophysiology. Suggested treatment thresholds lie in the area of 0.5–1.0 g/l (Bolton-Maggs et al. 2004; Acharya and Dimichele 2008).

11.2.1.4 Monitoring

Tests for fibrinogen were proposed in the middle of the last century: the Schulz method in 1955 and the Clauss method in 1957 (Schulz 1955; Clauss 1957; Nieuwenhuizen 1995; Lowe et al. 2004). Interestingly, Hartert had published his work on thromboelastography several years before that, in 1948, but functional fibrinogen tests for viscoelastic point-of-care (POC) devices (including functional "fibrinogen" tests on ROTEM, TEG, and related devices) were only standardized and validated much later (Hartert 1948).

The Schulz method is an antigenic test performed in citrate plasma: fibrinogen is heat denatured and the precipitable protein is measured in a graded tube. One of the pitfalls of this test is the presence of other precipitable proteins, not related to fibrinogen, which falsely increase outcomes. Turnaround time is approximately 60 min.

The Clauss method is a functional test of fibrinogen in which a coagulation time is measured in prediluted plasma, rendering fibrinogen the rate-limiting reagent. The addition of (bovine) thrombin is the start signal and formation of soluble fibrin is the stop signal. This coagulation time can be converted into a fibrinogen concentration. Strong inhibitors of thrombin (including direct anti-FIIa inhibitors), excessively high levels of fibrin degradation products (including D dimers), and other inhibitors may falsely lengthen the coagulation time resulting in falsely low fibrinogen results. Turnaround time is approximately 40 min.

Fibrinogen tests in viscoelastic POC devices represent functional tests. The addition of tissue factor induces whole blood to coagulate. Platelet function is inhibited by specific inhibitors. The maximum clot firmness, or maximum amplitude, is measured after a defined time. The results are not only dependent on the fibrinogen concentration, but may be influenced by hematocrit, FXIII, heparin, hydroxyl-ethyl starch, gelatin, and albumin (Solomon et al. 2011; Ogawa et al. 2012; Schlimp et al. 2013). None of these tests is standardized, and the international, gold standard test is currently debated.

11.2.1.5 Efficacy and Safety

To date, there is only limited evidence from three, small randomized controlled trials (RCTs) evaluating fibrinogen concentrate in acutely bleeding patients. A cystectomy trial ($n = 20$), a coronary artery bypass grafting (CABG) trial ($n = 20$), and an elective thoracic/thoracoabdominal aneurysm trial have been published. The cystectomy trial showed that fibrinogen concentrate increased maximum clot firmness and reduced postoperative transfusion in patients whose blood loss was substituted by hydroxyl-ethyl starch (Fenger-Eriksen et al. 2009b). In the CABG trial, patients were randomized to 2 g of fibrinogen concentrate preoperatively or placebo. This raised fibrinogen levels by 0.6 g/l. No adverse effects of fibrinogen substitution were observed (Karlsson et al. 2009). The largest trial, including 62 patients scheduled for elective thoracic/thoracoabdominal surgery, showed that thromboelastography-guided hemostatic therapy using fibrinogen concentrate was more effective than placebo to control bleeding. Fibrinogen substitution was also compared with cycles of FFP/platelets and found to be superior to one cycle and at least as effective as two cycles of the prespecified transfusion protocol. This trial's approximate target level of fibrinogen was 3.6 g/l (Rahe-Meyer et al. 2013a).

The RCT cited above are too small to draw any conclusions regarding safety. In the Rahe-Meyer RCT, one patient in the treatment group died after cardiorespiratory arrest, potentially of thromboembolic origin. In the placebo group, there were four deaths and two thromboembolic events. Based on the limited evidence, reviews describe fibrinogen concentrate as being safe (Fenger-Eriksen et al. 2009a; Levy et al. 2012; Warmuth et al. 2012).

The manufacturer of fibrinogen concentrate conducted a post-marketing program of pharmacovigilance between 1986 and 2008. More than one million grams of fibrinogen were administered, with 48 adverse events reported and 9 cases of arterial or venous thromboembolism. Of these nine patients, seven had congenital fibrinogen disorders and two had acquired fibrinogen disorders (Fenger-Eriksen et al. 2009a). The numbers cited suggest an estimated incidence of thromboembolic events of less than 1 per 10,000. Allergic reactions occurred at a frequency of less than 1 per 10,000. Underreporting of adverse events in the post-marketing phase is a well-known problem, so these numbers need to be interpreted with caution and corrected when data from large RCT become available.

11.2.1.6 Dosing

The following dosing regimen has been suggested in the context of classic coagulation testing: dose (g) = desired increase in g/l × plasma volume (plasma volume = 0.07 × (1-hematocrit) × body weight (kg)) (Acharya and Dimichele 2008). In the context of thromboelastographic/metric testing, 2 g of fibrinogen in a 70-kg patient generally increase the FIBTEM by 4 mm (Rahe-Meyer et al. 2009). The manufacturer of fibrinogen concentrate recommends 30–60 mg/kg or 2–4 g in a 70-kg patient (Fenger-Eriksen et al. 2009a). This dose will increase plasma fibrinogen by approximately 1 g/l (Solomon et al. 2010). Threshold and target values for fibrinogen have changed considerably in the recent years (see Sect. 11.3) (Sorensen et al. 2011b). In the recent Rahe-Meyer RCT, the target post-substitution fibrinogen level was 3.6 g/l or a maximum cloth firmness (MCF) of 22 mm in ROTEM in patients undergoing major aortic replacement surgery.

11.2.1.7 Key Points and Prospects

Preliminary evidence from these three RCTs indicates that fibrinogen concentrates can play an important role in the management of perioperative bleeding. Further research is needed to confirm the treatment's efficacy and safety for this indication.

11.2.2 Factor XIII Concentrate

11.2.2.1 Background

Factor XIII (FXIII) was the last coagulation factor to be discovered. First indications of its existence date back to the 1920s. Fibrin clots that formed in the presence of calcium became insoluble in the presence of weak bases (Barkan 1923). A similar experiment was performed in 1944 with purified fibrinogen. The authors concluded that an additional "stabilizing factor" to calcium was necessary to explain their findings (Robbins 1944). Duckert first described human FXIII deficiency in 1960 (Duckert et al. 1960). The protein was attributed with its current name in 1963 by the International Committee on Blood Clotting Factors (Muszbek et al. 2011).

11.2.2.2 Description

FXIII is a transglutaminase, an enzyme that cross-links proteins. This clearly distinguishes it from the classic coagulation factors that are serine proteases – enzymes that cleave proteins. In plasma, FXIII bound to fibrinogen forms a tetramer with two catalytic A domains and two inhibitory B domains. Cellular FXIII, present in platelets, monocytes, and bone marrow-derived cells, has two catalytic A domains (Muszbek et al. 2011; Levy and Greenberg 2012).

The catalytic A domain is an 83 kDa protein that can be activated by proteolytic activation (by thrombin) or non-proteolytic activation (in the presence of high calcium concentrations).

The FXIIIA encoding genes reside on chromosome 6 (6p24-25). It is expressed in bone marrow-derived cells including megakaryocytes, macrophages/monocytes, and in hepatocytes. The B domain, which lacks enzymatic activity, is an 80 kDa protein. The FXIIIB gene is located on chromosome 1 (1q31-32.1) and is expressed primarily in hepatocytes (Hsieh and Nugent 2008).

In the context of the fibrin clot, FXIII has two functions with fibrin and fibrinogen as its main substrates. FXIII-mediated cross-linking of soluble fibrin monomers results in the generation of an insoluble or stabilized fibrin strand that is essential for in vivo hemostasis. Furthermore, FXIII mediates the cross-linking of fibrinolysis inhibitors to fibrinogen, e.g., the α2-plasmin inhibitor (α2-PI, also called α2-antiplasmin) (Mosesson et al. 2008; Fraser et al. 2011). Fibrinogen circulating in a context of sufficient FXIII will be rich in α2-PI cross-linked to it. This type of fibrinogen will eventually give rise to fibrin strands rich in α2-PI. The presence of the fibrinolysis inhibitor in the fibrin strands hypothetically assures an increased stability of the hemostatic plug. Fibrinogen with low α2-PI supposedly gives rise to fibrin strands that are more prone to plasmin's fibrinolytic activity and may thus be associated with an increased risk of bleeding.

11.2.2.3 Indications

11.2.2.3.1 Acquired FXIII Deficiency

Acquired FXIII deficiency has been described in a variety of clinical settings due to consumption of the coagulation factor and due to inhibition by acquired inhibitors (Levy and Greenberg 2012). Consumption of FXIII can occur in massive bleeding, but its incidence is not very well defined in the literature. A study in 1,004 adult patients in a university hospital setting showed a prevalence of 21 % of patients with values below the reference range. A 62 % incidence of acquired FXIII deficiency was found in a population of patients with acute leukemia. In view of this high frequency, some published algorithms for bleeding management incorporate FXIII. Conditions associated with large wound areas, such as chronic inflammatory bowel disease (IBD: ulcerative colitis and Crohn's disease), massive burns, extensive orthopedic surgery of the spine, etc., are known to be associated with low FXIII levels. However, whether low levels of FXIII are associated with a clinical bleeding diathesis in the context of IBD, for example, is contested (Van Bodegraven et al. 1995; Chamouard et al. 1998). Acquired deficiency due to autoantibody formation is an extremely rare event, with less than 100 reported cases to date (Boehlen et al. 2013).

11.2.2.3.2 Congenital FXIII Deficiency

The prevalence of congenital FXIII deficiency is estimated at 1 per million. Areas with high rates of consanguinity have higher incidences. Treatment of the rare patients who require FXIII substitution in this context should be carried out in specialized centers. Heterozygote carriers of FXIII deficiency, with FXIII levels below the reference range (in the range of 50 %), will generally not present with a bleeding tendency under normal circumstances. Under special conditions, including postpartum bleeding, major trauma, and severe perioperative bleeding, FXIII levels may fall to levels that are conducive to a clinically relevant coagulopathy (Hsieh and Nugent 2008) (and personal observation).

11.2.2.4 Monitoring

FXIII monitoring can be done using functional and antigenic tests. The usual test is clot solubility in monochloroacetic acid solution, but this functional test is neither standardized nor quantitative. Quantitative FXIII activity tests use activated FXIII to assay its transglutaminase activity. This can be done in two main ways: (1) measurement of ammonia released as an early byproduct of the transglutaminase reaction (ammonia release assays) and (2) measurement of amine substrates that are covalently linked to another substrate (amine-incorporation assays). More commercial kits use the first method than the second. As there are non-FXIII-dependent ammonia-releasing reactions that can account for up to 15 % of the measured activity, FXIII measurements <20 % should be interpreted with caution and confirmed in an experienced laboratory. It should be noted that high ammonia concentrations in severe hepatic dysfunction can interfere with ammonia release assays. Antigenic tests can be directed against subunit A, subunit B, or the combination of both (Hsieh and Nugent 2008; Karimi et al. 2009). In the context of perioperative FXIII monitoring, any automated, rapid, reproducible, and precise test is suitable. Knowing the lower detection limit and test range used in one's institution is important. Peyvandi's review shows that FXIII correlates badly with clinical bleeding (Peyvandi et al. 2012b).

Some literature suggests that, due to absent or inadequate testing strategies, acquired FXIII deficiency goes largely undetected (Lawrie et al. 2010). Classic global coagulation tests, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), are "blind" to FXIII (see Fig. 11.2). Specialized tests, such as thrombin time and fibrinogen according to Clauss, do not incorporate FXIII activity. The common stop signal for all the coagulation time-based tests is the appearance of soluble fibrin monomers in the test vial. Fibrin monomers can be detected optically or mechanically. Whatever the method, coagulation time measurements stop prior to the onset of FXIII's action.

11.2.2.5 Efficacy and Safety

Two RCTs evaluating human FXIII concentrate have been published to date. Rasche et al. compared FXIII substitution versus placebo in 60 patients with acute leukemia (Rasche et al. 1982). Although FXIII treatment resulted in increased FXIII levels,

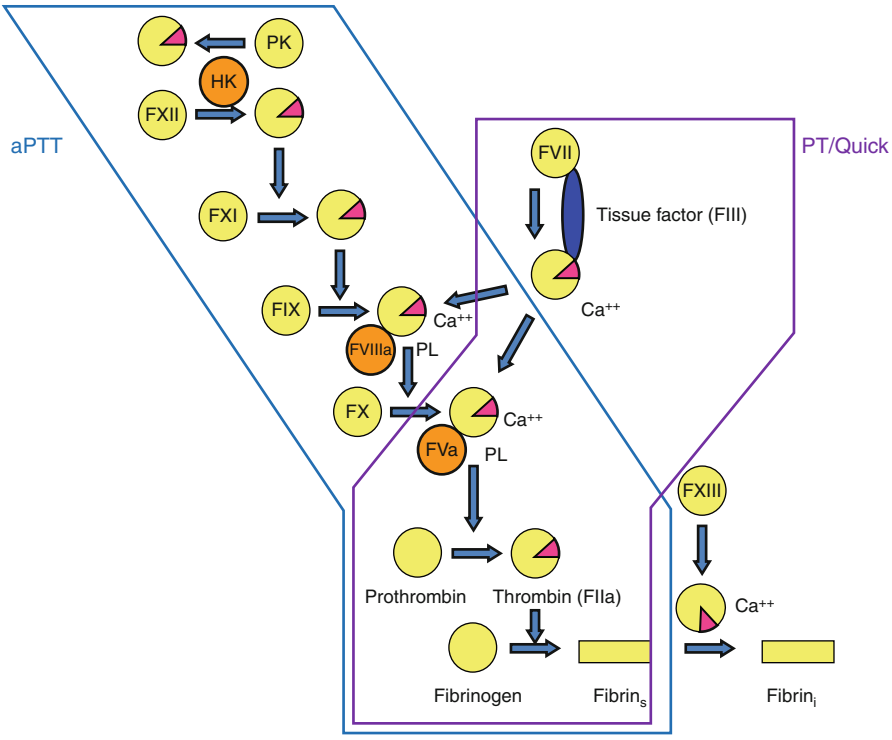

Fig. 11.2 The cascade model of coagulation and coagulation tests. Coagulation factors are depicted as circles. *Yellow circles* indicate enzymatically active coagulation factors (exception: fibrinogen, which is not enzymatically active, but a substrate). *Yellow circles* with a *pink insert* represent activated coagulation factors. *Orange circles* indicate cofactors. Tissue factor is depicted in *blue*, as it normally does not circulate in plasma. The factors involved in the activated partial thromboplastin time (*aPTT*) and prothrombin time according to Quick (*PT*) are circled by *light blue* and *purple polygons*, respectively. It is important that both FXIII and von Willebrand factor (not depicted) are not assayed in the so-called standard coagulation tests. Prothrombin complex concentrates contain FIX, FX, and FII and FVII to a variable degree. Substitution with PCC thus influences both PT and aPTT. Abbreviations: *Ca^{2+}* calcium, *$Fibrin_s$* soluble fibrin, *$Fibrin_i$* insoluble fibrin, *HK* high molecular weight kininogen, *PL* phospholipids, *PK* prekallikrein

there were no statistically significant differences in the number of bleeding complications or transfusions.

Korte et al. investigated maximal clot firmness using ROTEM measurement as the primary outcome in 22 cancer patients undergoing abdominal surgery. Patients were randomized to receive 30 IU/kg of human FXIII or placebo within the first 15 min of surgery. The trial was halted prematurely (prespecified primary outcome difference at interim analysis) because of an 8 % decrease in MCF in the treatment group compared with a 38 % decrease in the placebo group – a statistically significant difference (Korte et al. 2009).

11.2.2.6 Dosing

No prospectively evaluated treatment thresholds or target values have been established for the frequently acquired FXIII deficiencies.

In cases of congenital deficiency and in patients at a high risk of bleeding, 10 IU/kg of FXIII are given at 4–6 week intervals (Bolton-Maggs et al. 2004) for prophylaxis. This translates into 500–1,000 IU per application. In settings of acute bleeding, 10–20 IU/kg are recommended. This corresponds to single doses of 750–1,500 IU/kg for a patient of approximately 75 kg.

11.2.2.7 Key Points and Prospects

Similarly to fibrinogen, there are only preliminary data on the efficacy and safety of FXIII in the perioperative setting.

11.2.3 Von Willebrand Factor/Factor VIII Concentrates

11.2.3.1 Background

Von Willebrand factor (vWF) is named after the Finnish internist Erik A von Willebrand, who first described a family with the disease in 1926 (von Willebrand 1926; Federici et al. 2006). The family came from the Åland Islands in the Baltic Sea. In contrast to the hemophilias, both sexes were affected. The disease was characterized by a prolonged bleeding time, despite a normal platelet count, normal PT, (described by Quick in 1935), and normal-to-increased aPTT (described by Langdell in 1953). The disease's description was published under the designation "hereditary pseudohemophilia." In the 1950s, it became possible to measure FVIII and the first cases of "pseudohemophilia" were described in patients of both sexes who had reduced FVIII levels. In 1963, reduced platelet adhesiveness in affected patients became detectable (Salzman 1963). In 1971, using a specific antibody against FVIII, Zimmermann was able to show that there was another protein responsible for the phenotype (Zimmerman et al. 1971), initially called FVIII-related protein. In 1971, Howard and Firkin showed that an antituberculosis agent, ristocetin, could trigger platelet agglutination in normal subjects, but not in patients with von Willebrand's disease (Howard et al. 1973). Von Willebrand factor was finally isolated in 1972 (Bouma et al. 1972), and as there are several distinct underlying pathophysiological mechanisms, von Willebrand syndrome (vWS) is the recommended designation.

11.2.3.2 Description

VWF is a multimeric glycoprotein with monomers approximately 2,050 amino acids long. These monomers are assembled into dimers, which are subsequently polymerized into multimers of 2–20 units with a molecular weight of up to 20×10^6 D. VWF is encoded on the short arm of chromosome 12. It is primarily expressed and stored in endothelial cells (Weibel–Palade bodies) and megakaryocytes (α granules). Endothelial cells express DDAVP receptors that can induce vWF secretion. DDAVP stimulation can lead to three- to five-fold increase in plasma levels of vWF. Platelet activation and degranulation will also lead to a release of stored vWF (Laffan et al. 2004).

The vWF monomer has 4 N terminal D domains (D1, D2, D', D3), then 3 A domains (A1, A2, A3) followed by another D domain (D4), a B domain, and three terminal C domains (C1, C2, CK). VWF has three main functions, the first of which is binding and stabilizing FVIII. FVIII binds to the vWF N terminal D′-D3 domains. Its second function is interaction with platelets through glycoprotein GP Ibα expressed on the platelet surface. Platelet GP Ibα interacts with the vWF A1 domain. Third, vWF can bind to collagen in the subendothelium. Collagen-binding sites on vWF are in the A3 or A1 domains (Schneppenheim and Budde 2011). The vWF-cleaving protease, ADAMTS13, cleaves vWF in the A2 domain (Crawley et al. 2011).

VWF is a key molecule in hemostasis as it interacts with all three of its subsystems. It interacts with vascular wall collagen in cases of trauma or other causes of denudation of the vascular lining; it provides the landing strips for platelets by binding to their GP 1bα, thereby immobilizing them in the subendothelial matrix; and it stabilizes plasmatic FVIII. Similarly to fibrinogen, vWF plays a role in both primary and secondary hemostasis.

Endothelial cells release vWF as long chains of covalently linked dimers. These multimers are degraded by ADAMTS13 as they circulate. As the molecules decrease in size, they become less "sticky" (Schneppenheim and Budde 2011).

11.2.3.3 Indications

11.2.3.3.1 Acquired Deficiency

Unlike other coagulopathies, such as fibrinogen or FXIII deficiencies, where acquired deficiencies are more frequent than inherited forms, acquired vWS is less frequent than its congenital variant. By 2000, fewer than 200 cases had been reported (Sucker et al. 2009). Based on those figures and the author's personal experience, underreporting is very likely. Acquired vWS has been described in association with underlying disorders including myeloproliferative disorders (where affected cells may bind and consume vWF), lymphoproliferative disorders (autoantibodies against vWF), other neoplasms, autoimmune disorders, cardiovascular disorders (vWF consumption due to aortic stenosis, i.e., Heyde syndrome), and drug effects (hydroxyl-ethyl starch is reported to reduce vWF antigen (vWF:AG), but interference with vWF function is also possible) (Mohri 2006; Federici et al. 2013). A high frequency of a new form of acquired vWS has been associated with patients using ventricular assist devices. The supposed mechanism is the mechanical destruction (versus the action of ADAMTS13) of the molecule (Dassanayaka et al. 2013). Interestingly, in the context of acute bleeding, consumption of vWF without any of the underlying disorders cited above is a rarely reported problem. This clearly distinguishes vWF from fibrinogen, which is the first molecule to reach critical levels in acute bleeding. This is possibly due to vWF's multiple production sites (megakaryocytes in bone marrow, endothelial cells) and storage pools (platelets, endothelial cells).

11.2.3.3.2 Congenital Deficiency

VWS is the most frequent congenital bleeding disorder, with a population frequency of approximately 1 % (Schneppenheim and Budde 2011). It can be categorized into three subtypes (Federici 2009a; Favaloro 2011):

- Partial quantitative deficiency or type I vWS
- Qualitative vWF deficiency or type II vWS (several type II forms are distinguished)
- Virtually complete quantitative deficiency or type III vWS

Regarding the perioperative assessment of bleeding risk and prophylactic measures, a distinction needs to be made between "real" vWS patients and those with low vWF levels related to other factors, including the association of low vWF with blood group O. However, in the context of acute bleeding, all these patients may potentially benefit from vWF substitution.

11.2.3.4 Monitoring

Perioperatively, vWF testing should be based on pretest probability. If a validated bleeding questionnaire is positive, then preoperative hemostasis testing is indicated (Tosetto et al. 2006). VWF:AG, vWF ristocetin cofactor (vWF:RCo), and their ratio are sufficient to detect most of the clinically relevant manifestations of vWS.

Historically, vWF:AG was the first to be measured. This can be done manually using ELISA technology, but also using modern tests. The discovery that ristocetin could agglutinate platelets was used to design the first functional vWF:RCo test. Large vWF molecules tend to have vWF:RCo to vWF:Ag ratios of close to 1. When vWF consumption increases, due to a stenotic heart valve, for example, there is an increased proportion of smaller, less "sticky" vWF molecules, and the vWF:RCo to vWF:Ag ratio will drop. Ratios of less than 0.70 are considered indicative of acquired vWS or forms of congenital type II vWS, characterized by qualitative vWF defects.

Exact subtyping of vWS can be done by specialized laboratories capable of measuring vWF collagen-binding capacity (vWF:CB), vWF FVIII-binding capacity (vWF:FVIII), and performing vWF multimer (vWF:MM) analysis (Laffan et al. 2004; Sucker et al. 2009).

11.2.3.5 Efficacy and Safety

In the perioperative setting, there are no RCT-based treatment algorithms available for either congenital or acquired vWF deficiencies. With regard to safety, it must be noted that vWF concentrates contain both vWF and FVIII. When substituting vWF, it must be remembered that over substitution of vWF may be associated with an increased risk of venous and arterial thromboembolism (VTE and ATE). Furthermore, in a vWF-deficient patient who is substituted using concentrates, the previously normal or even increased FVIII level (FVIII is an acute phase reactant) will be boosted by the concentrate. This may result in supranormal levels of FVIII, which are similarly associated with VTE and ATE (Federici 2009a, b). The relative content of vWF:RCo to FVIII varies depending on the product. For Haemate P®, the ratio is 2.5 to 1. The ratio is lower for other concentrates, with a minimum ratio of 1.1 to 1 (Federici 2005).

In the 1980s, cryoprecipitate and DDAVP were the only available treatment options for vWS patients. Cryoprecipitate is poorly standardized, and not all patients are responsive to DDAVP; thus, initial attempts were made toward

standardizing factor concentrates. The mid-1980s catastrophe of plasmatic products contaminated with hepatitis B, hepatitis C, and human immunodeficiency virus shocked both patients and treating physicians alike (Alter et al. 1972; Evatt et al. 1985; Kuo et al. 1989). The catastrophe led to the introduction of viral inactivation methods (Alter and Klein 2008), followed by donor screening in the 1990s (Vamvakas and Blajchman 2009). These steps dramatically reduced the risks associated with plasmatic products down to current levels of less than 2 cases per 100,000 (Legler et al. 2000).

11.2.3.6 Dosing

Treatment of vWS aims to correct the deficient adhesion of platelets to the subendothelium and to redress FVIII deficiency if necessary. Dosing recommendations are mostly based on similarities to congenital vWF deficiency contexts and some limited experience with acquired vWS (AvWS) (Federici 2005; Franchini 2008; Tiede et al. 2011). As a rule of thumb, substitution of 1 IU of vWF (RCo) per kg bodyweight will raise vWF activity by approximately 2 %. VWS acquired due to severe aortic stenosis (Heyde syndrome) or other valvular defects is probably one of the most frequent forms of AvWS. Either no substitution or a single preoperative dose of Haemate P® 500–1,000 IU IV can be considered (not evidence based, in line with (Mohri 2006; Federici et al. 2013) and personal experience). Once a defective heart valve has been replaced, vWF levels return to normal and within hours the bleeding diathesis will disappear. As in other indications, the severity of the AvWS, the clinical context (active bleeding or not, previous bleeding complications), and potential treatment complications, particularly thromboembolism, must be taken into consideration. Treatment thresholds and targets are discussed later in Sect. 11.3. There are differing vWF concentrates on the market. They can be categorized according to purification method, viral inactivation, vWF:RCO to vWF:AG ratio, vWF:RCO to FVIII ratio, and vWF MM content (Franchini 2008). The one for which most experience exists is Haemate P®. The pharmacokinetics of concentrates may also show interindividual variability (Kessler et al. 2011).

11.2.3.7 Key Points and Prospects

There is a lack of RCT data for vWF concentrates in the perioperative setting.

11.2.4 Prothrombin Complex Concentrates

11.2.4.1 Background

Prothrombin complex concentrates (PCC) were historically also referred to as PPSB. This latter abbreviation summarized the four coagulation factors: prothrombin (FII), proconvertin (FVII), Stuart–Prower factor (FX), and antihemophilic factor B (FIX). The first description of PCC dates back to more than 50 years ago when Didisheim described the preparation of this human plasma fraction and its potential application in humans (Didisheim et al. 1959). Surgenor described the original isolation procedure – barium sulfate elution – in 1959, and methodology improved over the

following years. In 1965, Tullis reported on the clinical use of prothrombin complexes in the New England Journal of Medicine (Tullis et al. 1965). First reports on the adverse thromboembolic effects of PCC led to the addition of heparin (Kasper 1975; Menache 1975). When cases of PCC-associated transmission of hepatitis B and further thromboembolism-associated deaths were described, an international task force was convened. This led to products being retracted from the market, stronger regulation regarding isolation procedures, product surveillance regarding the contamination by activated coagulation factors, the addition of inhibitors (antithrombin, protein C, and protein S) to the products, viral inactivation procedures, and a formal recommendation by the European Medicines Agency (EMEA) regarding minimal and desired potencies for the various factors (Hellstern 1999; Hellstern et al. 1999).

11.2.4.2 Description

PCC are subdivided into two major categories based on their composition: three-factor concentrates (containing FII, FIX, and FX – some contain traces of FVII) and four-factor concentrates (containing all four factors, FII, FVII, FIX, and FX). PCC were originally intended for the treatment of hemophilia B or hereditary deficiency of FIX. In view of this, PCC were "labeled" according to their FIX content. Most current PCC contain 500 or 600 IU of FIX per vial and thus have this figure in their brand name. Procedures aimed at increasing product safety are frequently carried out (and an appropriate suffix added to the product name), such as nanofiltration (N or NF or F), pasteurization (P), solvent detergent treatment (SD or D), and vapor and/or heat (VH or T). It is important to know that PCC from different producers differ significantly in their relative and absolute content of the various coagulation factors (Samama 2008; Sorensen et al. 2011a). Based on the variable yield achieved during production, different lots from the same producer also vary in composition, which is the reason why their factor content is generally indicated as a range and not a single figure.

A further categorization of PCC is possible based on whether or not activated coagulation factors are included in the formulation. Current PCC, registered for most of the indications noted below, are nonactivated PCC. Activated PCC (aPCC) represent a formulation that was designed and intended for use with hemophilia patients who had acquired antibodies directed against the coagulation factor that they had a deficiency for – so-called inhibitor patients. Factor eight inhibitor bypassing agent (FEIBA) is the only registered plasma-based aPCC. It contains FII, FIX, and FX, primarily but not solely in their nonactivated forms, and FVII largely in its activated form (FVIIa) (Cromwell and Aledort 2012).

11.2.4.3 Indications

11.2.4.3.1 Acquired Disorders

Most coagulation factors are synthesized in the liver, including FII, FVII, FIX, and FX. After synthesis in the hepatocyte, they are modified prior to secretion into the blood stream. One of the modification steps is mediated by γ carboxylase, the vitamin K-dependent enzyme that is the site of action of vitamin K antagonists.

Acquired deficiencies of FII, FVII, FIX, and FX can occur for several reasons, including (1) coagulation inhibition due to vitamin K antagonists (VKA), (2) coagulation factor consumption in the context of coagulopathy or uncontrolled bleeding, (3) inhibition of coagulation by direct anticoagulants, and (4) other rare causes.

The most frequent cause of an acquired prothrombin complex deficiency is the use of VKA. Approximately 1 % of the population is estimated to be anticoagulated at any given time. In randomized trials for atrial fibrillation, the bleeding risk of patients treated by VKA ranged from 1.3 to 4.2 % per year (Wiedermann and Stockner 2008).

Coagulation factor consumption in uncontrolled bleeding will lead to a critical prothrombin complex factor deficiency after loss of approximately 200–240 % of the calculated blood volume (Hiippala et al. 1995). Coagulation factor consumption can also occur in the absence of active blood loss, e.g., in disseminated intravascular coagulopathy.

While the reversal of VKA effects on coagulation is a well-established indication for PCC, the data on PCC use to reverse the effects of novel oral anticoagulants (NOAC), including direct FIIa inhibitors (dabigatran) and direct FXa inhibitors (including apixaban, edoxaban, rivaroxaban, and others), is only now emerging (Eerenberg et al. 2011). The FEIBA aPCC has recently been included in European guidelines for the treatment of NOAC-related bleeding (Kozek-Langenecker et al. 2013). However, to date, no RCTs have been published on PCC or aPCC use in actively bleeding patients (Siegal and Cuker 2013).

Rare causes of acquired deficiencies involving one or more factors of the prothrombin complex include severe nutritional vitamin K deficiency, an acquired inhibitor (antibody) directed against FIX in hemophilia B patients, a propeptide mutation of the FIX gene leading to pseudohemophilia B in patients treated with VKA (Ulrich et al. 2008), absorption of FX to amyloid protein in systemic AL amyloidosis, and inhibitors directed against thrombin (FIIa) in patients with the same disease (Thompson et al. 2010).

11.2.4.3.2 Congenital Disorders

The deficiency of FIX, or hemophilia B, as one of the "more" frequent congenital bleeding disorders has a frequency of 1:60,000. Since the licensing of FIX concentrates, these products have largely replaced PCC as first-line treatment of hemophilia B. In principal, however, they remain a treatment option for hemophilia B replacement therapy. In several countries, individual concentrates for "rare" coagulation disorders (less frequent than hemophilia A or B) including severe FVII deficiency (frequency $1{:}0.3–0.5 \times 10^6$), FX deficiency (frequency 1×10^6), and FII deficiency (frequency $1{:}2 \times 10^6$) are not readily available or do not exist. For these conditions, three- and four-factor PCC remain relevant treatment options for managing bleeding (Bolton-Maggs et al. 2004).

The FEIBA aPCC is indicated in hemophilia patients, particularly those who have developed inhibitors (Aledort 2008).

11.2.4.4 Monitoring

Factors II, VII, and X are key factors in determining PT; thus PT will detect deficiencies of these factors and is suitable for PCC monitoring (see Fig. 11.3). The activity and antigen levels of these three factors can also be used for this purpose. Characteristics including plasma half-lives are given in Table 11.1. FIX is a vitamin K-dependent (VKD) factor, as are the three mentioned above. However, it is not a key determinant of PT. For FIX, aPTT and FIX determinations are the sensitive tests necessary to monitor substitution.

Point-of-care (POC) technologies including rotational thromboelastometry (ROTEM) and thromboelastography (TEG), as well as other systems, can assay

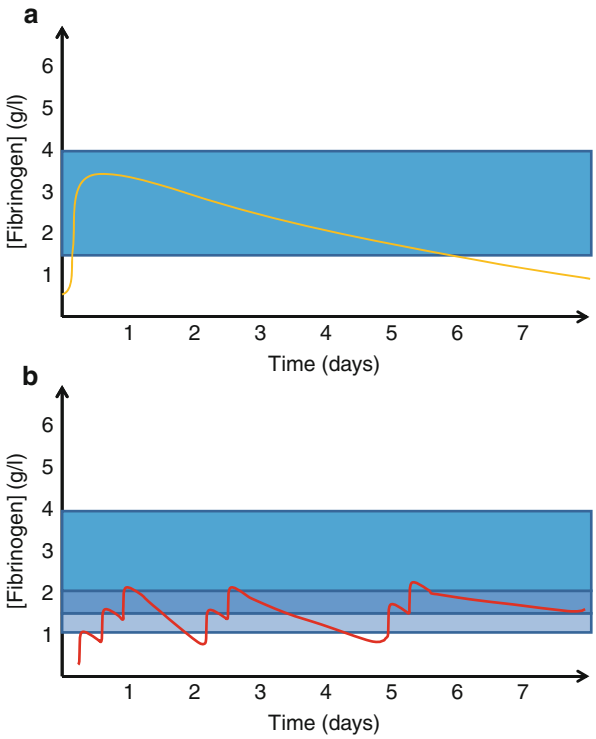

Fig. 11.3 The threshold and target question. (**a**) Depicts the time course of plasma fibrinogen concentration in a fictive patient, e.g., with hereditary afibrinogenemia (*yellow curve*). After (one big) substitution, the concentration increases into the normal range (depicted by *dark blue* area) and drops off with a half-life of approximately 72–100 h over the following days. (**b**) Illustrates the time course of a fictive perioperatively bleeding patient (*red curve*). The transfusion threshold in this example is set at 1.0 g/l (*lower border of dark blue box*) and the transfusion target at 2.0 g/l (*upper limit of light blue box*). Initially multiple (small) substitutions are needed to reach the transfusion target value. After two more instances of substitution, the fibrinogen levels stabilize as the fictive patient ceases to bleed. Note that in the acutely bleeding patient, the observed half-life of fibrinogen is initially much shorter than 72 h and only later approaches the value described under physiological conditions

Table 11.1 Factors relevant for coagulation

Name	Abbreviation	Function	MW (kDa)	µg/ml	µmol/l	IU/ml	t1/2 (h)
Fibrinogen	FI	Substrate of coagulation: forms fibrin	340	3,000	8.8235	n.a.	72–100
Prothrombin	FII	Serine protease (VKD): multiple targets	72	100	1.3889	0.60–1.40	60
Labile factor	FV	Cofactor to FX	330	10	0.0303	0.60–1.40	15
Stable factor	FVII	Serine protease (VKD): activates FX (and FIX)	50	0.5	0.0100	0.60–1.40	5
Antihemophilic factor	FVIII	Cofactor to FIX	185	0.1	0.0005	0.50–2.00	12
Christmas factor	FIX	Serine protease (VKD): activates FX	56	5	0.0893	0.60–1.40	18
Stuart–Prower factor	FX	Serine protease (VKD): activates FII	56	10	0.1786	0.60–1.40	30
Plasma thromboplastin antecedent	FXI	Serine protease: activates FIX	160	5	0.0313	0.60–1.40	45
Hageman factor	FXII	Serine protease: activates FXI	80	30	0.3750	0.60–1.40	
Fibrin-stabilizing factor	FXIII	Cross links soluble fibrin monomers ($fibrin_s$) to insoluble fibrin strand ($fibrin_i$)	320	60	0.1875	0.50–1.50	216
von Willebrand factor	vWF	Mediates platelet adhesion to collagen, stabilizes and transports FVIII	225xn	10	n.a.	0.50–2.00	10
Tissue factor	FIII	Main initiator of coagulation in vivo: cofactor to FVII/FVIIa	45	n.a.	n.a.	n.a.	n.a.

Coagulation factors I–XIII and von Willebrand factor are listed together with their abbreviation, function, molecular weight (MW), mean concentration in µg/ml and in µmol/l, reference range in IU/ml, and plasma half-life (under physiological conditions). Plasma half-life may be considerably shorter in the presence of bleeding. Tissue factor, the main initiator of coagulation in vivo, is principally a membrane-bound protein expressed on subendothelial cells. Under pathophysiological conditions it may (1) circulate bound to microparticles or monocytes, (2) circulate in truncated form as a free protein, or (3) be ectopically expressed on endothelial and other cells. Vitamin K-dependent (VKD)

FII-, FVII-, FIX-, and FX-dependent pathways. Tests targeting the "extrinsic" system (using tissue factor as the starting reagent) are available for thromboelastometric/graphic test systems. PCC influence the clotting times of such tests, including EXTEM and RapidTEG. However, as anticoagulated patients may present normal

clotting or R times in these whole blood tests, sensitivity is an issue. POC testing systems have the advantage of shorter turnaround times than routine coagulation tests. However, the fact that they generally use whole blood can have a negative impact on their sensitivity toward VKA, other anticoagulants, and possibly PCC.

11.2.4.5 Efficacy and Safety

Only a few RCTs have been published regarding the use of PCC in different settings. A French study with 59 patients evaluated two dosing regimens for urgent VKA reversal (Kerebel et al. 2013). An interesting study monitoring coagulopathic cardiac surgery patients showed reduced allogenic blood transfusion in 100 patients randomized to POC-based monitoring or standard care. The predefined treatment algorithm included PCC (Weber et al. 2012). Most of the data stems from cohort studies (Makris et al. 1997; Lubetsky et al. 2004; Riess et al. 2007; Pabinger et al. 2008).

PCC trials in an anticoagulant reversal setting have reported rates of thromboembolism, possibly related to PCC, in the percent range: approximately 1 % for VTE and up to 3 % for ATE (Majeed et al. 2012). A meta-analysis of 27 trials by Dentali reported a mean thromboembolism rate for PCC (three- and four-factor PCC combined) of 1.4 % (95 % CI 0.8–2.1 %) (Dentali et al. 2011). Sorensen reported thromboembolism in 1.5 % of PCC study patients (Leissinger et al. 2008; Sorensen et al. 2011a). The review also discusses the pathophysiology potentially related to the accumulation of coagulation factors with long half-lives, FII in particular. However, these thromboembolic complications may also be related to the underlying causes that mandate anticoagulation in the first place (Sorensen et al. 2011a). Nevertheless, thromboembolism in these settings appears to be more frequent than is observed in settings of fibrinogen or FXIII substitution.

11.2.4.6 Dosing

Clinical trials have not been able to resolve questions about the optimal dose of PCC. Doses reported in the studies cited above range from 7 to more than 80 IU/kg bodyweight. As RCT data is lacking, guidelines and other official dosing information are helpful (Makris et al. 1997; Mannucci and Douketis 2006; Weber et al. 2013). Algorithms dependent on the international normalized ratio (INR) exist. In perioperative bleeding, 20–30 IU/kg bodyweight has been suggested by a group of Austrian experts (OEGARI). The numerous confounding factors include differing target values for the INR; the fact that dosing algorithms are often based on pharmacological models which may or may not be applicable to a given patient; the question of whether the product is applied to an actively bleeding or non-bleeding patient; and the clinical context in which PCC are prescribed. Whenever possible, dosing should be standardized within institutions or clinics and should follow an evidence-based algorithm appropriate to the patient's clinical context (van Aart et al. 2006).

Factors reported to be associated with adverse outcome include repeated dosing (with potential accumulation of coagulation factors with a long half-lives, such as FII), coadministration with other coagulation products, and nonobservance of recommended infusion speeds (Pabinger et al. 2010).

11.2.4.7 Key Points and Prospects

There remains a paucity of RCT evidence on PCC. The evidence available points to a potential safety issue regarding thromboembolic events in the range of 1–3 %.

11.2.5 Recombinant Activated Factor VII

11.2.5.1 Background

Recombinant human activated factor seven (rFVIIa) was developed more than 20 years ago for hemophilia patients suffering from inhibitor formation. Antibodies directed against FVIII, or inhibitors, may complicate the treatment of hemophilia patients who are treated by FVIII products. The inhibitors may then neutralize the patient's own and the exogenous FVIII, leading to severe bleeding complications. Bypassing agents that circumvent the FIX/FVIII complex can stop bleeding in these patients. Pure plasma-derived FVIIa showed clinical efficacy in proof-of-principle experiments. Subsequently, recombinant FVIIa was developed and tested in clinical trials (Hedner 2007, 2012).

Distinguishing the clinical setting in which patients are treated with FVIIa appears relevant. On-label indications include only hypocoagulable patients. In off-label indications patients may be normo- or even hypercoagulable.

11.2.5.2 Description

FVIIa circulates in plasma and comprises approximately 1 % of the circulating plasma FVII pool. The precursor single-chain FVII molecule is synthesized in the liver and is one of the vitamin K-dependent coagulation factors. FVII is a 50 kD protein that has the shortest plasma half-life among coagulation proteins (see Table 11.1). The activation of FVII to two-chain FVIIa involves cleavage at a single peptide bond. This activation can be mediated by FXa, FVIIa itself, and other coagulation factors. By binding to surface-bound tissue factor, the enzymatic activity of FVIIa is dramatically increased. The cell surface-bound complex of calcium/tissue factor/FVIIa is capable of activating FX and FIX (Hedner and Brun 2007; Vadivel and Bajaj 2012).

Two mechanisms of action have been postulated for rFVIIa. The first is the tissue factor-mediated process described above on the surface of cells expressing tissue factor. The second is tissue factor independent and believed to occur by direct binding of FVIIa to the surface of activated platelets (Hoffman 2003; Logan and Goodnough 2010).

11.2.5.3 Indications

On-label indications include hemophilia A or B with inhibitors, congenital FVII deficiency, and acquired hemophilia. The treatment of these rare disorders goes beyond the scope of this chapter and will not be discussed in detail. Off-label indications for which clinical trial evidence exists, include body trauma, brain trauma, cardiovascular surgery, intracerebral hemorrhage, upper GI bleeding in the context of cirrhosis, liver transplantation, and hematopoietic stem cell transplantation (Logan and Goodnough 2010).

11.2.5.4 Monitoring

Monitoring of FVIIa treatment requires specialized coagulation tests. Classic coagulation tests including prothrombin time, activated partial thromboplastin time, and FVIII or FIX activity are unsuitable for this purpose. Some specialized tests, including thrombin generation tests, thromboelastography/rotational thromboelastometry, and aPTT waveform analysis, have been used (Hoffman and Dargaud 2012).

11.2.5.5 Efficacy and Safety

In the trauma setting two main studies have been published. The multicenter blunt trauma study ($n = 70$) showed a significant decrease of red blood cell transfusion and a reduced frequency of acute respiratory distress syndrome. Mortality did not differ between FVIIa and placebo in either study (Beste et al. 2012).

In the cardiovascular surgery context, two RCTs could show a significant decrease in RBC transfusion (Diprose et al. 2005; Gill et al. 2009).

In coagulopathic patients with liver disease, most RCTs showed negative results; only one study could show a reduction in RBC transfusion requirements (Bosch et al. 2004; Lodge et al. 2005; Planinsic et al. 2005; Pugliese et al. 2007; Bosch et al. 2008).

Thromboembolic complication rates of up to 11 % have been reported in the off-label setting of normo- and hypercoagulable patients (Levi et al. 2010).

11.2.5.6 Dosing

Off-label use of FVIIa requires an individualized risk–benefit assessment, with a particular focus on thromboembolic complications.

Reported dosing schemes in the on-label context range from 15 to 30 μg/kg every 4–6 h to 90 μg/kg every 2 h IV. In the off-label context, doses ranging 5–200 μg/kg were studied (Warren et al. 2007; Logan and Goodnough 2010). In cases where an off-label use appears unavoidable, it is the author's opinion that the lowest possible dose should be used (van de Garde et al. 2006; Narayan et al. 2008).

11.2.5.7 Key Points and Prospects

For on-label indications the evidence suggests efficacy and safety.

For off-label indications, few RCTs have been able to show clinical benefit. Safety is a relevant issue with thromboembolic events up to 11 %.

11.3 The Threshold and Target Question

One of the big unanswered questions in perioperative coagulation management is that of the treatment threshold. Which level is appropriate for a given parameter? For example, at which fibrinogen concentration is it indicated to substitute the patient? Some recent transfusion guidelines either do not define a threshold at all or give a wide range of thresholds (Dzik et al. 2011; Sniecinski et al. 2012).

One widely held misconception is that a test's reference range holds the answer to the threshold question. This is false: a reference range is defined in a population of healthy individuals. Ideally, the number of individuals tested is large (>20) and

the population covers both sexes and all relevant age groups. The reference range reflects the distribution of normal values for a given parameter and typically includes the central 95 or 99 % of individuals. There is no evidence to suggest that values below the lower limit of this range are associated with bleeding or that they might represent a useful threshold for transfusion in the perioperative setting.

If the reference range is not the appropriate tool to define the parameter's threshold, another procedure must be agreed upon. To address this issue, there is a need for large RCTs that show reduced mortality in transfused or substituted patients and that define thresholds. Currently, such studies are not available. In their absence, threshold levels are best defined locally. What are the important factors to consider when defining a threshold?

The threshold question is test dependent on at least three levels. Classic coagulation tests measure coagulation factor antigen or activity levels. Antigen assessments are defined by weight per volume, while activity assays test a biological function in relation to the amount of coagulation factor contained in 1 ml of plasma. It is unclear which value is the more reliable for use in a transfusion algorithm. Moreover, for a given test type, e.g., functional fibrinogen, test results can vary depending on which test kit is used. Furthermore, fibrinogen measured using the same test can vary between individual laboratory platforms.

The clinical context is another relevant factor to be considered when setting a coagulation factor threshold; threshold levels for different indications may vary. For hereditary disorders, such as afibrinogenemia or FXIII deficiency, guidelines and experts propose 0.5 g/l and 5–10 % as levels generally sufficient for hemostasis (Ciavarella et al. 1987; Anwar et al. 2002; Mannucci 2010). Recent data show that these numbers are not appropriate in states of acquired deficiency. Instead, in the setting of hypofibrinogenemia induced by acute bleeding, fibrinogen levels from 0.8 to 2.0 g/l have been proposed (Spahn et al. 2007; Rossaint et al. 2010).

Another relevant clinical factor is the hemostatic state. An actively bleeding patient with acquired fibrinogen deficiency below a given cutoff may require treatment. In the absence of bleeding, the treatment is likely to be different. Transfusion thresholds for bleeding (therapeutic intention) and non-bleeding patient populations (prophylactic intention) need to be established. If the volume of blood loss is used as the transfusion trigger, then target concentrations should be defined. In fact, Rahe-Meyer et al. published a randomized trial in major aortic surgery where the threshold for fibrinogen transfusion was defined by the volume of blood loss; the target concentration was defined for a FIBTEM MCF of 22 mm, corresponding approximately to a fibrinogen level (Clauss) of 3.6 g/l (Rahe-Meyer et al. 2013b).

The timing of testing is another complicating factor. Classic coagulation tests are performed in citrate plasma. The centrifugation of whole blood and the production of cell-free citrate plasma necessitate time. Between drawing the blood, centrifugation, and producing the test result, a turnaround time of 30–40 min is common. However, within this time span, an acutely bleeding patient's coagulation status can change dramatically, undergoing multiple transfusions and substitutions. To minimize turnaround time in acutely bleeding patients, whole blood tests have been designed utilizing POC testing devices. Fibrinogen tests exist for such POC test

devices (FIBTEM for ROTEM and functional fibrinogen for TEG). These fibrinogen tests are performed on whole blood and measure other aspects of fibrinogen than the classic coagulation tests. Because of their design as whole blood tests, POC-based tests have a higher degree of outcome variability (Okuda et al. 2003; Theusinger et al. 2010).

Large outcome-based studies are necessary to properly answer the transfusion threshold question. These studies are scarce or nonexistent for isolated coagulation factor products. In the absence of appropriate evidence, institutions should standardize their approach and define test procedures in order to optimize treatment efficacy and patient safety. Locally defined thresholds should be reevaluated regularly and changed in response to new evidence.

11.4 Conclusions and Prospects

Isolated coagulation factor concentrates including fibrinogen, FXIII, vWF, and PCC represent some of the therapeutic options for patient management in perioperative settings. Evidence based on RCT is only beginning to emerge. Safety signals include thromboembolic rates in the range of 1–3 % for PCC. These risks appear to be less important for other isolated coagulation factor concentrates. Besides safety, healthcare cost needs to be integrated into the final risk–benefit evaluation of the use of coagulation products. RCTs designed for perioperative settings and investigating predefined treatment algorithms will help define the evidence-based strategies of the future.

Key Points

With current knowledge and in the absence of RCT-based strategies, an individualized risk–benefit evaluation should be performed for every patient prior to the use of isolated coagulation factor concentrates.

Transfusion thresholds and targets depend on the clinical context (congenital versus acquired hemostatic disorders, active bleeding versus no bleeding).

Transfusion thresholds and targets need to be validated locally.

Transfusion thresholds and targets need to be established in an evidence-based context.

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Procoagulant Drugs

12

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12.1 Procoagulant Drugs

Procoagulant drugs are non-transfusional agents that are primarily used when bleeding is the consequence of a specific defect of hemostasis. In this chapter, the pharmacological properties and uses of desmopressin, antifibrinolytics, and vitamin K will be reviewed. Desmopressin, with its various procoagulant pharmacological effects, is used in the prevention and treatment of bleeding related to congenital and acquired coagulation factor deficiencies or platelet function disorders. Antifibrinolytics (inhibitors in particular steps of fibrinolysis) are the treatment of choice in bleeding caused by hyperfibrinolysis. Because of their low cost and their mild side effects, desmopressin and antifibrinolytics are also used as blood-saving agents in surgery. Vitamin K is given in states of vitamin K deficiency which lead to vitamin K deficiency bleedings. This is relevant to patients taking vitamin K antagonists in cases of urgent invasive procedures, asymptomatic and excessively elevated INR values, and bleeding.

12.2 Desmopressin

12.2.1 Description

Desmopressin is an analogue of the naturally occurring human antidiuretic hormone, vasopressin. It was first synthesized in 1967 by removing the N-terminal amino

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group and substituting L-arginine with D-arginine (DDAVP, desamino-d-arginine vasopressin; full name, 1-desamino-8-D-arginine vasopressin). This modification leads to an extensive loss of the molecule's vasopressive effect, while the duration of its antidiuretic activity is significantly prolonged. These clinically useful attributes made it the drug of choice for the treatment of central diabetes insipidus (Vavra et al. 1968; Kohler and Harris 1988; Mannucci 2008). In the 1970s, it was observed that desmopressin also raises the level of plasma coagulation factor VIII when infused into healthy volunteers (Cash et al. 1974; Mannucci et al. 1975). This effect is due to the selective binding of desmopressin to the vasopressin receptor subtype 2 (V2R). When endothelial V2R are activated, they cause cyclic adenosine monophosphate (cAMP)-mediated signaling, leading to the exocytosis of Weibel-Palade bodies, where von Willebrand factor (vWF) is stored and then released. After the administration of desmopressin, a fast increase of vWF levels in plasma can be observed. The details of the simultaneous increase of factor VIII levels in plasma are still not fully understood, although the mechanism can be explained as an indirect increase due to vWF secretion, making more factor VIII binding sites available.

The Weibel-Palade bodies also store tissue plasminogen activator (t-PA), which is released in the same way as vWF. This leads to profibrinolytic activity, as t-PA converts plasminogen to plasmin and thus initiates fibrin degradation. This activity is enhanced by fibrin binding (Irigoyen et al. 1999; Kaufmann and Vischer 2003). For that reason, the concurrent administration of tranexamic acid is discussed.

In addition to the increased vWF, factor VIII, and t-PA levels in plasma, other procoagulant mechanisms are induced by desmopressin, e.g., its effect on platelet function. It was possible to show that desmopressin enhances platelet adhesion to the subendothelium. This is unaffected by the vWF concentration in plasma. Therefore, other agonists must facilitate the adhesion of platelets; however, the mechanism of their response to desmopressin is not fully understood (Sakariassen et al. 1984; Lethagen 1997; Balduini et al. 1999). Several findings suggest that intercellular messengers, secreted by monocytes, may play a role in the hemostatic effects of desmopressin. As a consequence of the vWF release, P-selectin, a component of the membrane of Weibel-Palade bodies and an important cell adhesion molecule for thrombocytes and monocytes, is integrated in the membrane of the endothelial cells. This enhances platelet adhesion and adhesion of monocytes to the extracellular matrix of endothelial cells. Furthermore, the monocytes upregulate the expression of tissue factor through a simultaneous expression of inflammatory cytokines (Galvez et al. 1997; Pereira et al. 2003).

12.2.2 Clinical Uses

The different procoagulant pharmacological effects of desmopressin make it an oft used drug for the treatment of several congenital and acquired bleeding disorders (Mannucci 1998). It is also being evaluated as a blood-saving agent in surgery or trauma (Mannucci and Levi 2007), as recent studies have shown that red blood

cell transfusion is significantly associated with infection, ischemic postoperative morbidity, prolonged hospital stays and increased associated costs, and decreased long-term survival (Murphy et al. 2007).

12.2.2.1 Desmopressin in Inherited Bleeding Disorders (von Willebrand Disease, Hemophilia A, Factor XI Deficiency, Platelet Function Disorders)

The chief virtue of desmopressin – the direct release of vWF – has two main functions in hemostasis. VWF is an adhesion protein that redirects circulating platelets to sites of vascular injury, particularly through larger multimers, which is essential for platelet plug formation. Furthermore, in plasma it forms a complex with coagulation factor VIII, thereby protecting it from inactivation and clearance (Weiss et al. 1977; Wise et al. 1991; Sadler 1998). This accounts for its most established applications in several inherited bleeding disorders, first of all von Willebrand disease (vWD) and mild hemophilia A. The mainstay of treatment in these patients is the replacement of the deficient protein at the time of spontaneous bleeding such as hemarthrosis or mucosal bleeding or before invasive procedures are performed (Franchini 2007).

VWD is categorized into three major types with several subtypes (Favaloro 2011). In patients with type 1 vWD and baseline vWF and factor VIII levels higher than 10 IU/dL, desmopressin is most effective (Mannucci 1997). In vWD types 2A, 2M, and 2N, a variable response pattern occurs, and the decision to use desmopressin should be made based on the results of a test infusion. Its use in vWD type 2B is traditionally considered contraindicated because of the transient appearance of thrombocytopenia, but there are a few case reports where it has been used safely. Patients with vWD type 3 are usually unresponsive to desmopressin (Gralnick et al. 1986; Casonato et al. 1994; Mannucci 2001).

The magnitude of the response of factor VIII to desmopressin usually varies in patients with hemophilia A as well and is not always linked to the basal levels of factor VIII coagulant activity (FVIII:C). However, an effective application of desmopressin is only reasonable in patients with mild hemophilia A (FVIII:C >5 %). A test infusion should be carried out to assess the efficacy in each patient to be treated. Therapeutic indications must, furthermore, take into account the type of bleeding episode or surgical procedure and the factor VIII levels that must be attained and maintained. Patients with severe hemophilia A do not respond to desmopressin at all (Castaman 2008).

A number of patients with vWD and hemophilia A are unresponsive or display adverse effects to desmopressin. In these cases recombinant interleukin-11 is being tested as an alternative hemostatic agent (Ragni et al. 2013).

Although limited, data from the available literature suggest a potential role for desmopressin in patients with milder factor XI defects for the treatment of bleeding episodes and the prevention of postoperative bleeding (Franchini et al. 2009).

The increase in adhesiveness of platelets to the subendothelial matrix and the augmentation of platelet aggregation by means of desmopressin has been proved to be efficacious in platelet function disorders (Cattaneo 2002). Independently of their classification (Podda et al. 2012), these are characterized by impaired platelet-dependent

hemostatic functions, associated with bleeding diatheses of varying severity, and manifested in mild to severe mucocutaneous bleeding. Due to the rarity and heterogeneity of these disorders, results of the treatment with desmopressin are only reported in a few case series and have not been corroborated by means of thorough clinical trials (Coppola and Di Minno 2008). The types of inherited platelet function disorder for which some evidence of the efficacy of desmopressin has been shown include delta-storage pool diseases, disorders of granule secretion, signal transduction disorders, thromboxane receptor deficiency, and May-Hegglin anomaly. Weaker evidence has been provided for Bernard-Soulier syndrome, Hermansky-Pudlak syndrome, and arachidonate metabolism defects. In severe platelet dysfunctions, such as Glanzmann's thrombasthenia, which is characterized by a missing or dysfunctional glycoprotein (GP) IIb/IIIa receptor on platelets, desmopressin has no clinically relevant efficacy (Nurden et al. 2012).

12.2.2.2 Desmopressin in Acquired Bleeding Disorders (Acquired vWD or Hemophilia A, Liver Cirrhosis, Uremia, Drug-Induced Platelet Disorders)

Desmopressin has been used in several acquired bleeding disorders, most importantly in acquired von Willebrand disease (AvWD) and acquired hemophilia A.

AvWD occurs in association with a variety of underlying disorders, most frequently in lymphoproliferative and myeloproliferative disorders, other malignancies, and cardiovascular disease. The bleeding pattern and the laboratory findings are similar to the congenital form of vWD. Classification, diagnosis, and the mechanism of the vWF deficiency in patients with AvWD are largely influenced by the underlying disorder or causative agent. Treatment should pursue two strategies: treating the underlying disorder if possible and treating AvWD itself (Sucker et al. 2009; Tiede et al. 2011). Desmopressin can be used to prevent and control bleeding in some patients with AvWD. However, success rates depend on the underlying disorder: they were low in cardiovascular (10 %) and myeloproliferative disorders (21 %), but higher in autoimmune (33 %), lymphoproliferative (44 %), and other neoplastic disorders (75 %) (Federici et al. 2013).

Acquired hemophilia A is a rare bleeding disorder in which patients present with bleeding episodes that are often spontaneous and life-threatening. It is caused by autoantibodies to factor VIII. While a minority of cases are associated with a variety of conditions, e.g., pregnancy, autoimmune disorders, cancers, and drugs, it occurs mostly in patients without concomitant diseases. Predictors of a clinical response to desmopressin include a low inhibitor titer (<5 Bethesda units) and a residual FVIII:C level greater than 5 % (Franchini and Lippi 2011). Current registry data reveal a good response in acquired hemophilia treated with desmopressin as a first-line agent (Baudo et al. 2012).

Desmopressin can also be used in patients with acquired platelet function disorders such as uremia, a complex metabolic disorder with a platelet dysfunction being the main factor responsible for hemorrhagic problems (Mannucci et al. 1983; Lee et al. 2010). In patients with liver cirrhosis who need invasive procedures, a benefit from treatment with desmopressin was shown several times (Burroughs et al. 1985;

Mannucci et al. 1986; Agnelli et al. 1995), but could not be confirmed in later trials (Wong et al. 2003; Pivalizza et al. 2003).

Finally, drug-induced bleeding disorders, especially if caused by antiplatelet agents, can be treated successfully with desmopressin (Levi et al. 2011). Theoretically, desmopressin could also be used in an attempt to control acute bleeding caused by novel anticoagulants (Brem et al. 2013).

12.2.2.3 Desmopressin as a Blood-Saving Agent in Surgery

Since it was first suggested in the mid-1980s that desmopressin could reduce blood loss and transfusion requirements in surgery (Salzman et al. 1986), numerous studies and several meta-analyses have proved, and failed to prove, a positive effect from its administration. One of the two latest analyses concluded that there was no convincing evidence that desmopressin minimizes transfusion or blood loss in surgical patients who do not have congenital bleeding disorders (Carless et al. 2004). The other analysis concluded that desmopressin reduces blood loss and transfusion requirements only slightly, but without a reduction in the proportion of patients who received transfusions (Crescenzi et al. 2008). Stratifying these trials into patients with a high risk of bleeding due to aspirin intake and/or a surgical intervention with expected high blood loss on the one hand and patients with a low risk of bleeding on the other, it can be shown that the use of desmopressin significantly reduces blood loss and the number of red blood cell units transfused in the high-risk group. In contrast, in subjects with low risk of bleeding, no significant benefit from using desmopressin was found (Zotz 2009).

12.2.3 Administration and Dosage

Desmopressin is usually administered by intravenous infusion and should be diluted in saline solution and slowly infused over the course of approximately 30 min. To obtain a maximum response from factor VIII and vWF, the optimal dose is 0.3 μg/kg. After 1 h the peak plasma levels are 3–5 times higher than baseline for factor VIII and almost 3–5 times higher than baseline for vWF. Half-life varies as well: in the ranges of 2–5 h for circulating factor VIII and of 6–9 h for vWF. A subcutaneous injection of 0.3 μg/kg produces a similar response, but peak plasma levels are reached more slowly. The recommended dose for children is similar to that for adults. When body weight is greater than 10 kg, the drug should be diluted in 50 mL of fluid, whereas in young patients weighing less than 10 kg, the volume of fluid should be 10 mL (Villar et al. 2002). In children under the age of 1 year, desmopressin should be used with caution because of adverse effects (see below).

The preferred route for home treatment is intranasal administration with an optimal dose of 300 μg in two puffs; in children this should be reduced to one puff. As intranasal administration elicits a slower and less marked response (maximum factor VIII level of approximately 2.5 times higher than baseline value), subcutaneous or intravenous routes of administration should be chosen if the maximum response is desired (Villar et al. 2002).

Repeated doses of desmopressin over short intervals of time are associated with a phenomenon known as tachyphylaxis – the progressively lower rises in the factor VIII and vWF levels. This must be taken into account when planning treatment for a prolonged period of time, e.g., in surgery with treatment lasting 7 days or longer. The factor VIII level should be checked daily, and blood samples should be taken 1 h after the completion of the infusion. In such cases it is particularly important to monitor the plasma sodium level (Vicente et al. 1993).

12.2.4 Side Effects and Contraindications

Desmopressin can cause side effects in about 30 % of patients, but in the vast majority of cases, these are transient and mild. Administration is frequently accompanied by headache, facial flushing, and a mild decrease in blood pressure and heart rate (Mannucci 1998). More severe, but rarer, are episodes of fluid overload, severe hyponatremia, and seizures due to the modest antidiuretic effect of the hemostatic agent. This affects mostly very young patients after the administration of several doses or patients receiving hypotonic fluids. Thus, desmopressin should be used with caution in small children and patients with congestive heart failure or renal insufficiency. Fluid intake should also be regulated.

There are reports of the occurrence of arterial thrombotic episodes associated with the use of desmopressin, but no significant difference in the frequency of venous and arterial thrombosis could be shown in cardiac, orthopedic, or other major surgeries. Nevertheless, in patients with a history of cardiovascular events or diffuse atherosclerosis, caution should be exercised when considering desmopressin treatment (Castaman 2008).

Finally, desmopressin is not contraindicated in an uncomplicated pregnancy. A recent review determined it had a good safety record and was effective in selected cases in reducing bleeding complications associated with pregnancy and childbirth (Trigg et al. 2012). However, as with all drugs, in this indication desmopressin should be used with caution.

12.3 Antifibrinolytics

12.3.1 Description

Antifibrinolytics work by inhibiting particular steps of fibrinolysis. There are three agents that have antifibrinolytic activity in humans: the kallikrein inhibitor, aprotinin, and two synthetic derivates of the amino acid lysine, tranexamic acid and aminocaproic acid. As aprotinin has been withdrawn from the world market because of safety issues (Fergusson et al. 2008), this chapter focuses on the lysine analogues that are effective alternatives and may be safer for patients (Hutton et al. 2012). Most of the clinical and efficacy data concern tranexamic acid, as it is the only available antifibrinolytic agent in some places. It also has a favorable risk-benefit ratio,

and it has been used for years in cases of most types of bleeding or surgery in patients with congenital or acquired bleeding disorders (Schulman 2012).

The antifibrinolytic amino acids tranexamic acid (*trans*-4-(aminomethyl)cyclohexane carboxylic acid) and aminocaproic acid (6-aminohexanoic acid) both operate by blocking the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin and therefore inhibiting fibrinolysis. Tranexamic acid is about ten times more potent than aminocaproic acid and binds to both the strong and weak sites of the plasminogen molecule to a higher extent (Mannucci 1998). The mechanism also has a protective effect on thrombocytes, because the inhibited conversion of plasminogen to plasmin prevents the plasmin-induced cleavage of several receptors on thrombocytes (Quinton et al. 2004).

12.3.2 Clinical Uses

Because of their mode of action, antifibrinolytic amino acids are used in disease patterns with an expected local or generalized hyperfibrinolysis. This is relevant for nonsurgical and surgical bleeding. Recent studies and reviews have shown evidence that tranexamic acid reduces blood transfusion particularly in patients undergoing nonelective surgery.

12.3.2.1 Antifibrinolytic Amino Acids in Nonsurgical Bleeding (Upper Gastrointestinal Bleeding, Bleeding in the Urinary Tract, Menorrhagia, Congenital and Acquired Bleeding Disorders)

For patients with upper gastrointestinal bleeding, clinical trials testing tranexamic acid have presented differing results. A meta-analysis from 1989 including patients with peptic ulcers, mucosal erosions, and other causes of bleeding found considerable reductions in recurrent bleeding, the need for surgery, and mortality (Henry and Oconnell 1989). When compared with a placebo, a recently prepared review demonstrated a beneficial effect of tranexamic acid on mortality, but not on bleeding or transfusion requirements (Gluud et al. 2012). As no randomized clinical trials on the benefits and harms of antifibrinolytic amino acids for upper gastrointestinal bleeding in patients with liver diseases have been conducted so far, their use in these patients can neither be recommended nor advised against (Marti-Carvajal et al. 2012).

Bleeding in the urinary tract may occur after prostatectomy resulting in hematuria. In clinical trials tranexamic acid or aminocaproic acid reduced blood loss in patients who had undergone prostatectomy by up to 50 %, as compared with a placebo. There was no reduction in mortality or the need for transfusion. In patients with bleeding from the upper urinary tract, this kind of treatment is contraindicated because of the risk of residual clots in the ureter and bladder (Mannucci 1998).

In women with heavy menstrual bleeding not induced by organic causes, tranexamic acid reduces blood loss by about 40–50 % (Bonnar and Sheppard 1996; Lukes et al. 2010).

Patients with congenital or acquired bleeding disorders may also benefit from the use of antifibrinolytic amino acids in cases of epistaxis, gingival bleeding, or menorrhagia. Furthermore, these agents are useful for the prevention of bleeding following minor surgical procedures or dental extractions (Seligsohn 2012).

12.3.2.2 Antifibrinolytic Amino Acids in Surgical Bleeding (Cardiac Surgery, Total Knee and Hip Arthroplasty, Orthotopic Liver Transplantation, Trauma)

Antifibrinolytic drugs are widely used in surgery. A 2011 review confirmed relevant reductions in blood loss and the use of allogeneic red cell transfusion when compared with placebo in adult patients scheduled for nonurgent surgery. There were no serious adverse events (particularly vascular occlusion, renal dysfunction, or death) when antifibrinolytic acids were applied (Henry et al. 2011).

The use of antifibrinolytic amino acids in surgery has been studied most thoroughly for cardiac surgery. In a meta-analysis from 2009, including 49 trials where all 3 antifibrinolytic agents were evaluated, the need for transfusion was reduced with tranexamic acid, aminocaproic acid, and aprotinin. Although aprotinin did not increase the risk of death, compared with a placebo, the point estimate was higher in the indirect comparison with tranexamic acid, there was a strong statistical trend in the direct comparison with tranexamic acid, and there were similar numbers in the direct comparison with aminocaproic acid. There was no increase in the risk of myocardial infarction with these agents (Henry et al. 2009).

In total hip and knee arthroplasty, there are currently 50 published peer-reviewed studies that evaluate the effectiveness of tranexamic acid. Meta-analyses of this literature have demonstrated that the use of tranexamic acid leads to significant reductions in both perioperative blood loss and the proportion of patients requiring postoperative transfusion (Watts and Pagnano 2012).

There is some evidence that antifibrinolytic drugs show efficacy in reducing red blood cell requirements in patients undergoing orthotopic liver transplantation. The effect depends not only on the patient's preoperative condition but also on the donor's liver quality as well as surgical conditions during the hepatectomy and anhepatic stages. Therefore, it will be important to identify patients who could benefit from prophylactic treatment in further evaluations (Sabate et al. 2012).

Along with its inhibiting function on fibrinolysis and its protective effect on thrombocytes, tranexamic acid has also been shown to modulate the inflammatory response to injury. However, the exact mechanism in surgery and trauma is as yet poorly understood (Rappold and Pusateri 2013). Studies on the use of tranexamic acid in trauma populations have only been conducted for the last few years. A recently published retrospective review (MATTERs study), including critically injured combat victims treated with tranexamic acid, demonstrated that unadjusted mortality was reduced in the group receiving tranexamic acid and the survival advantage was greatest in patients who received massive transfusions. The use of tranexamic acid was also, in an adjusted analysis, independently associated with survival (Morrison et al. 2012). A 2010 randomized prospective trial in patients

after traumatic injury (CRASH-2 trial) reported a reduction of in-hospital mortality in the group that received tranexamic acid. Furthermore, when tranexamic acid was given within 3 h of injury, mortality attributable to bleeding was reduced (Shakur et al. 2010; Roberts et al. 2011). In patients with traumatic brain injury, neither moderate benefits nor moderate harmful effects can be excluded (CRASH-2 Collaborators (Intracranial Bleeding Study) 2011). There is evidence that tranexamic acid reduces blood transfusions in patients undergoing emergency or urgent surgery (Perel et al. 2013).

12.3.3 Administration and Dosage

The half-lives of tranexamic acid and aminocaproic acid are 2.3 and 2 h, respectively. They can be administered orally (in the form of tablets or as an oral solution) or intravenously.

For the treatment of acute bleeding syndromes, due to elevated fibrinolytic activity, it is suggested that 5 g of aminocaproic acid be administered during the first hour of treatment, followed by a continuous rate of 1 g/h. This method of treatment should be continued for about 8 h or until the bleeding situation is under control. In trials regarding the reduction of perioperative blood loss, dose regimens for aminocaproic acid varied significantly. Loading or bolus doses ranged from 75 to 150 mg/kg; maintenance doses ranged from 1 to 2 g/h or 12.5 to 30 mg/kg/h infused over varying time periods (Henry et al. 2011).

The dosage recommendations for tranexamic acid are as follows: as intravenous injection in local fibrinolysis, 0.5–1 g two to three times daily, and in generalized hyperfibrinolysis, 1 g (15 mg/kg) every 6–8 h. The general recommendations for oral application are 3–4 g daily. In trials regarding the reduction of perioperative blood loss, dose regimens for tranexamic acid differed significantly with varying doses and time frames for drug administration. In trials involving cardiac surgery, the loading or bolus doses ranged from 2.5 to 100 mg/kg. The maintenance doses for these cardiac trials ranged from 0.25 to 4.0 mg/kg/h delivered over 1–12 h. A similar variation was observed in trials not involving cardiac surgery (Henry et al. 2011). Dosing of tranexamic acid must be reduced in patients with renal dysfunction.

12.3.4 Side Effects and Contraindications

The side effects of tranexamic acid and aminocaproic acid are dose dependent. They usually involve the gastrointestinal tract (nausea, vomiting, abdominal pain, and diarrhea). Headache and dizziness can also be observed. Sometimes allergic reactions may occur. No striking increase in the risk of thrombosis was observed when the drugs were used during operations (Mannucci 1998; Henry et al. 2011). The use of tranexamic acid in moderate (24 mg/kg) to high doses ($\geq$100 mg/kg) is associated with convulsive seizures after cardiopulmonary bypass (Kalavrouziotis et al. 2012; Koster et al. 2013).

12.4 Vitamin K

12.4.1 Description

Vitamin K was discovered by chance in 1929 and was immediately associated with blood coagulation. Vitamin K is a group of structurally similar, fat-soluble vitamins that cannot be synthesized by the human body, but are provided via nutrition and gastrointestinal bacterial flora. This group of vitamins includes two natural vitamers: vitamin K_1 and vitamin K_2. Vitamin K_1 – also known as phylloquinone, phytomenadione, or phytonadione – is synthesized by plants, and the highest concentration is found in leafy green vegetables. Vitamin K_2 – also known as menaquinone – constitutes the main storage form in animals and has several subtypes which differ in isoprenoid chain length. Vitamin K enables the posttranslational γ-carboxylation of coagulation factors II (prothrombin), VII, IX, and X and proteins C, S, and Z. Prothrombin and factors VII, IX, and X represent the classic vitamin K-dependent plasma clotting factors and participate in the formation of a fibrin clot. In contrast, proteins C, S, and Z are inhibitors of the procoagulant system. Protein C exerts its inhibitory activity by inactivating factors Va and VIIIa and enhances fibrinolysis with protein S as a cofactor. Protein Z serves as a cofactor for the inhibition of factor Xa by protein Z-dependent protease inhibitor (Ferland 2012).

12.4.2 Clinical Uses

The only verified area of application of vitamin K is the therapy and prevention of states of vitamin K deficiency which lead to vitamin K deficiency bleedings that cannot be cured by nutrition. This includes vitamin K prophylaxis in neonates immediately after delivery. The prophylactic administration of vitamin K to pregnant women treated with anticonvulsives, antituberculosis drugs, or coumarin derivates does not seem to prevent deficiency in the newborn infants (Puckett and Offringa 2009). Vitamin K deficiency bleeding has a low incidence in neonates and infants as well as in adults. Reasons for vitamin K deficiency in adults include chronic liver disease, short bowel syndrome, chronic inflammatory bowel disease, and biliary tract obstruction leading to poor nutrition and malabsorption of fat-soluble vitamins (De Simone and Sarode 2013). Until now, no randomized clinical trials have been conducted to assess the benefits and harms of vitamin K use for upper gastrointestinal bleeding in patients with acute or chronic liver disease. Its use in this treatment can neither be recommended nor advised against (Marti-Carvajal and Sola 2012). Impaired vitamin K synthesis can also be caused by a disturbance of gut flora by a broad-spectrum antibiotic therapy.

The most frequent reason for severe vitamin K deficiency bleeding in adults is the intake of vitamin K antagonists (coumarin derivates). Intracranial hemorrhage, for instance, is seen in up to 2 % of patients receiving these drugs and has a mortality rate as high as 79 %. Patients with superwarfarin poisoning represent special

cases. Superwarfarin, available as rodenticide, is 100 times more potent than medicinal vitamin K antagonists and has a half-life of 20–62 days (De Simone and Sarode 2013).

12.4.3 Administration and Dosage

Vitamin K can be taken orally and parenterally by means of intramuscular, intravenous, or subcutaneous injection.

A 2009 review demonstrated that a single dose (1.0 mg) of intramuscular vitamin K after birth is effective in the prevention of classic vitamin K deficiency bleeding in neonates. Oral vitamin K has not been tested in randomized trials for its effect in this indication, neither as a single nor as a multiple dose (Puckett and Offringa 2009).

In patients treated with vitamin K antagonists, there is a need for strategies to reverse the effect of the oral anticoagulation. This is the case when an urgent invasive procedure is required, when an asymptomatic patient presents with excessively elevated international normalized ratio (INR) values, or in bleeding patients. Therapeutic options include interruption of treatment with vitamin K antagonists, administration of vitamin K, and the administration of blood derivatives such as fresh frozen plasma, prothrombin complex concentrates, or even recombinant activated factor VII. The dosage of vitamin K in these indications consists of oral intake or a slow infusion of 5–10 mg of vitamin K, repeated after 12 h if necessary. This leads to an increase in coagulation factor activities within 8–16 h. The half-lives of the various vitamin K antagonists are different: 9 h for acenocoumarol, 6–42 h for warfarin, and 90 h for phenprocoumon. In phenprocoumon, additional doses of vitamin K after 3–4 days may be necessary to avoid new increases in INR and bleeding (Ageno et al. 2012). In patients with superwarfarin poisoning, major acute bleeding should be treated with prothrombin complex concentrates and intravenous vitamin K (10 mg daily for several days) followed by the administration of high doses of long-term oral vitamin K (25–50 mg daily over several months until the superwarfarin efficacy has faded away) (De Simone and Sarode 2013).

12.4.4 Side Effects and Contraindications

The side effects and contraindications of vitamin K depend on the route of administration. The main disadvantages of oral administration are that complete absorption is not certain and can be adversely affected by vomiting or regurgitation. With regard to intramuscular vitamin K administration, hematomas are possible. Intravenous vitamin K administration carries the risk of allergic and anaphylactic reactions, which might be lower when slow administration in saline solution is used, e.g., over 30 min. Subcutaneous administration exhibits a lower risk of hematoma or anaphylaxis; however, drug absorption has been shown to be inconsistent (Burke 2013).

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Patient Blood Management

13

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13.1 Introduction

Although blood transfusions may be lifesaving in critical bleeding, treatment with allogeneic blood products has been shown to be associated with increased mortality and morbidity in all surgical specialties, as well as in intensive care medicine. Ischemic complications in particular, can lead to increased morbidity after blood transfusion (Vincent et al. 2002; Malone et al. 2003; Corwin et al. 2004; Koch et al. 2006; Surgenor et al. 2006, 2009; Murphy et al. 2007; Jakobsen et al. 2012; Jans et al. 2012). The World Health Organization (WHO) urges member states to search for and apply transfusion alternatives, and to introduce individualized patient blood management programs (http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf) (Spahn et al. 2008). Existing evidence supports the use of low-hemoglobin transfusion triggers, even in patients with cardiovascular disease (Carson et al. 2012a), and shows a reduction in in-hospital mortality without influencing hospital or intensive care length of stay (Carson et al. 2012a).

Blood transfusion is one of the most expensive treatments in medicine (Shander et al. 2007, 2010; Morton et al. 2010). Summing all transfusion related costs, including long-term side effects, blood transfusion accounts for up to 5 % of the health care

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Table 13.1 The basics of patient blood management

Patient blood management
Detect and correct preoperative anemia and iron deficiency
Iron (i.v.) + ESA perioperatively
Reduce perioperative RBC loss
Meticulous surgical technique
Acute normovolemic hemodilution
Cell salvage and re-transfusion
Avoidance of coagulopathy with an individualized, goal-directed coagulation algorithm and the use of antifibrinolytics and factor concentrates
Low CVP, no hypertension, normothermia
Harness and optimize physiogical reserve of anemia
Tolerate low hemoglobin values
Administer high FiO_2
Minimize metabolic demand

ESA erythropoiesis stimulating agent, *CVP* central venous pressure, *FiO_2* inspired oxygen fraction

budget of developed countries (Morton et al. 2010). The known and hidden costs, including the treatment of side effects, have been estimated close to USD 2,000 per red blood cell (RBC) unit in the USA (Shander et al. 2010; Ferraris et al. 2012). As blood donations are generally decreasing and previously regular blood donors grow older, a shortage of blood products is predicted (Borkent-Raven et al. 2010).

The Society for the Advancement of Blood Management defines patient blood management as "the appropriate use of blood and blood components, with a goal of minimizing their use".

The aim of patient blood management is to preoperatively identify patients at risk and offer individualized therapy to decrease the likelihood of transfusion (Williams and McCarthy 2003; Goodnough and Shander 2007; Spahn et al. 2008; Gombotz et al. 2011b), thereby improving outcome, and reducing side effects and overall costs. Avoiding RBC transfusion completely by introducing a patient blood management program is not possible, nevertheless a decrease in provided and used blood products has been shown after implementation (Wells et al. 2002; Cobain et al. 2007; Gombotz et al. 2007; Moskowitz et al. 2010; Kotze et al. 2012).

Patient blood management is a multi-disciplinary approach built upon three pillars: treatment of preoperative anemia, minimizing intraoperative blood loss, and increasing tolerance of anemia (Gombotz et al. 2011a; Spahn et al. 2012) (Table 13.1). Ideally, improvements in all three are strived for, but optimizing even one pillar reduces transfusion needs drastically. In 94 % of elective interventions, intraoperative RBC transfusion needs can be predicted from the preoperative hemoglobin level, possible blood loss, and individual transfusion triggers (Gombotz et al. 2007; Gombotz 2011). In May 2010, the WHO recognized patient blood management as a significant means to improve transfusion safety, and since then it has promoted its implementation in order to improve patient care.

The following chapter provides an overview of all the aspects that have to be taken into consideration and suggests what such a program could, or should, look like.

13.2 The Adverse Effects of Blood Transfusion (Table 13.2)

One unit of RBCs transfused to adults increases the hemoglobin level by approximately 1 g/l and the hematocrit by about 3 % (Liumbruno et al. 2009, 2011).

Blood products are frequently administered to older and sicker patients, therefore causing more serious complications and various side effects. Current estimates of viral transmission via blood products are 1:280,000–1:357,000 for hepatitis B, 1:1,149,000 for hepatitis C, and 1:1,467,000 for human immunodeficiency virus (HIV) (Epstein and Holmberg 2010). Although viral and bacterial transmission via RBC units is considered to be under control in developed countries (Pomper et al. 2003; Goodnough 2005), RBC transfusion increases morbidity and mortality several fold (Klein et al. 2007; Murphy et al. 2007; Spahn et al. 2008; Jakobsen et al. 2012). Effects on mortality are most commonly seen close to the time of transfusion, but effects have been shown up to 5 years after the

Table 13.2 Complications of blood transfusion

	Complications	Author	Year
RBC's	Viral transmission	Epstein and Homberg	2010
	Cancer recurrence	Amato and Pescatori	2006
	Postoperative infections		
	TRALI	Rana et al.	2006
		Khan et al.	2007
		Chaiwat et al.	2009
	Non Hodgkin Lymphoma	Castillo et al.	2010
	Chronic lymphotic leukemia		
	Small lymphotic lymphoma		
	Alzheimer's disease	Morales et al.	2011
		de Calignon et al.	2012
	Multi organ failure	Moore et al.	1997
	Thromboembolic events		
	Myocardial infarction		
	Renal dysunction	Rogers et al.	2006
	Sepsis	Ferraris et al.	2012
FFP's	Allergic reaction	Dara et al.	2005
	TRALI, TACO	Buddeberg et al.	2008
	Infections	Toy et al.	2005
Platelets	Infections	Norda et al.	2006

RBC red blood cells, *FFP* fresh frozen plasma, *TRALI* transfusion related acute lung injury, *TACO* transfusion-associated circulatory overload

initial transfusion (Reeves and Murphy 2008a, b; Jakobsen et al. 2012). Because of transfusion-related immunomodulation (TRIM), a higher incidence of postoperative infection and cancer recurrence is observed (Amato and Pescatori 2006). Immunosuppression is caused by a decreased activity of T-cells, macrophages, and other natural killer cells. Blood transfusion is also associated with an increased risk of developing non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia, and small lymphocytic lymphoma, up to 15 years after transfusion (Castillo et al. 2010). Furthermore, it is assumed that protein misfolding diseases such as Alzheimer's disease might be transmitted through blood transfusions, however further studies need to be performed (Morales et al. 2011; de Calignon et al. 2012).

Besides an increased frequency of MOF, thromboembolic events such as myocardial infarction and stroke are correlated to blood transfusion (Moore et al. 1997).

Overall, around 4 % of RBC transfusions are associated with transfusion-related complications.

It is therefore fundamental to accept intraoperative hemoglobin levels of between 6 and 7 g/dl in order to reduce possible side effects (Spahn and Madjdpour 2006; Spahn et al. 2008). Perioperative anemia does not increase postoperative mortality or morbidity in cardiac surgery, whereas restrictive transfusion recommendations decrease complications (Moskowitz et al. 2010).

Adverse effects are directly dependent on the number of units transfused and the mean storage time (Offner 2004; Shorr et al. 2004; Koch et al. 2008; Spinella et al. 2009; Ness 2011; Tung et al. 2012). Even transfusion of a single unit has been associated with increased mortality, renal dysfunction, and sepsis (Rogers et al. 2006; Ferraris et al. 2012). Longer stored erythrocytes have significantly more harmful effects, such as increased in-hospital mortality, increased 1 year mortality, renal failure, and sepsis (Spahn et al. 2008; Belizaire et al. 2012). Ventilator associated pneumonia is increased by 1 % per day of mean storage time (Shorr et al. 2004; Bernard et al. 2009). This is due to the time-dependent metabolic, biochemical, and molecular changes undergone by stored RBCs. These include: adenosine triphosphate (ATP) depletion; bioactive generation of histamine, cytokines, and lipids; reduction of nitric oxide; and a decrease of 2.3-diphosphoglycerate leading to a left-shift of the oxyhemoglobin dissociation curve (Chin-Yee et al. 1997; Offner 2004; Raat et al. 2005). Further, stored RBCs have a higher inflammatory potential, due to increased vascular endothelial growth factor levels; they are also stiffer. Increased hemolysis of aged RBCs after massive transfusion has recently been shown in a guinea pig model. Cell-free, plasma hemoglobin led to vascular injury and renal insufficiency (Upile et al. 2009; Urner et al. 2012). Hemoglobin toxicity was prevented by co-infusion of haptoglobin, showing possible protective effects (Urner et al. 2012).

Unfortunately it is not yet clear exactly when negative effects occur, though a storage time over 14 days has been associated with negative outcomes such as increased in-hospital mortality, renal failure, sepsis, and intubation prolonged beyond 72 h (Koch et al. 2008; Blasi et al. 2012).

Correlation between RBC transfusion and increased postoperative incidence of infections has been shown in all surgical fields (Hill et al. 2003).

Whereas the transmission of hepatitis and HIV has decreased in developed countries over the last 10 years, nosocomial infections have increased and are enhanced by 9.7 % with each unit transfused (Claridge et al. 2002; Taylor et al. 2006). The median onset of infection is around 5 days after transfusion (Rachoin et al. 2009).

Gram-positive and Gram-negative organisms were both detected more frequently in transfused patients than in non-transfused ones. Acinetobacter – a Gram-negative coccobacillus – is frequently identified (Rachoin et al. 2009).

Transfusion-related acute lung injury (TRALI) occurs once in every 1,000–4,000 units transfused (Rana et al. 2006; Khan et al. 2007; Chaiwat et al. 2009), thus being the leading cause of death correlated with blood therapy (Vamvakas and Blajchman 2010). The reaction usually starts within 6 h of transfusion. TRALI is defined by acute onset of non-cardiogenic pulmonary edema, dyspnea, fever, and hypertension. A mortality rate of 5–10 % has been reported (Popovsky et al. 1992; Gude 2012).

A great number of TRALIs are caused by antibody carrying blood products of female blood donors with a positive pregnancy history. Therefore, plasma is only accepted from female donors who have either a negative pregnancy history or negative HLA- and HNA-antibody results (Nguyen et al. 2011).

13.3 The Three Pillars of Patient Blood Management (Fig. 13.1)

13.3.1 Detection and Treatment of Preoperative Anemia: Pillar One

13.3.1.1 Definition and Risk of Perioperative Anemia

The WHO defines anemia as hemoglobin (Hb) levels below 12 g/dl in women and below 13 g/dl in men, or hematocrit (Hct) levels lower than 36 % in woman and less than 39 % in men (Goodnough 2007; Theusinger et al. 2007).

Preoperative anemia is seen in 5–75 % of patients scheduled for elective surgery (orthopedic, cardiac, visceral), depending on age, the underlying pathology, and the definition of anemia (Shander et al. 2004; Patel and Carson 2009; Gombotz et al. 2011a; Musallam et al. 2011). A reduced preoperative circulating erythrocyte mass, as estimated by the patient's hemoglobin concentration (Cosgrove et al. 1985), is also a major risk factor for perioperative RBC transfusion, and is associated with increased mortality, morbidity, and length of hospital stay (Khanna et al. 2003; Murphy et al. 2007; Isbister et al. 2011; Leichtle et al. 2011). Moreover, preoperative anemia is an independent risk factor for increased 30-day mortality in cardiac and non-cardiac surgical patients (Glance et al. 2011; Musallam et al. 2011). Even preoperative hemoglobin levels between 10 and 12 g/dl lead to a 40 % increase in

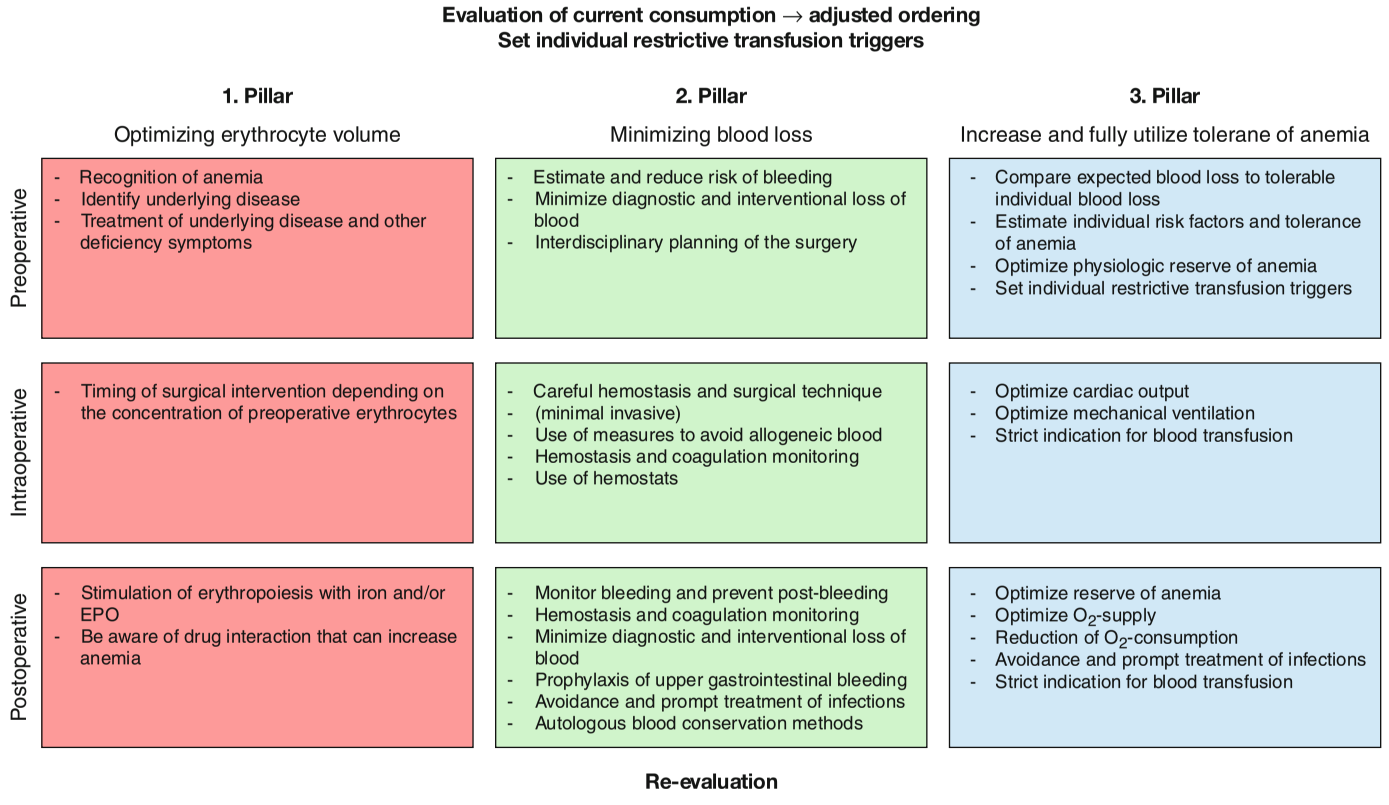

Fig. 13.1 Strategies for Pre-, per- and postoperative Patient Blood Management

mortality and a 30 % increase of morbidity. This risk is doubled when blood products are transfused (Musallam et al. 2011).

Postoperative anemia is common. Moderate postoperative anemia does, however, not influence rehabilitation (Carson et al. 2011; Vuille-Lessard et al. 2012). In order to minimize the degree of postoperative anemia or to reduce its incidence, patient blood management focuses on the detection and treatment of preoperative anemia and the reduction of RBC loss during surgery (Westenbrink et al. 2011).

13.3.1.2 Screening and Treatment of Preoperative Anemia

In addition to an in-depth coagulation history, preoperative laboratory tests need to be performed in order to detect anemia or a coagulation disorder ahead of surgery (Pfanner et al. 2007). Preferably, elective surgery is rescheduled if anemia, coagulopathy, or any other concomitant disease needs to be treated.

According to the National Blood Authority of Australia, preoperative tests include full blood count, iron studies including ferritin levels, C-reactive protein (CRP), and renal function tests. Ferritin can be elevated in malignancy, liver disease, and inflammation, therefore a thorough investigation is essential in these cases. Furthermore, gastrointestinal bleeding needs to be ruled out in patients with unexplained iron deficiency.

Correction should be achieved with intravenous iron, erythropoietin (EPO), and Vitamin B12 and/or folic acid at least 2 weeks before elective surgery. Oral iron is not absorbed during inflammatory processes due to the presence of hepcidin and patient compliance is low due to side effects (Goodnough et al. 2010). Intravenous iron, however, can be administered in much higher doses (Chang et al. 2002; Mircescu et al. 2006; Auerbach and Rodgers 2007).

Optimally, patients should be seen 4 weeks before surgery in order to increase hemoglobin levels (Gombotz et al. 2011a; Goodnough et al. 2011) up to around 15 g/dl at the time of surgery, nevertheless short-term therapy is possible and better than no therapy at all (Weltert et al. 2010; Na et al. 2011; Yoo et al. 2011). Avoiding higher hemoglobin levels is advisable in order to prevent possible thromboembolic complications (Cuenca et al. 2004). In patients with carcinoma and chronic kidney failure, hemoglobin levels should not exceed 11 g/dl (Addeo et al. 2009; Brookhart et al. 2010); this requires a close cooperation between primary care physicians and hospital staff.

Autologous donations are not very cost effective (Etchason et al. 1995; Bierbaum et al. 1999) and are associated with serious side effects such as possible mistaken identity, storage lesions, and bacterial contamination (Tokuno et al. 2012). In addition, most patients arrive at the hospital anemic after their prior donation, forcing early re-transfusion of their own RBCs (Spahn 2010). Autologous predonation has thus been abandoned in most centers, except for patients with extremely rare blood groups or multiple anti-bodies.

In summary, the first pillar calls for individual preoperative therapy to optimize the RBC mass and consequently tolerance of blood loss. Existing preoperative

anemia influences the course of diseases negatively (Endres et al. 2009). Preoperative iron treatment, as well as the use of EPO in orthopedic surgery, reduces the rate of allogeneic blood transfusions and infections (Spahn 2010). Today, 90 % of existing preoperative anemia is not treated prior to surgery with expected significant blood loss, resulting in a three to fourfold increase in the transfusion rate (2nd Austrian Benchmark study; http://www.bmg.gv.at).

13.3.2 Avoiding Intraoperative Coagulopathy: Pillar Two

13.3.2.1 Intraoperative Techniques

Optimizing intraoperative hemostasis is a multi-disciplinary task: surgical techniques and anesthesiological management are equally important. Using a harmonic scalpel, argon beam coagulation, fibrin glue, or bone wax to reduce intraoperative blood loss and thereby allogeneic blood transfusions, are just some of the surgical possibilities (Cuenca et al. 2004; Freischlag 2004; Madjdpour and Spahn 2005; Munoz et al. 2005; Spahn 2010; Emmert et al. 2011). Minimal invasive surgery is also considered to be blood saving. The patient's body position plays an important role too, as arterial and venous pressure during surgery should be kept to a minimum (Australian Patient Blood Management Guidelines). Additionally, coagulopathy due to blood loss increases the risk of mortality and morbidity (Spahn and Rossaint 2005; Hess et al. 2008).

Fluid resuscitation using Ringer's lactate and placing the patient in the Trendelenburg position are major aspects of ideal anesthesiological perioperative management. In addition, maintaining body temperature above 35 °C (to prevent coagulopathy), and controlled hypotension with a mean arterial pressure of 50–55 mmHg also reduce intraoperative blood loss (Fukusaki et al. 1997; Fukusaki and Sumikawa 2000; Theusinger et al. 2012). Maintaining postoperative mean arterial pressure between 60 and 70 mmHg is recommended (Emmert et al. 2011). Normovolemic hemodilution reduces the total amount of intraoperative RBC loss. It should be considered in patients undergoing surgery in which substantial RBC loss is anticipated (Australian Patient Blood Management Guidelines).

13.3.2.2 Pharmacotherapy

Calcium is crucial in all phases of coagulation and plasma concentration of ionized calcium should be kept between 1.15 and 1.29 mmol/l in bleeding patients (Lier et al. 2008). In lactic acidosis (blood loss, vasoconstrictions, hypoxia), plasma lactate and free ionized calcium levels are inversely related. It has been shown that acidosis affects clot firmness and is not restored by sodium bicarbonate infusion (Martini et al. 2006). Calcium is further depleted by the transfusion of citrate containing allogeneic blood products (Vivien et al. 2005). Hence, acidosis, hypothermia, and hypocalcaemia must be avoided and treated at all times.

To reduce intraoperative blood loss, the Western Australian Blood Authority recommends the use of perioperative vasoconstrictors such as diluted epinephrine in

combination with local anesthesia. Topical agents, like collagen or thrombin, are additional means of reducing intraoperative blood loss (Achneck et al. 2010).

Other blood saving techniques include catecholamine administration and the application of systemic antifibrinolytics, such as aminocaproic acid or tranexamic acid (Gombotz 2011). Both compounds are synthetic lysine analogues that inhibit fibrinolysis by blocking the lysine-binding site on plasminogen, thus preventing fibrin from binding to plasminogen (Holcomb 2004; Zufferey et al. 2006).

13.3.2.3 Blood Products

Although fresh frozen plasma (FFP) is administered in massive bleeding due to multifactor deficiency, for the reversal of vitamin K antagonist, and for treating thrombotic thrombocytopenic purpura, the clinical effect of FFP transfusion remains unproven (Stanworth et al. 2004; Spahn et al. 2007; Yang et al. 2012).

Various adverse effects are connected with the administration of FFP: allergic reactions, TRALI, transfusion-associated circulatory overload (TACO), and transmission of infectious pathogens. Furthermore, a threefold increase of nosocomial infections has been reported (Dara et al. 2005; Toy et al. 2005; Buddeberg et al. 2008). Up to now, the administration of FFP has been reliant on trust in expert opinion alone. Despite this, large quantities of FFP (>15 ml/kg body weight) are recommended in cases of massive bleeding (Ho et al. 2005; Gajic et al. 2006; Spahn et al. 2007; Theusinger et al. 2009), given that a 1:1 ratio of plasma to RBCs is connected with a decreased mortality in massively transfused trauma patients (Nunez and Cotton 2009).

Furthermore it is suggested that freshly thawed plasma, in contrast to post thawed storage, is endothelium-protective in shock (Pati et al. 2010). It should be noted that 1 ml/kg body weight of plasma, leads only to an increase of coagulation factors of 1 %.

The indication of transfusing platelets should be restrictive because of the high risk of bacterial contamination of platelet concentrates (1:2,000–1:8,000) (Norda et al. 2006). So far only expert opinions are available. Nevertheless, in bleeding patients platelets should be kept over 50×10^9/l, and over 100×10^9/l in patients with traumatic brain injuries (Rossaint et al. 2006, 2010; Spahn et al. 2007). By administering one platelet concentrate containing 3×10^{11} platelets, platelet count is increased by $20–40 \times 10^9$/l in a healthy adult patient.

13.3.2.4 Monitoring

Point of care (POC) monitoring devices, such as TEG® (Haemonetics® Corporation, Braintree, MA, USA) or ROTEM® (TEM® International GmbH, Munich, Germany), are increasingly used to monitor coagulation in vivo. Hemostatic tests are performed on whole blood, evaluating platelet interaction with coagulation factors in all three phases of coagulation: initiation, propagation, and lysis of the clot (Ganter and Hofer 2008; Theusinger et al. 2010). Because the results are shown in real time, clinicians can distinguish between surgical bleeding, hemostasis disorders, and hyperfibrinolysis, and assess the extent of dilutional coagulopathy.

The results of POC tests can guide the transfusion of blood products or the administration of coagulation factors. The use of a POC, goal directed transfusion algorithm improves outcomes in cases of massive hemorrhage (Spahn et al. 2008, 2012; Ganter and Spahn 2010; Gorlinger et al. 2011; Liumbruno et al. 2011; Young et al. 2011; Theusinger et al. 2014).

Ideally, coagulation should be monitored using viscoelastic POC tests before and after therapy, and 30 min after every administration of Factor XIII (Fibrogammin®). Figure 13.2 illustrates just one possible means of handling massive bleeding in a clinical setting and needs to be adjusted to local recommendations. The early use of coagulation factors combined with POC testing leads to a reduction of RBC transfusions, decreased incidence of thrombotic events, and better outcomes (Gorlinger et al. 2011; Weber et al. 2012). Finally, the intraoperative collaboration between anesthesiologists and surgeons can reduce intraoperative blood loss up to 50 % (Filicori et al. 2010; Zwart et al. 2010).

13.3.3 Low Hemoglobin Transfusion Triggers: Pillar Three

Due to a correlation between physical symptoms and the amount of blood loss, the American Society of Anesthesiologists (ASA) recommends using physiological transfusions triggers to identify transfusion needs (Ferraris et al. 2011; Carson et al. 2012a). Examples are tachycardia, hypotension, mixed venous oxygen pressure of less than 32 mmHg, electrocardiogram (ECG) changes, oxygen extraction greater than 50 %, or an increase in lactate (Madjdpour and Spahn 2005; Spahn and Madjdpour 2006; Ferraris et al. 2007) (Table 13.3). With hyperoxic ventilation in patients with critical hemoglobin values, tissue oxygenation is not impaired (Meier et al. 2004; Weiskopf 2010). Thus a high fraction of inspired oxygen (FiO_2) is a possible bridge until blood products are available (Weiskopf 2010).

Low hemoglobin transfusion triggers should be applied. While the use of restrictive transfusion triggers has not been shown to increase adverse outcomes, a reduction in the RBC transfusion and infection rate can be found, leading to decreased mortality and overall cost (Carless et al. 2010; Carson et al. 2012a). If cardiovascular comorbidities are treated preoperatively, postoperative hemoglobin values of 8 g/dl in orthopedic patients are well tolerated (Grover and McManus 2006).

The individual minimal hematocrit depends on the patient and his/her comorbidities. In general surgical patients, hemoglobin levels of <7 g/dl are tolerated (Carless et al. 2010), and <8 g/dl is accepted in high risk patients (Carson et al. 2011, 2012b). Elderly patients without cardiovascular disease tolerate hemoglobin values of 9 g/dl (Spahn et al. 1996).

Diagnostic	Intervention
Preoperative history 1. Drugs affecting coagulation - Antiplatelet drugs - Heparin - Oral anticoagulation (Vit. K antagonists, Xa antagonists, IIa antagonists) 2. Coagulation status? 3. HIT II?	ROTEM® after anesthesia induction - Transplant surgery - Cardiac and vascular surgery - Difficult cancer surgery - Liver insufficiency - Intra-abdominal sepsis - Emergency room entry
Blood loss > 50% with diffuse bleeding	
ROTEM® analysis - EXTEM, INTEM, FIBTEM, APTEM - HEPTEM in heart and vascular surgery	Target values - Normothermia (Temp. > 35°C) - Normocalcemia (Ca >1.15 mmol/l) - No acidosis (pH > 7.2) - Hematocrit > 0.21 - Hypotension (MAP 55–60 mmHg) Crystalloid and/or colloid volume substitution
FIBTEM < 7 mm	Fibrinogen 2–4 g iv (maximal 3×2g), after a total of 6 g give FXIII
INTEM (CT and CFT prolonged) and HEPTEM normal OR ACT pathological and heparinase ACT normal	Protamine sulfate 1:1 to heparin crystalloid and colloid volume substitution
EXTEM/INTEM: Decrease of MCF after maximum was reached APTEM: normal ⇨ HYPERFIBRINOLYSIS	Tranexamic acid - 15 mg/kg BW as bolus iv - 1–2 mg/kg/h during surgery iv as perfusion
On-going diffuse bleeding	
EXTEM/INTEM MCF < 40 mm CT EXTEM/INTEM normal MCF FIBTEM < 7 mm Hematocrit > 0.21 MCF FIBTEM > 7 mm Platelets < 50 G/L (< 100 G/L in cardiac surgery or in patients suffering from traumatic brain injury) Coagulation test incl. F XIII, F V, INR, PT, aPTT	Fibrinogen up to 6 g, followed by Factor XIII 15 U/kg BW crystalloid and colloid volume substitution Platelet concentrates Target of Factor XIII: > 60% (Factor XIII 15 U/kg BW) Target of Factor V: > 20% (in particular in liver insufficiency /trauma or intra-abdominal sepsis: 2–4 U FFP)
On-going diffuse bleeding	
Quick's value < 30% and Factor V > 20% OR EXTEM/INTEM: CT, CFT prolonged	4 factor prothrombin complex concentrate 1000–2000 IU - Factor II, VII, IX and X Depending on the patients' body weight
In case of massive transfusion	Target Hematocrit: 0.21–0.24
In massive diffuse bleeding continues and	
Treated acidosis Treated hypothermia Hypocalcaemia excluded Hematocrit: 0.21–0.24 DIC excluded Fibrinogen was substituted Platelets > 50 G/L (> 100 G/L in cardiac surgery or in patients suffering from traumatic brain injury)	Recombinant Factor VIIa 60 µg/kg Body weight iv A second dose of 60 µg/kg Body weight iv can be given again after 2–4 hours, if bleeding has not completely stopped.

Fig. 13.2 Second version of the transfusion algorithm of the University Hospital of Zürich 2012©, Switzerland with permission from Theusinger et al. (2014)

Table 13.3 Physiologic transfusion triggers

Physiologic transfusion triggers
Cardiopulmonary symptoms
Tachycardia
Hypotension
Dyspnea
Decrease in blood pressure of unknown origin
Ischemic ECG changes
Cardiac arrhythmia
ST elevation or deviation
Echocardiographic signs of myocardial dysfunction
Global indices of inadequate oxygenation
Increase in global oxygen extraction >50 %
Decreased oxygen uptake of >10 % of initial value
Decreased mixed venous oxygen saturation <50 %
Decreased central venous oxygen saturation <60 %
Decreased mixed venous oxygen partial pressure <32 mmHg
Lactic acidosis

Lauscher et al. (2012)

13.4 Implementation of Patient Blood Management

In recent years, the doctrine for resuscitation of patients suffering from massive bleeding has changed from a supportive treatment with crystalloids/colloids and RBC units, to a standardized massive transfusion protocol (Young et al. 2011). In 2002, the Province of Ontario, Canada, introduced the pioneering Ontario Nurse Transfusion Coordinators Provincial Blood Conservation Program (ONTraC). A decrease of RBC transfusion of 14–24 % was noticed 1 year after implementation (Freedman et al. 2005). To date, based on decreased mortality and morbidity, patient blood management programs have shown themselves to be efficient in all medical fields, in various countries (Moskowitz et al. 2010; Spahn 2010; Goodnough et al. 2011; Kotze et al. 2012).

Western Australia's patient blood management program is probably the best known: it is very well organized and administered by the state government and all major hospitals are included.

By carrying out RBC transfusion only when there is no other alternative and thus reducing the use of blood products, health care costs are reduced. Due to improved collection, testing and processing, the direct costs of blood products have progressively increased (Kamper-Jorgensen et al. 2010; Abraham and Sun 2012). As stated in the introduction, the known and hidden costs have been estimated to be USD 2,000 (Ferraris et al. 2012; Shander et al. 2010) per RBC unit. USD 1.62 to USD 6.03 million per year and hospital are spent on transfusion

related activities in surgical specialties only. Only 30 % of patients who have their blood-typed and screened eventually receive peri- or postoperative transfusions. These non-transfused patients contribute substantially to overall costs (Shander et al. 2010). The introduction of a patient blood management program significantly reduces the prevalence of anemia, transfusion rates, the length of hospital stays, and re-admission rates, while also reducing costs (Kotze et al. 2012; Spahn et al. 2012).

The patient blood management paradigm shift in transfusion medicine (Farrugia 2011) not only saves lives, but reduces health care costs (Spahn et al. 2012). It should be therefore part of good clinical practice.

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Part II

Per-operative Hemostasis

Perioperative Coagulation in Cardiovascular Surgery

14

Fabrizio Gronchi and Marco Ranucci

14.1 Introduction

The evolution of scientific knowledge in cardiac surgery and cardiopulmonary bypass (CPB) has enabled the reduction of perioperative complications, despite an increase in patient-related risks and in the complexity of surgical procedures. However, the management of hemostasis and coagulation remains a difficult issue, and it is of note that the rates of allogeneic blood transfusion and surgical revision in bleeding patients have not declined in recent years. It is widely recognized that allogeneic blood transfusion carries risks of increased morbidity and mortality (Koch et al. 2006) and that there is a wide difference in transfusion thresholds and practice among hospitals. Transfusion is a controversial issue in cardiac surgery, and there are still gaps in knowledge with respect to indications, efficacy, and even safety.

It is currently recognized that a restrictive transfusion policy, guided by point-of-care (POC) tests, significantly reduces the number of transfused packed red blood cell (RBC) and fresh frozen plasma (FFP) units. Restrictive transfusion strategies do not alter perioperative morbidity (Hajjar et al. 2010) or postoperative quality of life.

A number of risk factors help identify patients at high risk of receiving transfusions, including:

- Chronic renal failure (CRF)
- Chronic heart failure (CHF)

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- Chronic obstructive pulmonary disease (COPD) in elderly patients
- Perioperative anticoagulation or antiaggregation
- Reduced RBC volume (preoperative anemia and/or small body surface)
- Complex surgery (emergency surgery, reoperation, aortic surgery, surgery other than coronary artery bypass grafting (CABG), long-lasting CPB)

Different models for predicting the transfusion risk have been proposed and validated in cardiac surgery (Magovern et al. 1996; Litmathe et al. 2003; Karkouti et al. 2006; Alghamdi et al. 2006; Ranucci et al. 2009b). The guidelines in this chapter are supported by the recommendations of the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) clinical practice guidelines on blood conservation (Society of Thoracic Surgeons Blood Conservation Guideline Task Force et al. 2011). Additional information is provided by clinical practice, expert opinions, and other guidelines and recommendations.

14.2 Preoperative Treatment with Anticoagulants and/or Antiaggregant Agents

Due to the nature of their disease, cardiac surgery patients are usually treated with anticoagulants and/or antiaggregant agents. The optimal timing for surgery on these patients is still debated, and decisions should balance the risk of thrombosis and postoperative bleeding.

A guideline to perioperative antithrombotic treatment management is summarized in Table 14.1.

14.2.1 Unfractionated Heparin (UFH) and Low-Molecular-Weight Heparins (LMWH)

In order to prevent excessive bleeding, LMWH should be stopped 12–24 h prior to surgery, given the fact that LMWH are only partially reversible by protamine (Class IIb, level of evidence C). Heparin can be reversed by protamine, making its use simple, so that intravenous infusion of UFH (in patients with unstable angina or acute coronary syndrome) is not usually stopped before surgery.

14.2.2 Oral Anticoagulants (OAC)

Patients treated with vitamin K antagonists (VKAs) are generally switched to LMWH a few days before surgery. In case of emergency surgery, VKA may be antagonized with a prothrombin complex concentrate (PCC) and vitamin K every 24 h. This treatment has largely proven its superiority over FFP (Class IIa, level of evidence B). Patients with residual VKA effects, as well as patients with poor liver function, have low levels of coagulation factors and a reduced capacity to generate

Table 14.1 Common antithrombotics seen for cardiac surgery patients

Drug	Class	Half-life (h)	Timing to surgery	Reversibility
Heparin	Thrombin and FXa inhibitor	1–1.5	Up to skin incision	Protamine
LMWH	Thrombin and FXa inhibitor	2.5–4	12–24 h	Partial, protamine
Dabigatran	Thrombin inhibitor	8–17	[a]	No
Apixaban	FXa inhibitor	8–15	[a]	No
Rivaroxaban	FXa inhibitor	9–13	24 h	No
Bivalirudin	FXa inhibitor	0.5	2 h before surgery (depending on renal function)	No, but rapidly metabolized and removed by hemofiltration
Warfarin	Vitamin K inhibitor	40	5 days before surgery	Yes, prothrombin complex, FFP
Acenocoumarol	Vitamin K inhibitor	8–11	4 days before surgery	Yes, prothrombin complex, FFP
Phenprocoumon	Vitamin K inhibitor	160	7 days before surgery	Yes, prothrombin complex, FFP
Aspirin	Cyclooxygenase inhibitor	Life of platelet	Usually not discontinued	No
Clopidogrel bisulfate	Thienopyridine ADP receptor antagonist	Life of platelet	5–7 days before surgery, Multiplate AUC >40	No
Ticlopidine hydrochloride	Thienopyridine ADP receptor antagonist	Life of platelet	7 days before surgery	No
Prasugrel hydrochloride	Thienopyridine ADP receptor antagonist	Life of platelet	7 days before surgery	No
Ticagrelor	Thienopyridine ADP receptor reversible antagonist	8–13	5 days before surgery	No
Abciximab	GP IIb/IIIa receptor antagonist	24	24 h before surgery	Fibrinogen (controversial)
Eptifibatide	GP IIb/IIIa receptor antagonist	4–6	6–12 h before surgery	Fibrinogen (controversial)
Tirofiban	GP IIb/IIIa receptor antagonist	4–6	6–12 h before surgery	Fibrinogen (controversial)

FXa activated factor X, *ADP* adenosine diphosphate, *GP* glycoprotein
[a]No data available

thrombin. For these reasons they usually require lower doses of UFH to reach and maintain adequate anticoagulation during CPB.

In recent years, VKAs have been partially replaced by novel oral anticoagulants that probably will gain even wider popularity in years to come. The most commonly used are the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban. Patients treated with these drugs cannot easily be treated with PCC, and the timing of surgery should be based on their half-life (Table 14.1).

14.2.3 Antiplatelet Therapy

14.2.3.1 Aspirin

Antiplatelet therapy has the most important role in the prevention of acute coronary syndromes. Aspirin treatment may increase perioperative bleeding and transfusion requirements; however, these side effects seem limited, and discontinuation of the treatment is not recommended. In addition, withdrawing the treatment would unreasonably increase the risk of ischemic events (Class IIa, level of evidence A).

14.2.3.2 $P2Y_{12}$ Receptor Antagonists

The optimal delay between the last dose of clopidogrel and surgery has still to be defined. The 2007 version of the STS/SCA guidelines (Society of Thoracic Surgeons Blood Conservation Guideline Task Force et al. 2007) suggested at least 5–7 days of discontinuation, but the most recent version (Society of Thoracic Surgeons Blood Conservation Guideline Task Force et al. 2011) shortened this period to 3 days. A position statement by the Canadian Cardiovascular Society (Fitchett et al. 2009) suggests at least 5 days of discontinuation, and the European guidelines from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (Task Force on Myocardial Revascularization of the European Society of, C., S. the European Association for Cardio-Thoracic et al. 2010) also confirm 5 days as the minimal discontinuation time for thienopyridine treatment for elective patients undergoing coronary surgery.

Identifying patients resistant to antiplatelet therapy may prevent unnecessarily postponing surgery; conversely, postponing patients who are strongly anti-aggregated may limit the risk of severe postoperative bleeding. A recent study using impedance aggregometry confirmed the interindividual response variability to clopidogrel bisulfate and also showed that its duration of action is not predictable (Ranucci et al. 2011). However, patients who experienced severe postoperative bleeding were identifiable using a preoperative platelet function test (Multiplate®). Therefore, it seems reasonable to test platelet function to establish clear cutoffs for surgical timing (e.g., area under the curve (AUC) <30 on receptor $P2Y_{12}$ measured on Multiplate®).

Prasugrel hydrochloride is a new-generation thienopyridine with a more pronounced effect on platelet function and no, or a very limited number of, resistant patients. It has been associated with a fourfold increase in the risk of bleeding after CABG, compared to patients on clopidogrel (Wiviott et al. 2007). It is therefore recommended to withdraw treatment 5–7 days prior to surgery, when feasible (Class IIb, level of evidence C).

Ticagrelor is a $P2Y_{12}$ receptor antagonist that does not belong to the thienopyridine family. Its action is different from clopidogrel and prasugrel; it reversibly inhibits platelet function and recovery can be expected 5 days after discontinuation (Butler and Teng 2010).

14.2.3.3 Double Antiaggregant Therapy

Double antiaggregation by aspirin and $P2Y_{12}$ inhibitors carries an increased risk of bleeding in patients undergoing CABG (Hongo et al. 2002; Yende and Wunderink 2001; Berger et al. 2008; Pickard et al. 2008; Purkayastha et al. 2006).

Continuing the treatment with aspirin and stopping clopidogrel prior to surgery are currently the best compromise between hemorrhagic and thrombotic risks (Class I, level of evidence B).

14.2.3.4 GP IIb/IIIa Inhibitors

The management of patients under GP IIb/IIIa inhibitors is more controversial; short-acting drugs, such as eptifibatide or tirofiban, can be stopped 4–6 h before surgery, whereas long-acting ones, such as abciximab, need a 24 h interval. In case of emergency surgery, some authors recommend platelet transfusion (Lemmer et al. 2000) (Class IIb, level of evidence C).

14.3 Pathophysiology of Blood Clotting Disorders Induced by CPB

The activation of the coagulation system induced by CPB is multifactorial and involves all pathways. It can lead to microthrombi formation during CPB, excess bleeding after CPB weaning, or a postoperative hypercoagulable state with an increased risk of thrombotic complications.

14.3.1 Primary Hemostasis

During CPB, a significant increase in platelet activation markers, such as granule membrane 140, P-selectin protein, PF4, and β-thrombomodulin, can be observed (De Somer et al. 2002; Vallely et al. 2009; Diago et al. 1997). Platelet dysfunction begins at the same time, with a subsequent decreased platelet response to thrombin. The dysfunction is partially due to mechanical factors (CPB circuit, aspiration, and pump interactions with platelets) and partially due to fibrinogen bound to the CPB circuit. Fibrinogen links to the GP IIb/IIIa platelet receptor and induces the release of procoagulant factors and platelet thrombin production.

Plasmin contributes to the platelet dysfunction by splitting the GP Ib receptor (de Haan and van Oeveren 1998), partially activating the platelet and rendering it less sensitive to agonists such as adenosine diphosphate (ADP) and arachidonic acid (Slaughter et al. 2001; Velik-Salchner et al. 2009). Plasmin can also activate platelets through protease-activated receptor 4 (PAR4), triggering aggregation and degranulation with the release of procoagulant factors (Mao et al. 2009; Quinton et al. 2004).

14.3.2 Secondary Hemostasis

Activation of the extrinsic pathway starts at the operative site, and in spite of the administration of heparin (aiming an ACT >400 s), the initiation of CPB induces a surge in thrombin and fibrin generation (Chandler and Velan 2003; Hunt et al. 1998) even though the level of hemostatic proteins in the plasma is decreased by 30 % at

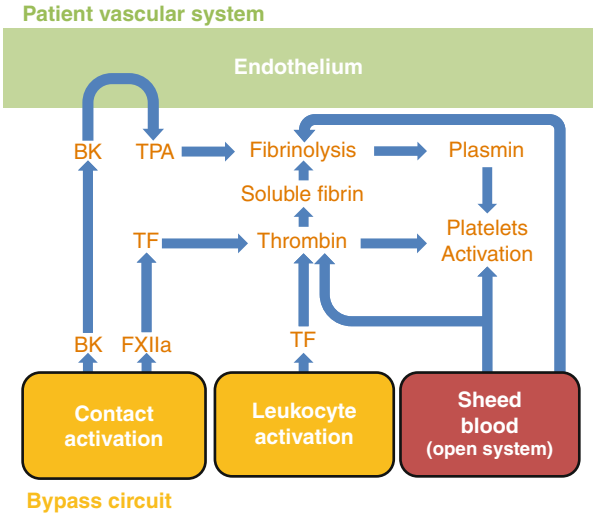

Fig. 14.1 Hemostatic activation mechanisms of cardiopulmonary bypass. *BK* bradykinin, *FXIIa* activated factor XII, *TF* tissue factor, *TPA* tissue plasminogen activator

that time. Hemodilution, blood loss, and volume replacement are responsible for this decrease, whereas the role of consumption is variable and strongly dependent on the duration of the CPB.

During cardiac operations both the extrinsic and the intrinsic coagulation pathways are activated, leading to thrombin generation (Fig. 14.1). However, thrombin generation is largely due to the release of tissue factor (TF) (De Somer et al. 2002) with the consequent activation of the extrinsic pathway. TF is expressed at the site of surgical trauma but is also expressed by platelets due to an interaction with circulating leucocytes (Chung et al. 2007). And, since inflammatory pathways, such as the complement pathway, are intrinsically linked to the hemostatic system, the CPB circuit's surface can increase the release of TF by monocytes and neutrophils. (Tabuchi et al. 2003; el Habbal et al. 1995).

After the onset of CPB, the intrinsic pathway (composed of factors XII and XI, kininogen, and prekallikrein) is activated by interaction with the artificial surfaces (Campbell et al. 2001). Factor XII is activated into factor XIIa, which converts prekallikrein into kallikrein. Kallikrein then cleaves kininogen into kinin, which has two effects: a potent hypotensive effect and a pathway amplifying effect, with a positive feedback on bradykinin production and FXII activation. Factor XII also cleaves inactive plasminogen into its active form plasmin, triggers the complement pathway, and activates FXI into FXIa, initiating the intrinsic pathway.

Prekallikrein and kininogen levels decrease during CPB not only because of hemodilution but also because of consumption and binding to the CPB circuit. On the contrary, bradykinin levels are increased tenfold, through activation of the contact system on the one hand and decreased pulmonary blood flow on the other; the lung and the kidney are responsible for bradykinin metabolism (Campbell et al. 2001).

14.3.3 Fibrinolysis

Increased levels of bradykinin enhance endothelial release of TPA. On average, TPA levels increase tenfold during CPB (Chandler et al. 2000), which in turn increase plasmin by a factor of 10–100. The result is an increase in fibrinolytic activity by a factor of 10–20 (Chandler and Velan 2004). As a consequence, the rates of fibrin generation and fibrinolysis (normally 1 %) are very similar, reflecting predominantly systemic fibrinolysis, not limited to the site of surgery. This hyperfibrinolytic state consumes fibrinogen, decreasing levels available in the postoperative phase. Conversely, during the 24 h after the operation, the patient may experience a hypofibrinolytic state, due to a 15-fold increased level of plasmin activator inhibitor 1 (PAI-1) (Chandler and Velan 2004; Freyburger et al. 1993; Lu et al. 1994). This level can further increase, carrying an associated risk of thrombosis.

14.3.4 Anticoagulation, Antithrombin III, and Protein C

During CPB, 30 % of antithrombin III (AT III) is consumed because its natural anticoagulant activity is markedly increased by UFH. Indeed, UFH increases the catalytic activity of AT III by a factor of 1,000. Inactive thrombin-antithrombin III complexes are formed and then eliminated, allowing for an effective anticoagulation during CPB. If levels of AT III are too low, heparin resistance will be observed. The clinical consequence of this will be the impossibility to reach an ACT >480 s after UFH doses of 300–400 UI/kg. Hence, it is imperative to keep AT III levels high enough to prevent excessive coagulation and inflammation activation, leading to increased bleeding and transfusions (Ranucci et al. 2005a; Paparella et al. 2009). AT III is a circulating plasma protein and can be administered through FFP; alternatively, concentrated recombinant AT III is available and reduces volume load. Although administration of recombinant AT III has proven to lower coagulation and inflammation activation, no study has been able to demonstrate any impact on postoperative bleeding and transfusion rates (Levy et al. 2002; Koster et al. 2003; Avidan et al. 2005).

While thrombin production increases during CPB, protein C activity and endothelial expression of its receptor decrease (Weiler 2010; Danese et al. 2010).

Hemodilution, negative protein C feedback on its own receptor, and negative thrombomodulin feedback on the endothelium all participate in the increase of thrombin formation.

14.3.5 Shed Blood

There also is marked activation of coagulation in shed blood, where large amounts of TF generate thrombin, activating platelets and triggering fibrinolysis (de Haan et al. 1993). Hence, the reinfusion of saved mediastinal blood can potentially

increase hemostasis activation and, as a consequence, the hemorrhagic risk. During both CPB (Class IIb, level of evidence C) and postoperatively (Class IIb, level of evidence B), the processing of mediastinal shed blood using a cell salvage device may decrease lipid emboli, decrease the concentration of inflammatory cytokines, and limit transfusions (De Somer et al. 2002).

14.4 Blood Conservation During CPB

It is currently recognized that measures that aim to reduce hemostasis activation during CPB contribute to both the decrease of preoperative microvascular bleeding and the requirement for blood transfusion (Sniecinski and Chandler 2011). Different strategies may be used to limit the deleterious effects mentioned above.

14.4.1 Avoiding Excessive Hemodilution

The nadir hematocrit in CPB has been associated with postoperative morbidity and mortality (Ranucci et al. 2005b; Karkouti et al. 2005; Fang et al. 1997; DeFoe et al. 2001). Hemodilution during CPB is dependent on the priming volume, cardioplegia volume, and any additional fluid. Any strategy aimed at limiting infused volumes will allow for a higher hematocrit during CPB and its postoperative phase and, consequently, a lower transfusion rate. Many strategies are available in order to diminish the priming volume, such as reducing the length and size of the CPB circuits (Class I, level of evidence A), using vacuum-assisted venous drainage (Class IIb, level of evidence C), and applying retrograde autologous priming (Class IIb, level of evidence B). Reducing priming volume from 1,400 to 800 ml has been proven to significatively reduce transfusion rates. Another technique available for minimizing hemodilution is modified ultrafiltration (MUF): after CPB weaning, blood is ultrafiltrated through a hemofilter connected to the venous and aortic cannulae (Class I, level of evidence A). MUF ensures not only the removal of excess water, minimizing hemodilution, but also the removal of inflammatory cytokines, resulting in a reduction of blood loss and transfusion requirements.

14.4.2 Shed Blood Management

The recuperation of pericardial or pleural shed blood can potentially contribute to saving blood units, since it returns blood and coagulation factors to the patient. Nevertheless, hemostasis, inflammation, and fibrinolysis are very active in this blood volume and if reinfused could worsen fibrinolysis and platelet dysfunction. The treatment of salvaged shed blood using a cell salvage device, which includes washing and centrifugation, reduces the activation of hemostasis and inflammation and is associated with a decrease in blood loss and transfusion rates (Wang et al. 2009) (Class IIb, level of evidence B).

14.4.3 Pumps and Circuits

Biocompatible circuits and oxygenators, by definition, decrease inflammatory responses, limit hemostasis activation, and preserve platelet function. Closed circuits are designed to reduce the foreign material contact surface and to minimize blood-air contact by suppressing the cardiotomy reservoir. When used in combination with closed systems, heparin-coated circuits allow for a reduction in the heparin dose, with loading doses of less than 300 UI/kg still achieving an ACT of at least 300 s. Two meta-analyses have confirmed the role of biocompatible circuits in reducing allogeneic transfusion (Mangoush et al. 2007; Ranucci et al. 2009a). The type of pump used in the CPB circuit may play a limited role in sparing blood. Roller pumps are occlusive pumps that sequentially compress a segment of the CPB circuit, propelling blood through the tubing. Centrifugal pumps are nonocclusive, generating blood flow by centrifugal force. This latter type of pump preserves platelet count and functions better than the former (Wheeldon et al. 1990) (Class IIb, level of evidence B). Hence, it is thought that the use of centrifugal pumps can reduce postoperative blood loss and the associated transfusion rate.

14.4.4 Anticoagulation

It is common to achieve anticoagulation for CPB by using a loading dose of 300–400 UI/kg of heparin to obtain an ACT >400 s. Yet this strategy is based more on tradition than on actual evidence. The response to an intravenous loading dose of UFH is highly variable across patients (Young et al. 1978). Individual sensitivity to heparin is influenced by nonspecific binding to plasma proteins and endothelial cells and by AT III availability (Finley and Greenberg 2013). During CPB, measurement of the plasma heparin level decay is problematic because its metabolism is altered by hemodilution and hypothermia.

ACT monitoring during CPB is essential to accurately titrate the doses of heparin and protamine. When compared with ACT-based anticoagulation management, individualized heparin and protamine management during cardiac surgery with CPB is associated with greater heparin doses, a lower protamine to heparin ratio, and reduced platelet and plasma transfusions (Despotis et al. 1995). For individualized management, heparin-ACT dose-response curves can be manually constructed by measuring the ACT at baseline and after the administration of the loading dose of heparin (Szalados 1994). The heparin concentration at the end of CPB and the protamine dose needed can then be extrapolated from the curve. Today automated devices are available that construct the patient-specific dose-response curves and calculate the appropriate doses of heparin and protamine.

One prospective randomized study has demonstrated that the target ACT can be achieved using a loading dose of 200 UI/kg and that patients having received smaller amounts of heparin suffer less postoperative blood loss (Shuhaibar et al. 2004).

Few issues are more controversial than the adequate heparin dose during cardiac surgery, with some authors supporting high-dose regimens and others suggesting heparin dose reduction through the use of closed and biocompatible circuits.

14.4.5 Fibrinolysis

The hyperfibrinolytic state induced by CPB can be attenuated by the administration of antifibrinolytic agents such as lysin inhibitors (tranexamic acid and aminocaproic acid) or nonspecific serine protease inhibitors (aprotinin). Tranexamic acid is more potent than aminocaproic acid, has a longer elimination half-life, and is the better studied agent in cardiac surgery (Ozier and Bellamy 2010). The prophylactic administration of lysin inhibitors is associated with an overall reduction in blood loss, as well as a reduction in the number of patients transfused (Class I, level of evidence A).

14.4.6 Mini Circuits

Although all of the abovementioned strategies can be applied to a conventional CPB circuit, using mini circuits can prove even more beneficial (Class I, level of evidence A). These circuits are small closed loop CPB systems with or without a flexible reservoir and driven by a centrifugal pump, minimizing hemolysis. The priming volume is less than 1,000 ml, and the surfaces are biocompatible, providing protection for blood components. Blood aspirated from the pericardial area is treated separately in a cell salvage device. The total dose of heparin needed is significantly reduced with these circuits. All these strategies, combined in a mini extracorporeal circuit, result in a 60 % decrease in the transfusion rate (Ranucci and Castelvecchio 2009).

14.5 Management of Perioperative Bleeding and Transfusion

The management of intraoperative bleeding encompasses the maintenance of adequate oxygen delivery to tissues and the specific treatment of bleeding disorders. Early intervention will prevent the occurrence of the fatal triad of hypothermia, acidosis, and coagulopathy.

14.5.1 Anemia and Transfusion Triggers

The evaluation of intraoperative bleeding consists of a visual inspection of the surgical field, the number of swabs, an estimation of aspirated blood, measurement of hemoglobin (Hb) and hematocrit (Ht), and monitoring of body tolerance to anemia. The latter is done by monitoring oxygen delivery, mixed venous oxygen saturation, and lactic acidosis. Monitoring regional cerebral oxygen saturation helps estimate brain tolerance to anemia. ST segment monitoring and evaluation of myocardial wall motion by transesophageal echocardiography estimate the heart's tolerance to anemia.

Evidence supporting packed RBC transfusion is thin, and Hb and Ht thresholds are arbitrary. Transfusion rates in cardiac surgery patients vary across different hospitals, from 10 to 95 % (Stover et al. 1998; Snyder-Ramos et al. 2008). This wide range of practice suggests that many transfusions and their related complications could have been avoided.

Clinicians nevertheless face the challenge of identifying the ideal parameter on which to base their decision to transfuse or not. Even if the prevention and treatment of inadequate tissue oxygenation are generally accepted indications, it has yet to be proven that blood transfusion actually increases oxygen delivery to the microcirculation.

Indeed, in patients with Hb of 75–85 g/l, it has been demonstrated that the transfusion of one to two blood units, when the fraction of inspired oxygen (FiO_2) is 0.4, has little effect on intramuscular oxygen partial pressure, whereas the latter is significatively increased when the FiO_2 is raised to 1.0 (Suttner et al. 2004).

Therefore, increasing FiO_2 to 1.0 is an integral part of acute anemia management.

Combining the use of transfusion thresholds with the monitoring and understanding of physiological parameters seems to be the best available tool to optimize peripheral oxygenation (Spahn et al. 2004; Madjdpour et al. 2006).

If RBC transfusion is deliberately limited, the circulating volume should still be maintained. Crystalloids and colloids will help maintain normovolemia, but care must be taken not to worsen the hemodilution. Furthermore, the choice of the solution can worsen coagulopathy, particularly in massive hemorrhage. Colloids can be responsible for a decrease in factor VIII and von Willebrand activity, as well as a decrease in platelet adhesion (Franz et al. 2001; Gallandat Huet et al. 2000).

14.5.2 Hypothermia and Acidosis

Hypothermia is relatively common in the intraoperative period and can significatively contribute to bleeding (Arthurs et al. 2006). In vitro, viscoelastic tests show a significant decrease in clot initiation and strength from temperatures below 35 °C. At less than 16 °C, the coagulation cascade is completely inactivated. On the one hand, hypothermia decreases coagulation factor activity, and on the other, it decreases platelet activation and adhesion (Rivard et al. 2005).

The development of acidosis is the result of inadequate tissue perfusion and oxygenation, and with hypothermia it synergistically worsens coagulopathy. In vitro, the effect on aggregometry of a pH <7.0 can be compared to that of hypothermia <30 °C (Engstrom et al. 2006). Acidosis worsens coagulopathy by decreasing the activity of pH-sensitive coagulation factors, such as FVIIa (activity is decreased by 90 % in an environment with pH <7.0) (Meng et al. 2003). The use of blood units and blood-derived products can aggravate acidosis due to the fact that the pH of stored products ranges from 6.0 to 7.0.

In summary, intraoperative bleeding in cardiac surgery is related to surgical trauma but can also be caused by the development of a coagulopathy; in this case, bleeding will be diffuse. The main mechanisms of the hemostasis dysfunction are:

- Preoperative use of anticoagulants or antiaggregants
- CPB-induced thrombopenia and platelet dysfunction
- Hemodilution with a decrease of procoagulant factor levels
- Increased fibrinolysis
- Insufficient neutralization of heparin after CPB weaning
- Excess protamine
- Presence of physiological anticoagulants, inducing procoagulant factor consumption
- Hypothermia and acidosis

14.5.3 Diagnosis and Treatment of Coagulopathy

Considering the complexity of the mechanisms of hemostasis and the multifactorial pattern of postoperative coagulopathy in cardiac surgery, the therapeutic pathway should be guided by the objective measurement of the various steps contributing to coagulation. The targets are to rationalize bleeding management, to tackle the underlying coagulopathy, to avoid the potentially deleterious effects of transfusion, to improve patient outcome, and eventually to control transfusion-related costs.

The first line of treatment consists of identifying patients at high risk of hemorrhage and applying strategies to decrease coagulation activation (Class I, level of evidence A).

The use of POC transfusion algorithms in the perioperative phase has been shown to better correlate with post-CPB bleeding than standard laboratory tests (Davidson et al. 2008; Cammerer et al. 2003). Algorithms including viscoelastic and platelet function tests in particular target the coagulation deficit and its specific treatment more precisely (Shore-Lesserson et al. 1999). This is currently the most efficient method of reducing transfusion after cardiac surgery and improving patient outcomes (Weber et al. 2012) (Class IIa, level of evidence C). A possible algorithm including the exploration of the viscoelastic properties of the clot and platelet function is proposed in Fig. 14.2.

The use of viscoelastic tests (TEG® or ROTEM®) reveals the specific contribution of coagulation factors, fibrinogen, and platelets in clot formation, as well as the influence of fibrinolysis or anticoagulation. It is important to keep in mind that platelet dysfunction caused by antiaggregants such as aspirin or thienopyridines is not revealed in viscoelastic coagulation tests (TEG® or ROTEM®) and will only be highlighted by platelet function tests using specific agonists.

In Germany, K. Goerlinger's team compared bleeding management guided by standard laboratory tests to bleeding management guided by thromboelastometry combined to multiple electrode impedance aggregometry (Weber et al. 2012). The latter, POC-guided, management group received significantly less RBC, FFP, and platelets. Interestingly, fibrinogen and PCC dosages were also inferior in the POC group, even though the frequency of use was comparable. Finally, The POC-guided

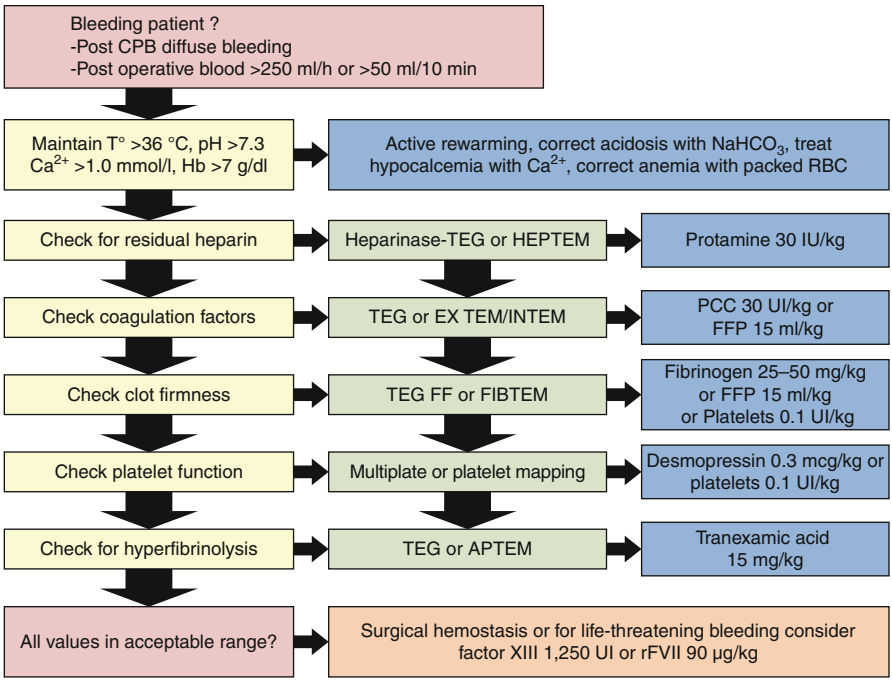

Fig. 14.2 Hemostatic therapy algorithm. *CPB* cardiopulmonary bypass, *RBC* red blood cells, *TEG* thromboelastography, *TEG FF* TEG-based functional fibrinogen assay, *EXTEM* tissue factor-activated ROTEM assay, *INTEM* ellagic acid-activated ROTEM assay, *HEPTEM* heparinized ROTEM assay, *APTEM* aprotinin-based ROTEM assay, *PCC* prothrombin complex concentrate, *FFP* fresh frozen plasma

group received less rFVIIa. The conventional group, on the other hand, showed more blood loss, a lower PaO_2/FiO_2 index, prolonged postoperative ventilation, an increased rate of undesirable events, and a higher 6-month mortality rate. These results confirm that a POC-guided approach is superior to an approach based on standard laboratory tests. Whereas standard tests provide only quantitative information on hemostasis, POCs rapidly provide qualitative information, allowing the clinician to act faster and target a specific problem.

It should be noted that, even if controlling a bleeding defect is advisable, picking out the main culprit is difficult. This is due to the multitude of potential mechanisms causing the coagulopathy. Luckily, there is rarely a need to target a single factor or specific clotting or fibrinolysis pathway. Indeed, acting on one part of the clotting pathway is often sufficient to compensate for the disorder present elsewhere in it.

Our pharmacological array allows us to promote hemostasis and fibrin formation (and to slow down fibrinolysis) by interfering in the delicate balance between coagulation activation and physiological anticoagulation (Mannucci and Levi 2007). Nevertheless, the use of pharmacological agents carries the potential risk of thrombotic complications. A transfusion algorithm is shown in Fig. 14.2.

The use of fibrinogen, factor XIII, PCC, desmopressin, recombinant factor VII, and antifibrinolytics is discussed in Chaps. 11 and 12.

14.5.4 Heparin and Protamine

Antagonization of heparin's anticoagulant effects after CPB weaning is achieved with protamine. Protamine is an alkaline arginine-rich (70 %) polypeptide extracted from salmon sperm. It neutralizes heparin by binding to its acidic sulfate group, preventing interaction with AT III. Controversy exists about which dose of protamine should be administered after CPB. Dosing regimens range from 0.8 to 1.3 mg of protamine for 100 IU of heparin. The calculation is often based on the initial or total dose of heparin, without taking its elimination into account. This can lead to a relative overdose of protamine with deleterious effects on coagulation and platelet function, since protamine itself has anticoagulant as well as antiaggregant properties. Protamine enhances endothelial release of t-PA and binds to thrombin, inhibiting its capacity to convert fibrinogen into fibrin. Furthermore, protamine-heparin complexes transiently decrease platelet count and function.

Ideally, the protamine dose should be based on the plasma heparin level (Despotis et al. 1995; Jobes et al. 1995). After protamine administration, a residual heparin effect can be caused by insufficient antagonization or heparin rebound – a reappearance of anticoagulant activity after adequate neutralization. Residual heparin effects can be responsible for pathological bleeding (Frick and Brogli 1966). Considering its low sensitivity to low plasmatic heparin concentrations, ACT is an inadequate measure for the detection of residual heparin effects. It is advisable to use specific heparinase-based tests (ROTEM® HEPTEM or heparinase-TEG®).

14.5.5 Side Effects of Protamine

The undesired effects of protamine administration are mainly hemodynamic and can be classified into three types.

The type I effect – the most frequent – is hypotension caused by mast cell release of histamine and can be prevented by injecting protamine slowly (over 5 min).

Type II effects are classified as type IIa, anaphylaxis; type IIb, nonimmune-dependent anaphylactoid reactions; and type IIc, delayed, non-cardiogenic pulmonary edema probably linked to direct drug toxicity. Although type IIa reactions can occur at any dosage and speed of infusion, careful titration is recommended with high-risk patients (past exposure to protamine, insulin-dependent diabetes treated with Hagedorn insulin, fish allergy, personal history of vasectomy) (Nybo and Madsen 2008).

A type III reaction consists of severe pulmonary vasoconstriction (probably mediated by activation of complement by pulmonary macrophages) causing acute right ventricular failure and systemic hypotension. This pulmonary hypertension can be short lived or long enough to justify going back on the CPB circuit until the hemodynamic parameters normalize. This phenomenon can be prevented by slow administration of diluted protamine.

In a case of protamine allergy, a 5 mg/kg dose of platelet factor 4 (PF4) and 5–7 mg/kg of heparinase have been proposed as alternatives for the reversal of a dose of 300 UI/kg of heparin (Dehmer et al. 1995; Michelsen et al. 1996).

When no treatment is available, omitting heparin neutralization will cause heavy bleeding (up to 5 l in 13 h (Campbell et al. 1984)) which can lead to a consumption coagulopathy. In order to reduce the need for allogeneic blood transfusion, it is recommended, in this specific case, to recycle blood collected from chest tubes in a cell salvage device.

14.6 Heparin-Induced Thrombocytopenia (HIT) in Cardiac Surgery

14.6.1 Pathophysiology of HIT

Unfractionated heparin remains the gold standard for anticoagulation in cardiac surgery, with or without CPB, given its easy titration, safety margin, reversibility, and low cost. However, its use carries the risk of developing heparin-induced thrombocytopenia (HIT). Heparin binds to PF4 and 50 % of cardiac surgery patients develop antibodies (Ab) to these heparin-PF4 complexes (anti-heparin-PF4 Ab). In 1–5 % of these patients, the anti-heparin-PF4 Ab will activate platelets by binding its Fc fragment to the platelet FcRII receptor (Warkentin et al. 2000).

The anti-heparin-PF4 Ab-mediated platelet activation and the resulting release of proclotting factors increase the production of thrombin. The continuing exposure, or reexposure, to heparin can lead to venous thrombosis (17–55 % of cases) (Warkentin and Kelton 1996; Warkentin et al. 2000) or arterial thrombosis (3–10 % of cases) (Warkentin and Kelton 1996). Although rare, it can also cause anaphylactoid reactions after intravenous injection, cutaneous necrosis at the site of injection, adrenal hemorrhage, or disseminated intravascular coagulation (DIC).

In cardiac surgery, the most common complication of untreated or unrecognized HIT is arterial thrombosis, which carries an associated mortality of 5–10 %.

14.6.2 Diagnosis of HIT

The diagnosis of HIT is based on a typical clinical presentation and the presence of anti-PF4 Ab in patients treated with UFH or LMWH (although it is ten times less frequent with the latter). HIT typically appears between the fifth and tenth day of heparin treatment or within 24 h if anti-heparin-PF4 Ab are still circulating after prior sensitization (<100 days). Less frequently, HIT can occur up to 3 weeks after the cessation of heparin. In cardiac surgery, the pattern of HIT differs from the thrombocytopenia generally seen after CPB: a patient who undergoes CPB generally experiences a platelet drop immediately on arrival in the intensive care unit; subsequently, the platelet count starts recovering, reaching preoperative values

around 5–6 days after the operation (Pouplard et al. 2005). In this setting, HIT is more often represented by a continuous drop in platelet count or a very late recovery (Pouplard et al. 2005).

An easy tool for the clinical diagnosis of HIT is the 4Ts score (Table 14.2). A low 4Ts score implies a very low probability of the patient actually having a HIT (0–0.3 %) (Lo et al. 2006; Pouplard et al. 2007); however, some patients with a high 4Ts score (24–61 %) do not have HIT at all (Lo et al. 2006; Pouplard et al. 2007). In cardiac surgery, the usefulness of the 4Ts score is limited because 2 of the 4 Ts are always present after the procedure anyway (Thrombocytopenia and other causes) and a third (Time) is unreliable.

HIT is associated with a daily thrombosis rate of 5 % (Lubenow et al. 2005). Thus, considering the long laboratory turnaround times for HIT tests and the nondiagnostic presence of isolated anti-PF4 Ab, a fast *clinical* diagnosis of HIT is imperative.

14.6.3 Treatment of HIT

After cardiac surgery, patients with strongly suspected or confirmed HIT, whether or not complicated by thrombosis, should be treated with an alternative, nonheparin anticoagulant such as danaparoid, lepirudin, argatroban, fondaparinux, or bivalirudin (Linkins et al. 2012). Any treatment with VKA must be interrupted until the platelet count has substantially recovered (usually, to at least 150×10^9/l). VKA

Table 14.2 Estimating the pretest probability of HIT with the 4Ts score: low probability, 0–3 points; moderate probability, 4–5 points; and high probability, 6–8 points

	Score = 2	Score = 1	Score = 0
Thrombocytopenia	>50 % fall or $>20 \times 10^9$/l	30–50 % fall or $10–20 \times 10^9$/l	<30 % fall or $<10 \times 10^9$/l
Timing of platelet count fall or thrombosis (day 0 = first day of most recent heparin exposure)	Platelet fall days 5–10 after start of heparin Platelet fall within 1 day and exposure to heparin within past 5–30 days	Platelet fall > day 10 Platelet fall within 1 day and exposure to heparin within past 31–100 days Platelet fall days 5–10 but not clear (e.g., missing counts)	Platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae)	Confirmed new thrombosis Skin necrosis at injection site Anaphylactoid reaction to IV heparin bolus Adrenal hemorrhage	Recurrent venous thrombosis in patient receiving therapeutic anticoagulants Suspected thrombosis (awaiting confirmation) Erythematous skin lesions at heparin injection sites	Thrombosis suspected
OTher causes of Thrombocytopenia	No alternative explanation for platelet fall is evident	Possible other cause is evident	Probable other cause is evident

therapy can only be resumed with low maintenance doses (maximum 5 mg of warfarin or 6 mg of phenprocoumon), and the nonheparin anticoagulant has to be continued until the platelet count has reached a stable plateau and the international normalized ratio (INR) has reached the intended target range. There must be a minimum overlap of 5 days between nonheparin anticoagulation and VKA therapy before the nonheparin anticoagulant is withdrawn (Linkins et al. 2012).

14.6.4 Cardiac Surgery in Patients with HIT

Patients with a history, or a severe suspicion, of previous HIT should be tested for anti-heparin-PF4 Ab. These usually disappear about 100 days after the last exposure to heparin. If anti-heparin-PF4 Ab are no longer present, cardiac surgery can be performed using standard UFH (Warkentin et al. 2008), but after receiving protamine, no further doses of heparin should be administered, and the prophylaxis of thrombotic events should be based on alternative anticoagulants. Conversely, if active antibodies are still present, the operation should be postponed (if feasible) until they disappear. An algorithm for the management of patients with HIT who need cardiac surgery is presented in Fig. 14.3.

Different strategies have been proposed for patients with active antibodies whose cardiac surgery cannot be postponed. A first possibility is to replace heparin with another anticoagulant, such as argatroban (Edwards et al. 2003; Furukawa et al. 2001), lepirudin (Koster et al. 2000a; Riess et al. 2007), or bivalirudin (Koster et al. 2000a, 2007; Dyke et al. 2007). However, caution should be applied in patients with impaired renal function, especially when bivalirudin or, in particular, lepirudin is used.

In patients with acute HIT, there is no direct evidence supporting the use of one alternative nonheparin anticoagulant over another. Although off-label, bivalirudin is

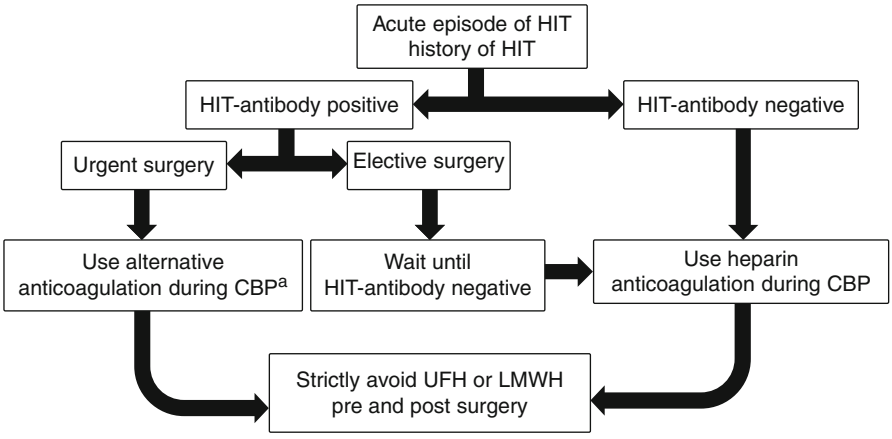

Fig. 14.3 Heparin-induced thrombocytopenia (HIT) management algorithm. *CBP* cardiopulmonary bypass, *UFH* unfractionated heparin, *LMWH* low-molecular-weight heparin. [a]See text for details

Table 14.3 Alternative anticoagulation with bivalirudin for urgent cardiac surgery in patients diagnosed with HIT

Drug	Start	Bolus	Infusion	Monitoring	Additional doses	Stop
Bivalirudin (Koster et al. 2007)	Before cannulation	1 mg/kg IV and 50 mg in CPB prime	2.5 mg/kg/min	ACT >400 s or 2.5 times of baseline value	During CPB: 0.1–0.5 mg/kg IV After weaning: 50 mg in *CPB* followed by 50 mg/h infusion	10–15 min before weaning

For details, see text

the only one that is supported by prospective multicenter cohort studies of patients with HIT, who require urgent cardiac surgery, and indirectly by small randomized heparin-controlled trials in patients without HIT (Dyke et al. 2007; Koster et al. 2007, 2009). This hirudin-derived peptide does not cross-react with anti-PF4 Ab. Bivalirudin is a reversible thrombin inhibitor with a half-life of 25 min; it is eliminated by plasmatic proteolysis and renal excretion (20 %) and can be ultrafiltrated.

Bivalirudin is administered with an initial bolus of 1 mg/kg IV, followed by an infusion of 2.5 mg/kg/h (Koster et al. 2007) (Table 14.3). Targeting an ACT >300 s (or 2.5 times the baseline), additional 0.1–0.5 mg/kg boluses can be given. The infusion should be stopped 10–15 min before weaning. In the case of CPB, 50 mg has to be added to the priming volume, and due to bivalirudin's metabolic properties, its use demands certain changes. First, surgery has to be normothermic. Second, since stasis of blood can enhance the enzymatic breakdown of bivalirudin, the following modifications of the CBP circuit are recommended:

- The use of a closed-circuit CPB when possible or replacing cardiotomy suction by a citrate anticoagulated cell saver.
- Avoiding hemofiltration during CPB.
- Inserting shunt lines from arterial filter to the cardiotomy reservoir.
- Intermittent flushing of soft venous reservoirs.
- After weaning from CPB, add a bolus of 50 mg followed by a continued infusion of 50 mg/h in the circuit.
- After weaning, once return on bypass is excluded, process the blood in the circuit with a citrate anticoagulated cell saver for reinfusion.

In the case of CABG surgery, assessments of graft patency or leakage must be performed with unheparinized normal saline. When grafting an internal mammary artery, the vessel should be transected as late as possible before grafting.

Another strategy involves combining heparin with a short-acting potent antiplatelet agent, such as a prostacyclin analog (e.g., epoprostenol, iloprost) (Antoniou et al. 2002) or a glycoprotein (GP) IIb/IIIa inhibitor (e.g., tirofiban) (Koster et al. 2000b) to attenuate platelet activation (Table 14.4). Prostacyclin analogs inhibit platelet activation by increasing adenylate cyclase activity and have very short half-lives (6 min for epoprostenol and 15–30 min for iloprost). The most important side effect reported is profound hypotension. Tirofiban has a half-life of about 2 h and is eliminated by renal and biliary excretion.

Table 14.4 Anticoagulation with platelet inhibitors and heparin for urgent cardiac surgery in patient diagnosed with HIT

Drug	Start	Bolus	Infusion	Heparin	Monitoring	Additional doses	Stop
Prostacyclin (Antoniou et al. 2002)	After induction of anesthesia	Avoid	6–12 ng/kg/min	100–300 UI/kg when HIPA negative	ACT HIPA test	Increase perfusion by 6 ng/kg/min until HIPA negative	20 min after protamine
Tirofiban (Koster et al. 2001)	Before cannulation	10 mcg/kg	0.15 mcg/min	300 UI/kg after tirofiban bolus	ACT >480 s	None	1 h before end of CPB

HIPA heparin-induced platelet aggregation

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Perioperative Hemostasis in Hepatic Surgery

15

Klaus Görlinger, Eva Schaden, and Fuat H. Saner

15.1 Coagulopathy in Liver Cirrhosis

Blood coagulation is based on complex interactions between cells and plasmatic coagulation factors, with elaborate feedback mechanisms including amplifying and inhibiting loops. It is best described by the term "hemostasis," highlighting the sensible equilibrium between pro- and anticoagulants as well as fibrinolytic and antifibrinolytic factors.

Because most the coagulation factors are synthesized in the liver, their levels are decreased in cases of chronic liver disease. This is particularly true for the vitamin K-dependent coagulation factors II, VII, IX, and X, as well as for factor V; it is also true for the vitamin K-dependent coagulation inhibitors protein C and protein S, as well as for antithrombin (Schaden et al. 2013; Tripodi and Mannucci 2011). Notable exceptions are von Willebrand factor (vWF) and coagulation factor VIII, which are synthesized in the vascular endothelium and in compensation reach elevated levels in patients with liver cirrhosis. On the other hand, the activity of the vWF-cleaving enzyme ADAMTS13 (a metalloprotease exclusively produced in hepatic stellate cells) is reduced in liver cirrhotic patients. Deficiency of ADAMTS13, particularly

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in the presence of elevated levels of large vWF multimers, increases platelet microthrombi formation and can therefore result in sinusoidal microcirculatory disturbances and subsequent progression of liver injury. This can eventually lead to multiple organ failure (Lisman et al. 2006; Pereboom et al. 2009a; Uemura et al. 2011). A marked imbalance between decreased ADAMTS13 activity and increased production of large vWF multimers has been shown to be closely related to functional liver capacity, hepatic encephalopathy, hepatorenal syndrome, and intractable ascites in advanced liver cirrhosis; it may also be useful in predicting long-term survival of cirrhotic patients (Uemura et al. 2011; Takaya et al. 2012). Therefore, some end-stage liver cirrhotic patients show conditions similar to thrombotic thrombocytopenic purpura (TTP). Besides sequestration of platelets in the spleen due to portal hypertension and subsequent hypersplenism (Al-Busafi et al. 2012; Bhavsar et al. 2012; Kedia et al. 2012), this mechanism may substantially contribute to thrombocytopenia in liver cirrhotic patients. This thrombocytopenia seems to rebalance the increased platelet adhesion and aggregation resulting from increased levels of large vWF multimers in plasma and decreased ADAMTS13 activity. Therefore, platelet transfusion should be restricted to bleeding complications since it may result in further liver damage and exacerbated portal and portopulmonary hypertension (Elias et al. 2013). Notably, platelet dysfunction and acquired dysfibrinogenemia may also occur in liver cirrhosis (Caldwell and Sanyal 2009; Math et al. 2010; Tripodi and Mannucci 2011). Furthermore, changes in pro- and antifibrinolytic drivers have been reported. Here, plasminogen and alpha$_2$-antiplasmin levels decrease while tissue-plasminogen activator and plasminogen activator inhibitor-1 levels simultaneously increase (Schaden et al. 2013; Tripodi and Mannucci 2011). Endotoxemia and subsequent tissue factor expression on monocytes are common in patients with liver cirrhosis or following liver transplantation (Esch et al. 2010). Therefore, infections can quickly result in alterations in hemostasis in cirrhotic patients by inducing disseminated intravascular coagulation (DIC) (Smalberg and Leebeek 2009; Chavez-Tapia et al. 2011b). Similar, but more pronounced changes of pro- and anticoagulant factors are observed in acute liver injury/failure (Agarwal et al. 2012), but data regarding fibrinolysis in acute liver dysfunction are inconclusive (Agarwal et al. 2012; Lisman et al. 2012a, b). Recently published data showed evidence of reduced fibrinolytic activity in acute liver failure, similar to that shown in early phase sepsis (Adamzik et al. 2010; Brenner et al. 2012; Lisman et al. 2012a, b). Taken together, blood coagulation in chronic liver dysfunction is rebalanced, even though at an earlier stage it is prone to tipping toward thrombosis or hemorrhage, depending on concomitant risk factors (Fig. 15.1) (Schaden et al. 2013; Tripodi and Mannucci 2011). Recent studies have nevertheless shown that patients with liver cirrhosis are at greater risk of thrombosis than bleeding, even if routine plasmatic coagulation tests suggest hypocoagulability (Lisman et al. 2010; Ditisheim et al. 2012; Tripodi and Mannucci 2011; Tripodi et al. 2011). Therefore, prophylactic correction of laboratory values by transfusion of blood products may have a deleterious effect on liver cirrhotic patients (Ditisheim et al. 2012; Schaden et al. 2013; Tripodi and Mannucci 2011).

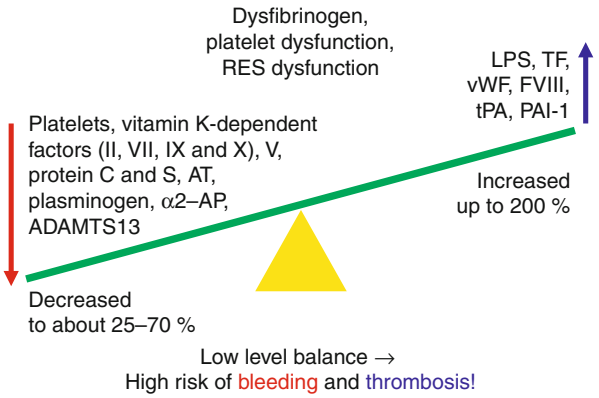


Fig. 15.1 Hemostatic changes in liver cirrhotic patients. *AT* antithrombin, *α2-AP* alpha 2-antiplasmin, *LPS* lipopolysaccharides, *PAI-1* plasminogen activator inhibitor-1, *RES* reticuloendothelial system, *tPA* tissue plasminogen activator, *vWF* von Willebrand factor

15.2 Coagulation Tests in Liver Dysfunction

In order to understand the concept of balanced blood coagulation in liver dysfunction, knowledge of the scope and limits of coagulation tests performed in central laboratories or at the point of care (POC) is essential.

15.2.1 Routine Coagulation Testing

The prothrombin time (PT) test, first described in 1935, was developed and implemented to monitor anticoagulation with vitamin K antagonists (VKA) (Owren and Aas 1951). Thromboplastins of different origin are added to recalcified citrated plasma, and the time until coagulation starts is measured. This test only reflects the activity of vitamin K-dependent procoagulant factors in plasma; it is neither capable of measuring the activity of the vitamin K-dependent anticoagulants proteins C and S, nor the complex interaction of cells and coagulation factors in whole blood (Schaden et al. 2013; Tripodi and Mannucci 2011). Due to the use of different thromboplastins, results from different laboratories are not comparable. The INR was established – and is indeed useful – to monitor anticoagulation in patients on VKA. Later, the INR was used to detect and quantify coagulopathy in many other clinical settings without ever having been validated for them, e.g., to predict bleeding in elective surgery, to guide hemostatic therapy in massive bleeding after trauma or surgery, and also to define coagulopathy in liver disease. Meanwhile, it has been shown that the correlation between INR and bleeding in patients scheduled for surgery is poor (Koscielny et al. 2004). This has been demonstrated in patients with liver cirrhosis as well (Stravitz et al. 2012; Tripodi and Mannucci 2011). In particular, no correlation could be observed between PT and the bleeding time observed directly on the liver surface during laparoscopic liver biopsy (Ewe 1981). However, the validity of the INR as a prognostic parameter in liver dysfunction is not affected by this finding (Stravitz et al. 2012).

15.2.2 Thrombin Generation Assays

Thrombin generation (TG) assays measure the endogenous thrombin potential (ETP) by adding phospholipids and thromboplastin to platelet-poor plasma: the main parameters are the lag time, velocity, and area under the reaction curve. Using this basic TG assay as a guide, TG seems to be reduced in patients with liver cirrhosis. However, the imbalance between pro- and anticoagulant activity – due to the decrease in activity of proteins C and S in liver cirrhotic patients – cannot be reflected by this basic TG assay performed in the absence of thrombomodulin. This is because the thrombin-thrombomodulin complex is essential to the activation of the protein C system (Tripodi and Mannucci 2011). Notably, results following ETP tests in patients with acute and chronic liver disease were indistinguishable from those in healthy volunteers and may even show higher TG in the presence of soluble thrombomodulin (Lisman et al. 2012a, b; Tripodi and Mannucci 2011). A similar result can be achieved by the addition of Protac® (Pentapharm, Basel, Switzerland), a snake venom that activates protein C in a manner similar to thrombomodulin (Agarwal et al. 2012; Gatt et al. 2010; Green et al. 2012; Tripodi et al. 2010). Furthermore, the results of TG assays are modified by the presence or absence of platelets (Tripodi et al. 2006). Notably, platelet factor 4 modulates the substrate specificity of the thrombin-thrombomodulin complex by selectively enhancing protein C activation, while inhibiting thrombin-activatable fibrinolysis inhibitor (TAFI) activation (Mosnier 2011). Altogether, modified TG assays can be useful for the determination of coagulation function in patients with liver dysfunction, but they have the major drawback of not being available as a routine laboratory test.

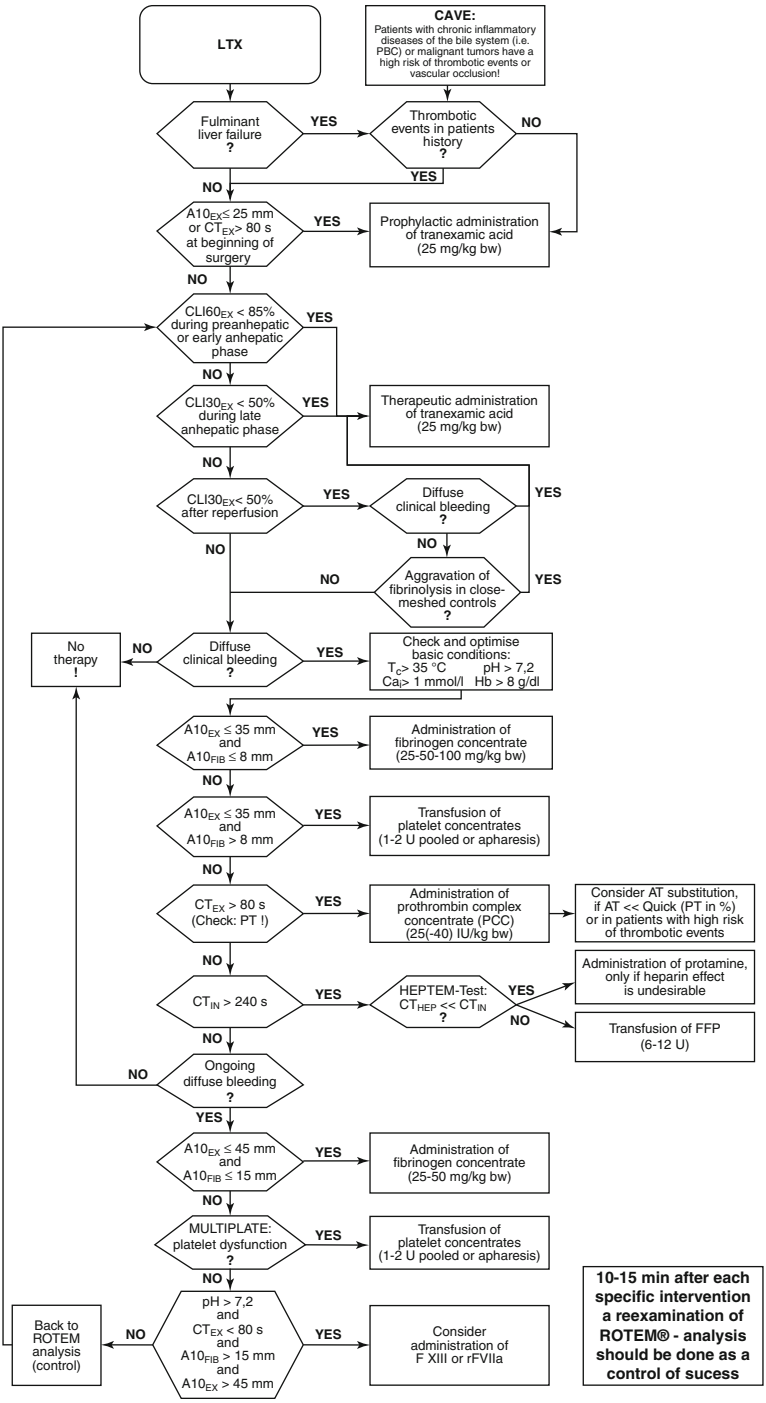
15.2.3 Viscoelastic Tests (Thromboelastometry/ Thromboelastography)

Viscoelastic tests such as thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) and thromboelastography (TEG®, Haemonetics, Niles, IL) are performed on whole blood, reflecting the interaction between blood cells (platelets, leukocytes, and erythrocytes) and plasmatic coagulation factors (pro- and anticoagulants). In addition to the dynamics of clot formation (CT, CFT, alpha angle and r time, k time, alpha angle), they provide essential information about clot firmness (A5, A10, MCF and MA) and clot stability (ML, LI30, LI60). These timely values for clot firmness (e.g., amplitude of clot firmness 5 or 10 min after CT (A5, A10)) allow for fast, reliable prediction of thromboelastometric maximum clot firmness (MCF) in patients with hypo-, normo-, and hypercoagulability; they can therefore be used to guide hemostatic therapy in severe bleeding, including patients undergoing liver transplantation (Görlinger et al. 2013). The short turnaround times of thromboelastometric tests (15–25 min) are particularly important for guiding therapy and preventing any inappropriate blood transfusions during

surgery and in intensive care units (Haas et al. 2012a, b). Furthermore, the diagnostic performance of a panel of specific reagents and additives used in thromboelastometry has been shown to be superior to mono-analysis using kaolin-based tests (Larsen et al. 2011). On the one hand, algorithms based on the use of kaolin-activated tests alone, usually lead to platelet transfusion in cases of reduced clot firmness (Larsen et al. 2011; Sakai et al. 2012). On the other hand, algorithms based on a panel of ROTEM® reagents may avoid platelet transfusion when goal-directed fibrinogen substitution is more appropriate (Figs. 15.2 and 15.3a–h) (Larsen et al. 2011; Görlinger et al. 2010, 2011a, b). This is of special importance in liver transplantation since platelet transfusion is associated with a significant reduction in 1-year survival (74 % vs. 92 %; $P < 0.001$) in this clinical setting (Pereboom et al. 2009b). Notably, viscoelastic tests showed normo- (Stravitz et al. 2012) or even hypercoagulability (Agarwal et al. 2012) in patients with acute liver failure, further challenging the bleeding tendency concept in liver dysfunction. Here, hypercoagulability seems to be better detected by whole blood thromboelastometry than by TG tests using platelet-poor plasma (Fig. 15.3a) (Tripodi et al. 2009a). Furthermore, tissue factor expression on monocytes, detected by thromboelastometry in septic patients as well as in patients undergoing liver transplantation or extracorporeal organ support, may play an important role in hypercoagulability and thrombosis in liver cirrhotic patients (Fig. 15.3b) (Adamzik et al. 2010; Esch et al. 2010; Görlinger et al. 2012a).

15.3 Bleeding Management in Patients with Liver Dysfunction or Undergoing Liver Transplantation

Following the concept of balanced hemostasis in liver dysfunction, the administration of blood products and coagulation factors in order to correct laboratory values (e.g., prior to interventions) is inappropriate (Agarwal et al. 2012; Tripodi and Mannucci 2011). Nevertheless, FFP and platelet transfusion are still used for pre-procedural prophylaxis in cirrhosis patients (Shah et al. 2012; Violi et al. 2011), and in the UK, liver cirrhosis is one of the factors associated with a greater use of prophylactic plasma transfusion (Hall et al. 2012). However, a high proportion of current FFP transfusion is of unproven clinical benefit and has to be considered inappropriate (Stanworth et al. 2011a, b). In severe bleeding, FFP transfusion is often recommended, but its risks and benefits should be assessed critically (Kozek-Langenecker et al. 2011; Tripodi et al. 2012). High amounts of FFP have to be applied for the correction of coagulopathy; this often results in increased portal pressure and subsequently leads to increased bleeding and acute lung injury (ALI) due to transfusion-associated circulatory overload (TACO). Therefore, intravenous fluid restriction, rather than prophylactic administration of large volumes of FFP, is recommended for patients with gastrointestinal bleeding or undergoing major liver surgery (Kozek-Langenecker et al. 2013; Stellingwerff et al. 2012). Moreover, transfusion-related acute lung injury (TRALI),


LTX
CAVE:
Patients with chronic inflammatory diseases of the bile system (i.e. PBC) or malignant tumors have a high risk of thrombotic events or vascular occlusion!
Fulminant liver failure ?
YES
Thrombotic events in patients history ?
NO
YES
NO
A10EX≤ 25 mm or CTEX> 80 s at beginning of surgery
YES
Prophylactic administration of tranexamic acid (25 mg/kg bw)
NO
CLI60EX < 85% during preanhepatic or early anhepatic phase
YES
NO
CLI30EX < 50% during late anhepatic phase
YES
Therapeutic administration of tranexamic acid (25 mg/kg bw)
NO
CLI30EX< 50% after reperfusion
YES
Diffuse clinical bleeding ?
YES
NO
NO
Aggravation of fibrinolysis in close-meshed controls ?
YES
No therapy !
NO
Diffuse clinical bleeding ?
YES
Check and optimise basic conditions:
T> 35 °C pH > 7,2
Ca> 1 mmol/l Hb > 8 g/dl
A10EX ≤ 35 mm and A10FIB ≤ 8 mm
YES
Administration of fibrinogen concentrate (25-50-100 mg/kg bw)
NO
A10EX ≤ 35 mm and A10FIB > 8 mm
YES
Transfusion of platelet concentrates (1-2 U pooled or apharesis)
NO
CTEX > 80 s (Check: PT !)
YES
Administration of prothrombin complex concentrate (PCC) (25(-40) IU/kg bw)
Consider AT substitution, if AT << Quick (PT in %) or in patients with high risk of thrombotic events
NO
CTIN > 240 s
YES
HEPTEM-Test: CTHEP << CTIN ?
YES
Administration of protamine, only if heparin effect is undesirable
NO
Transfusion of FFP (6-12 U)
NO
Ongoing diffuse bleeding ?
NO
YES
A10EX ≤ 45 mm and A10FIB ≤ 15 mm
YES
Administration of fibrinogen concentrate (25-50 mg/kg bw)
NO
MULTIPLATE: platelet dysfunction ?
YES
Transfusion of platelet concentrates (1-2 U pooled or apharesis)
NO
pH > 7,2 and CTEX < 80 s and A10FIB > 15 mm and A10EX > 45 mm
NO
Back to ROTEM analysis (control)
YES
Consider administration of F XIII or rFVIIa
10-15 min after each specific intervention a reexamination of ROTEM® - analysis should be done as a control of sucess

immunomodulation, increased nosocomial infection rates, and, last but not least, therapy delay due to the thawing process all have to be considered when using FFP (Pandit and Sarode 2012). Data from patients with liver cirrhosis are not available yet (Levy et al. 2012; Sørensen et al. 2011). Results obtained in cardiac surgery and liver transplantation, however, prove that when guided by POC coagulation monitoring with thromboelastometry, the administration of specific coagulation factor concentrates, like fibrinogen and 4-factor prothrombin complex concentrates, corrects coagulopathy without increasing the thrombotic risk (Fig. 15.2) (Görlinger et al. 2010; Görlinger et al. 2011a, 2012b; Kirchner et al. 2012; Weber et al. 2012). Furthermore, several other authors reported on the advantages of coagulation management guided by thromboelastometry in liver transplantation (Blasi et al. 2012; Minov et al. 2012; Noval-Padillo et al. 2010; Roullet et al. 2010; Stancheva et al. 2011; Tripodi et al. 2009b; Trzebicki et al. 2010). Platelet transfusion can also be guided by POC monitoring (Figs. 15.2 and 15.3c–d) (Larsen et al. 2011; Görlinger et al. 2010, 2011a, b, 2012a, b). However, platelet transfusion has been shown to be associated with a significant reduction in 1-year survival (74 % vs. 92 %; $P < 0.001$) in liver transplantation, independent of whether the platelet count was below or above 50/nL before platelet transfusion (Pereboom et al. 2009b). Therefore, the indication to transfuse platelets should be considered carefully. Cryoprecipitate, containing fibrinogen and factor XIII, but also vWF and factor VIII, would further increase the already high levels of the latter two, possibly contributing to a procoagulant switch with subsequent thrombosis (see below) (Dasher and Trotter 2012). Notably, the factor XIII Val34Leu mutation, either alone or in combination with the PAI-1 4G/5G mutation, has been shown to be a risk factor for an increased rate of liver fibrosis development in patients with chronic hepatitis B or C (Dik et al. 2012).

15.4 Calculated First-Line Therapy with Fibrinogen and Prothrombin Complex Concentrate Guided by Thromboelastometry

Our algorithm for thromboelastometry-guided coagulation management during liver transplantation, first published in 2006, clearly defines the indication, dosage, and sequence of each hemostatic intervention in bleeding patients (Fig. 15.2)

Fig. 15.2 Point-of-care algorithm for thromboelastometry-guided coagulation management during liver transplantation. *A10* amplitude 10 min after CT, *AT* antithrombin, *bw* body weight, *Cai* ionized calcium, *CLI30* clot lysis index after 30 min, *CLI60* clot lysis index after 60 min, *CT* clotting time, *EX* EXTEM®, *FXIII* factor XIII concentrate, *FFP* fresh frozen plasma, *FIB* FIBTEM®, *IN* INTEM®, *Hb* hemoglobin, *HEP* HEPTEM®, *IU* international units, *LTX* liver transplantation, *MCF* maximum clot firmness, *MULTIPLATE* multiple electrode impedance aggregometry, *PCC* 4-factor prothrombin complex concentrate, *PT* prothrombin time, *ROTEM®* rotational thromboelastometry, r*FVIIa* activated recombinant factor VII, *Tc* core temperature, *U* units

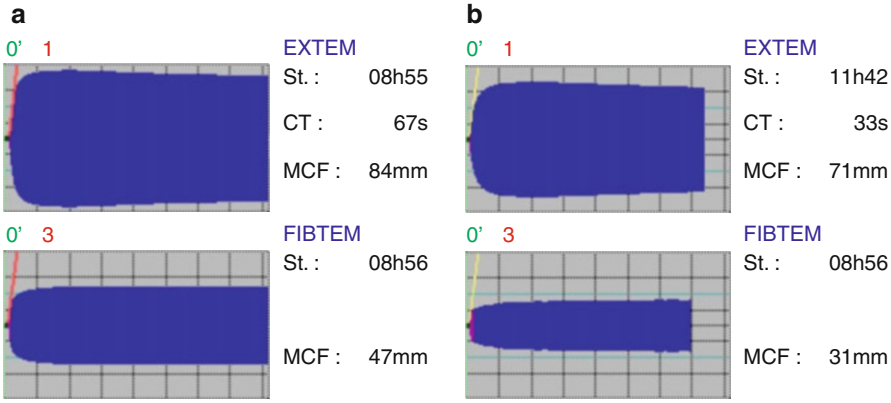


Fig. 15.3 Interpretation of ROTEM® analyses in patients undergoing liver transplantation. (**a**) Hypercoagulability in an infant with Budd-Chiari syndrome (hepatic vein thrombosis). Platelet count 796/nL; plasma fibrinogen concentration >10 g/L; D-dimer 228 µg/dL; Quick 68 %; aPTT 33.8 s; AT 111 %. (**b**) Hypercoagulability due to infection and tissue factor expression on monocytes. Quick 18 %; INR 3.5; aPTT 62.8; plasma fibrinogen concentration 6.56 g/L. The mismatch between an increased INR (PT) in routine plasmatic coagulation tests and a reduced CT in whole blood viscoelastic tests (ROTEM®) is typical for tissue factor expression on circulation cells (monocytes or malignant cells). (**c**) Fibrinogen deficiency. Administration of fibrinogen concentrate (cryoprecipitate) is indicated according to the POC algorithm in Fig. 15.2 in case of bleeding and $A10_{EX}$ ≤35 mm and $A10_{FIB}$ ≤8 mm (corresponding to MCF_{EX} ≤45 mm and MCF_{FIB} ≤10 mm). Fibrinogen dosage (mg) = targeted increase in $A10_{FIB}$ (mm) × 6.25 mg/kg fibrinogen × kg bw. (**d**) Thrombocytopenia compensated by a high plasma fibrinogen level. Platelet count 22/nL; plasma fibrinogen concentration 4.2 g/L. Transfusion of platelet concentrates is indicated according to the POC algorithm in Fig. 15.2 in case of bleeding and $A10_{EX}$ ≤35 mm and $A10_{FIB}$ >8 mm (corresponding to MCF_{EX} ≤45 mm and MCF_{FIB} >10 mm). (**e**) Fulminant fibrinolysis in the anhepatic phase of liver transplantation. Clot firmness in EXTEM® is reduced to zero within 15 min; flat line in FIBTEM®. Recommended therapy according to the POC algorithm in Fig. 15.2: 25 mg/kg tranexamic acid and 50 mg/kg fibrinogen concentrate (cryoprecipitate if fibrinogen concentrate is not available). (**f**) Self-limiting fibrinolysis after reperfusion in a liver transplantation with a good graft function. In the absence of bleeding, there is no need for therapeutic intervention. (**g**) Liberation of heparinoids from the liver graft after reperfusion. Marked prolongation of CT and CFT in INTEM® and almost normal CT in HEPTEM® (reference range for CT in INTEM® and HEPTEM®. 100–240 s). The effect of heparinoids usually is short acting and does not require any therapy in the absence of bleeding. In principle, administration of FFP or PCC is not indicated here. (**h**) Deficiency of vitamin K-dependent coagulation factors (II, VII, IX, X). Administration of PCC (or FFP if PCC is not available) is indicated according to the POC algorithm in Fig. 15.2 in case of bleeding and normalization of clot firmness (A10 or MCF) in EXTEM® and FIBTEM®, and CT_{EX} >80 s (reference range for CT in EXTEM®. 40–80 s). Dosage of PCC = 25 (−40) IU/kg bw; dosage of FFP = 15 (−30) mL/kg bw. *alp* alpha angle, *AT* antithrombin, *bw* body weight, *CFT* clot formation time, *CT* clotting time, *EX* EXTEM®, *FFP* fresh frozen plasma, *FIB* FIBTEM®, *HEP* HEPTEM®, *IN* INTEM®, *MCF* maximum clot firmness, *PCC* 4-factor prothrombin complex concentrate, *Quick* activity as % of normal based on PT, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *Run* run time of the test, *St.* start time of the test

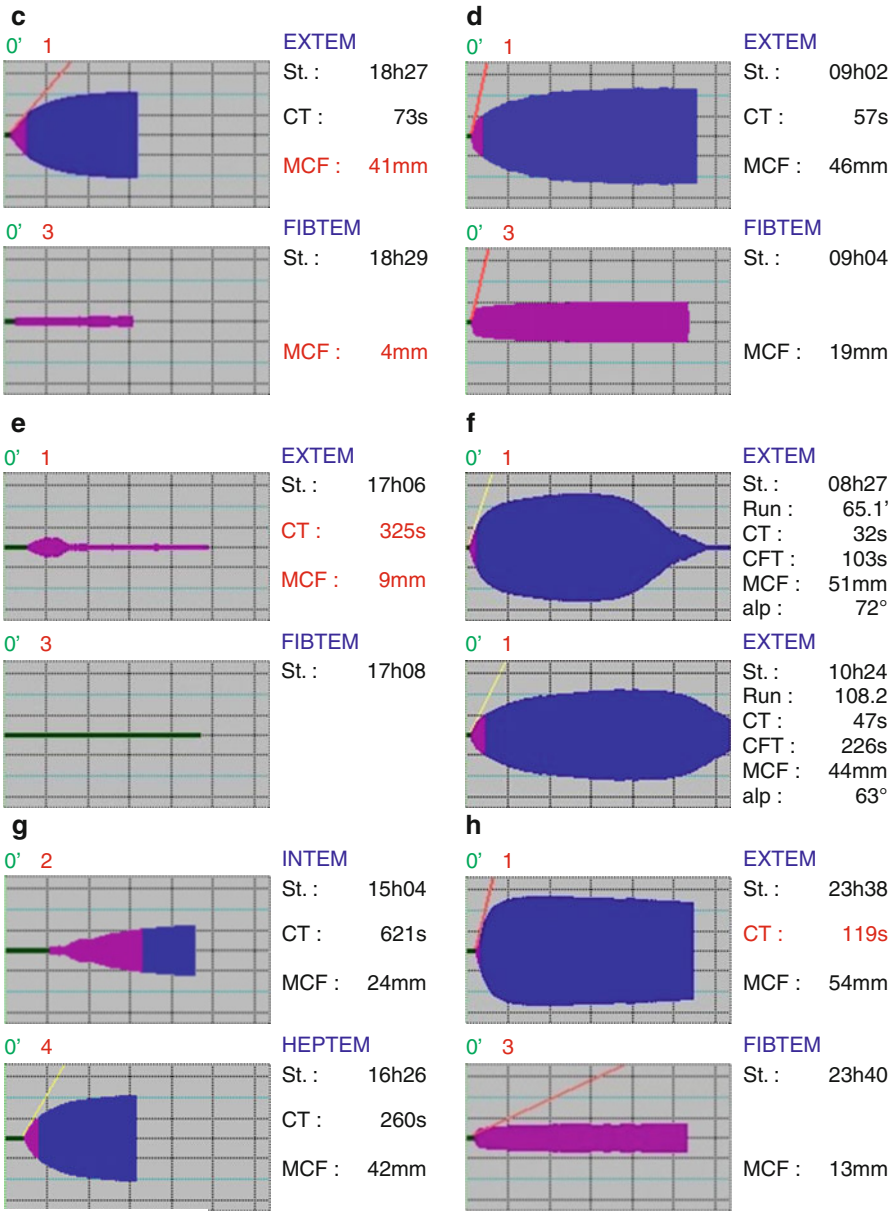


Fig. 15.3 (continued)

(Görlinger 2006; Görlinger et al. 2011b). This algorithm has been shown to reduce transfusion requirements in patients undergoing liver transplantation, without increasing the incidence of thrombotic/thromboembolic events (Görlinger et al. 2010, 2012b; Kirchner et al. 2012). Use of ROTEM®/TEG® for perioperative coagulation monitoring and targeted therapy of coagulopathy in patients undergoing visceral and transplant surgery is highly recommended in the European Society of Anesthesiology's guidelines for the management of severe perioperative bleeding (Kozek-Langenecker et al. 2013). However, all therapeutic interventions which reduce the need for blood transfusion and help avoid thrombotic/thromboembolic events should be investigated further since the strongest predictor of survival in patients undergoing liver transplantation is the number of blood transfusions (Esmat Gamil et al. 2012).

15.4.1 Antifibrinolytic Drugs (Tranexamic Acid)

Apart specific cases of prophylactic intervention (see thereafter), ROTEM®-guided haemostatic therapy has been administered in cases of diffuse bleeding. Tranexamic acid has been given prophylactically in a dose of 25 mg/kg bw in cases where thromboelastometry detected severe coagulopathy (CT in EXTEM® >80 s and/or A10 in EXTEM® <25 mm) at the beginning of surgery. A therapeutic dose of 25 mg/kg bw tranexamic was administered in case of thromboelastometric detection of hyperfibrinolysis (CLI30 <50 % or CLI60 <85 %) in presence of clinical diffuse bleeding (Figs. 15.2 and 15.3e). In case of self-limiting fibrinolysis after reperfusion without clinically relevant bleeding, no therapeutic intervention has been performed in about 30 % of patients presenting fibrinolysis (Fig. 15.3f).

15.4.2 Fibrinogen Concentrate or Cryoprecipitate

According to our ROTEM®-guided algorithm, fibrinogen concentrate (Haemocomplettan® P, CSL Behring GmbH, Marburg, Germany; marketed in the US under the name RiaSTAP®) has been given as a first-line therapy in case of clinically relevant diffuse bleeding and a decreased A10 value in both EXTEM® (A10 ≤35 mm) and FIBTEM® (A10 ≤8 mm) (Figs. 15.2 and 15.3c). Usually, 25 mg/kg bw fibrinogen concentrate was administered in order to increase A10 in FIBTEM® by 4 mm or 50 mg/kg bw to increase A10 in FIBTEM® by 8 mm (Görlinger et al. 2012b; Lier et al. 2013). If bleeding continued, further fibrinogen concentrate was administered until reaching a targeted A10 >15 mm in FIBTEM® and an A10 >45 mm in EXTEM®. Fibrinogen concentrate has been approved in Germany since 1985 for hereditary hypo-, dys-, and afibrinogenemia, as well as for any case of acquired hypofibrinogenemia when cryoprecipitate is not in use. However, cryoprecipitate can be used instead of fibrinogen concentrate in countries where fibrinogen concentrate is not available or approved for this indication (Kozek-Langenecker et al. 2013).

15.4.3 Platelet Concentrate

Platelet transfusion was administered in cases of clinically relevant diffuse bleeding and a low platelet count not compensated by higher fibrinogen levels (EXTEM® A10 ≤35 mm and FIBTEM® A10 >8 mm) (Figs. 15.2 and 15.3d). Notably, platelet transfusion during liver transplantation was associated with an increased incidence of acute lung injury and a decreased 1-year survival rate (Pereboom et al. 2009b). Therefore, the potential benefits of platelet transfusion have to be balanced against their risks.

15.4.4 Prothrombin Complex Concentrate (PCC)

According to our ROTEM®-guided algorithm, four-factor PCCs (Beriplex® P/N, CSL Behring GmbH, Marburg, Germany, or Octaplex®, Octapharma AG, Lachen, Switzerland) were administered at a dose of 20–25 IU/kg bw in cases of clinically relevant diffuse bleeding, with adequate clot firmness in EXTEM® and FIBTEM® (A10 >35 mm and 10 mm, respectively) but with prolonged CT in the EXTEM® (>80 s). In case of ongoing diffuse bleeding, further PCC administration (up to 40 IU/kg bw) was considered if the CT in the EXTEM® assay did not reach values below 80 s (Figs. 15.2 and 15.3h) (Görlinger et al. 2012b). Antithrombin concentrate was not routinely substituted for PCC. The four-factor PCCs used in Europe (such as Beriplex® and Octaplex®) contain balanced amounts of all vitamin K-dependent coagulation factors (II, VII, IX, and X), as well as the vitamin K-dependent anticoagulants proteins C and S (Holland et al. 2009; Sørensen et al. 2011; Kalina et al. 2008). Since 1996 in Germany, these four-factor PCCs have been approved for the prophylaxis and therapy of bleeding in patients with a hereditary or acquired deficiency of vitamin K-dependent coagulation factors. The safety profile of these four-factor PCCs has been considered good (Sørensen et al. 2011; Hanke et al. 2013).

15.4.5 Fresh Frozen Plasma (FFP)

A transfusion of FFP as a sole treatment was administered in cases of clinically diffuse bleeding and hyperfibrinolysis associated to a deficiency of fibrinogen, platelets, and vitamin K-dependent coagulation factors while an effect of heparinoids liberated from the liver graft could be excluded (Figs. 15.2 and 15.3g). In these cases, we assumed that a coagulation factor was missing and not included in the coagulation factor concentrates we used in the perioperative setting, e.g., factor V, VIII, or IX. Accordingly, 6–12 units of FFP were transfused as a hemostatic intervention. It is of note that large FFP transfusion are linked with transfusion-associated circulatory overload, acute lung injury, multiple organ failure, hepatic artery thrombosis, nosocomial infections, and sepsis (Dara et al. 2005; Hatano et al. 1997; Khan et al. 2007; Sarani et al. 2008; Watson et al. 2009). The potential benefits of FFP transfusion therefore have to be balanced against their risks.

15.4.6 Recombinant Activated Factor VII (rFVIIa)

It is of note that rFVIIa (NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) is not labeled for use in liver dysfunction and liver transplantation, and studies have failed to demonstrate a significant benefit in bleeding of the upper gastrointestinal tract or in liver transplantation (Chavez-Tapia et al. 2011a; Dasher and Trotter 2012; Pandit and Sarode 2012; Simpson et al. 2012). Keeping a potential increased risk of thrombosis in mind, the off-label use of rVIIa in patients with severe bleeding that is unresponsive to other hemostatic interventions can be considered (Kozek-Langenecker et al. 2013). According to our ROTEM®-guided algorithm, the administration of rFVIIa can be considered as a rescue therapy in case of ongoing diffuse bleeding despite optimization of hemostasis, surgical hemostasis, and ROTEM®-guided hemostatic therapy (Fig. 15.2). However, this has not been necessary in any cases since the implementation of our ROTEM®-guided algorithm (Görlinger et al. 2010).

15.5 Venous Thromboembolism in Liver Dysfunction

In line with the observations described above, patients with liver dysfunction are not "auto-anticoagulated" (Pincus et al. 2012; Schaden et al. 2013; Tripodi et al. 2011), but according to the findings of more global coagulation tests (thromboelastometry and thrombin generation assays), they tend rather to hypercoagulability with the inherent risk of thrombosis (Agarwal et al. 2012). Besides deep vein thrombosis, portal vein thrombosis and pulmonary embolism thrombosis can also affect the arterial system (hepatic artery thrombosis, myocardial infarction, or stroke). Even the progression of liver fibrosis in chronic liver disease might be a consequence of procoagulant imbalance (Tripodi et al. 2011). Hence, venous thromboembolism (VTE) prophylaxis is required during the hospitalization of patients with liver dysfunction (Koliscak and Maynor 2012). Despite this, 75 % of these patients do not receive VTE prophylaxis (Dabbagh et al. 2010; Aldawood et al. 2011).

15.6 Venous Thromboprophylaxis in Patients with Liver Dysfunction

VTE prophylaxis can be performed by pharmacological and/or mechanical means (compression stockings, intermittent pneumatic compression). The American College of Chest Physicians guidelines are updated every 4 years and present and grade the available evidence regarding thrombosis and thromboprophylaxis (Guyatt et al. 2012). Interestingly, these comprehensive guidelines do not offer any recommendations for VTE prophylaxis in patients with liver disease. This might be due to the lack of evidence, as in most studies dealing with thromboprophylaxis, patients with liver dysfunction are excluded. A recent study investigating the prevention of portal vein thrombosis in patients with chronic liver disease proved the efficacy and safety of enoxaparin application (4,000 U subcutaneously once daily) in cirrhotic patients (Villa et al. 2012). Prophylactic use of low-molecular-weight heparins

(LMWH) in patients with cirrhosis appears to be safe (Bechmann et al. 2011). A decreased anti-Xa value in cirrhotic patients and a negative correlation with liver function challenge the unconditional use of anti-Xa assays in LMWH monitoring in cirrhotic patients; it also reveals a potential limitation of anti-Xa analysis in these patients. A low level of AT, due to reduced hepatic synthesis, is the most likely cause of this phenomenon (Bechmann et al. 2011).

Early anticoagulation treatment, in both cirrhotic and non-cirrhotic patients with portal vein thrombosis and acute variceal bleeding, resulted in a satisfactory rate of recanalization with minimal procedure-associated morbidity (Hall et al. 2011; Maruyama et al. 2012). Since argatroban is mainly metabolized in the liver, it should be used with caution in patients with liver dysfunction (Garcia et al. 2012) and/or hyperbilirubinemia (Doepker et al. 2012). Despite some absolute contraindications (e.g., peripheral vascular disease), mechanical deep vein thrombosis (DVT) prophylaxis can be used in most patients and is of particular benefit to patients with a suspected bleeding risk. Nevertheless, mechanical DVT prophylaxis is used only in a minority of patients in intensive care units (Schaden et al. 2012).

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Perioperative Hemostasis in Pediatric Surgery

16

Thorsten Haas

16.1 Pediatric Hemostasis

The development of hemostasis during childhood is a complex physiological process which aims to build a stable clot in situations of vascular injury, but which is also responsible for clot dissolution to maintain blood flow (Andrew et al. 1987, 1988, 1992). Although the most significant changes in this maturation process can be observed during the first 6 months of life, the hemostatic system continues to mature thereafter (Andrew et al. 1992; Miller et al. 1997). These changes include lower quantities of most of the coagulation factors (except for factor VIII and von Willebrand factor, vWF), decreased platelet activity, and a fetal dysfunctional fibrinogen (Guzzetta and Miller 2011). However, as the anticoagulant system (such as plasmin generation and fibrinolytic activity) is also diminished at birth, the overall hemostasis potential in neonates and young infants can be evaluated as good, with no increased risk of thrombosis or hemorrhage in the face of minor challenges (Kuhle et al. 2003). However, this maturation process is certainly not rigidly coupled to a child's age group, but rather it is highly individual. It is therefore essential that careful anamnesis, physical examination, and laboratory work-up should be adapted to actual age and underlying medical condition.

16.2 Perioperative Coagulation Testing in Children

16.2.1 Preoperative Screening of Hemostasis

At present, guidelines and recommendations for perioperative coagulation management do not support routine coagulation screening tests in otherwise healthy patients

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if their bleeding history shows negative results (Dzik 2004; Koscielny et al. 2004; Chee et al. 2008; Kozek-Langenecker 2010; Samkova et al. 2012). This approach is based on the fact that the prediction of perioperative bleeding could not be reliably determined by routine coagulation screening tests, while the combination of a clinical examination, together with a detailed (family) history, showed superior results in ensuring the detection of impaired hemostasis. For example, von Willebrand syndrome type I is the most common type of a clinically relevant congenital bleeding disorder, with an incidence of 1 in 500; because it cannot be detected by a prolonged activated partial thromboplastin time (aPTT), it will most likely come to light via a detailed bleeding history. Templates of standardized questionnaires can be downloaded from the Austrian Society of Anesthesiology (ÖGARI) (http://www.oegari.at/web_files/dateiarchiv/116/Recommendation%20questions%20bleeding%20symptoms%202009.pdf), the Canadian Pediatric Bleeding Questionnaire (http://www.ahcdc.ca/inheritedbleeds.html), and the International Society on Thrombosis and Haemostasis bleeding assessment tool (http://www.isth.org/default/assets/file/bleeding_type1_vwd.pdf).

If this preoperative approach reveals evidence of impaired hemostasis, or a child suffers from a congenital or known acquired coagulation disorder, an interdisciplinary work-up with a hematologist or another dedicated physician specialized in pediatric bleeding disorders is indicated.

16.2.2 Intraoperative Coagulation Testing

16.2.2.1 Standard Plasmatic Coagulation Testing

Intraoperative coagulation testing is a cornerstone of the identification of an underlying coagulation disorder, but is also an essential tool for guiding appropriate coagulation management. Unfortunately, routine plasmatic coagulation tests are of limited help for timely management of perioperative bleeding; this is due to long turnaround times, insufficient differential diagnosis of complex acquired intraoperative coagulopathy, and insensitivity to fibrinogen function, hyperfibrinolysis, and platelet dysfunction (Kozek-Langenecker 2010). Other important limitations are that the measurement of fibrinogen levels using the photometric Clauss assay can be considerably altered after massive fluid resuscitation, and that colloids may erroneously induce increased levels of fibrinogen (Fenger-Eriksen et al. 2010; Kozek-Langenecker 2010).

16.2.2.2 Thromboelastometry

Although data on the use of rotational thromboelastometry for intraoperative coagulation management in children were scarce (Haas et al. 2008, 2012c; Hayashi et al. 2011; Romlin et al. 2011), a recently published meta-analysis showed significant reduction in requirements of allogeneic blood products if thrombelastography/thromboelastometry was used to guide transfusion strategy (Afshari et al. 2011). In addition, the use of thromboelastometry for pediatric care is recommended by the European guidelines for perioperative bleeding management (Kozek-Langenecker et al. 2013). Thus it seems reasonable to also use this advanced coagulation test for coagulation management in children once it has been implemented as routine for adults.

While keeping in mind the functional maturity of the coagulation system, age-dependent reference ranges for the ROTEM® (Oswald et al. 2010) or TEG® (Miller et al. 1997) should be taken into account. The most striking finding from the evaluation of these reference ranges is that children aged 0–3 months exhibited accelerated coagulation and strong clot firmness, despite showing prolonged standard plasma coagulation test results. Similarly to adults, fibrinogen concentrations, platelet count, and FXIII in children also contribute to clot firmness as measured using ROTEM® assays. Furthermore, it was demonstrated that children aged 4–24 months showed the lowest 2.5 % percentiles for clot strength, indicating low reserve when exposed to hemodilution and blood loss. However, as a rule of thumb, from the 6th month of life, adult reference ranges from ROTEM® can safely be used to guide intraoperative coagulation management.

16.2.2.3 Pre-analytical Considerations

Depending on local resources, the following coagulation tests could reasonably be used for baseline measurements, for regular check-ups, and in situations of increased bleeding tendency or severe bleeding:

- ROTEM® INTEM, EXTEM, FIBTEM, and APTEM
- Plasmatic coagulation testing (including FXIII, if possible)
- Blood count (platelet count, hemoglobin level, hematocrit)
- Blood gas analysis

This full panel of coagulation tests can be performed with a total withdrawal of only 3.6 ml blood.

Thought must be given to the possibility of pre-analytical errors that can have considerable impact on the interpretation of laboratory results. These can include important but avoidable errors, such as an artificial activation of the blood sample by forced aspiration through the small diameters of pediatric cannulas, temperature effects, and an alteration of the correct whole blood/citrate ratio. Although laboratory tests should be repeatedly analyzed during any surgical procedure with massive or expected bleeding, only the minimum volume necessary should be withdrawn in order to prevent artificial anemia.

16.3 Perioperative Coagulation Management

16.3.1 Preoperative Considerations

Several publications have investigated coagulopathies in the clinical setting of cardiac surgery. However, if a cardiac bypass were used, additional disturbance to the coagulation system, such as platelet dysfunction, excessive fibrinolysis, or consumption of coagulation factors might aggravate dilution following administration of the priming volume (Friesen et al. 2006). Thus, coagulation testing and management should be adapted to the type of surgery.

There are some important prerequisites for adequate hemostasis that need to be carefully checked and treated throughout the entire perioperative phase. Anesthetized children are particularly prone to becoming hypothermic which, like

acidosis, inevitably leads to impairment of the coagulation process and may worsen bleeding (Dirkmann et al. 2008). Thus, forced-air warming should be rigorously performed, and temperature, as well as pH values, continuously measured during pediatric surgery.

Meta-analyses of major pediatric surgery (Sethna et al. 2005; Tzortzopoulou et al. 2008; Schouten et al. 2009; Goobie et al. 2011) and scoliosis surgery in children (Tzortzopoulou et al. 2008) have nicely demonstrated that the prophylactic administration of antifibrinolytic agents (e.g. tranexamic acid or TXA) may decrease blood loss and reduce allogeneic blood transfusion significantly. Therefore, the prophylactic use of TXA can generally be recommended for major pediatric surgery with estimated high blood loss or need for transfusion. Optimum doses are still debated; reported dosing ranges from 10 to 100 mg/kg bolus, while high doses might provoke seizures. Recent studies favored an initial bolus followed by continuous infusion due to TXA's relatively short half-live of about 120 min. Based on recently published data it seems reasonable to use an initial dose of 10–15 mg/kg infused over 15 min, followed by continuous infusion of up to 5 mg/kg/h throughout the entire surgical phase and upon transfer to the postoperative ward (Goobie et al. 2013).

Alternative means to minimize blood transfusion in major pediatric surgery were recently reviewed (Lavoie 2011). Results showed that acute normovolemic hemodilution (mostly in adolescents) showed modest benefits. Other strategies such as preoperative autologous donations (partly in combination with administration of erythropoietin), intraoperative cell salvage (may be feasible if child's body weight is >10 kg), or deliberate hypotension (in the absence of a hypovolemic state), or a combination of them, might be helpful in reducing allogeneic blood transfusion. However, approaches must largely depend on individual expertise and local facilities.

16.3.2 Intraoperative Fluid Management

Prevention and treatment of hypovolemia during major pediatric surgery is essential and may be carried out by appropriate fluid management using crystalloids or colloids. Besides the 'traditional' usage of albumin for pediatric fluid resuscitation, modern synthetic colloids, e.g. gelatin solutions or hydroxyethyl starches, can be safely used even in neonates and small children (Standl et al. 2008; Sumpelmann et al. 2012). As with adults, the use of any synthetic or natural colloids may lead to volume-dependent changes in the hemostatic profile and eventually to dilutional coagulopathy and occurrences of generalized microvascular oozing (Osthaus et al. 2009; Haas et al. 2012b). One can only speculate as to whether early vasopressor therapy might have a beneficial impact on perioperative bleeding by reducing the amount of fluids administered during major surgery. However, to date, no conclusive statement can be made about which type of fluid should be used to stabilize hemodynamics in children, but caution should be exercised in clinical scenarios were colloids are administered to children with an increased risk of bleeding.

16.3.3 Intraoperative Laboratory Findings and Therapy

It is important to note that the reported triggers of standard plasmatic coagulation tests for assessment of coagulopathy or initiation of bleeding therapy are based on empirical rather than evidence based data. In addition, the results of standard laboratory tests and ROTEM® data cannot be used interchangeably for the detection of hemostatic disorders. As an example, the results of standard laboratory tests (prothrombin time, PT, or aPTT) alter frequently during early stages of surgery, thus indicating transfusion of fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC), while abnormal ROTEM® clotting time is a late phenomenon that may be observed after severe disturbances of hemostasis (Haas et al. 2012c). Thus, transfusion requirements will be completely different according to the underlying laboratory methods and transfusion triggers. The European guidelines for perioperative bleeding recommend the use of thromboelastometry in this setting (Kozek-Langenecker et al. 2013) (Table 16.1).

16.3.3.1 Impaired Clot Firmness

16.3.3.1.1 Fibrinogen Deficiency: Diagnostic and Therapy

Functional fibrinogen/fibrin activity can be quickly and reliably assessed using the ROTEM® FIBTEM assay. If the maximum clot firmness (MCF) at 10 min (A10) showed values <7 mm (which is approximate to a Clauss assay of ≤150 mg/dl) in a scenario of significant bleeding, fibrinogen should be administered (Fries et al. 2010; Kozek-Langenecker et al. 2013). It should be noticed that besides of fibrinogen deficiency, a low FIBTEM MCF may be also caused by inadequate amounts of FXIII necessary to stabilize the clot.

Table 16.1 Intraoperative laboratory findings and therapy

Hemostatic disorder	ROTEM®	Standard laboratory test	Therapy
Fibrinogen deficiency	FIBTEM A10 <7 mm	Clauss assay 150–200 mg/dl *(Cave: overestimation in presence of colloids)*	Fibrinogen concentrate: 30–50 mg/kg Cryoprecipitate: 5 ml/kg (or 15–30 kg bodyweight = 5 Units; >30 kg = 10 Units) FFP: 20 (–30) ml/kg
FXIII deficiency	FIBTEM MCF remains low despite adequate substitution with fibrinogen	FXIII activity <60 %	FXIII concentrate: 20 IU/kg FFP: 20 (–30) ml/kg
Low platelet count	EXTEM MCF <40 mm with normal FIBTEM MCF	Platelet count <50,000–100,000/µl	10 (–20) ml/kg of apheresis platelet concentrate (to a maximum of 1 Unit)
Inadequate thrombin generation	EXTEM or INTEM CT prolonged	Needs to be determined	FFP: 20 (–30) ml/kg PCC: about 20 IU/kg (Cave: thromboembolic risk)

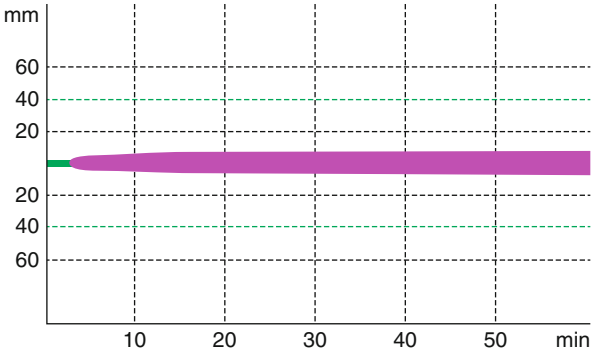

Fig. 16.1 ROTEM® trace of fibrinogen deficiency. FIBTEM MCF weak (6 mm)

Using the conventional Clauss assay, current recommendations (for adult patients) emphasize a trigger level of 150–200 mg/dl for initiating fibrinogen substitution therapy. However, if colloids were administered, fibrinogen levels analyzed using the Clauss assay may be erroneously high (Fenger-Eriksen et al. 2010).

Treatment of acquired fibrinogen deficiency consists of the administration of purified fibrinogen concentrate, transfusion of cryoprecipitate, or FFP (Fig. 16.1).

16.3.3.1.2 Fibrinogen Deficiency: Rationale

Fibrinogen plays several key roles in the maintenance of hemostasis (Levy et al. 2012; Sorensen et al. 2012). Fibrinogen acts by bridging activated platelets and is the key substrate by which thrombin forms a mechanically stable clot. Accumulating data suggest that acquired fibrinogen deficiency seems to be the leading determinant in dilutional coagulopathy in adults and children (Fries 2006; Levy 2006; Kozek-Langenecker 2007; Fenger-Eriksen et al. 2009; Innerhofer and Kienast 2010; Haas et al. 2012b). Clinical trials and observations indicated a beneficial role for intraoperative substitution with human fibrinogen concentrate to treat fibrinogen deficiency (Danes et al. 2008; Fenger-Eriksen et al. 2008; Haas et al. 2008; Weinkove and Rangarajan 2008; Fenger-Eriksen et al. 2009a; Rahe-Meyer et al. 2009) with a very good safety profile (Dickneite et al. 2009; Manco-Johnson et al. 2009).

FFP and cryoprecipitate may also serve as alternative sources of fibrinogen, although this is not supported by evidence from good-quality randomized trials (Stanworth et al. 2004). Cryoprecipitate contains higher concentrations of fibrinogen than FFP, but was withdrawn from several European countries because of the risk of immunologic reactions and potential transmission of infectious agents. Recommended dosages for FFP of 10–15 ml/kg may not be adequate to achieve a clinically meaningful improvement in hemostatic potential, but the considerable necessary volume load often limits higher doses.

16.3.3.1.3 FXIII Deficiency: Diagnostic and Therapy

For clinical purposes, weak factor activity of FXIII can be either accurately analyzed in a laboratory (FXIII <60 % and severe bleeding indicative for therapy), or can be estimated in a clinical case, when clot firmness in the ROTEM® FIBTEM

assay remains relatively low despite adequate substitution with fibrinogen. Although it was shown that the FXIII-dependent increase in clot firmness can be displayed using the ROTEM®/TEG® (Nielsen et al. 2004; Theusinger et al. 2010), to date no commercially available point-of-care test for measuring FXIII activity is available. Recommended means of substitution for FXIII include administration of a purified factor concentrate, or FFP.

16.3.3.1.4 FXIII Deficiency: Rationale

Factor XIII is a significant ingredient in achieving clot stability by cross-linking fibrin monomers, and preventing clot lysis by covalent binding of α2-plasmin inhibitor to fibrin molecules. Although congenital FXIII deficiency is a very rare bleeding disorder, there is growing evidence that acquired FXIII deficiency can also be frequently observed in perioperative settings in the pediatric age group (Korte 2006; Haas et al. 2012a). More recent data point towards the importance of FXIII in clot stabilization during major surgery and consequent blood loss (Gerlach et al. 2002; Korte et al. 2009; Korte 2010). However, improvement of clot firmness and the concomitant decreased bleeding tendency following substitution of FXIII in pediatric surgery is currently based on clinical observation, not on evidence based data.

16.3.3.1.5 Low Platelet Count: Diagnostic and Therapy

Platelet transfusion should be considered if platelet counts fall to levels between 50,000–100,000/μl during major surgery with the presence of severe bleeding. To distinguish a platelet-based weakening of clots from a deficiency in fibrinogen and/or FXIII, results of EXTEM MCF and FIBTEM MCF were gathered and analyzed. An MCF <40 mm in the EXTEM test, in combination with a normal FIBTEM MCF, will be indicative of a low platelet count. Transfusion of 10–20 ml/kg of apheresis platelet concentrate (to a maximum of 1 Unit) should raise the platelet count by 50,000/μl (Fig. 16.2).

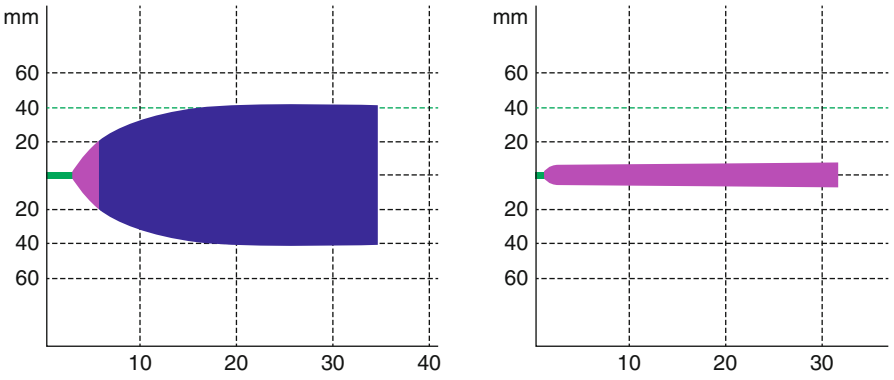

Fig. 16.2 ROTEM® trace of low platelet count. INTEM MCF decreased (40 mm); FIBTEM MCF normal (10 mm)

16.3.3.1.6 Low Platelet Count: Rationale

Recommendations for a safe lower platelet count threshold vary significantly in current literature. However, a significant decrease in platelet count seems to be a rather late phenomenon. In a retrospective analysis of 150 children who had undergone craniofacial surgery only 2 showed a platelet count ≤50,000/μl (Stricker et al. 2011). Note that the transfusion of platelet concentrate carries the highest risk of side-effects of all allogeneic blood products and should therefore be performed with caution.

16.3.3.2 Inadequate Thrombin Generation

16.3.3.2.1 Diagnostic and Therapy

Inadequate thrombin generation due to a deficiency of coagulation factors can be quite accurately estimated by prolonged clotting time (CT) in both the EXTEM and the INTEM assay, although no clear cut-off value was defined by now. Additionally, results from the ROTEM® HEPTEM assay may more usefully distinguish the impact of heparin, compared to the results of an INTEM test, if heparin was used during the procedure. It should be noticed that arbitrarily defined threshold for aPTT or PT prolonged >1.5–1.8 times are still used in the literature although no evidence based data exists to justify these values in this setting. Transfusion of FFP at a dose of about 20 ml/kg was routinely used if any signs of impaired hemostasis were observed, however, evidence based data to support its general use are weak. Administration of PCC (about 20 IU/kg) might offer an alternative approach, although no high quality data from pediatric trials are available (Fig. 16.3).

16.3.3.2.2 Rationale

Adequate thrombin generation is inevitably needed to induce the building of a stable clot. Notably, a perioperative decrease in thrombin generation, to levels that are unlikely to initiate clot building, is typically found late on in severe bleeding, even in neonates with lower vitamin K dependent coagulation factor levels. Unfortunately, neither aPTT nor PT correlates with clinically relevant coagulopathies or bleeding conditions (Johansson et al. 2010). Little evidence supports the use of standard coagulation tests for the guidance of perioperative coagulation therapy (Spahn et al. 2013). As viscoelastic tests are not used everywhere, empirical thresholds still exist to serve as rough estimates of disturbed hemostasis. In contrast, the prolonged coagulation times of thromboelastometry, in conjunction with increased bleeding tendency, might be interpreted as a relevant deficiency in coagulation factors and can

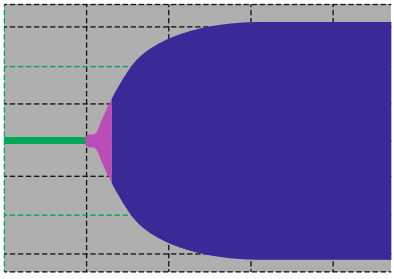

Fig. 16.3 ROTEM® trace of inadequate thrombin building

be treated with either an administration of PCC or a transfusion of FFP (Schochl et al. 2009, 2010). The accepted indication for administering PCC is reversal of the effects of vitamin K antagonists, but also for prophylaxis and treatment of factors of the prothrombin complex. Although numerous publications have shown the effective use of PCC in the latter indication, no evidence for its safe use in children exists to date. However, in severe bleeding episodes, where FFP is unavailable as a source of coagulation factors, or where there is a risk of hypervolemia due to large amounts of FFP, using PCC might offer a useful approach.

16.3.3.3 Hyperfibrinolysis

Besides the recommendation to use antifibrinolytic agents as prophylactic treatment, there is no evidence based data published that hyperfibrinolysis is a common problem during major surgery in children. However, due to the fact that hyperfibrinolysis is significantly associated with higher morbidity and mortality (Schochl et al. 2009), and in light of current recommendations for adults, it seems adequate to treat signs of hyperfibrinolysis (ROTEM® maximum lysis >15 % and maintenance of MCF using the APTEM test) in children with 10–20 mg/kg tranexamic acid, if relevant bleeding occurs (Fig. 16.4).

16.3.3.4 Bleeding Without Abnormal ROTEM® Results

Anesthesiologists can be challenged by intraoperative diffuse bleeding which neither the results from standard laboratory tests nor ROTEM® can explain. The usual reasons are the presence of congenital or acquired von Willebrand disease, or platelet disorders. In both cases, a timely, reliable diagnosis can be hard to achieve. First, the patient's bleeding anamnesis should be checked, as should any possible hypothermic, acidotic, or hypocalcemic condition, and then surgical bleeding should be ruled out. Thereafter, a clear work-up procedure, preferably involving a hematologist or a physician specialized in pediatric hemostasis, should be put in place. For severe cases, an empirical administration of tranexamic acid (bolus of up to 20 mg/kg over 15 min) is reasonable. Depending on the effectiveness of the antifibrinolytic therapy, a supplementary desmopressin infusion of 0.3 µg/kg over 15–30 min can be administered if a mild von Willebrand syndrome or impaired platelet function is suspected. It is important to keep in mind that the highest levels FVIII and von

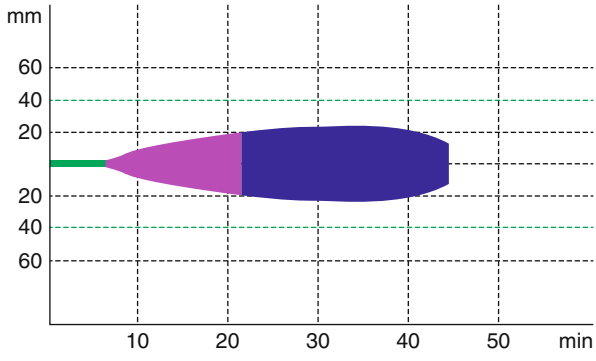

Fig. 16.4 ROTEM® trace of hyperfibrinolysis. Moderate lysis. Severe lysis

Willebrand factor (vWF) released from their storage sites within endothelial cells occur 30–60 min after desmopressin administration. If bleeding persists, administration of either vWF/FVIII concentrate (50 IU vWF:c/kg) or a platelet transfusion (20 ml/kg in children <15 kg; 1 apheresis unit platelets for children >15 kg) may be initiated, depending on the assumed underlying coagulation disorder.

16.3.3.5 Rescue Therapy

Final rescue therapy encompasses transfusion of at least FFP 20 ml/kg and/or administration of recombinant activated factor VII 90 μg/kg (rFVIIa). Final rescue therapy should only be considered after sufficient and timely treatment with standard therapy (as previously mentioned) has failed.

The licensed indications for rFVIIa are treatment of patients with hemophilia A or B with inhibitors, and patients with congenital FVII deficiency. In Europe, additional approval was granted for treatment of Glanzmann's thrombasthenia. Off-label treatment using rFVIIa to stop severe bleeding in children has been published concerning neurosurgical procedures (Heisel et al. 2004; Uhrig et al. 2007) and cardiac surgery (Ekert et al. 2006), but there is insufficient data to prove it is effective in off-label indications. It has been hypothesized that administration of rFVIIa for treatment of severe bleeding may only be efficacious if critical amounts of fibrinogen and platelets have been established or if extremely high doses of rFVIIa were administered (Spahn et al. 2013). Care should be taken to avoid excessive treatment with rFVIIa and PCC, as both substances may increase thromboembolic risk considerably. For this reason, rFVIIa is no longer recommended outside its licensed indications (Simpson et al. 2012).

This chapter reviewed acquired changes to hemostasis that may occur during major pediatric surgery. It also gave clinically useful trigger levels for ROTEM® as well as thresholds for standard laboratory tests for initiating structured and timely coagulation therapy. Further studies are urgently needed to elucidate optimal and safe thresholds for transfusion/coagulation management. As a general rule, treatment of laboratory findings without clinically relevant bleeding should be avoided, or considered very carefully, only if there is a high risk of bleeding.

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Perioperative Hemostasis in Obstetrics

17

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17.1 Introduction

Coagulation in pregnant women undergoes profound changes that lead to a hypercoagulable state, thus raising the risk of thrombosis (Cerneca et al. 1997; Holmes and Wallace 2005; Uchikova and Ledjev 2005). This increased coagulability is the body's means of reaching its primary objective—reducing bleeding during delivery. Postpartum hemorrhage (PPH) represents a major birth complication, with an overall incidence that has been shown to be close to 5 % (Dupont et al. 2009). Severe forms of PPH occur in nearly 1 % of births (Dupont et al. 2011), and they remain the primary cause of maternal mortality during pregnancy (Bouvier-Colle et al. 2004). PPH is often purely obstetric in origin, but whatever the precise etiology, severe PPH is frequently aggravated by coagulation disorders, which can worsen bleeding and even be life threatening. In rare cases, coagulopathies themselves may constitute the principal cause of PPH, often resulting in fatal hemorrhages.

In France and in many countries, there is a strong consensus around the use of guidelines. These advocate early detection of PPH and speedy obstetrical management as the crucial factors for a good prognosis. Conversely, there is no national or international consensus on the diagnosis and treatment of obstetric coagulopathies. This situation means that there is a great diversity of practice. The 2009–2011

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guidelines of the United Kingdom's Royal College of Obstetricians and Gynaecologists underlined the importance of coagulopathy management and recommended the involvement of a hematologist (RCOG 2011). In the absence of appropriate studies in obstetrics and due to the specificities of pregnant women, including pregnancy-associated changes in coagulation, treatment is primarily based on data from elective surgery or the management of polytrauma victims.

In cases of acute hemorrhage, any secondary coagulopathy will be governed by a lower fibrinogen level—the central factor in coagulation—at the interface of the intrinsic and extrinsic coagulation pathways with the fibrinolysis pathways. In recent decades, the role of fibrinogen in clinical practice has probably been underestimated. Clinical and experimental data are virtually unanimous in suggesting that the target fibrinogen levels used for indicating the transfusion of procoagulant blood derivatives (fibrinogen, fresh frozen plasma, cryoprecipitates, etc.) are usually too low (Rossaint et al. 2010). The data which lead to these conclusions were drawn almost exclusively from non-obstetrical hemorrhages: they were therefore not directly transferable to pregnant women, and no expert guidelines currently exist to propose a transfusion algorithm which takes into account the changes in coagulation associated with pregnancy.

17.2 Specificities of Hemorrhage Linked to Placental Expulsion

17.2.1 Hemorrhages During Placental Expulsion

PPH is defined as blood loss >500 mL within 24 h of vaginal delivery (Subtil et al. 2004). Apart from certain exceptional cases, the occurrence of bleeding is unpredictable. There are multiple hemorrhage mechanisms (e.g., wounds to the birth canal, post-cesarean hemoperitoneum), and not all of them correspond to placental expulsion pathologies. Primary uterine atony is the most frequent cause of PPH, while uterine inertia may be secondary and can complicate any type of PPH.

PPH can be aggravated by uncontrollable uterine bleeding, caused by two main mechanisms: tissue hypoxia associated with acute anemia or reduced circulation or the occurrence of a coagulopathy leading to abnormal bleeding of the placental bed.

17.2.1.1 Normal Placental Expulsion

Placental expulsion—the third and final stage of labor—can be defined as the set of mechanisms leading to the placenta and membranes coming out of the birth canal. Placental expulsion systematically involves a certain amount of blood loss, which can vary from a few tens of mL to several liters. Hemorrhage will usually occur in the first 2 h following birth.

Natural placental expulsion is induced by spontaneous uterine contractions. If this has not taken place 30 to 60 min of birth, there is an increased risk of hemorrhage (Tessier and Pierre 2004), and it is recommended that the expulsion should be

actively assisted via manual removal of the placenta from the uterus. Placental expulsion is systematically followed by a uterine examination, mainly in order to check that the uterine cavity is empty.

Four phases can be distinguished in a normal placental expulsion:

- Phase one: uterine contraction immediately after the fetus is pushed out. Because the uterus is less distended, it undergoes a simple phenomenon of passive elastic retraction. This phase is usually followed by a few minutes of rest during which the contractions are less intense.
- Phase two: characterized by renewed, more intense uterine contractions. These contractions will lead to a reduction of the placental insertion site and will put a strain on the chorionic villi in the compact layer of the basal plate. This creates a gap between the compact outer layer and the spongy intermediate layer of the decidua, and the lesion of these uteroplacental blood vessels leads to the formation of a hematoma. The hematoma widens the gap and completes the detachment of the placenta.
- Phase three: processus of hemostasis. This crucial phase is carried out by:
- The formation of clots in the affected uteroplacental blood vessels. Hemostasis is set off by an abundant liberation of tissue factor as the gap between the layers grows. It is reinforced by the modifications to coagulation which develop during pregnancy.
- Uterine contractions that will seal off the open blood vessels embedded in the uterine wall.
- Phase four: the migration of the freed placenta down the birth canal and its expulsion from the vagina.

Relaxation of the uterus, or an intrauterine retention of placental tissue, may lead to the development of a hemorrhage. It is imperative to carry out a uterine examination and to keep the patient under strict observation.

In case of a cesarean section, placental expulsion is actively managed or it is manually extracted; uterine examination is systematic. Cesarean birth is associated with an increased risk of hemorrhage: intrinsically (sectioning of veins during hysterotomy, hemoperitoneum, and hematoma), due to its causes (*e.g.*, placenta previa, HELLP syndrome), and due to more frequent uterine atony.

17.2.1.2 Principal Causes of PPH

The causes of PPH are numerous, and in the majority of cases, they are of obstetrical origin. It is rare for primary coagulation disorders to be the principal etiology of PPH.

Uterine atony is the leading cause of PPH and several conditions will readily increase its likelihood (e.g., long working hours, uterine distention, and uterine fibroids). Secondary atony may also occur after cases of severe PPH. In such cases, it maintains bleeding and can lead to a worsening of PPH. A retained placenta (e.g., membranes, cotyledon of full placenta retention) can also lead to hemorrhage. Surgical causes of PPH are frequent: hemorrhagic hysterotomy, wounds to the birth canal (e.g., vaginal tearing, uterine rupture), etc. Uterine inversions are a classic, although now rare, cause of PPH.

An abnormal position of the placenta can be a source of massive PPH. This is notably the case with placenta previa and placenta accreta for which antenatal identification is vital so as to prepare birth and delivery in the best possible conditions.

17.2.2 Coagulopathies in PPH

Hemostasis of the uterine placental bed plays an important role in reducing the risks of hemorrhage. The hemostatic system enters into action as soon as the placenta detaches itself, allowing the formation of clots in the blood vessels. The modifications in coagulation activity linked to pregnancy are designed to increase the effectiveness of hemostasis.

17.2.3 Modifications to Coagulation During Pregnancy

Fibrinogen is the blood factor which undergoes the greatest variations in concentration during pregnancy, but coagulation modifications are by no means limited to fibrinogen. Fibrin formation depends directly on the capacity to generate thrombin. Understanding all these modifications is therefore fundamental to understanding its impact on the blood clot.

17.2.3.1 Evolution of Fibrinogen Levels

The level of fibrinogen increases progressively throughout pregnancy. Personal data collected by this chapter's authors on 4,022 women in their third trimester showed that the 5th and 95th percentiles were 3.5 g/L (95 % CI [3.4–3.5]) and 6.4 g/L (95 % CI [6.3–6.5]), respectively. This increase in the level of fibrinogen is accompanied by an increase in the firmness of the clot as measured by thromboelastometry. Clot formation is firmer towards the end of pregnancy, which certainly helps to improve hemostasis of the placental bed at birth. The increase in fibrinogen levels during pregnancy can fulfill two objectives: first to improve the firmness and hemostatic effectiveness of clotting and second to constitute rapidly available reserves in case of PPH.

17.2.3.2 Changes in the Different Pathways of Hemostasis

- *Primary hemostasis* is subject to major upheavals. Levels of von Willebrand factor (vWF) increase considerably during pregnancy (Clark et al. 1998; Wickstrom et al. 2004). The contribution of platelets to hemostasis is warranted despite the reduction in platelet count that often occurs in the third trimester: firstly because the reduction is small and the count rarely goes below 100,000/mm^3 and secondly because there may be increased platelet adhesion linked to over-activation. Data related to the increased activation of platelets during normal pregnancies are the subject of some controversy, however (Nicolini et al. 1994; Star et al. 1997).
- *The coagulation stage* is subject to many changes. Concentrations of almost all the coagulation factors either increase or remain stable. The only factor which shows a significant reduction throughout pregnancy is factor XI (Hellgren and Blomback

1981), which plays an important role in the generation of thrombin. The reduction of this factor occurs in order to counterbalance increases in the other factors (Holmes and Wallace 2005). Tissue factor plays a key role in triggering coagulation in vivo. The absence of an increase in soluble tissue factor (Bellart et al. 1998b), the reduction in monocyte tissue factor (Holmes et al. 2002), and the increase in tissue factor pathway inhibitor (TFPI) (Sandset et al. 1989) may contribute to limiting the risks of activating coagulation during pregnancy.

- *The factors inhibiting coagulation pathways* are also affected by pregnancy. The level of antithrombin remains stable (Hellgren and Blomback 1981; Stirling et al. 1984) or increases slightly (Dargaud et al. 2010). The level of protein C hardly changes or also increases slightly, perhaps due to the influence of increased levels of thrombomodulin; concentrations of its inhibitor do increase (Hellgren 2003). The levels of the free form of protein S and the total level of protein S both diminish (Clark et al. 1998; Kjellberg et al. 1999). Holmes and Wallace suggested that these modifications were aimed at a reducing coagulation inhibition (Holmes and Wallace 2005).
- *The fibrinolytic system* is also subject to changes. Overall fibrinolytic activity is reduced despite increases in plasminogen and its activators, tissue plasminogen activator (tPA) and urokinase (Nakashima et al. 1996). This is because of parallel increases of plasminogen activator inhibitor 1 (PAI-1) and especially of plasminogen activator inhibitor 2 (PAI-2) secreted by the placenta. The level of PAI-2, which is very low outside of pregnancy, rises considerably and may lead to strong inhibition of the conversion of plasminogen to plasmin (Nakashima et al. 1996; Bellart et al. 1997). However, the concentration of thrombin-activatable fibrinolysis inhibitor (TAFI) is not affected by pregnancy (Chetaille et al. 2000), and the level of α2-antiplasmin remains stable or increases slightly (Hellgren and Blomback 1981).

Pregnancy has little effect on standard plasmatic tests such as prothrombin time (PT, or Quick's time) or activated coagulation time (ACT), and they are poor at detecting hypercoagulable states (Holmes and Wallace 2005; Huissoud et al. 2009).

During pregnancy, there is an increase in activation markers for coagulation, such as the thrombin-antithrombin complex (TAT) and fragments Fi and F2 released by the degradation of prothrombin (Clark et al. 1998; Holmes and Wallace 2005; Uchikova and Ledjev 2005). Dargaud et al. (2010) suggested that the increase in F1 and F2 is linked to the significant increase of FVII. Likewise, during pregnancy, there is an increase in the levels of fibrinopeptide A (which is a product of the conversion of fibrinogen to fibrin) and of D-dimers (Bellart et al. 1998a, b; Uchikova and Ledjev 2005; Dargaud et al. 2010). The best way to evaluate coagulability is to calculate the capacity to generate thrombin or the endogenous thrombin potential (ETP). Recent work by Dargaud et al. demonstrated that ETP levels increased from the first to the third trimester (Dargaud et al. 2010). These results support data from thromboelastometry which show an increase in the α angle and a reduction in clot formation time (CFT) as gestation progresses. All these results reflect an increase in the "capacity to coagulate" which occurs from the first through to the third trimester (Huissoud et al. 2009; Dargaud et al. 2010).

The third trimester of pregnancy is thus characterized by:

- Increased reserves of coagulation factors and of fibrinogen in particular
- Increased capacity for coagulation which reduces clotting time
- A clot whose firmness is maximized by strong fibrinogen concentrations

All these changes work together to promote better conditions for hemostasis at birth.

Above all, successful management of PPH from its earliest phase requires treatment of the bleeding and thus its direct causes. The appropriate obstetric measures should be taken promptly at each phase in order to stop hemorrhage rapidly. Obstetric treatment follows several essential steps: verification that the uterus is empty and that the birth canal is undamaged and a rapid initiation of uterotonic treatment using oxytocin and prostaglandins. If bleeding persists, a specific uterine balloon tamponade should be used. If this is not available or fails, then a uterine artery embolization procedure, or a surgical intervention, will become essential. Surgery is primarily based on techniques involving vascular ligatures or uterine compression. It is possible to combine both of these methods by using a total uterine ligation note: the total uterine ligation is the name of the technique that simultaneously combines multiple arterial ligations and compression of the uterus; this has the notable advantage of causing the least damage to the uterine cavity (Huissoud et al. 2012). Should all these stabilization techniques fail, then a hemostatic hysterectomy may become necessary.

In most cases, disruptions of hemostasis at the beginning of PPH are either nonexistent or moderate. These disruptions often develop progressively and generally follow the same chronological sequence. Once coagulation problems have manifested themselves, they can prolong PPH or even worsen bleeding through such different mechanisms as:

- A worsening of the hemorrhage at its initial site
- A secondary hemorrhage following an initial successful hemostasis of the placental site (e.g., an overlooked wound in the birth canal)
- Reactions such as tissue hypoxia that can promote uterine atony
- A worsening of the coagulopathy itself via a self-perpetuating process linked to disseminated intravascular coagulopathies or the consumption of coagulation factors through bleeding
- The hemodilution frequently induced by fluid administration of non-blood transfusion products
- A worsening of maternal hemodynamics

Inversely, there are rare instances where primary hemostatic problems are the cause of PPH, such as:

- An obstetric pathology (e.g., placental abruption, an amniotic fluid embolism, intrauterine fetal demise, HELLP syndrome, acute fatty liver of pregnancy, and even more rarely intrahepatic cholestasis of pregnancy)
- A quantitative or functional congenital hemostatic disorder, some of which are actually improved by pregnancy
- A treatment with anticoagulant or antiplatelet drugs

Regardless of the circumstances, the existence of a coagulopathy, whether primary or secondary, constitutes an aggravating factor for the mother's functional prognosis and even her prognosis for survival. The onset of a coagulopathy is undoubtedly a critical point in the development and management of PPH.

17.3 Hemostatic Management of PPH

PPH is a true race against time. Gaining hemostatic control of macroscopic bleeding remains an absolute priority, whether this must be done using surgery or via embolization using interventional radiology.

At the same time, resuscitation management must be aggressive: the early use of hemostatic products associated with constant monitoring of coagulation efficacy is mandatory. As with any serious situation, the existence of written protocols is essential. Adequate management of these patients will require nonstop collaboration between specialist obstetricians, anesthetists, and radiologists.

17.3.1 General Management

- Monitoring. Early cardiac monitoring of vital signs is essential. Changes in arterial blood pressure, heart rate, and capillary refill are useful for the diagnosis of hypovolemia, but are not correlated to its intensity; their predictive impact is often too late, especially if blood loss is superior to 30 %. Therefore, an ensuing diagnosis of hypotension is a serious sign. Before clinical evidence of poor tolerance, it is essential to quantify a patient's blood loss using a specialized graduated collection bag and, furthermore, to ensure continuous monitoring of her hemoglobin level using a micromethod. The time factor is a fundamental part of the prognosis; early use of today's widespread alert scores (such as Modified Obstetric Early Warning Scoring, MOEWS) by maternity ward personnel in the period following birth aids the early detection of any modifications to patient's vital signs.
- Therapeutic measures linked to transfusion.
- The first treatment of hypovolemia must be symptomatic and initially based on the use of crystalloid volume expanders, while awaiting blood-based products. Hydroxyethyl starches have their own side effects on hemostasis and on fibrinogen in particular; thus, it is important to limit their use. Maintaining sufficient perfusion and tissue oxygenation is essential in order to avoid progression towards organ dysfunction; lactic acid levels have been shown useful in monitoring the adequacy of resuscitation in traumatology; rising lactic acid levels are closely correlated to the risk of onset of a coagulopathy.

Fighting acidosis is essential: this should be done by optimizing blood volume, if necessary by using alkaline solutions when blood pH values drop below 7.20, so as to best preserve coagulation factor functionalities.

- Monitoring hypercalcemia, by measuring free (unbound) ionized calcium, should be carried out as soon as a transfusion procedure administering calcium intravenously is started (1 g for every 4–6 units of packed red blood cells, pRBC); maintaining normal levels of calcium is indispensable for optimizing patients' coagulation.
- Finally, continuous monitoring of body temperature must be ensured along with other vital signs. There is a variety of means of fighting hypothermia such as thermal blankets and above all by warming blood products before administration.

In all cases, the objective must be to keep body temperature above 34 °C so as to maintain sufficient platelet aggregation and coagulation factor activity.

17.3.2 Transfusion Strategy

Stopping obstetrical hemorrhage remains difficult; it requires the development of clear procedures within hospital maternity units. These procedures must ensure that blood products and coagulation factors are rapidly available as any transfusion strategy must begin early.

Correction of anemia is paramount in order to avoid developments towards organ dysfunction when hemorrhaging is severe.

The target level of hemoglobin should therefore be above 8 g/L. This level not only enables a better transport of oxygen but also improves the hemostatic process. The rheological role of red blood cells themselves favors platelet adhesion at the site of the endothelial injury, and via their surface receptors, these red blood cells also participate in setting off the initiation phase of coagulation.

Finally, anemia's deleterious role in the onset of myocardial ischemia in severe forms of PPH has been demonstrated (34); its role can be even more damaging in the presence of strong doses of prostaglandins.

Should the clinical situation demand it (extremely high blood loss), then a perfusion of fresh frozen plasma (FFP) can be initiated before the results of the hemostatic tests are available; in cases with lower bleeding kinetics, perfusion of FFP should be carried out using guidance from the results from standard coagulation tests or thromboelastometry.

Thus, in situations involving massive transfusion, the strategy proposed here rests essentially on data obtained from non-obstetric studies. These have shown that morbidity and mortality are significantly reduced by initiating transfusion early, with a fixed rate of FFP to pRBC; however, these arguments are based mainly on biased retrospective studies. Perfusion of significant quantities of plasma increases the risks inherent to transfusion itself. The ideal FFP/pRBC ratio remains unknown, but results currently available in the literature, notably Murad et al.'s meta-analysis, show that transfusions of FFP, in ratios about one-third, are associated with a significant reduction in mortality (35).

FFP ratios are increased when the objective is to correct the coagulopathy by increasing the intake of coagulation factors, notably fibrinogen: each unit of FFP contains around 400 mg of fibrinogen. Using plasma also enables an increase in blood volume when oncotic pressure is high, thus reducing hemodilution. However, the use of high ratios of FFP in a massive transfusion protocol should be reserved for patients showing massive bleeding, which only represents a minority of situations. Using such high ratios on patients presenting only minor hemorrhage could, in fact, lead to an increase in morbidity- and mortality-related complications.

Prothrombin complex concentrates (PCC) can be a good alternative in situations involving obstetric hemorrhage for a number of reasons: they provide easily prepared and administered coagulation factors with immediate availability and few

side effects. PCC therefore seem to be a potential solution for the management of such hemorrhages despite the fact that there are currently no specific guidelines. Several retrospective studies have emphasized the value of PCC during perioperative bleeding, especially in combination with the administration of fibrinogen. The advantages of a strategy combining the targeted transfusion of coagulation factors with thromboelastographic monitoring seem to be an interesting alternative to the conventional transfusion strategies which are still often quite empirical. However, the thromboembolic risks linked to using PCC have yet to be properly evaluated: vigilance is recommended when using these products during PPH.

As with severe trauma, platelet levels should be maintained at over 100,000/mm^3 during active bleeding: Simon et al.'s retrospective analysis identified a lower threshold to be a risk factor independent of PPH. Thus, the more the platelet level decreases, the greater the number of pRBC that should be administered.

The administration of fibrinogen is recommended if the perfusion of FFP is unable to maintain fibrinogen levels above 2 g/L. Indeed, in the study by Charbit et al., fibrinogen concentration was the only independent parameter to be associated with PPH developing a severe course (a fibrinogen level of less than 2 g/L gave a 100 % positive predictive value of serious bleeding).

In addition to fibrinogen's role in clot formation, it has the other advantages of only requiring a low infusion volume and very little preparation time. Thus, fibrinogen use allows a reduction of transfusion volume requirements during massive bleeding. These studies also underlined the importance of regularly measuring fibrinogen levels during PPH, while keeping in mind that normal fibrinogen levels during late pregnancy are around 4 g/L.

United Kingdom recommendations emphasize that a level of at least 1.5 g/L is needed to improve hemostasis.

Thromboelastometry allows for close monitoring of fibrinogen levels in plasma: in patients suffering PPH, this level is highly correlated to the amplitude of the fibrin clot measured after 5 min, using rotational thromboelastometry (ROTEM®). When using an algorithm with appropriate transfusion thresholds, ROTEM® can thus help save on transfusion requirements, as in cardiac surgery. A FIBTEM® or TEG amplitude measured below 12 mm (about 2 g/L fibrinogen) is a sign that justifies early administration of fibrinogen. Finally, monitoring fibrinogen levels using ROTEM's FIBTEM® test highlights the potential effects that fluids can have on coagulopathy: in vitro clot firmness decreases significantly after hemodilution using colloids rather than crystalloids.

Several case studies, case series, and registry studies have been published on the use of recombinant activated factor VII (rFVIIa). Results suggest that rFVIIa provides a reduction in transfusion requirements and facilitates surgical hemostasis in 60–80 % of obstetric cases. The dose is variable: 90–120 μg/kg. rFVIIa can be used after the failure of other medical and surgical treatments but also prior to hysterectomy. In order to optimize rFVIIa's efficacy, the patient's blood should have a pH >7.20, a temperature >34 °C, a fibrinogen level >1 g/L, and platelets above 50,000/mm^3.

Ferrer et al.'s meta-analysis showed that tranexamic acid reduces obstetric bleeding. Since then, a randomized multicenter study evaluating high doses of tranexamic

acid for use in PPH (4 g in the first hour, then 1 g/h for 6 h) versus placebo showed significant reductions in blood loss and transfusion requirements in the group receiving tranexamic acid. Side effects (nausea, vomiting, or problems of vision) are more common however, and appear to be linked to the high doses; an international randomized trial (WOMAN Trial) is underway using lower doses. There has been a great deal of recent interest in antifibrinolytics in the context of traumatic hemorrhage: they are inexpensive products, reduce blood product use, and do not appear to increase the risk of thromboembolism. In short, the significant efficacy of antifibrinolytic agents demonstrates the importance of fibrinolysis in the pathophysiology of PPH.

In practice, the evaluation of hyperfibrinolysis using conventional biological tests (D-dimers, fibrin degradation products, and euglobulin lysis time) is not easily applicable in emergency situations. On the other hand, thromboelastometry permits a rapid diagnosis of acute hyperfibrinolysis, such as coagulopathies associated with catastrophic amniotic fluid embolism.

Overall, optimal management of PPH necessitates:

- The existence of protocols adapted to the institution's organization of critical obstetric care and transfusion services, in order to optimize timely coordination
- Bearing in mind the limits of standard hemostasis tests in this type of situation and acknowledging the increasing preference for using thromboelastometric techniques to guide the transfusion process
- Several weeks of monitoring for patients who have suffered a severe hemorrhagic event (this appears indispensable; indeed, in a series of 317 patients with severe PPH, 22 % of them, in fact, had a constitutional defect of hemostasis: hypofibrinogenemia, drops in von Willebrand factor or factor XI)

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Perioperative Hemostasis in Trauma

18

Catherine Heim and Karim Brohi

18.1 Introduction

Injury is a major public health problem: it is the leading cause of death in the first four decades of life (Krug et al. 2000; Eastridge et al. 2006). Exsanguination accounts for up to 50 % of trauma deaths in the first 24 h and for up to 80 % in the operating theater (Association of Anaesthetists of Great et al. 2010). Despite significant advances in trauma care, exsanguination remains the leading cause of preventable death (Sauaia et al. 1995; Demetriades et al. 2004; Kauvar and Wade 2005; Gruen et al. 2006; Kauvar et al. 2006; Cothren et al. 2007). Caring for a severely injured and bleeding patient is to face a challenge of timely and effective hemorrhage control and rapid restoration of physiology.

Coagulopathy is common after trauma and directly related to poor outcome (Brohi et al. 2003; MacLeod et al. 2003; Maegele et al. 2007). Over the last years, transfusion strategies for patients with severe trauma-related bleeding have undergone important changes due to a better understanding of epidemiology, the mechanisms and consequences of bleeding and coagulopathy (Spinella and Holcomb 2009). Impaired hemostasis following trauma was thought to be essentially due to a loss or inhibition of coagulation proteases, similar as in surgical haemorrhage. In 2003, two large observational studies found that 1 in 4 trauma patients presents impaired coagulation on hospital arrival, independent of exogenous factors (Brohi et al. 2003; MacLeod et al. 2003). This identification of early coagulopathy has progressed to the recognition of an endogenous component of trauma-related hemostatic impairment, and the term "acute traumatic coagulopathy" (ATC) has been adopted (Brohi et al. 2003). ATC is

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characterized by systemic anticoagulation and fibrinolysis. It is secondarily exacerbated by dilution, inhibition, and consumption of clotting factors. The combination of tissue injury and shock is a key factor in the development of ATC.

Coagulopathy on hospital arrival is associated with increased bleeding, higher morbidity, and death (Brohi et al. 2003; MacLeod et al. 2003; Frith et al. 2010). Early identification is therefore crucial to rapid, goal-directed interventions and thus improved outcome (Borgman et al. 2007; Hess et al. 2008). Laboratory-guided transfusion strategies have been shown to result in delayed correction of ATC and suboptimal use of blood products (Hess and Hiippala 2005; Gonzalez et al. 2007). Rapid control of bleeding and early administration of hemostatic blood components, restoration of volume status, and limiting amounts of clear fluids have all been shown to improve outcomes (Hess et al. 2006; Borgman et al. 2007; Holcomb et al. 2007; Gunter et al. 2008; Maegele et al. 2008; Cotton et al. 2009; Jansen et al. 2009; Duchesne et al. 2010). This strategy has been termed "hemostatic resuscitation" or "damage control resuscitation." The concept of ATC has revolutionized the comprehension of trauma-related bleeding and therefore influenced clinical management. However, the exact underlying pathophysiological mechanisms are not yet fully understood, and there is no generally accepted algorithm for hemostatic resuscitation and blood product use. The innate physiological responses to trauma, and optimal therapeutic strategies for hemostatic resuscitation and organ protection, are subject to extensive ongoing research (Brohi et al. 2008; Frith et al. 2010).

18.2 Acute Traumatic Coagulopathy, a Component of Trauma-Induced Coagulopathy

One in four trauma patients presents signs of established coagulopathy on hospital admission, independently of fluid administration or hypothermia (Brohi et al. 2003; MacLeod et al. 2003; Maegele et al. 2007). ATC occurs within minutes of the traumatic event (Brohi et al. 2003, 2007a, b; Floccard et al. 2012). The presence of ATC is associated with mortality close to 50 %, higher transfusion requirements, and significantly increased morbidity in terms of acute lung injury, infections, and multiple organ failure (Brohi et al. 2003; MacLeod et al. 2003; Maegele et al. 2007). Lengths of hospital stay are consequently increased too. However, 10 years after its description, the functional characterization of the causes and effects of ATC is still not fully understood. Current knowledge suggests an innate physiological response to tissue injury and cellular hypoperfusion, which together lead to a systematic activation of anticoagulation and fibrinolysis (Brohi et al. 2008). The simultaneous presence of severe tissue trauma and shock seem to be necessary for the development of ATC; the worst coagulopathy is seen in patients with a high injury severity score (ISS) and very low base excess (Frith et al. 2010). Endothelial activation and protein C seem to be key actors in the concept of ATC. Several studies suggest that tissue injury and hypoperfusion lead to increased expression of thrombomodulin, resulting in increased activation of protein C (aPC). aPC impairs clotting factors V and VIII and reduces thrombin generation. Furthermore, aPC has an inhibitory

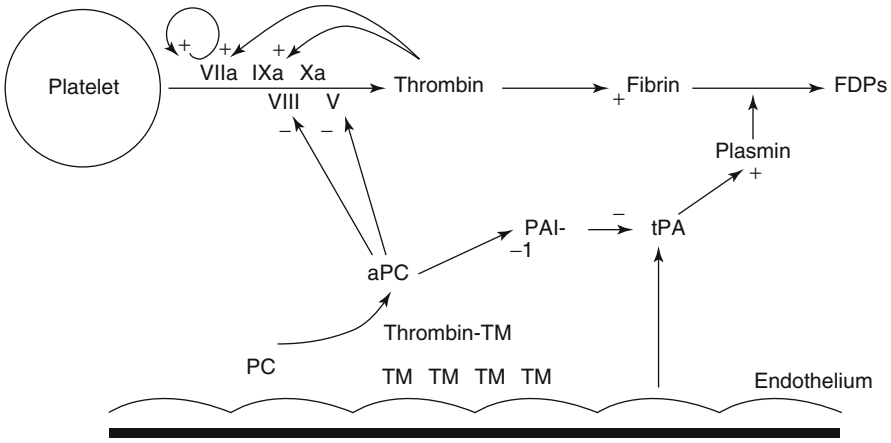

Fig. 18.1 The ATC pathway (From Brohi et al. (2007a) with permission)

effect on plasminogen activator inhibitor 1 (PAI-1). The resulting combination of high levels of tissue plasminogen activator (tPA) and low levels of PAI-1 leads to a hyperfibrinolytic state with unregulated tPA activity and fibrinolysis (Hrafnkelsdottir et al. 2001; Brohi et al. 2007a, b, 2008; Frith et al. 2010; Cohen et al. 2012) (Fig. 18.1).

Hyperfibrinolysis (HF) is a significant component of ATC, presenting as an excessive, inappropriate process leading to accelerated clot breakdown and enhanced bleeding (Brohi et al. 2008). The purpose of enhanced fibrinolysis after trauma might be the body's attempt to limit clotting to the site of vascular injury (Hess et al. 2008). HF after trauma has been reported in up to 34 % of cases; it correlates positively with transfusion requirements; and it has a mortality rate of close to 80 % (Kashuk et al. 2010a, b; Schochl et al. 2010, 2011; Tauber et al. 2011). A large randomized control trial (RCT) on trauma supports the role of fibrinolysis in trauma-related coagulopathy, as administration of tranexamic acid (TXA) was associated with a significant reduction of mortality (CRASH-2 trail Collaborators et al. 2010). Factors contributing to HF include high ISS, shock, and hypothermia. Some authors suggest that crystalloids promote HF (Cotton et al. 2012).

Platelet counts are generally preserved early after trauma, but there seems to exist some degree of traumarelated dysfunction (Brown et al. 2011; Wohlauer et al. 2012). Known factors impairing platelet function, such as hypothermia, acidosis, consumption and dilution of coagulation factors, and HF, are frequent after trauma. Activation of platelets and generation of fibrin are mutually dependent processes. Injury to the endothelium will activate platelets leading to the transformation of glycoprotein IIb/IIIa into high-affinity receptors for fibrinogen, promoting a solid plug (Varga-Szabo et al. 2008). Further, the platelet membrane acts as an amplifier of the hemostatic process and facilitates activation and binding of coagulation factors (Furie and Furie 2008). Overall, it seems likely that platelets are a bigger contributor to clot strength than fibrin (Chakroun et al. 2006). Correlation between

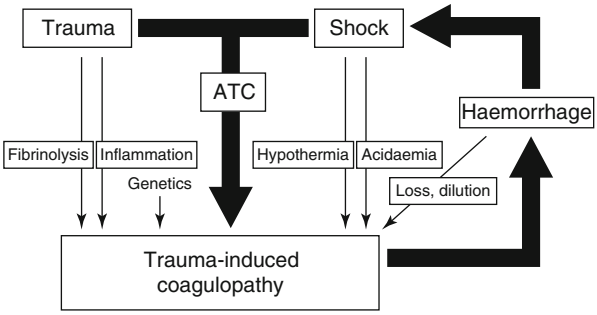

Fig. 18.2 Recognized mechanisms leading to trauma-induced coagulopathy (TIC) (From Davenport and Khan (2011) with permission)

platelet count and clot integrity, as analyzed by viscoelastic tests, has been demonstrated. However, studies examining functional characterization of platelets after trauma are sparse, and the pathophysiological role of platelets in this condition has yet to be defined (Rugeri et al. 2007; Plotkin et al. 2008).

Trauma-related impairment of hemostasis has been described with multiple terms, the most frequently used being acute traumatic coagulopathy (ATC), acute coagulopathy of trauma shock (ACoTS), endogenous acute coagulopathy (EAC), and trauma-induced coagulopathy (TIC). In this chapter, we use ATC as the term describing the endogenous component of trauma-related coagulopathy, while TIC describes the concomitant factors worsening coagulopathy further (Frith et al. 2010). While ATC occurs immediately after the injury, other mediators of TIC develop over time and in conjunction with measures against shock and resuscitation. TIC is multifactorial and involves all the components of the hemostatic system, notably dysfunctional platelets and activation of the endothelium (Fig. 18.2).

Six key initiators of TIC have been identified (Hess et al. 2008):

- Tissue trauma
- Shock
- Hemodilution
- Hypothermia
- Acidemia
- Inflammation

18.2.1 Tissue Trauma

Tissue damage activates coagulation via the exposure of subendothelial collagen and increased expression of tissue factor (TF). This leads to binding of von Willebrand factor (vWF), platelets, and activated factor VII (Mann 1999), as well as concomitant generation of large amounts of thrombin and fibrin (Roberts et al. 2006). Further, endothelial injury will also promote HF via a direct release of tPA and induce clot breakdown (Hrafnkelsdottir et al. 2001). All trauma patients have tissue injury to some extent. However, according to the type and mechanism of injury, the tissue damage load, expressed as an ISS, can be variable – crush or blast

injuries destroy more cells than an isolated penetrating injury. As mentioned above, tissue injury is a prerequisite, but in isolation is not sufficient to have a full picture of ATC (Frith et al. 2010).

18.2.2 Shock

Shock – next to tissue injury – seems to be the other key driver of ATC. Several studies have shown a linear relationship between the extent of systemic hypoperfusion, measured by base deficit (BD), and the degree of coagulopathy (Brohi et al. 2007a, b; Niles et al. 2008; Frith et al. 2010; Jansen et al. 2011). Systemic hypoperfusion seems to activate protein C via increased generation of the thrombin-thrombomodulin complex. aPC exerts an anticoagulant effect by irreversibly deactivating factors Va and VIIIa (Brohi et al. 2007a, b). Further, in shock, fibrinolysis is exacerbated through the combined effects of endothelial tPA release and the shock-mediated inhibition of PAI-1(Brohi et al. 2008). Cellular hypoperfusion and activation of inflammation are closely related. Hemorrhagic shock and resuscitation lead to alterations in microcirculation via the release of a multitude of inflammatory mediators, cytokines, and oxidants. The activation of inflammation and the induction of apoptotic cell death as a consequence of hypoxic cellular damage and ischemia-reperfusion phenomena are the presumed causes of secondary organ injury leading to organ failure and death (Duchesne et al. 2010). At the coagulation level, cellular hypoxia, thrombin, and various cytokines will together promote endothelial cell activation (ECA) (Faller 1999). ECA will induce a downregulation of thrombomodulin (TM) and enhance fibrinolysis via increased levels of PAI-1. Destruction of the endothelial glycocalyx limits activation of antithrombin and upregulates platelet-activating factor and the expression of TF (Johansson et al. 2011) (Fig. 18.3).

18.2.3 Hemodilution

During fluid resuscitation, the dilution of coagulation factors can be a major contributor to clinical coagulopathy (Armand and Hess 2003; Maegele et al. 2007). High volumes (>2,000 ml) of crystalloids or colloids during prehospital resuscitation are associated with a worse coagulation profile, an increased need for blood transfusion, and a higher incidence of organ failure (Wafaisade et al. 2010; Hubetamann et al. 2011; Hussmann et al. 2011). Further, administration of blood-products such as packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelets (PLT) may cause significant dilution due to the anticoagulant properties of their storage solutions. Coagulopathy is directly proportional to the volume of clear fluid infused, independent of their type (Haas et al. 2008a, b; Bolliger et al. 2009). Even in the absence of exogenous resuscitation, endogenous hemodilution occurs as a physiological response to hypovolemia. The shift of hypocoagulable fluid from the cellular and interstitial space into plasma will lead to minor dilution of

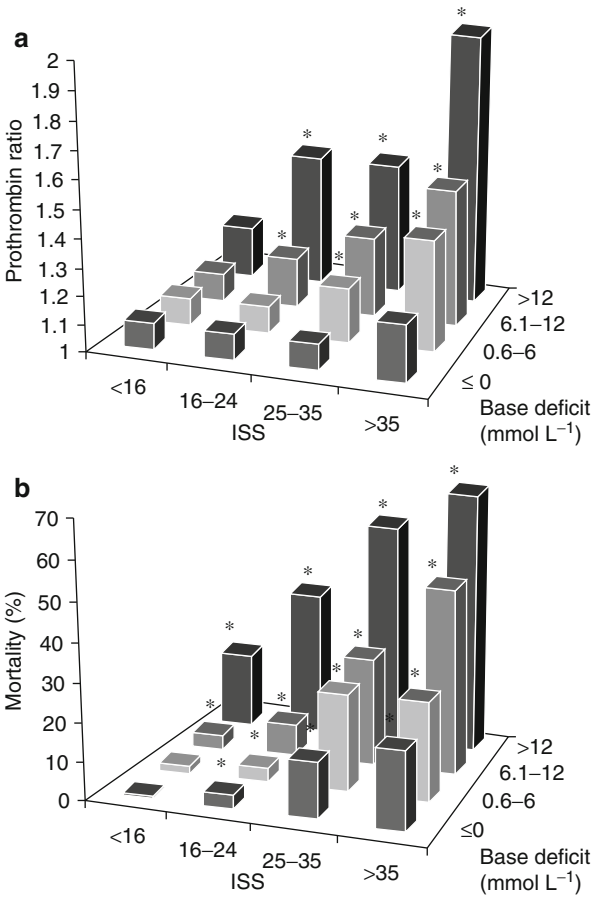

Fig. 18.3 Tissue trauma and systemic hypoperfusion appear to be the main drivers of ATC. (**a**) Median prothrombin ratios of patients grouped according to injury severity score (ISS) and base deficit (BD). (**b**) Mortality of patients grouped according to ISS and BD (From Frith et al. (2010) with permission)

coagulation factors but in insufficient quantities to explain established coagulopathy (Rizoli et al. 2011; Rourke et al. 2012). Fibrinogen is the first clotting factor to be reduced but initially remains above substitution thresholds (Martini 2011; Rizoli et al. 2011; Rourke et al. 2012).

18.2.4 Hypothermia

Trauma patients are prone to hypothermia. This is due to either environmental factors or administration of cold resuscitation fluids combined with the reduced heat production of maximally vasoconstricted musculature. Hypothermia has important, reversible effects on the functionality of coagulation factors, platelet protease activity, and fibrinolysis (Wolberg et al. 2004; Thorsen et al. 2011). The activity of TF or FVIIa complex decreases in a linear fashion with reduced body temperature. Hypothermia reduces platelet adhesion to vWF on endothelial surfaces, limiting the signal transduction from initial adhesion to activation. Whereas platelet function

starts to be impaired at temperatures below 35 °C, important functional decreases in protease activity occur only with severe hypothermia (Kermode et al. 1999; Martini 2009). Above 33 °C; however, isolated hypothermia probably has a minimal clinical impact on hemostasis, and some authors see hypothermia rather as a marker of the severity of shock and the resulting endogenous coagulopathy (Gruen et al. 2012).

18.2.5 Acidemia

Acidemia in trauma is most often due to hypoperfusion and may be enhanced by administration of large volumes of ionic chloride as found in normal saline (Hess et al. 2008). In animal models, inducing acidemia by infusing hydrochloric acid led to prolonged clotting times, reduced clot strength, and increased degradation of fibrinogen (Martini and Holcomb 2007). Low pH levels lead to structural changes of platelets (Djaldetti et al. 1979) and impairment of procoagulant protease functions (Meng et al. 2003). This reduces the activity of coagulation factor complexes, leading to impaired thrombin generation. Further, acidemia increases degradation of fibrinogen, promoting fibrinolysis (Martini and Holcomb 2007). At pH levels below 7.2, coagulation factor activity is reduced by 50 % and plasma protease activity is seriously impaired (Meng et al. 2003; Lier et al. 2008). Correction of acidemia alone, using buffer solutions such as sodium bicarbonate, for instance, has not been proven efficient for normalization of coagulopathy (Martini et al. 2006; Darlington et al. 2011).

18.2.6 Inflammation

Coagulation and inflammation are closely linked (Esmon 2005). The combination of tissue injury and shock is an important inducer of a systemic inflammatory response syndrome. Inflammation initiates clotting, decreases the activity of physiological anticoagulatory mechanisms, and impairs the fibrinolytic system (Gruen et al. 2012). The innate immune system is activated early after traumatic injury through the release of intracellular debris, exposure of the subendothelium, endothelial activation, and the hypoxic environment of the microcirculation. Further, resuscitation fluids have been shown to have immunomodulating properties. Crystalloids and colloids cause neutrophil activation in patients in hemorrhagic shock (Rhee et al. 1998, 2000), and crystalloids lead to degradation of glycocalyx, contributing to further activation of inflammation (Van der Linden and Ickx 2006). Immunomodulatory treatment strategies, limiting the activation of the inflammatory response, might constitute promising novel approaches in the future.

18.3 Diagnosis of Trauma-Induced Coagulopathy

There is no consensus about the definition and characterization of ATC. Diagnosis of ATC has so far been based on traditional plasma-based laboratory test results, such as abnormal aPTT, prothrombin time (PT), and international normalized ratio

(INR) (Brohi et al. 2003). Laboratory-based clotting tests have logistic issues, limiting their utility in acute trauma care, and there is an emerging consensus that such tests are inappropriate for monitoring coagulopathy and guiding therapy in trauma hemorrhage (Segal et al. 2005; Yuan et al. 2007; Toulon et al. 2009; Kashuk et al. 2010a, b). The absence of rapid diagnostic tools has been shown to lead to delayed correction of ATC and suboptimal use of blood products (Hess and Hiippala 2005; Gonzalez et al. 2007; Davenport et al. 2011). There is renewed interest in viscoelastic hemostatic assays (VHA), such as thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®). Several studies support the superiority of VHA in terms of guiding adequate blood product provision in comparison with traditional plasma-based coagulation tests (Afshari et al. 2011), and the use of TEG/ROTEM in massively bleeding trauma patients is recommended in current guidelines (Rossaint et al. 2010). Davenport et al. (2011) identified the typical thromboelastographic profile of ATC as slow clot formation and persistently reduced clot strength of around 40 %. This prospective study (the largest to date) on the diagnostic modalities of ATC identified a clot amplitude at 5 min (CA5) ≤35 mm as diagnostic marker of ATC; it had a greater sensitivity than PT in predicting the need for massive transfusion. Furthermore, all ROTEM parameters showed a negative predictive value of close to 100 % for massive transfusion, indicating that a normal ROTEM trace can be used for timely termination of massive hemorrhage protocols (Davenport et al. 2011). Based on current knowledge, it would seem reasonable to implement VHA-based algorithms allowing for a goal-directed resuscitation strategy, although evidence from clinical trials is still lacking (Dzik et al. 2011).

18.4 Management of Trauma-Induced Coagulopathy: Damage Control Resuscitation

A massively bleeding patient is a multidisciplinary challenge at every time point through the chain of resuscitation. Prompt recognition of established or pending hemorrhagic shock is crucial in order to minimize the time to hemostatic intervention and supportive care. Effective teamwork and communication are an essential part of this process.

Faced with trauma hemorrhage, the most important goal is to gain rapid control of the source of bleeding. In the 1990s, "damage control surgery" (DCS) was shown to improve survival for exsanguinating trauma patients (Duchesne et al. 2010). DCS advocates a focused effort to only correct life-threatening conditions during the initial intervention, while deferring definitive repair of less severe injuries to a later stage (Rotondo et al. 1993; Jaunoo and Harji 2009). In order to support the rapid restoration of patient homeostasis, it became clear that the focus had to go beyond the types and timings of operative interventions and that the nonsurgical part of resuscitation strategy had to follow a similar and supportive concept. Hemostatic resuscitation (HR), aimed at a carefully weighted and goal-directed restitution of lost volume and blood components, is crucial for improved outcome (Cotton et al. 2011; Curry et al. 2012). HR completes DCS to build a more comprehensive and multidisciplinary concept of "damage control resuscitation" (DCR). DCR aims to

rapidly restore physiological conditions, facilitate clotting, improve hypoperfusion, and restore endothelial integrity. HR relies principally on four pillars:

- Early hemorrhage control (damage control surgery)
- Permissive hypotension
- Limited fluids
- Rapid reversal of coagulopathy

Administration of large volumes of fluid before achieving control of a hemorrhage will, independently of the type of fluid, contribute to worsening coagulopathy (Bolliger et al. 2009). Bleeding will be enhanced through increased perfusion pressure, reversal of autoprotective vasoconstrictory reflexes, dislocation of spontaneous clotting, and dilution of coagulation factors (Stern et al. 1993, 1995). The recognition of these negative effects has led to the doctrine that for trauma patients in need of DCS, "only fluids that either clots or carry oxygen should be given" (Dutton 2012).

The concept of permissive hypotension advocates deliberate maintenance of blood pressure at subnormal values until surgical control of hemorrhage has been achieved. Systolic blood pressure is thus limited to the minimum necessary to maintain the perfusion of vital organs; in animal studies, this lead to reduced blood loss and improved survival (Bickell et al. 1994; Shoemaker et al. 1996; Burris et al. 1999; Jansen et al. 2009; Li et al. 2011). This concept is adequate only for a limited time, and systolic blood pressure values need to be adapted to higher values in case of concomitant traumatic brain injury (Li et al. 2011). Although RCTs showing improved survival and fewer complications using permissive hypotension are sparse, the concept of low-volume resuscitation has gained wide acceptance (Bickell et al. 1994; Shoemaker et al. 1996; Burris et al. 1999; Li et al. 2011; Morrison et al. 2011). The threshold for minimal systolic blood pressure remains controversial. Concerns about aggravating hypoperfusion through insufficient however perfusion pressure and enhancing post-injury coagulopathy with further activation of the innate immune response have not been conclusively addressed yet.

Early therapy with blood components is part of the core strategy for trauma-induced coagulopathy. Retrospective studies suggest that improved survival involves a transfusion strategy with a high ratio of FFP to PRBC (Godier et al. 2012). A high-dose approach has also been recommended for platelet transfusion and fibrinogen concentrates (Inaba et al. 2010; Rourke et al. 2012). However, RCTs providing evidence are still awaited. Preventing hypothermia, correcting acidosis by restoring adequate tissue perfusion, and avoiding dilution of coagulation factors are still valid doctrines and compose the core of strategy for avoiding worsening TIC.

18.5 Components of Hemostatic Resuscitation

18.5.1 Packed Red Blood Cells

Tissue oxygenation remains the principle goal of resuscitation. Due to the relationship between tissue oxygenation, impaired hemostasis, and mortality, the most important

blood component for the prevention and treatment of ATC are packed red blood cells (Hess et al. 2008; Dzik et al. 2011). Erythrocytes contribute to hemostasis by promoting marginalization of platelets and allowing their interaction with the endothelium (Valeri et al. 2007). An inverse correlation has been demonstrated between the hematocrit and bleeding time in vitro (Eugster and Reinhart 2005). Furthermore, erythrocytes support thrombin generation through the exposure of procoagulant phospholipids (Peyrou et al. 1999) and activate platelets via liberation of adenosine diphosphate (ADP) (Joist et al. 1998). Clearly defined targets for hemoglobin or hematocrit during active hemorrhage are lacking, but the most recent European guidelines recommend a hemoglobin target of 7–9 g/l (Spahn 2013).

18.5.2 Fresh Frozen Plasma

Transfusion of FFP in massively bleeding trauma patients is an essential part of most guidelines, even though the clinical efficacy of FFP is unproven (Stanworth et al. 2004). Nevertheless, most experts agree that FFP is beneficial in cases of important bleeding and concomitant coagulopathy. Several retrospective analyses suggest that early administration of FFP in a 1:1 ratio with PRBC might be beneficial (Borgman et al. 2007; Cotton et al. 2008; Gunter et al. 2008; Maegele et al. 2008; Spinella et al. 2008; Zink et al. 2009). This conclusion, however, might be subject to "survivor bias": FFP is often administered at a delayed time point; thus some patients did not survive because they received plasma, but rather they received plasma because they survived long enough (Snyder et al. 2009).

The optimal ratio of FFP to PRBC remains unclear. Despite the low quality of evidence, actual data seem to tend to a more liberal use of FFP, indicating that a higher FFP to PRBC ratio is associated with improved survival (Holcomb et al. 2008; Snyder et al. 2009; Murad et al. 2010; Johansson et al. 2012). The first RCT on this topic, the PROPPR trial (http://cetir-tmc.org/research/proppr), is ongoing and will hopefully bring more insights. Currently, the European guidelines recommend FFP administration with an initial dose of 10–15 mg/kg followed by goal-directed management (Spahn 2013).

18.5.3 Platelet Concentrates

Even in severely injured patients, PLT counts on admission are rarely below critical levels (Murthi et al. 2008; Stansbury et al. 2013). The fall in PLT count seen later in the resuscitation time course is probably due to dilution. Low PLT count at admission, however, is strongly related to mortality and a need for PRBC (Brown et al. 2011; Stansbury et al. 2013). High PLT to PRBC transfusion ratios have reportedly increased survival in massively transfused patients (Inaba et al. 2010; Holcomb et al. 2011; Johansson et al. 2012). However, evidence is even scarcer than for FFP ratios. Current recommendations indicate maintaining a PLT count above 100,000/µl with an initial dose of 4–8 platelet concentrates (Spahn 2013). However, there is

currently no clear evidence to support the use of up-front administration of PLT concentrates. In trauma patients previously treated with antiplatelet drugs, PLT transfusion does not reverse their action and no benefit has been demonstrated (Flower and Smith 2011).

18.5.4 Antifibrinolytic Drugs

Fibrinolytic processes are an essential part of ATC and HF has a mortality rate of close to 80 % (Brohi et al. 2008; Kashuk et al. 2010a, b; Schochl et al. 2011; Tauber et al. 2011). Antifibrinolytic agents reduce blood loss in patients (with both normal and exaggerated fibrinolytic response to surgery) by inhibiting plasminogen activation and therefore activation of fibrinolysis (Henry et al. 2011). The recent placebo-controlled randomized CRASH-2 trial including over 20,000 trauma patients has shown a significant reduction in all-cause mortality of approximately 10 % for trauma patients receiving TXA versus placebo and to an approximately 30 % reduction in transfusion requirements. Benefit was maximal when administration was early – within 3 h of injury (CRASH-2 trail Collaborators et al. 2010). This might be due to high levels of free tPA detected early after a traumatic event, resulting in enhanced plasmin generation and therefore increased fibrin degradation products (Brohi et al. 2007a, b, 2008; Rugeri et al. 2007; Levrat et al. 2008). However, administration later than 3 h after injury was associated with worsened outcome (CRASH-2 trail Collaborators et al. 2010). The risk for thromboembolic complications appeared to be relatively low. The use of antifibrinolytic drugs, such as TXA, is therefore recommended in patients suffering from, or at risk of, hemorrhagic shock (Association of Anaesthetists of Great et al. 2010).

18.5.5 Fibrinogen

Fibrinogen is an endogenous acute phase protein and an essential substrate for clot formation. Activated by thrombin, fibrinogen forms insoluble fibrin strands and functions as a ligand for platelet aggregation. After major trauma, fibrinogen is one of the first coagulant proteins to reach critically low concentrations, and hypofibrinogenemia has been associated with poor outcome (Harrigan et al. 1989; Hiippala et al. 1995; Rourke et al. 2012). Administration of crystalloids and colloids leads to dilution, functional deficiency, and abnormal fibrinogen polymerization. Furthermore, hypothermia increases the breakdown of fibrinogen as its production is impaired in acidemia. The use of fibrinogen concentrate results in reduced perioperative bleeding and transfusion requirements (Rahe-Meyer et al. 2009), improves clot strength in dilutional coagulopathy (Haas et al. 2008a, b), and shows that higher fibrinogen to PRBC ratios have been associated with improved survival (Stinger et al. 2008). Recent data indicate that coagulopathy induced by synthetic colloids may be reversed by fibrinogen administration (Fenger-Eriksen et al. 2009). Despite the lack of high quality RCT data supporting the benefit of fibrinogen supplementation, European

guidelines recommend supplementary fibrinogen in trauma hemorrhage in cases of significant bleeding when VHA show signs of functional fibrinogen deficit and/or a plasma fibrinogen level of <1.5–2 g/l (Spahn 2013).

18.5.6 Calcium

Hypocalcemia after trauma occurs during resuscitation with citrate-containing blood products, most importantly with FFP and PLT. Further, hypocalcemia can be attributed to the binding of calcium to lactate or through colloid-induced hemodilution (Vivien et al. 2005). Calcium has an important role in clotting, acting as a bridge between vitamin-K-dependent coagulation factors, phospholipids, and the endothelium. It protects fibrinogen from proteolysis, therefore contributing to the stabilization of fibrin polymerization. Low cytosolic calcium also impairs PLT activity (Lier et al. 2008). Despite the lack of solid evidence, recommendations suggest maintaining levels of ionized calcium above 1.1 mmol/l (Lier et al. 2008; Spahn 2013).

18.5.7 Prothrombin Complex Concentrate

Coagulation factor concentrates allow a more rapid reversal of established coagulopathy than that achieved with plasma alone. Several studies have demonstrated the successful use of prothrombin complex concentrate (PCC) in trauma-induced coagulopathy, leading to reduction in use of blood products and improved survival (Honickel et al. 2011; McSwain and Barbeau 2011; Patanwala et al. 2011). However, PCC does not provide any volume expanding, raising the question of whether it can be used concomitantly with FFP for restoring volume. To date, there have been no prospective RCT demonstrating a definite clinical benefit of PCC over FPP. Therefore, the use of PCC in traumatic hemorrhage is currently off-label, and the risk of thrombotic complications needs to be considered (Sorensen et al. 2011).

18.5.8 Factor XIII

Factor XIII (FXIII) is fundamental to clot firmness because it binds to platelets via their GP IIb/IIIa receptor. Furthermore, FXIII increases clot resistance against fibrinolysis by cross-linking to fibrin. In combination with functional platelets, it appears to have inhibitory effects on plasmin-mediated HF (Dirkmann et al. 2012). Trauma and major hemorrhage are known causes of acquired FXIII deficiency (Egbring et al. 1996). Its substitution has been shown to improve clot firmness and might therefore contribute to reduced bleeding (Nielsen et al. 2004). It has also been shown to have some compensatory effects in settings with low fibrinogen levels (Theusinger et al. 2010). A clinical combination suggesting the need for substitution of FXIII might be weak clot strength despite adequate fibrinogen levels. A clear role for FXIII administration to bleeding trauma patients, however, has yet to be defined.

18.5.9 Recombinant Activated Factor VII

Supraphysiological doses of recombinant activated factor VII (rFVIIa) induce a thrombin burst via the transformation of fibrinogen to fibrin and direct binding to platelets. In several case reports, administration in trauma-related bleeding has been shown to reduce PRBC requirements and improve hemostasis (Martinowitz et al. 2001; Dutton et al. 2004). A large multicenter RCT assessing the efficacy and safety of rFVIIa in bleeding trauma patients was unable to show any survival benefit but found an increased incidence of arterial thromboembolic events (Boffard et al. 2005; Hauser et al. 2010).

Although it is currently not an approved indication, the European guidelines for management of bleeding after trauma recommends considering rFVIIa as a "last-resort" drug in persistent major bleeding in blunt trauma (Rossaint et al. 2010). Prerequisites are control of surgical bleeding, restoration of adequate hematocrit, PLT and fibrinogen levels, as well as correction of acidosis, hypothermia, and hypocalcemia.

18.6 Resuscitation Strategies: Formula Driven Versus Goal Directed/Laboratory Driven

Clinical pathways in healthcare tend to improve the quality of the delivered care (Rotter et al. 2010). Timely provision of blood products to a massively bleeding patient is a challenge for any institution. The concept of hemostatic resuscitation calls for the immediate readiness of components so as to enable their delivery in an empirically agreed ratio on site. The implementation of massive transfusion protocols (MTP) has been shown to facilitate this process (Cotton et al. 2009; Young et al. 2011). Based on a mathematical model suggesting that a 1:1:1 ratio of PRBC to FFP to PLT will come close to the composition of whole blood, formula-driven resuscitation strategies have been advocated as the structural base for MTP (Hess et al. 2008). Retrospective studies suggesting that early transfusion of FFP at a fixed, high ratio will improve survival rates support the formula-driven approach (Borgman et al. 2007; Cotton et al. 2008; Gunter et al. 2008; Maegele et al. 2008; Spinella et al. 2008; Zink et al. 2009). However, in a study correcting for survivor bias, no similar reduction in mortality was seen (Snyder et al. 2009). Regarding the incidence of morbidity, there seems to be a controversy in the literature as to whether formula-driven care increases or decreases the risk of multiple organ failure and other complications in the trauma population (Maegele et al. 2008; Cotton et al. 2009). Furthermore, empirical administration of blood products can lead to over-transfusion and has been shown to result in delayed correction of ATC and suboptimal use of blood products (Hess and Hiippala 2005; Gonzalez et al. 2007). Lastly, identification of patients in need of this formula-based approach may be difficult as there is no evidence-based strategy allowing for adequate triggers of a MTP. To date, the vast majority of studies on formula-driven resuscitation focus essentially on finding the optimal ratio of empirical blood-product use. However, whether the concept of formula-driven resuscitation improves coagulation parameters and patient outcomes has not been reliably addressed yet.

In the absence of clear evidence, a 2011 conference on massive transfusion gave a consensus opinion that neither laboratory testing-based transfusion strategies nor predetermined blood component ratios would provide the optimal hemostatic support for bleeding trauma patients (Dzik et al. 2011). Emphasis is put on the importance of individually tailored therapy over rigid, predetermined protocols for hemostatic resuscitation strategies. In conclusion, a three-strategy management approach composed of "up-front hemostatic support, a foundation ratio of blood components, and a goal-directed adjustment of transfusion therapy" has been recommended (Box 18.1). Better and faster laboratory testing, rather than formula-driven transfusion practices, may be the preferred strategy (Callum et al. 2009). Point-of care testing, such as viscoelastic tests, seems to be a promising option for real-time transfusion decision making (Davenport et al. 2011; Curry et al. 2012).

Box 18.1
Three-strategy approach to transfusion in trauma patients at risk/with verified massive hemorrhage (Adapted from Dzik et al. (2011))

1. Early administration of tranexamic acid (1 g over 10 min followed by an infusion of 1 g over 8 h)
2. If critical bleeding, immediate administration of blood components (RBC and FFP) in a fixed ratio
3. Adjustments of the fixed ratio of transfusion support based on clinical course and results of goal-directed blood therapy

Conclusion

Coagulopathy after traumatic injury is incompletely understood and has a poor prognosis. Early identification and proactive management is crucial for optimal patient outcome. The concept of hemostatic resuscitation has become a pivotal part of major trauma management. However, solid evidence for optimal transfusion strategies is lacking. In the massively bleeding patient, a readily available up-front hemostatic support with a predefined foundation ratio of blood components seems adequate as first-line approach. This standardized initial step will ideally be followed by an individualized goal-directed therapy, guided by the clinical course and point-of-care testing.

Whichever strategy is chosen – the formula-driven or the individually tailored approach – the 4 pillars of damage control resuscitation remain the major determinants in achieving the best possible outcome:

- Early hemorrhage control
- Permissive hypotension
- Limited fluids
- Rapid reversal of coagulopathy

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Perioperative Hemostasis in Neurosurgery

19

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19.1 Particularities of Neurosurgical Patients

Neurosurgeons, intensive care specialists, and anesthesiologists who deal with neurosurgical management know the crucial factors surrounding coagulation and hemostasis disorders. However, it is striking to note that most neurosurgery textbooks hardly mention coagulation management. With regard to the particularities of neurosurgical patients, we will describe the pathophysiological backgrounds of the specific mechanisms that lead to hemostatic perturbations, the implications of neurological pathologies and surgical procedures on hemostasis, and the effects of specific drugs on coagulation.

19.1.1 Specific Mechanisms Leading to Hemostatic Disorders

19.1.1.1 Activation of Coagulation Processes

Various mechanisms launch and accelerate the coagulation process and platelet activation: endothelial injury, ischemia, and secondary inflammatory reactions all trigger the release of brain thromboplastins, thrombin, iron, and the degradation products of lysed red blood cells that will result in hemostatic perturbations.

19.1.1.2 Release of Thromboplastins

Hemostasis is a complex process; tissue factor, or thromboplastin, has a central role in the initiation of coagulation. Thromboplastins are widely expressed on the

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surface of normal brain tissue cells, and their thromboplastin content increases after brain trauma (Pathak et al. 2005; Goh et al. 2005). Thromboplastins can be expressed on the surface of injured blood vessels in brain lesions. This expression can also result from inflammatory or tumoral processes. Increased expression of tissue factor has been reported in astrocytic tumors and is correlated to their degree of malignancy (Guan et al. 2002).

Injured brains and certain tumors in particular have a direct effect on fibrinolysis (Goh et al. 1997). Tissue plasminogen activator (tPA) is an initiator of fibrinolysis, and increased levels of tPA are reported in brain tumors. Hyperfibrinolysis is also seen in trauma-related bleeding. This cascade of mechanisms can result in an exaggerated response called disseminated intravascular coagulation (DIC).

Hyperfibrinolysis can sometimes result from factor XIII deficiency, as this factor will catalyze fibrin cross-linking into stable polymers (Gerlach et al. 2002). Cases of postoperative bleeding have been reported in such situations (Vrettou et al. 2010), and some authors recommend screening factor XIII levels before neurosurgery (Gerlach et al. 2002).

19.1.1.3 Role of Thrombin and Iron

Recent advances in knowledge of the mechanisms underlying intracranial, hemorrhage-induced brain injuries have focused attention on the role of the thrombin and iron released by red blood cell lysis. In vitro, high concentrations of thrombin will cause neuronal and astrocyte death. The infusion of large doses of thrombin into brain tissue causes inflammatory reactions, with microglia activation, cell infiltration and proliferation, brain edema, and finally neuronal death (Xi et al. 2006). This early brain edema is partially due to an increased permeability of the blood-brain barrier (Lee et al. 1997). Interestingly, these effects seem to be attenuated by the infusion of nonclotting heparinized blood (Xi et al. 1998). However, thrombin can also have neuroprotective effects. As an essential component of the coagulation cascade, thrombin's first role is to stop bleeding (Mayer et al. 2005). Many studies have shown a beneficial effect on the brain of low concentrations of thrombin, with reduction of injury size in models of cerebral ischemia or hemorrhage (Xi et al. 2003).

Various studies suggest that brain edema after intracranial hemorrhage is attributable to red blood cell lysis (Wu et al. 2006). The importance of the edema appears to be related to an increased blood-brain barrier permeability resulting from the toxic effects of the degradation products of lysed red blood cells (Xi et al. 2001). Red blood cell lysis can result in iron release, and intracerebral iron infusion is shown to be a direct cause of brain edema or of the promotion of thrombin-induced brain edema (Huang et al. 2002).

19.1.2 Effects of Brain Injury and Neurosurgical Pathologies on Hemostasis

Brain injuries and brain tumors, as well as other neurosurgical procedures in general, can have an impact on overall coagulation, leading to thrombotic or hemorrhagic disorders (Seifman et al. 2011). This can be explained by an imbalance between

procoagulant and anticoagulant systems, both locally and systemically, and by the expression of several substances in physiological or pathological cerebral tissues. These substances include tissue plasminogen activator and tissue factor, the latter known as the main initiator of coagulation processes in the cell-based model of coagulation activation (Gerlach et al. 2009). Hemorrhagic coagulopathy from cerebral or systemic causes raises a significant risk of secondary central nervous system injury by the hemorrhagic progression of lesions. Thrombotic events, however, will only affect global outcome.

19.1.2.1 Thrombosis

Hypercoagulability can be detected during neurosurgical procedures as soon as the intraoperative period (Abrahams et al. 2002). Deep venous thrombosis and pulmonary emboli are frequent complications in the neurosurgical setting. Risk factors include intracranial surgery, age, active malignancy, and hemi/para-paresia or paraplegia. Surgery for brain tumors and vertebro-medullary trauma is considered to be at a high risk of thromboembolic complications. Symptomatic deep venous thrombosis can affect up to 32 % of patients undergoing brain tumor neurosurgery (Agnelli 1999). The incidence of symptomatic and asymptomatic deep venous thrombosis ranges from 4 to 34 % for all causes of intracranial surgery (Hamilton et al. 2011) and from 1.5 to 18 % for subarachnoid hemorrhage (Vespa et al. 2011). The risk of thrombosis is heterogenous during spinal surgery: vertebro-medullary traumas show a high incidence of symptomatic deep venous thrombosis (12–23 %) and asymptomatic deep venous thrombosis (81 % diagnosed by phlebography), whereas the risks for other surgical procedures are mild (osteosynthesis and extended laminectomy, 0.3–2.7 %) or low (herniated disc or less than two levels of laminectomy, <1 %) (Audibert et al. 2005). We have seen that thromboplastin release increases in traumatic brain injury (TBI) and tumoral lesions, but procoagulant mediators are also promoted in such situations. Significantly higher concentrations of plasma tissue factor pathway inhibitor have been reported in patients with brain tumors (Gerlach et al. 2003).

19.1.2.2 Bleeding

Coagulopathy resulting from brain injury has been extensively studied. It includes multiple mechanisms: release of cerebral tissue factor and activation/amplification of coagulation, disseminated intravascular coagulation, hyperfibrinolysis, platelet dysfunction, brain and global hypoperfusion, and activation of protein C.

These mechanisms are well documented in trauma settings (Laroche et al. 2012). They can occur in isolation or in association with acute traumatic coagulopathy, acidosis, and hypothermia. Coagulopathy due to TBI is statistically associated with the severity of injury, progression of hemorrhagic lesions, and increased morbidity and mortality. Mortality rises from 8 to 32 % in cases of hemorrhagic progression lesions (Allard et al. 2009). It is, however, difficult to establish a strong unilateral causal relationship between coagulopathy and the severity of brain injury: hemorrhagic progression of lesions seems to be partly predetermined by the primary injury whatever the state of coagulation (Kurland et al. 2012), and the severity of the primary injury determines the severity of coagulopathy. This is probably a phenomenon of autoamplification: the more severe the primary injury, the more severe the

consecutive brain hypoperfusion and the worser the coagulopathy, affecting the evolution of lesions and outcome. This could explain why it may not be possible to completely reverse outcome even while normalizing coagulation. However, acquired iatrogenic coagulopathy is a risk factor for bad outcomes. The incidence of TBI-related coagulopathy ranges from 10 to 97 % depending on severity and definition. Its mean incidence is 33 % (Harhangi et al. 2008). The time course of TBI coagulopathy has been studied. It occurs in the first 5 days, mostly in the first 24 h (mean 23 ± 2 h post admission). Early onset (<12 h) has been associated with greater severity and poorer outcome (Lustenberger et al. 2010). It is important to note that therapeutic hypothermia does not seem to cause hemorrhagic progression of brain contusions (Resnick et al. 1994). What is observed in brain trauma is also relevant in neurosurgery, and some of the mechanisms described in TBI coagulopathy have been documented in the perioperative period (Goh et al. 1997).

19.1.3 Effects and Management of Specific Drugs

Both congenital and acquired coagulation disorders can be involved in inducing or worsening brain injury, particularly intracerebral hemorrhage (ICH). Coagulation disorders induced by medical therapies are of particular interest because of the wide use of such drugs and procedures for other diseases.

19.1.3.1 Effects and Management of Antiepileptic Drugs

The use of antiepileptic drugs has been related to hemostatic disorders, mainly platelet dysfunction. Thrombocytopenia is the most frequently reported hemostatic side effect (Priziola et al. 2010). This has been reported with valproic acid (Lackmann 2004), carbamazepine (Finsterer et al. 2001; Taher et al. 2012), phenytoin (Holtzer and Reisner-Keller 1997), levetiracetam (Sahaya et al. 2010), and lamotrigine (Okur et al. 2012). In addition, gabapentin and valproic acid have been associated with hypofibrinogenemia, acquired von Willebrand syndrome, and lowered factor XIII (Gerstner et al. 2006; Pan et al. 2007). Despite these observations, the pathophysiological mechanisms of these disturbances and their association with increased bleeding or blood product administration remain unclear. The literature reveals many cases of thrombocytopenia in patients on valproic acid antiepileptic therapy. Topf et al. (2011) used calibrated automated thrombography to study the effects of valproate antiepileptic therapy on thrombin generation; however, they found no major differences between their 90 patient samples and controls not using the drug. Manohar et al. (2011) evaluated 84 children who had undergone epilepsy surgery and examined the effects of antiepileptic treatments on perioperative coagulation parameters, blood loss, and the amount of blood products transfused. They concluded that antiepileptic drugs did not appear to be associated with perioperative coagulation disorders or blood transfusion requirements.

Antiepileptic drugs have numerous positive effects which, despite their effects on hemostasis, must be taken into account in patients undergoing potentially hemorrhagic surgery.

19.1.3.2 Effects of Hydroxyethyl Starch on Coagulation

Hydroxyethyl starches (HES) are widely used to restore intravascular volume. This can be particularly important in neurosurgical procedures to maintain cerebral or medullary perfusion pressure. Recent developments have focused on the effects of HES on hemostasis, questioning its clinical use. The impairment of hemostasis is dependent on the physicochemical characteristics of HES solutions, such as molecular weight, pattern of hydroxyethyl substitution at carbon positions C2 and C6 (C2/C6 ratio), and molar substitution (Kozek-Langenecker 2005). HES use has been related to acquired von Willebrand syndrome and decreased coagulation factor VIII activity. The use of HES has been associated with increased risk of bleeding, alteration of fibrin function, and a decrease in platelet count in patients with cerebrovascular diseases (Treib et al. 1996a, b); however, many of these studies were conducted with old-generation HES (Treib et al. 1997). No clear association with increased transfusion requirements has been reported with the latest generation of 6 % hydroxyethyl starch 130/0.4, but studies are of poor-quality and further high-quality trials are needed (Gattas et al. 2012). No major changes in coagulation variables were found in patients with severe brain injury despite large HES 130/0.4 doses administered (Neff et al. 2003). Nevertheless, clinicians must be aware of these effects on hemostasis, particularly when HES is used repeatedly over several days, and maximal doses must absolutely be respected.

19.1.3.3 Effects of Hypertonic Saline and Mannitol on Hemostasis

Both hypertonic saline and mannitol are used in neurosurgery to decrease intracranial pressure (osmotherapy). They can also be used to quickly restore intravascular volume in hemorrhagic situations. Nevertheless, they do interfere with blood coagulation (Brummel-Ziedins et al. 2006), altering plasma clotting time and platelet aggregation (Reed et al. 1991). Hypertonic saline has also been shown to induce hyperfibrinolysis in vitro (Tan et al. 2002). These effects on coagulation are particularly obvious in thromboelastometric tests, which show altered fibrin clot firmness (Luostarinen et al. 2011). As these drugs cause significant side effects, such as hypernatremia, they must be considered as rescue drugs and their use limited to specific situations.

19.1.3.4 Effects of Desmopressin on Coagulation

Desmopressin is a synthetic analogue of the natural hormone vasopressin, characterized by its strong and prolonged antidiuretic effects but decreased pressor activity. Its use is common in the treatment of neurosurgically induced diabetes insipidus. Desmopressin is also a classic treatment for von Willebrand disease, mild hemophilia A, or platelet dysfunctions (Mannucci et al. 1977), and it can be proposed to reduce blood loss in surgical hemorrhage. Desmopressin will increase the plasmatic concentration of coagulation factor VIII, von Willebrand factor, and t-PA; it will also promote platelet adhesion. These effects are dose-dependent (Aberg et al. 1979), and the optimal hemostatic effect seems to be obtained with a dosage of 0.3 μg/kg administered intravenously (Lethagen 1994).

19.1.3.5 Effects and Management of Antiplatelet Agents in Neurosurgery

Patients undergoing neurosurgery often suffer from significant cardiovascular comorbidities. Antiplatelet (AP) therapies are thus commonly encountered. Theoretically, this treatment is usually interrupted before neurosurgical interventions because of the potential for perioperative bleeding. Data is more consistent with aspirin than with thienopyridines, which seem to have worse effects on bleeding. Risk of spontaneous ICH is very low in patients receiving aspirin (0.2 events per 1,000 patient years) (Gorelick and Weisman 2005). However, aspirin use before the onset of ICH has been shown to be associated with an increase in size of the hematoma and higher mortality (Saloheimo et al. 2006). This was confirmed in a meta-analysis comparing AP therapy to no-AP therapy at the time of intracranial hemorrhage (Thompson et al. 2010). It is interesting to note that AP therapy was associated with increased mortality, but not with poor functional outcome. Similarly, mortality after traumatic brain injury is higher in patients receiving AP medication, particularly if they present hemorrhagic contusions (Beynon et al. 2012).

However, this interruption itself can have dramatic consequences, as patients will be at a high risk of perioperative thromboembolism. Depending on the AP medication itself (aspirin, clopidogrel, or glycoprotein IIb/IIIa inhibitors), on its indication (coronary stent implantation vs. carotid artery stenosis), and the type of surgery (intracranial vs. spinal surgery, planned vs. emergency surgery), risks will be different and AP therapy disruption will have to be balanced against the risk of thromboembolic events. Glycoprotein IIb/IIIa inhibitors like abciximab, eptifibatide, and tirofiban have an intense and sustained effect on platelet function and therefore dramatically more pronounced effects on bleeding than aspirin.

Because AP medications do not decrease platelet count but rather alter their function, standard biological tests do not offer a proper assessment: a normal platelet count is no guarantee of satisfactory perioperative primary hemostasis. Whole-blood in vitro systems like the platelet function analyzer (PFA-100®) can be useful to investigate platelet function, helping clinicians to decide whether or not to interrupt AP therapy before planned surgery (Kottke-Marchant et al. 1999). Similarly, whole-blood POC platelet function (Multiplate®) can detect possible unknown AP medications in emergency situations or in comatose patients (Weber et al. 2008).

There are no guidelines or recommendations for the management of platelet function substitution in such situations. Decisional algorithms integrating clinical data, and both laboratory and POC information, can be proposed to help manage AP therapy in these patients (Figs. 19.1 and 19.2).

19.1.3.6 Vitamin K Antagonists

Vitamin K antagonists (VKA) are involved in 10–20 % of spontaneous ICH, representing an annual incidence of 2.2 % of treated patients (Quinones-Hinojosa et al. 2003). Furthermore, the onset of ICH in these patients is complicated by a higher frequency of hematoma enlargement (56 % vs. 26 % in patients without oral anticoagulation) and a higher mortality (62 % vs. 17 %) (Cucchiara et al. 2008). Ongoing

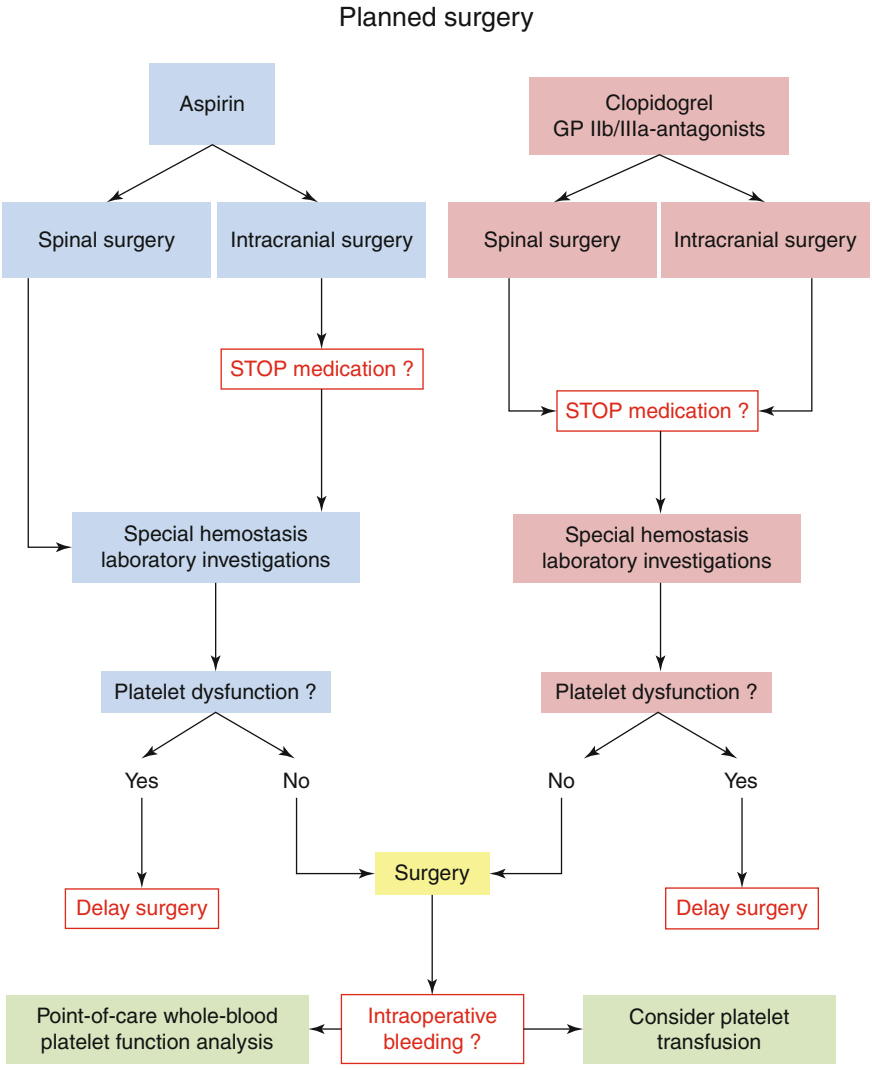

Fig. 19.1 Management of antiplatelet agents in planned neurosurgery (Gerlach et al. 2009; Beynon et al. 2012; Okano et al. 2014)

warfarin treatment also dramatically increases mortality in patients suffering traumatic brain injury (40 % vs. 21 %) (Lavoie et al. 2004). VKA should therefore be withheld from patients before a planned neurosurgical intervention. Usually, interrupting VKA treatment 4 days prior to surgery will normalize the international normalized ratio (INR). Depending on the therapeutic indication and the thrombotic risk and potential consequences, anticoagulation can be maintained using

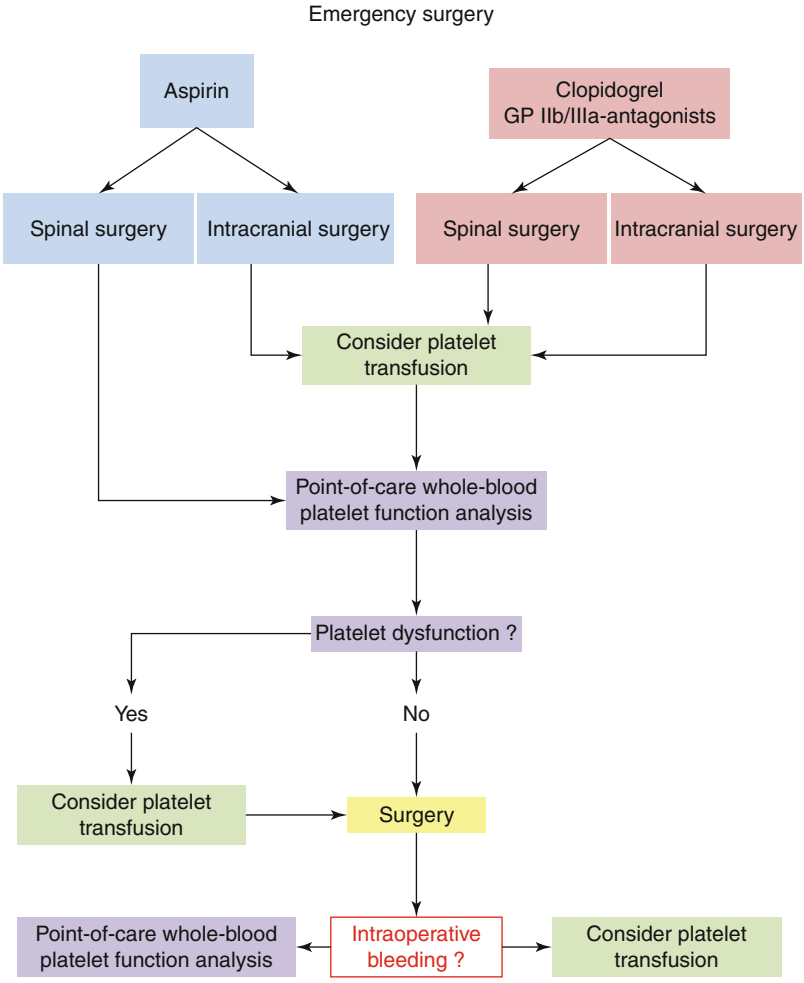

Fig. 19.2 Management of antiplatelet agents in emergency neurosurgery (Beshay et al. 2010; Batchelor and Grayson 2013; Beynon et al. 2013; Li et al. 2013)

unfractionated heparin, but this should be stopped 6 h before surgery. In case of emergency surgery, VKA therapy can be reversed without delay using prothrombin complex concentrates (PCC) and vitamin K.

19.1.3.7 New Oral Anticoagulants

This new family includes factor Xa inhibitors (apixaban, rivaroxaban) and direct thrombin inhibitors (dabigatran). These anticoagulants have all shown similar results in preventing primary and secondary ischemic stroke in atrial fibrillation, including a lower incidence of spontaneous ICH. There are concerns, however, about the reversal of these drugs, which seems to be more difficult than with vitamin K antagonists (Mittal and Rabinstein 2012).

19.1.3.8 Thrombolytics

Intravenous thrombolysis for myocardial infarction or pulmonary embolism shows a quite low incidence of spontaneous ICH (less than 2 %) (Patel and Mody 1999). However, the incidence is higher following thrombolysis for ischemic stroke: rates between 2.4 and 10.7 % have been described following intravenous thrombolysis, 7.8–15.4 % following intra-arterial mechanical plus chemical thrombolysis, and 6.3–9.9 % following intra-arterial procedures following intravenous thrombolysis (Mokin et al. 2012). This can be explained by the increased fragility of ischemic brain tissue, particularly due to the early disruption of the blood-brain barrier. In contrast, modern thrombolytic agents (alteplase) have very short half-lives, and there is usually no use in providing antagonization. Association with other medications which interfere with hemostasis and coagulation seems, of course, to increase the risk of bleeding.

Spinal complications are rare after thrombolytic therapy and usually present as epidural hematoma (Clark and Paradis 2002).

19.1.4 Neurosurgical Techniques

In addition to bleeding induced by surgery itself, certain neurosurgical techniques can be responsible for hemostatic disturbances. Patient positioning can induce bleeding as the upright position causes modifications to intracranial dynamics. Excessive cerebrospinal drainage and intraoperative mechanical brain shifting also contribute to bleeding. Decompressive surgery can also be responsible for a dangerous increase in blood flow that may lead to hemorrhagic complications in the edematous brain area.

19.2 Evaluation of Hemostatic Changes in Neurosurgical Patients

19.2.1 Clinical Evaluation of Hemostatic Disturbances in Neurosurgical Patients

The anatomical specificities of the central nervous system can lead to diagnostic and therapeutic difficulties, as even a small volume of blood can have dramatic consequences, and the diagnosis of bleeding can be delayed because of a lack of obvious hemorrhagic exteriorization. Sometimes, the first sign of a bleeding disorder will be a neurological deterioration in the patient. When available, the patient's medical history will be invaluable. Preexisting hemostatic defects can be detected at a preanesthetic consultation, and some authors have proposed standardized questionnaires to evaluate coagulation on admission (Koscielny et al. 2004). In some situations, hemostatic perturbations can be discovered during surgery. This is particularly true in emergency situations, with comatose or sedated patients, or with unknown coagulation diseases. Thus, the surgeon's appreciation of potential bleeding and hemostasis constitutes precious information that should not be neglected.

Multidisciplinary, intraoperative communication and cooperation are essential to manage hemostatic disorders in the operating room in a proper and timely fashion. The surgeon's opinion will be helpful in guiding hemostatic therapy and blood product transfusion. The brain has the particularity of being the only organ locked in a non-expandable box.

Postoperative hemorrhagic complications are most frequent in the first 6 h following surgery (Taylor et al. 1995), so when possible, waking the patient will be essential for a neurological follow-up that will provide precious information.

19.2.2 Classic Biological Tests

Classic hemostatic monitoring comprises activated partial thromboplastin time (aPTT), INR, platelets, and fibrinogen. Nevertheless, these conventional tests only monitor the initiation phase of coagulation and normal results cannot exclude a perioperative hemorrhagic complication.

Abnormal plasmatic coagulation tests have been shown to be associated with the progression of traumatic intracranial hemorrhage (Allard et al. 2009), but their use has never been properly validated. A more complete monitoring of hemostasis may be helpful for choosing a therapeutic strategy.

Recent European guidelines on the management of bleeding following major trauma recommend that "routine practice to detect post-traumatic coagulopathy include the early, repeated and combined measurement of prothrombin time (PT), aPTT, fibrinogen and platelets." However, they also suggest that PT and aPTT should not be used alone to guide hemostatic therapy and that thromboelastometry could be performed to assist in the characterization and treatment of posttraumatic coagulopathy (Spahn et al. 2013). These considerations can be reasonably extended to the perioperative management of bleeding patients.

19.2.3 Point-of-Care Assessment of Hemostasis

Not enough attention is paid to the complex pathophysiology and kinetics of acute coagulopathy: this is partly due to the limitations with usual hemostasis assays. In addition to the routine coagulation parameters, viscoelastic assays (ROTEM®/TEG®) can give an overall understanding of the coagulation status. Thromboelastometry/thromboelastography appears to be useful in the treatment of bleeding trauma patients and provides information about the speed and quality of clot formation (Spahn et al. 2013). They are performed in whole blood and thus provide clinically relevant data. Thromboelastometry assays are increasingly used to guide transfusion strategy; however, data on patients with isolated brain injury are lacking. A recent publication detailed thromboelastometric patterns of isolated brain-injured patients, but there are no prospective data on the subject (Schöchl et al. 2011).

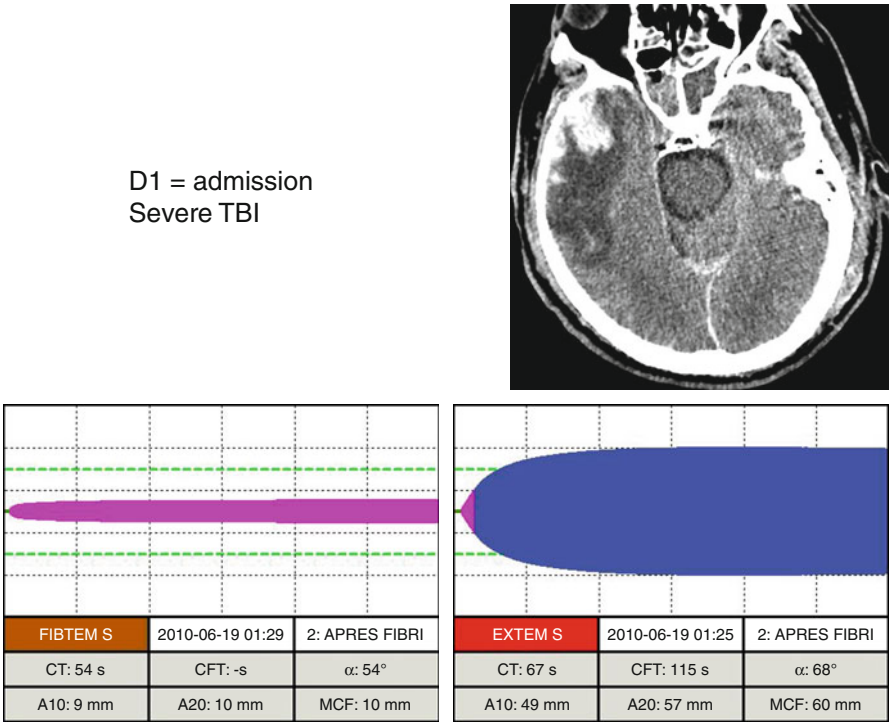

Fig. 19.3 Thromboelastometric (ROTEM) profile of a patient with severely traumatic brain injury on day 1 (hemorrhagic complication: extensive hemorrhagic brain contusions)

Thromboelastometry/thromboelastography is also an attractive technique for investigating the prothrombotic evolution of surgical patients. In a retrospective analysis of 152 critically ill surgical patients, Kashuk et al. (2009) reported that the presence of hypercoagulability – as identified by thromboelastography (r-TEG) – was predictive of thromboembolic events. A systematic review of the literature to investigate r-TEG's accuracy in predicting postoperative thromboembolic events concluded that more prospective studies were needed (Dai et al. 2009). The ability to predict thromboembolic events early is particularly significant for neurosurgical patients (Figs. 19.3 and 19.4).

POC whole-blood impedance aggregometry (Multiplate®) can detect the effects of aspirin, clopidogrel, and GP IIb/IIIa receptor blockers (Weber et al. 2008). It can also be used to detect unknown hemostatic disorders in comatose patients or to assess coagulation in patients treated with interfering medications. Indeed, AP drug-mediated dysfunction cannot be detected by platelet count.

The availability of repeated and rapid POC tests can guide intraoperative therapeutic management and goal-directed hemostatic therapy. This approach has been shown to reduce blood requirements in cardiovascular surgery and liver transplantation (Görlinger 2006). More recently, the use of thromboelastometry/

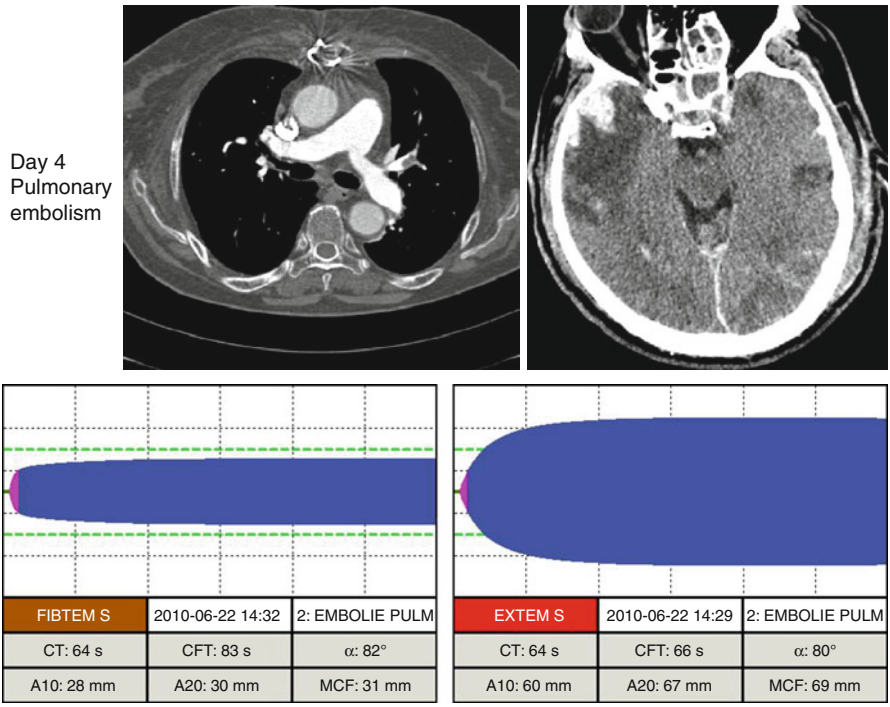

Fig. 19.4 Thromboelastometric (ROTEM) profile of a patient with severely traumatic brain injury on day 4 (thromboembolic evolution: bilateral pulmonary emboli)

thromboelastography has been reported in pediatric neurosurgery and after traumatic brain injury (Luostarinen et al. 2012; Kunio et al. 2012).

19.3 Management of Hemostasis in Neurosurgery

19.3.1 Blood-Derived Products

There are no evidence-based recommendations on the intraoperative use of blood-derived products in neurosurgery. For a detailed description of the various blood-derived or pharmacological products, we refer to Chaps. 9, 10, and 11. Here, we will focus on the particularities of their use in a neurosurgical context.

19.3.1.1 Platelets

Thrombocytopenia is directly associated to mortality and adverse outcome in traumatic intracranial hemorrhage patients (Allard et al. 2009). General recommendations are to maintain a platelet level greater than 100,000/μL, but a platelet count below 175,000/

μL has been correlated to greater intracranial hemorrhage progression (Schnüriger et al. 2010). Chan et al. (1989) showed an increase in postoperative hematoma formation when platelet count went below 124,000/μL in the immediate postoperative period. Risk of bleeding was greater in acute than in chronic thrombocytopenia.

19.3.1.2 Fibrinogen

European guidelines on the management of bleeding following trauma recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by a plasma fibrinogen level below 1.5–2.0 g/L. The development of thromboelastometric assays has focused attention on the role of fibrinogen. It plays a central role in the coagulation process and the literature suggests that its administration could reduce blood loss and requirements for blood-derived products in both cardiovascular surgery and trauma (Karlsson et al. 2008; Fenger-Eriksen et al. 2008).

Nevertheless, good-quality multicentered randomized trials are lacking, and it is currently not known whether the administration of high doses of fibrinogen is associated with an increased thromboembolic risk.

19.3.1.3 Fresh Frozen Plasma and Prothrombin Complex Concentrate

There are no recommendations specific to neurosurgery concerning the administration of either fresh frozen plasma (FFP) or PCC, but infusion of blood-derived products will always be associated with volume load, which can lead to brain swelling. Except the reversal of VKA therapy, there is no evidence-based recommendation for the use of PCC in a neurosurgical setting. Retrospective analyses of goal-directed protocols for thromboelastometry-guided fibrinogen and PCC administration have shown favorable survival rates (Schöchl et al. 2010), but data in neurosurgery and prospective trials are needed to establish the role of PCC administration in this context.

19.3.2 Pharmacological Hemostatic Interventions in Neurosurgery

19.3.2.1 Tranexamic Acid

Tranexamic acid competitively inhibits plasminogen binding to the fibrin which maintains clot stability. In a meta-analysis of 18 trials, the administration of tranexamic acid has been associated with a reduction in blood loss in elective surgery patients (Henry et al. 2007) and has recently been the subject of debate about reducing transfusion requirements in brain trauma (Perel et al. 2012). There are many case reports on the use of tranexamic acid in spinal (Cravens et al. 2006) or intracranial surgery (Sorimachi et al. 2005), to reduce either blood loss or hematoma growth, but controlled trials are lacking.

Nevertheless, if hyperfibrinolysis is either detected or suspected, the administration of tranexamic acid could be helpful in controlling bleeding.

19.3.2.2 Recombinant Activated Factor VII

Initially used to treat critical bleeding in hemophilic patients, recombinant activated factor VII (rFVIIa) has been successfully used in non-hemophilic patients. According to the cell-based coagulation model, rFVIIa enhances hemostasis by binding both exposed tissue factor at the injury site and activated platelets to produce thrombin (Grounds 2003). In neurosurgery, rFVIIa has been used during craniotomies for traumatic subdural or epidural hematomas, subarachnoid hemorrhage, and tumor resection or to treat warfarin-associated intracranial hemorrhage (Lin et al. 2003). Many case reports describe the correction of coagulation parameters in bleeding patients after rFVIIa administration, but the results of randomized clinical trials do not support its systematic administration for spontaneous intracranial bleeding. Mayer et al. (2005) reported on 399 patients with spontaneous intracranial hemorrhage who randomly received either a placebo or different doses of rFVIIa. They found the lowest increase in the volume of hemorrhage in the group given the highest dose of rFVIIa (160 μg/kg) in the first 4 h. However, a greater incidence of serious thromboembolic complications was observed in that group than in the placebo group. Further, large, controlled randomized clinical trials are necessary to determine the role of rFVIIa in the treatment of spontaneous intracranial bleeding. The data available concerning traumatic, surgical, and drug-induced bleeding essentially consist of case reports and retrospective studies. So the off-label use of rFVIIa cannot be considered a conventional therapy in neurosurgery and should be reserved to uncontrolled refractory bleeding.

19.3.2.3 Deferoxamine

Iron can induce brain damage. Deferoxamine – an iron chelator – has been shown to reduce hemoglobin-induced edema in a rat model (Nakamura et al. 2004). It has also been shown to reduce brain atrophy and improve neurological function after intracranial hemorrhage in the rat (Okauchi et al. 2010). There are nevertheless no clinical studies published.

19.4 Future Management of Hemostasis in Neurosurgical Patients

19.4.1 Early Hemostatic Goal-Directed Therapy in Neurosurgery

The mechanisms of hemorrhage and coagulopathy in neurosurgical patients are multifactorial, complex, and dynamic. The traditional biological tests have been surpassed. Damage control hematology is an emerging concept, and the ability to detect and treat coagulopathy early is essential to the management of neurosurgical patients.

Thromboelastometry/thromboelastography and whole-blood impedance aggregometry are advantageous POC tools that offer the clinician early information on both the hemorrhagic and procoagulant tendencies in complex situations. The

development of algorithms based on POC information and confirmed by classic laboratory tests will certainly help in the future.

19.4.2 From Bleeding to Clotting

Bleeding remains the most serious threat to neurosurgical patients, but the problem is certainly more complex when the early and massive activation of coagulation processes leads rapidly to a hypercoagulable state. Abrahams et al. (2002) studied the evolution of coagulability during neurosurgical procedures and found increased coagulability from the induction of anesthesia and skin incision through to intraoperative and postoperative periods (Abrahams et al. 2002). Interestingly, these changes were more pronounced in patients undergoing craniotomy than in patients undergoing spinal procedures.

Thromboembolic complications are known to be more frequent in neurosurgical patients. Classic risk factors including immobility, malignancy, trauma, and a delayed introduction of thromboprophylaxis certainly do play a role in the increased number of thromboembolic events observed in these patients, but they are not the only mechanisms. There is growing evidence that a hypercoagulable state can develop perioperatively in neurosurgical pathologies and interventions. Goobie et al. (2001) evaluated coagulation by using thromboelastography (TEG) data from 30 pediatric patients undergoing craniotomy; they found that peri- and postoperative hypercoagulable TEG profiles showed shortened coagulation times and increased maximal amplitude of clot strength, compared to preoperative profiles.

Experimental investigations have shown that thrombin is responsible for increased brain edema and neuronal death, and the intracerebral injection of thrombin inhibitors, such as argatroban, has been shown to significantly reduce edema in a rat model of ICH (Kitaoka et al. 2002); thus, supporting the concept that clotting and bleeding states are closely linked.

19.4.3 The Forgotten Secondary Brain Injury?

Neurosurgical bleeding is probably one of the most dreaded complications and in the field of neurocritical care, one of the most complex and fascinating problem.

Pathophysiological mechanisms of brain injury, and hemostatic cascades triggered by attacks on the central nervous system, tend to show that the same processes that lead to hemorrhagic complications will also lead to a hypercoagulable state and thromboembolic events.

Just as hypotension, anemia, hypoxia, hypoglycemia, hypercapnia, and hyperthermia are all now recognized as secondary factors that can worsen a primary brain injury, coagulopathy must also be considered as a potential contributing factor to poor outcomes. Many useful tools, currently in the development stage, will soon help clinicians to give an even earlier diagnosis and treatment of coagulopathy: the forgotten secondary brain injury.

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Bleeding Management in Elective Orthopedic Surgery

20

Oliver M. Theusinger

20.1 Introduction

Perioperative blood loss remains an important problem in elective orthopedic surgery (hip, knee, and spine surgery). For many years, allogenic blood transfusions were the standard approach to treating diminished hemoglobin (Hb) levels. The inherent risks of homologous transfusions persist despite all efforts to minimize them. Transmission of infections, transfusion-related acute lung injury (TRALI) or febrile reactions, red blood cell (RBC) transfusion-related immunomodulation, and increased mortality, morbidity, and adverse outcome have all been proven (Dodd 1992; Kopko and Holland 1999; Musallam et al. 2011; Spahn and Goodnough 2013).

The costs of RBC transfusions are largely underestimated. The reported price of one unit of packed RBC varies between USD 270 and 780, depending on the inclusion of costs related to storage, laboratory analyses (cross-matching tests, antibody tests, etc.), and prolonged hospital stays. In Switzerland, the cost of one unit of packed RBC administered in relation to surgery is estimated at close to USD 700 without taking into consideration transfusion-related complications, which have been estimated to cost around USD 1,000 (Shander et al. 2007, 2010; Ferraris et al. 2012).

Special attention should therefore not only be given to the costs of alternatives to blood transfusions but also at their possible surgery-specific drawbacks and acceptance by orthopedic surgeons. While the experience and skills of the surgeon are among the most important factors influencing intraoperative blood loss (Ishii and Matsuda 2005; Moonen et al. 2006), they are also the factors that cannot be managed by any other team member. Adequate hemostasis therefore remains the "gold standard" technique for eliminating potential complications. Its impact on

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transfusion decisions is evident: blood that is not lost does not have to be replaced. Preoperative anemia, which varies from 20 to 51 %, has been identified as another major issue. The World Health Organization (WHO) has defined this as a Hb level ≤12 g/dL in women and ≤13 g/dL in men, which corresponds to a hematocrit (Hct) of ≤36 % in women and ≤39 % in men (Rosencher et al. 2003; Theusinger et al. 2007; Kendoff et al. 2011). This has been shown to be an independent risk factor for increased 30-day mortality and major morbidity in all surgical patients (Musallam et al. 2011). In up to 30 % of patients, iron deficiency is the cause of anemia and should be corrected at least 4 weeks prior to surgery in order to achieve optimal results (Theusinger et al. 2007). Optimizing Hb mass before orthopedic surgery, as well as limiting intraoperative blood loss, is associated with improved outcomes after 90 days (Kotze et al. 2012).

20.2 Alternatives to Allogenic Blood Transfusions

A series of alternative methods for reducing or avoiding allogenic blood transfusions in orthopedic surgery have been described. These include identification of transfusion triggers for RBCs, pre-donation of autologous blood, iron substitution, administration of erythropoiesis-stimulating agents (ESA), adaptation of perioperative medication, body temperature adjustments, goal-directed transfusions, hypotensive epidural anesthesia, normovolemic hemodilution, platelet gel and fibrin sealant, autologous retransfusion indirect retransfusion of patients' shed blood (Cell Saver/C.A.T.S), and direct retransfusion of patients' shed blood (ABT, Bellovac).

20.2.1 Identification of Transfusion Triggers

The indications for RBC transfusions are controversial, and their liberal use versus their more restricted use is largely discussed. Current literature tends to support a more restrictive use, with Hb concentrations of 6–8 g/dL or awaiting physiological triggers (Klein et al. 2007).

20.2.1.1 Hemoglobin-Based Transfusion Triggers

The guidelines from the American Society of Anesthesiologists (ASA) and the American College of Physicians (ACP) recommend RBC transfusion for Hb levels below 6–10 g/dL (Carson et al. 2012). Transfusions in situations where the Hb level is higher than 10 g/dL are indicated in rare situations, whereas transfusions for levels below 6 g/dL seem to be nearly always indicated. In Europe, a Hb target range of 7–9 g/dL is largely accepted, even in cases of major trauma (Marik and Corwin 2008). However, Hb levels alone do not always justify transfusion. In the literature, Hb levels below 6.4 g/dL have been associated with impaired cognitive function, and Hb levels below 4.8 g/dL were associated with a mortality of 50 % (Weiskopf et al. 2003). For this reason, clinical parameters, including hemodynamic status, should be evaluated individually (Spence 1997; Madjdpour and Spahn 2005).

20.2.1.2 Physiological Transfusion Triggers

Physiological transfusion triggers can be used as a guide and these have been defined as tachycardia, hypotension, oxygen extraction greater than 50 %, mixed venous oxygen pressure of less than 32 mmHg, an increase of lactate, and electrocardiogram changes. The level of shock, the hemodynamic response to resuscitation, and the actual blood loss in the hemodynamically unstable patient should all be integrated into the indication for RBC transfusions. In any case, RBC transfusions should be used restrictively as clinical outcome has been shown to be improved by more restrictive transfusion triggers (Earley et al. 2006; Claridge 2002).

20.2.2 Preoperative Autologous Blood Donation

This method was a standard for many years but is barely used nowadays, as there is a poor cost-benefit relationship for the patient. Patients donate one or more units of their own blood preoperatively (4–6 weeks) and are allowed a recovery period of 4 weeks prior to surgery. The units are stored in a blood bank and then retransfused preoperatively. Patients have been shown to become anemic due to their donation (Vamvakas and Pineda 2000). Several studies have shown that pre-donation is no longer recommended in elective orthopedic surgery (Tartter et al. 1986; Theusinger et al. 2007) because such risks as transfusion reactions, circulatory overload, bacterial contamination, clerical errors, and negative outcome rates have all been demonstrated (Goldman et al. 1997).

The cost-effectiveness has also been discussed as more than 45 % of donated blood is discarded and patients become anemic due to this technique (Goldman et al. 1997; Habler and Messmer 1997; Franchini et al. 2008).

20.2.3 Preoperative Intravenous Iron Therapy

Anemia related to iron deficiency is the most common type of anemia among patients scheduled for elective orthopedic surgery (prevalence of up to 30 %) (Theusinger et al. 2007). Preoperative iron supplements have been proposed in order to elevate Hb levels (Weiss and Goodnough 2005) as they can be substituted orally and parenterally.

After significant blood loss, there is a fivefold increase of the erythropoietic response following intravenous (i.v.) iron administration (Weiss and Goodnough 2005). This, in combination with erythropoietin (EPO), has been shown to be associated with a decrease in mortality due to reduced transfusion and infection rates (Cuenca et al. 2004, 2005, 2006).

Iron therapy was found to be generally safe and effective, especially high molecular weight iron. Ferric carboxymaltose (Ferinject®, Vifor Int., St. Gallen, Switzerland) has been shown to be well tolerated, with no safety concerns (Kulnigg et al. 2008) for dosages up to 1 g of i.v. iron administered every 15 min. Life-threatening anaphylactic reactions have been described for solutions containing dextran (Chertow et al. 2006),

while minor reactions to Feraheme® (ferumoxytol) injection (AMAG Pharmaceuticals®, Inc., Waltham, MA, USA) can be of concern. Issues of dosage (502 mg of iron can be given to the patient in one dose) and a pH of between 6 and 8 could be of concern (Macdougall et al. 2014).

Iron substitution alone decreases endogenous erythropoietin reserves (Theusinger et al. 2007), while EPO administration alone increases the risk for thrombotic incidents (Franchini et al. 2008). For these reasons, the combination of iron and EPO is recommended and should be the gold standard (Goodnough et al. 2000; Coyne et al. 2007; Dahl et al. 2008).

An average patient requires 1 g of iron, whereas the cost for treatment with ferric carboxymaltose, for example, would be close to USD 300. This has been shown to be cheaper than one unit of RBC (Shander et al. 2010). Acceptance by surgeons is optimal, as no further involvement is required from their side.

20.2.4 Administration of Erythropoiesis-Stimulating Agents (ESA)

Erythropoietin is a glycoprotein hormone mainly produced in the kidneys. It acts as a growth factor for erythrocyte progenitor cells, promotes their proliferation, and accelerates the development of reticulocytes (Jelkmann 2008). It is an excellent choice in order to avoid allogenic blood transfusions in anemic patients undergoing major elective surgery (Faris et al. 1996; Goodnough 1996; Schmidt et al. 1998; Rohling et al. 2000; Couvret et al. 2004; Cuenca et al. 2006).

In 2005, Rosencher et al. showed that one to two doses of erythropoietin were sufficient to increase Hb to non-anemic levels in orthopedic patients (Chun et al. 1997; Rosencher et al. 2005). This treatment costs USD 550 to 1,100. Care should be taken at all times and EPO should not be administered if patients have a known personal or familial history of thromboembolic events, severe hypertension, or an allergy to the agent or other ingredients. Furthermore, pregnancy or breastfeeding are contraindicated. Finally, neocytolysis is a recently discovered concern. In this physiological process, a rapid fall in erythropoietin levels has a negative influence on erythropoiesis and triggers neocytolysis. The extent of this phenomenon's relevance in the context of EPO therapy needs to be further investigated (Rice and Alfrey 2005; Alfrey and Fishbane 2007).

Very recently, a new generation of ESAs called continuous erythropoiesis receptor activators (CERA) has been designed. They have a longer elimination half-life and different binding characteristics than previous ESAs, leading to benefits such as a significant increase in the level of Hb within 2 weeks (Kakimoto-Shino et al. 2014).

20.2.5 Adaptation of Perioperative Medication

Patients undergoing surgery are getting older and are on a variety of medications. While it was usual to discontinue anticoagulants such as vitamin K antagonists or aspirin several days before surgery, discontinuing clopidogrel and aspirin in patients with unstable

coronary perfusion and/or recently implanted stents before elective orthopedic surgery is strongly contraindicated (Spahn et al. 2006, 2007; Chassot et al. 2007a, b). Recommendations promote aspirin as a lifelong therapy, whereas clopidogrel should be used only as long as the coronary stents are not fully endothelialized. This usually takes 6–24 weeks depending on the technique used (Chassot et al. 2007a, b). The hemorrhagic risk due to antiplatelet therapy is modest: 2.5–20 % more blood loss with aspirin and 30–50 % with the combination of aspirin and clopidogrel (Chassot et al. 2007a, b).

Nonsteroidal painkillers (NSAID) are widely used for pre- and postoperative analgesia and might adversely affect hemostasis after the surgery. They should be stopped at least 24 h prior to surgery. NSAR inhibit prostaglandin synthesis and particularly block cyclooxygenase (COX), which is the central enzyme in the process of prostaglandin formation. COX-2-selective NSAR have no undesirable COX-1-related side effects such as impaired platelet aggregation and prolonged bleeding time or consecutive increased blood loss during surgery. If NSAR are considered for postoperative pain relief, COX-2-selective ones should be used (Slappendel et al. 2002; Weber et al. 2003). The costs of optimizing perioperative medication are negligible, but close attention should be paid to this issue during the preoperative surgical and anesthesiology consultations.

20.2.6 Intraoperative Body Temperature

Body temperature during surgery affects platelet aggregation and bleeding time. The pathophysiological effect of hypothermia on platelet activation/adhesion is due to the inhibition of the interaction between von Willebrand factor and the platelet glycoprotein Ib-IX-V complex. It also slows down the metabolic rate of coagulation factor enzymes. A decrease of 1.5 °C is associated with increased blood loss of about 50 % during total hip replacement (Schmied et al. 1996; Winkler et al. 2000). Maintenance of physiological body temperature is therefore an obligation, and all efforts should be taken to achieve this goal.

20.2.7 Goal-Directed Transfusions

The principle of goal-directed transfusion is to optimize the coagulation pathway by replacing coagulation factors identified as being missing or diminished. Fibrinogen, factor XIII, and the prothrombin complex (the concentrate of factors II, VII, IX, X, antithrombin III, and protein C) improve coagulation and minimize the blood loss (Fries et al. 2005, 2006; Theusinger et al. 2014). Point-of-care coagulation monitoring devices are essential. Rotational thromboelastometry (ROTEM®) has been shown to be useful (Theusinger and Levy 2013) in determining the causes of hemorrhage. Tests are performed using whole blood and allow conclusions to be made about the entire clotting process, fibrinolysis, and platelet function at bedside speed (Theusinger and Levy 2013). In combination with a transfusion algorithm, this has been shown not only to decrease transfusion requirements during surgery but also to be cost-effective (Shore-Lesserson et al. 1999; Spalding et al. 2007; Theusinger et al. 2014).

20.2.8 Antifibrinolytic Agents

Okamoto and coworkers began searching for substances that inhibit the action of plasmin during the 1950s. One of 200 lysin derivates studied was tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid, or TXA) (Okamoto et al. 1997). Its use has been shown to have significant beneficial blood-sparing effects in elective surgery (Henry et al. 2007), while a dose of 1 g reduced bleeding and blood loss for elective knee and hip arthroplasty (Aguilera et al. 2013; Delanois and Mont 2013). Costs and side effects are low at this dose, suggesting that a generalization of the use of antifibrinolytic agents in orthopedic surgery might be possible.

20.2.9 Hypotensive Epidural Anesthesia (HEA)

The technique of HEA is as yet not widely carried out for perioperative blood management in orthopedics. Nevertheless, it has been shown to be an effective method for reducing perioperative blood loss (Niemi et al. 2000). HEA aims to achieve an epidural dermatome block (at least as far as the T2 level) and to establish a sufficiently extensive and dense block of the cardioacceleratory fibers of the thoracic sympathetic chain. Bradycardia is usually prevented by using a continuous i.v. infusion of a low-dose epinephrine solution. This leads to reduced arterial pressure but maintains heart rate, central venous pressure, stroke volume, and cardiac output within normal ranges. Mean arterial blood pressure can be lowered to 50 mmHg resulting in a reduction of intraoperative (Nelson and Bowen 1986) and postoperative blood loss, as seen in several orthopedic trials (Juelsgaard et al. 2001; Tenholder and Cushner 2004; Eroglu et al. 2005). HEA seems, therefore, to be an attractive alternative for certain specific patients and situations.

20.2.10 Normovolemic Hemodilution

The principle of normovolemic hemodilution is based on replacing 2–4 units of the patient's whole blood with acellular fluids (e.g., crystalloids). The advantage of this procedure is that fewer valuable oxygen carriers (e.g., RBC) are lost in cases of bleeding due to the artificial dilutional anemia. Additionally, fresh whole blood is instantly available for retransfusion. This method has been shown to reduce the need for allogenic blood transfusion in different fields of surgery (Terada et al. 2001; Matot et al. 2002; Wong et al. 2002; Habler et al. 2004), including orthopedic surgery (Goodnough et al. 1999; Bennett et al. 2006). Contraindications for this technique are severe anemia, hemorrhagic shock related to trauma, severe sepsis, respiratory failure, and myocardial insufficiency (Morgan et al. 2002).

The estimated costs seem to be minimal (about USD 30) compared to other procedures (Monk et al. 1999). It has to be acknowledged, however, that hemodilution—when using hydroxyethyl starch (HAES/HES)—can lead to diffuse intraoperative bleeding (capillary bleeding) due to the reduced platelet aggregation caused

by colloids. In procedures where a well-controlled hemostasis is mandatory, normovolemic hemodilution might not be the ideal choice from a surgical point of view and particular care should be taken about HES usage (Kind et al. 2013).

20.2.11 Platelet Gel and Fibrin Sealant

Platelet gel is manufactured from platelet-rich plasma, which is obtained by sequestration of autologous whole blood by using a blood cell separator. Treatment involves direct application of concentrated platelets and their growth factors (TGF-ß = platelet-derived growth factor) and has been proven to have favorable effects on the wound healing cascade (Mustoe et al. 1987; Pierce et al. 1989; Wrotniak et al. 2007). Platelet gel is cheap (about USD 24 per unit of blood sequestrated), the work required is minimal, and its efficiency in orthopedic surgery has been well described. Furthermore, Lincoln et al. suggested that it has antibacterial properties due to its high concentrations of leukocytes and granulocytic neutrophils which contain myeloperoxidase (Lincoln et al. 1995).

Fibrin sealants, also known as fibrin glues, are plasma-derived surgical hemostatic agents. Two major components are usually present: fibrinogen and thrombin. Fibrin sealants can be applied to the wound surface using a dual-syringe system in either a liquid or an aerosol form. Their improved hemostatic effects have been shown in both animal and human models (Mankad and Codispoti 2001), with clinical efficiency described in cardiothoracic surgery, cosmetic surgery, and neurosurgery (Kjaergard and Fairbrother 1996; Mankad and Codispoti 2001). A few studies have been published in orthopedic surgery (Levy et al. 1999; Wang et al. 2001) using a non-autologous cryoprecipitate-based fibrinogen. Besides the improved hemostatic effect, a lower incidence of postoperative wound healing disturbances (Everts et al. 2006), fewer infections, and a shorter length of stay were all described (Pierce et al. 1989). However, the costs for these products are not negligible: 1 ml of fibrin glue is used for 10 cm^2 of wound surface at a price of USD 175 (Baxter®, Deerfield, IL, USA).

The use of these hemostatic agents is complementary to decreasing the need for allogenic blood transfusions. They are not a replacement for diligent surgical hemostasis and should be used judiciously to improve the surgical outcome (Mankad and Codispoti 2001).

20.2.12 Autologous Retransfusion

There are two different methods of autologous retransfusion. Suctioned blood is either washed mechanically before being given back to the patient (indirect retransfusion) or it is filtered before retransfusion (direct procedure).

20.2.12.1 Indirect Retransfusion

Two examples of indirect retransfusion systems are the discontinuous autotransfusion system (DATS, "Cell Saver®" system, Haemonetics Corp, Braintree, MA, USA)

and the continuous autotransfusion system (CATS, "C.A.T.S ®" system, Fresenius, Bad Homburg, Germany). Both systems centrifuge blood, divide corpuscular elements according to their density, and wash these with a physiological liquid (e.g., normal saline) (Dai et al. 2004).

The difference between the two methods is that in the discontinuous setting, each cycle processes a fully loaded blood reservoir, whereas the continuous system is almost independent of the blood volume (priming volume 30 mL). Another advantage of the continuous system is that smaller centrifugal forces are used to separate erythrocytes. Furthermore, a higher percentage of residual fat particles is removed, which is a relevant concern in orthopedic surgery. Leukocytes, on the other hand, are better removed by the discontinuous system (Dai et al. 2004). The quality of these washed RBCs is at least comparable to that of stored blood cells (McShane and Martin 1987).

The major contraindication to the use of indirect retransfusion is bacterial contamination of suctioned wound blood; tumor surgery is only a relative contraindication (Beck-Schimmer et al. 2004). Intraoperative cell salvage has been proven to be an effective method to avoid allogenic blood transfusion (Spahn and Casutt 2000). Using indirect retransfusion systems in orthopedic patients significantly reduces the need for allogenic blood transfusions from 70 to 23 % (Heddle et al. 1992).

The high costs associated with this indirect retransfusion technique (USD 2,400 for Cell Saver®, Haemonetics Corp, Braintree, MA, USA) might suggest that its intraoperative use be reserved for dedicated and specific surgery only.

20.2.12.2 Direct Retransfusion

Postoperative drainage can be used for the direct retransfusion (e.g., Bellovac ABT®, Astra Tech, Vienna, Austria) of filtered shed blood. This method has gained popularity in the field of orthopedic surgery as it is cost-effective and easy to use. Concerns over the safety of unwashed, filtered shed blood have been tempered by recent studies (Healy et al. 1994; Habler and Messmer 1997; Habler et al. 2004) showing that autologous retransfusion is safe provided the correct protocols are followed. These include abiding by maximum transfusion volumes, a blood loss over 250 ml, and a retransfusion time within 6 h of surgery, thereby minimizing any hematological or immune reactions (Henry et al. 2002). Six hours postoperatively, the system can still be used as a regular low-vacuum drain.

Different studies have shown the benefits (easy handling, low work load, low cost at around USD 100, reduced hospital stay) of autologous retransfusion in elective orthopedic surgery, especially after hip and knee replacements (Healy et al. 1994; Goodnough et al. 2000, 2003; Juelsgaard et al. 2001; Henry et al. 2002; Jelkmann 2008). Nevertheless, a few trials have described failings in this safe system (Ishii and Matsuda 2005) and an increase in complication rates of 10 % (febrile reactions or tachycardia) after the retransfusion of unwashed wound drainage blood after total hip arthroplasty (Reize and Wulker 2007).

Retransfusion of shed blood is most effective if all lost blood can be collected and given back, as in total knee arthroplasty, where tourniquets are used during surgery. In hip arthroplasty, where blood loss occurs mostly during surgery, this system does not seem to be the ideal solution (Juelsgaard et al. 2001), although

some studies have still reported a positive effect (Juelsgaard et al. 2001; Henry et al. 2002; Goodnough et al. 2003).

Conclusions

Concerns regarding the safety and high costs of allogenic blood products have led to increased research and efforts to implement patient-blood management programs in orthopedic surgery. A multidisciplinary approach to optimizing the care of patients who might need transfusions should be an obligation for patients undergoing orthopedic procedures. Both an individualized evaluation of the patient and clinical management of the transfusion decision-making process are necessary (including the application of appropriate indications), as are the minimization of blood loss and optimization of the patient's red cell mass. The need to reduce allogenic blood transfusions and healthcare costs while ensuring that blood components are available for the patients who need them is a cornerstone of appropriate team work.

Anemic patients (women, Hb <12 g/dL; men, Hb <13 g/dL: WHO) should be treated preoperatively with i.v. iron and EPO as this is the optimal method for preparing a patient for elective surgery (Goodnough et al. 2000; Coyne et al. 2007; Dahl et al. 2008; So-Osman et al. 2014a, b).

The use of intraoperative platelet gel and fibrin sealant may be an adequate option as they improve hemostatic effects, lower the incidence of postoperative wound healing disturbances, present fewer infections, and lead to shorter hospital stays (Cuenca et al. 2004).

Intraoperative salvage is effective in patients where excessive blood loss >1.5 L is expected (Goodnough et al. 1999). Due to the high costs associated with these systems, their utility should be critically assessed before surgery.

Postoperative salvage is still debated, with some controversy regarding possible side effects. So far, most of the concerns have been proven wrong and the method itself is inexpensive and easy to use (Healy et al. 1994; Goodnough et al. 2000, 2003; Juelsgaard et al. 2001; Henry et al. 2002; Cuenca et al. 2004, 2005; Jelkmann 2008).

Finally, it is not only important for surgeons and anesthesiologists to have early knowledge of the patient's preoperative Hb level and the expected blood loss during surgery, but they should also have detailed knowledge about the different alternatives available for reducing the need for allogenic blood products. All hospitals should adapt their methods with regard to the type of surgery to be performed and to their financial possibilities.

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Perioperative Coagulation in Neuraxial and Peripheral Nerve Blocks

21

Kyle Kirkham and Eric Albrecht

21.1 Introduction

The occurrence of hemorrhagic complications from the performance of neuraxial and peripheral anesthesia are rare events, making estimates of their incidence challenging. The most dreaded hemorrhagic complication following regional anesthetic techniques is the development of a symptomatic spinal hematoma with the concurrent risk of neurological ischemia and permanent paralysis. While spontaneous spinal hematoma can occur in even healthy patients, medical anticoagulant therapy increases the risk significantly. An extensive review of the literature examined 61 cases of spinal hematoma associated with neuraxial regional anesthesia and found that 68 % involved impaired coagulation, most commonly heparin or low molecular weight heparin (LMWH) (Vandermeulen et al. 1994). One quarter of procedures were identified as being challenging, with bleeding identified at the time of needle or catheter placement. The overall incidence of spinal hematoma after neuraxial blockade is unknown; however, commonly quoted frequencies are calculated to be less than 1 in 150,000 epidural and 1 in 200,0000 spinal procedures (Tryba 1993). However, it may be as high as 1 in 3,600 procedures for the highest risk groups (Moen et al. 2004). Risk factors contributing to this supplementary risk include increased age, female sex, history of excessive bruising or bleeding, continuous catheter technique, large needle gauge, multiple passes, and moderate or difficult needle placements (Horlocker et al. 1995).

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Given that most of these factors are either unmodifiable or unpredictable at the start of a procedure, most of the attention placed on the prevention of hemorrhagic complications has been towards coagulopathies induced by anticoagulant or antithrombotic medication. The 2010 American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines on regional anesthesia and antithrombotic medications summarized a total of 26 case reports of hemorrhagic complication: 13 were associated with peripheral or plexus nerve blocks and antithrombotic therapy, while 13 others occurred without concurrent antithrombotic therapy (Horlocker et al. 2010). The majority of serious outcomes in this series were related to major hemorrhage, which is theoretically more easily managed than a neuraxial hematoma. However, this series demonstrated that hospital admission may be prolonged by this outcome, discomfort may be significant, transient neurological deficits may occur, and consequences may be severe enough to result in death (Maier et al. 2002).

When deciding whether to proceed with a regional technique, consideration must be given to the site of needle placement and to the consequences of a hemorrhagic complication specific to that site. Current guidelines therefore advocate caution when considering peripheral or plexus regional techniques in cases involving anticoagulated patients. ASRA's formal recommendation is that these techniques be considered equivalent to neuraxial procedures (Horlocker et al. 2010). The European Society of Anaesthesiology (ESA) similarly suggests that deep blocks, including lumbar plexus and paravertebral blocks as well as the removal of indwelling catheters, should be considered under neuraxial guidelines (Gogarten et al. 2010) if there is a newer one. In general, a cautious approach is justified for any patient on anticoagulant medication. Even superficial procedures like axillary or popliteal neural blockade, where accompanying vessels are directly compressible, should be carefully weighed up from a risk-benefit perspective and where reasonable medication should be withheld for appropriate time periods before needle or catheter placement.

21.2 Anticoagulants and Regional Anesthesia

21.2.1 Antiplatelet Agents

Antiplatelet medications include a broad range of agents with significantly different implications for the performance of regional anesthesia. As a class, this group includes aspirin and other nonsteroidal anti-inflammatory drugs (NSAID); the thienopyridine derivatives, most notably clopidogrel and ticlopidine; and the GP IIb/IIIa platelet receptor antagonists, including eptifibatide, tirofiban, and abciximab. Each of these groups differs greatly in its pharmacological impact on platelet aggregation and function and must therefore be examined separately when considering a patient for a regional anesthetic technique.

The Collaborative Low-dose Aspirin Study in Pregnancy, published in 1994 (CLASP Lancet 1994), was conducted to investigate the management of preeclampsia. Of those patients randomized to receive aspirin, approximately 750

Table 21.1 Guideline recommendations for antiplatelet agents

	ESA guidelines[a]		ASRA guidelines[b]	
	Time before procedure/ catheter removal	Time after procedure	Time before procedure/ catheter removal	Time after procedure
Aspirin	Not specified	Not specified	None	None
NSAID	In isolation, no adjustment required		In isolation, no adjustment required	
Clopidogrel	7 days	After catheter removal	7 days	
Ticlopidine	10 days	After catheter removal	14 days	
Abciximab	48 h		24–48 h	
Tirofiban/ eptifibatide	8–10 h		4–8 h	

[a]Gogarten et al. (2010)
[b]Horlocker et al. (2010)

continued their dose until at least 1 day prior to delivery, resulting in only one occurrence of traumatic cannula placement in the intervention group vs. two in the control group and no spinal hematoma. While 3 of the 61 cases described by Vandermeulen et al. (1994) were using NSAID concurrently, prospective case series have failed to demonstrate an increased risk associated with continuing aspirin or NSAID during the performance of neuraxial procedures (Horlocker et al. 1995, 2002).

As a result, NSAID dosing alone does not require adjustment for the purpose of regional anesthesia. However, the balance of evidence from case reports suggests that combining nonselective NSAID with other forms of thromboprophylaxis increases the risk of major hemorrhagic complications (Ruff and Dougherty 1981; Moen et al. 2004). The practical implication of this observation is that a cautious approach should be taken, as reflected in current guidelines. These limit postoperative use of NSAID therapy to COX-2 selective agents if the administration of thromboprophylaxis is anticipated, and patients on pre-procedure combination therapy should have their nonselective NSAID withheld for 12–24 h prior to the planned procedure.

Thienopyridine derivatives have been associated with increased bleeding in surgical settings and are generally considered contraindications for regional anesthesia. The pharmacokinetics of these agents determines the recommendations for safe time periods before invasive procedures. There is consensus that clopidogrel should be discontinued 7 days prior to a regional anesthetic procedure (see Table 21.1). Ticlopidine has a variable half-life that depends on the duration of its administration, and there is disagreement between European and North American recommendations. The ESA minimum recommended period is 10 days (Gogarten et al. 2010), whereas ASRA guidelines recommend 14 days (Horlocker et al. 2010). These agents have, for example, been associated with both neuraxial and retroperitoneal hematoma after lumbar plexus blockade.

Antagonist agents of the platelet GP IIb/IIIa receptor include abciximab, eptifibatide, and tirofiban. They have considerably different durations of effect on platelet function, with a return to normal function requiring only 4–8 h after eptifibatide or

tirofiban, but a minimum of 24–48 h after abciximab therapy. The antiplatelet effect of these agents is profound: it is prudent to target the upper limits of these ranges when planning the removal of an indwelling catheter and to carefully monitor neurological function afterward. In addition to their intrinsic activity, these agents generate a risk of significant thrombocytopenia that may last beyond their pharmacological duration (Berkowitz et al. 1997). As such, it is recommended that a platelet count be performed for any patient who has received a GP IIb/IIIa inhibitor.

21.2.2 Unfractionated Heparin

The administration of low-dose subcutaneous unfractionated heparin (UFH), primarily for the purpose of thromboprophylaxis, has a considerable accumulated body of practice. Overall, there is little evidence to suggest a significant increase in risk associated with the performance of regional anesthetic techniques in patients who are receiving this therapy. Liu and Mulroy (1998) summarized the early, published experience of neuraxial anesthesia in the presence of subcutaneous UFH and found no epidural hematomas in over 9,000 cases. When administered subcutaneously, a 1–2 h delay exists before peak anticoagulant effect. Some authors therefore advise a delay of 4–6 h before needle placement. Controversy exists as to whether any interval is necessary however, given the low perceived risk of complications in current North American guidelines; these do not advocate any specific delay when daily doses of 5,000 U are administered twice daily (Horlocker et al. 2010).

Higher daily doses or more frequent dosing intervals carry a potential, but uncertain, increased risk. European recommendations for prophylactic dosing include withholding heparin therapy for a minimum of 4–6 h prior to a regional procedure, with a further delay to 8–12 h in a setting of therapeutic subcutaneous dosing; the re-initiation of therapy should be delayed for 1 h after completion of the procedure.

Systemic intraoperative, intravenous heparinization, for indications such as vascular surgery, carries a potential significant impact on the risk of neuraxial complications. For patients who have undergone a regional anesthetic technique, intraoperative i.v. heparin should be delayed a minimum of 1 h after needle or catheter placement. In the setting of a traumatic needle placement, most authors advocate a risk-benefit discussion between the patient and surgical team to determine whether to continue with the procedure at all (Liu and Mulroy 1998). European guidelines (Gogarten et al. 2010) suggest an even more cautious approach where possible, including delaying heparinization for 6–12 h and, when possible, postponement of the operation.

The removal of an indwelling catheter should be considered the equivalent to an invasive procedure and similar delays to therapy are recommended. In addition, due to the potential for patients to develop heparin-induced thrombocytopenia (HIT), a platelet count is advisable prior to needle placement for any patient who has received therapy for greater than 4–5 days (Linkins et al. 2012) (Table 21.2).

Table 21.2 Guideline recommendations for unfractionated heparins

	ESA guidelines[a]		ASRA guidelines[b]	
	Time before procedure/ catheter removal	Time after procedure	Time before procedure/ catheter removal	Time after procedure
Prophylaxis	4–6 h (<15,000 IU/day)	1 h	No delay (<10,000 IU/day)	
Therapeutic S.C.	8–12 h	1 h	Not established	
Intravenous	4 h and normal laboratory values	1 h	2–4 h	1 h
Traumatic needle placement	Delay low-dose therapy 1–2 h; delay intraop heparinization 6–12 h; consider surgical delay		Individual patient risk-benefit discussion with surgical team	

[a]Gogarten et al. (2010)

[b]Horlocker et al. (2010)

21.2.3 Low Molecular Weight Heparin

The performance of regional anesthesia in cases using low molecular weight heparins (LMWH) deserves special consideration for three reasons. Firstly, in many centers, LMWH has replaced UFH or oral anticoagulants as the thromboprophylaxis of choice. As a result, significant numbers of patients are exposed to this class of medication annually. Secondly, traditional coagulation tests such as activated partial thromboplastin time (aPTT) and activated clotting time (ACT) are unaffected by LMWH, making monitoring challenging. Thirdly, the introduction of LMWH, particularly in North America, had a demonstrable impact on the reported number of hemorrhagic complications from neuraxial needle placement in a relatively short period of time. Between 1993 and 1998, 60 cases of spinal hematoma were reported after the introduction of LMHW to the United States (Horlocker et al. 2010). It has been estimated that this represented a frequency of approximately 1 in 3,100 epidural catheter procedures and 1 in 40,800 spinal procedures (Schroeder 1998). These observations contrasted with prior European experience where, in one example, Bergqvist et al. (1992) pooled 9,013 neuraxial patients receiving LMWH from 11 studies and found no incidence of hematoma. This geographical difference may partially be accounted for by different dosing regimen, with North American patients often receiving twice-daily dosing.

The increased risk of twice-daily dosing is reflected in both current North American and European guidelines. Recommendations include delaying needle placement or catheter removal for a period of 10–12 h after prophylactic once-daily dosing and then restarting therapy for a minimum of 2–4 h after the procedure. Initiation of postoperative therapy should begin no earlier than 6–8 h after needle placement. Twice-daily or therapeutic dosing should be withheld for a minimum of 24 h before a regional procedure or the removal of an indwelling catheter. In this setting, therapy may be restarted a similar 2–4 h after the procedure. However, ASRA guidelines further recommend delaying the initiation of postoperative

Table 21.3 Guideline recommendations for low molecular weight heparins

	ESA guidelines[a]		ASRA guidelines[b]	
	Time before procedure/catheter removal	Time after procedure	Time before procedure/ catheter removal	Time after procedure
Pre-procedure LMWH	12 h	4 h	10–12 h	2 h
Higher dose or twice daily	24 h	4 h	24 h	2 h
Postoperative LMWH			Once-daily dosing: delay LMWH for 6–8 h Twice-daily dosing: delay LMWH for 24 h and remove catheter 2 h pre-therapy	
Traumatic needle placement			Consider delaying therapy for 24 h	

[a]Gogarten et al. (2010)
[b]Horlocker et al. (2010)

twice-daily dosing by 24 h after a neuraxial technique, as well as removing indwelling catheters 2 h before therapy begins.

As described above, the concurrent administration of thromboprophylaxis may increase the hemorrhagic risk of otherwise benign antiplatelet agents like NSAID. Thus careful attention should be paid to the complete medical history of these patients to ensure that no other agents which might increase the risk of a serious complication (beyond that considered in these recommendations) are being co-administered. The risk of HIT associated with LMWH is real but uncommon, with some series failing to show any significant incidence of this condition (Warkentin et al. 1995) (Table 21.3).

21.2.4 Vitamin K Antagonists

The administration of vitamin K antagonists, particularly warfarin for perioperative thromboprophylaxis, remains common in many centers in North America. As such, there remains considerable interest in the optimal management of these medications, the specifics of their monitoring, and which levels of anticoagulation place patients at increased risk during regional anesthetic procedures. All recommendations are strongly opposed to performing procedures on patients who are therapeutically anticoagulated. However, there has been some relevant debate in recent literature regarding how strict recommendations should be, particularly with respect to the initiation of treatment.

Generally, levels of factors II, VII, IX, or X below 40 % of the normal have been quoted as posing a high risk of bleeding (Raj et al. 2004). This level is felt to occur around an international normalized ratio (INR) of 1.5; however, the differing half-lives of each factor determine their relative level when this laboratory result is

Table 21.4 Guideline recommendations for warfarin

	ESA guidelines[a]		ASRA guidelines[b]	
	Time before procedure/catheter removal	Time after procedure	Time before procedure/catheter removal	Time after procedure (may initiate therapy pre- or post-procedure
Initiation of therapy		After catheter removal		Catheter removal INR ≤1.4 INR <3.0 with no other agents and neuromonitoring
Preexisting therapy	INR ≤1.4		4–5 days and normal INR	

[a]Gogarten et al. (2010)
[b]Horlocker et al. (2010)

reached. North American guidelines recommend that preexisting therapy be stopped 4–5 days before a regional technique and that the INR be normalized. For newly initiated therapy, concurrent administration of medication affecting hemostasis is discouraged, the INR should be monitored daily, and neurological function examined routinely. Indwelling catheters should preferably be withdrawn with the INR <1.5, but an INR <3.0 may be permissible in the presence of otherwise normal hemostasis and appropriate monitoring (Horlocker et al. 2010). Several case series demonstrate that INR values in this higher range are likely to be safe during the initiation phase of therapy (Parvizi et al. 2006; Liu et al. 2011), although a cautious approach is justified.

Reversal of vitamin K antagonists may be accelerated using oral or intravenous vitamin K supplementation or may be clinically reversed through the administration of prothrombin complex concentrates or plasma. In most centers the administration of plasma or plasma-derived products would be supported if required for urgent surgery, but not specifically for the purpose of performing an elective or semi-elective regional anesthetic technique (Table 21.4).

21.2.5 Anti-Xa Agents and Direct Thrombin Inhibitors

This class of medication has recently expanded, with new agents in development and approved for clinical use. Many of these drugs present unique challenges to the regional anesthesiologist. The anti-Xa drug with the longest history, in both Europe and North America, is fondaparinux, but the introduction of rivaroxaban, apixaban, and others has led to an increasing number of patients presenting for chronic anticoagulation. The half-lives of these agents are typically long (allowing for once-daily dosing), but are varied: fondaparinux near 20 h and rivaroxaban closer to 6 h. The literature supporting periprocedural guidelines is developing. Recommendations are typically cautious and based directly on what is known of the agents' pharmacology. For example, the manufacturer of the univalent direct thrombin inhibitor dabigatran

Table 21.5 Guideline recommendations for anti-Xa agents

	ESA guidelines[a]		ASRA guidelines[b]	
	Time before procedure/ catheter removal	Time after procedure	Time before procedure/ catheter removal	Time after procedure
Fondaparinux (2.5 mg daily)	36–42 h	6–12 h	Single injection, atraumatic needle placement or alternate prophylaxis. Avoid indwelling catheters	
Rivaroxaban (10 mg daily)	22–26 h	4–6 h		
Apixaban (2.5 mg BID)	26–30 h	4–6 h		
Dabigatran (150–220 mg)	Contraindicated	6 h		
Argatroban	4 h	2 h	Recommend against neuraxial techniques	
Hirudins (e.g., lepirudin, desirudin)	8–10 h	2–4 h	Recommend against neuraxial techniques	

[a]Gogarten et al. (2010)
[b]Horlocker et al. (2010)

suggests that regional procedures should be contraindicated in patients receiving it. It is recommended that physicians who anticipate encountering these agents familiarize themselves with their individual pharmacology, as specific considerations exist for each one. To illustrate this, dabigatran is up to 80 % renally cleared and clearance half-time may be greatly affected in cases of renal insufficiency; the lack of any monitoring test makes prediction of adequate reversal challenging.

In a series of patients receiving fondaparinux 2.5 mg thromboprophylaxis postoperatively, 1,631 patients underwent neuraxial or deep peripheral regional anesthesia and no major hemorrhagic complications were noted. However, first doses were administered 6–12 h after surgery, while treatment was withheld for 36 h before surgery, and restarted 12 h after indwelling catheter removal (Singelyn et al. 2007). Ultimately, little clinical evidence has been reported and extreme caution is recommended, particularly when considering a neuraxial technique. Table 21.5 summarizes current guideline recommendations.

21.2.6 Thrombolytics

Thrombolytics, like the exogenous plasminogen activators streptokinase or anistreplase, are only administered in emergency situations and thus often unpredictably for the regional anesthesiologist. If this situation is encountered after performance of a regional technique, vigilance is necessary and frequent neurological examinations should be performed to assess for the possibility of a hemorrhagic complication. Consideration should be made for leaving indwelling catheters in situ until thrombolytic activity has ceased.

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Part III

Post-operative Hemostasis

Coagulation Disorders in Intensive Care Patients

22

Marcel Levi

22.1 Introduction

Critically ill patients commonly suffer from coagulation abnormalities (Levi and Opal 2006). A myriad of altered coagulation parameters is often detectable, such as thrombocytopenia, longer global coagulation times, reduced levels of coagulation inhibitors, or high levels of fibrin split products. Each of these clotting derangements may derive from a variety of different pathophysiological mechanisms. Some patients may have a marked coagulopathy, yet it can go largely undetected when measured using routine coagulation assays. Proper identification of the underlying cause for these coagulation abnormalities is required since different coagulation disorders may necessitate different diagnostic and therapeutic management strategies. This chapter reviews the most frequently occurring coagulation abnormalities in patients in intensive care units (ICUs). Emphasis is put on the differential diagnosis, the underlying molecular and pathogenetic pathways, and the appropriate diagnostic and therapeutic interventions.

22.2 Incidence

The incidence of thrombocytopenia (platelet count $<150 \times 10^9$/l) in critically ill patients is 35–44 % (Vanderschueren et al. 2000). A platelet count of $<100 \times 10^9$/l is seen in another 30–50 % of patients. A longer global coagulation time, such as prothrombin time (PT) or the activated partial thromboplastin time (aPTT), occurs in 14–28 % of ICU patients (Levi and Opal 2006).

ICU patients with coagulation defects have a four to five times higher risk of bleeding than patients with a normal coagulation status (Vanderschueren et al.

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2000). The risk of intracerebral bleeding in critically ill patients during ICU admission is relatively low (0.3–0.5 %), but 88 % of patients with this complication have platelet counts $<100 \times 10^9$/l. Moreover, a decrease in platelet count may indicate ongoing coagulation activation, which contributes to microvascular failure and organ dysfunction. Early identification of these patients is crucial to the provision of adequate supportive care (Ahmed et al. 2009; Schultz 2009). Regardless of the cause, thrombocytopenia is an independent predictor of ICU mortality in multivariate analyses, with various studies showing a relative risk of 1.9–4.2 (Fig. 22.1) (Strauss et al. 2002; Vanderschueren et al. 2000). Other coagulation test abnormalities frequently observed in ICU patients include elevated fibrin split products and reduced levels of coagulation inhibitors. Fibrin split products, such as D-dimer, were detectable in 42 % of a consecutive case series of ICU patients, in 80 % of trauma patients, and in 99 % of patients with sepsis (Bernard et al. 2001; Shorr et al. 2002). Low levels of coagulation inhibitors, such as antithrombin and protein C, are found in 40–60 % of trauma patients and 90 % of sepsis patients (Bernard et al. 2001).

22.3 Coagulation and Inflammation in Critically Ill Patients

The simultaneous and interdependent activation of inflammation and coagulation is important in the pathogenesis of many systemic inflammatory states that can be found in critically ill patients. Endothelial cells and natural anticoagulant pathways have a central position in the interaction between coagulation and inflammation pathways; the restoration of defective anticoagulant pathways in patients with sepsis has therefore received considerable attention (Levi and van der Poll 2008). There is ample evidence that there exists extensive crosstalk between inflammation and coagulation,

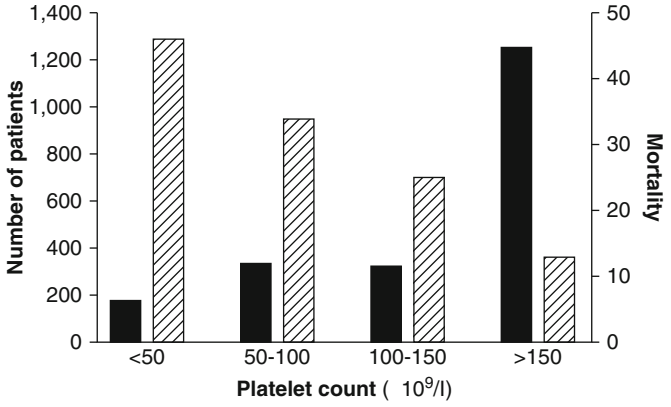

Fig. 22.1 Distribution of nadir platelet count (*black bars*) and survival (*striped bars*) in a pooled analysis of four clinical studies of consecutive groups of patients admitted to an ICU (From Levy and Opal (2010) with permission)

whereby inflammation not only leads to activation of coagulation, but coagulation also markedly affects inflammatory activity (Levi et al. 2008). Procoagulant activity is regulated by three key anticoagulant pathways: antithrombin, the protein C/thrombomodulin system, and tissue factor pathway inhibitor (Esmon 2001). Notably, activated protein C (APC) appears to play a central role in the pathogenesis of sepsis and associated organ dysfunction (Griffin et al. 2007). There is ample evidence that an insufficient functioning of the protein C pathway contributes to the derangement of coagulation in sepsis (Esmon 1987; Levi et al. 2001). The circulating zymogen protein C is activated by the endothelial cell-bound thrombomodulin once this is activated by thrombin (Esmon 1987). APC acts in concert with its cofactor protein S and is able to proteolytically degrade the activated cofactors V (FVa) and VIII (FVIIIa) which are essential to coagulation; hence, it is an effective anticoagulant. The endothelial protein C receptor not only accelerates activation of protein C several times over but also serves as a receptor for APC, and the binding of APC to this receptor may amplify its anticoagulant and anti-inflammatory effects (Esmon 2000). In patients with sepsis, plasma levels of the zymogen protein C are low or very low due to impaired synthesis, consumption, and degradation by proteolytic enzymes, such as neutrophil elastase (Eckle et al. 1991; Mesters et al. 2000; Vary and Kimball 1992). Furthermore, a significant downregulation of thrombomodulin, caused by pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1, has been demonstrated, resulting in diminished protein C activation (Faust et al. 2001; Nawroth and Stern 1986). Low levels of free protein S may further compromise an adequate function of the protein C system. In plasma, 60 % of the cofactor protein S is complexed to a complement regulatory protein, C4b-binding protein (C4bBP). As a consequence of the acute phase reaction in inflammatory diseases, increased levels of C4bBP in plasma may result in a relative deficiency of protein S, which further contributes to a procoagulant state during sepsis. Finally, but importantly, the endothelial protein C receptor has been shown to be downregulated in sepsis, and this may negatively affect the function of the protein C system (Taylor et al. 2000). Interestingly, all three anticoagulant systems are located at the endothelial surface, where they can direct both anticoagulant and anti-inflammatory functions. During inflammation-induced activation of coagulation, the functions of all three pathways may be impaired (Levi et al. 2004). Pro-inflammatory cytokines and chemokines, as well as endothelial cell perturbation, affect all physiological anticoagulant mechanisms, and vice versa, activated coagulation proteases and physiological anticoagulants can modulate inflammation via specific cell receptors.

22.4 Causes of Thrombocytopenia

There are many causes of thrombocytopenia in critically ill patients. Table 22.1 summarizes the most frequently occurring diagnoses.

Sepsis is a clear risk factor for thrombocytopenia in critically ill patients, and the severity of sepsis correlates with the decrease in platelet count (Mavrommatis et al. 2000). The main factors contributing to thrombocytopenia in patients with sepsis

Table 22.1 Differential diagnosis of thrombocytopenia in the ICU

Differential diagnosis	Relative incidence (%)	Additional diagnostic clues
Sepsis	52.4	Positive (blood)cultures, positive sepsis criteria, hematophagocytosis in bone marrow aspirate
DIC[a]	25.3	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	7.5	Major bleeding, low hemoglobin, longer aPTT and PT
Thrombotic microangiopathy	0.7	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency
Heparin-induced thrombocytopenia	1.2	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin–platelet factor IV antibodies), rebound of platelets after cessation of heparin
Immune thrombocytopenia	3.4	Antiplatelet antibodies, normal or increased number of megakaryocytes in bone marrow aspirate, thrombopoietin (TPO) decreased
Drug-induced thrombocytopenia	9.5	Decreased number of megakaryocytes in bone marrow aspirate or detection of drug-induced antiplatelet antibodies, rebound of platelet count after cessation of drug

Seven major causes of thrombocytopenia (platelet count $<150 \times 10^9$/l) are listed. Relative incidences are based on two studies in consecutive ICU patients. Patients with hematological malignancies were excluded.

[a]Patients with sepsis and DIC are classified as DIC

are impaired platelet production, increased platelet consumption or destruction, or platelet sequestration in the spleen or on the endothelial surface. In patients with sepsis, impaired platelet production within the bone marrow may seem contradictory to the high levels of platelet production-stimulating pro-inflammatory cytokines (such as tumor necrosis factor-α and interleukin-6) and high concentrations of circulating thrombopoietin. These cytokines and growth factors should theoretically stimulate megakaryopoiesis in the bone marrow (Folman et al. 2000). However, marked hemophagocytosis may occur in a significant number of patients with sepsis. This pathological process consists of active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages, due hypothetically to their stimulation by high levels of macrophage colony-stimulating factor in sepsis (Francois et al. 1997). Platelet consumption probably also plays an important role in patients with sepsis, due to ongoing generation of thrombin (which is the most potent activator of platelets in vivo) in its most fulminant form, known as disseminated intravascular coagulation (see below). Platelet activation, consumption, and destruction may also occur at the endothelial site as a result of the extensive endothelial cell–platelet interaction in sepsis, although this may vary between different vascular beds in various organs (Levi and Lowenberg 2008).

Heparin-induced thrombocytopenia (HIT) is caused by a heparin-induced antibody that binds to the heparin–platelet factor IV complex on the platelet surface (Warkentin et al. 2003). This may result in massive platelet activation, and as a consequence, a consumptive thrombocytopenia and arterial and venous thrombosis

occur. A consecutive series of critically ill ICU patients who received heparin revealed an incidence of 1 % in this setting (Verma et al. 2003). Unfractionated heparin carries a higher risk of HIT than low molecular weight heparin (LMWH). Thrombosis may occur in 25–50 % of patients with HIT (with fatal thrombosis in 4–5 %) (Warkentin 2003). The diagnosis of HIT is based on the detection of HIT antibodies in combination with the occurrence of thrombocytopenia in a patient receiving heparin, with or without concomitant arterial or venous thrombosis. It should be mentioned that the commonly used ELISA (enzyme-linked immunosorbent assay) for HIT antibodies has a high negative predictive value (100 %), but a very low positive predictive value (10 %) (Verma et al. 2003). The gold standard for the diagnosis of HIT is a sensitive platelet activation assay; however, this test is not routinely available. Normalization of the number of platelets 1–3 days after discontinuation of heparin may further support the diagnosis of HIT.

The category of thrombotic microangiopathies encompasses syndromes such as thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome, severe malignant hypertension, chemotherapy-induced microangiopathic hemolytic anemia, and the HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) (Moake 2002). A common pathogenetic feature of these clinical entities appears to be endothelial damage, causing platelet adhesion and aggregation, thrombin formation, and impaired fibrinolysis. The multiple clinical consequences of this extensive endothelial dysfunction include thrombocytopenia, mechanical fragmentation of red blood cells with hemolytic anemia, and obstruction of the microvasculature of various organs such as the kidneys and the brain (leading to renal failure and neurologic dysfunction, respectively). Despite this common final pathway, the various thrombotic microangiopathies have different underlying etiologies. Thrombotic thrombocytopenic purpura is caused by congenital or acquired (autoimmune) deficiency of von Willebrand factor-cleaving protease (ADAMTS13); this results in endothelial cell-attached ultra-large von Willebrand multimers that readily bind to platelet surface glycoprotein Ib and cause platelet adhesion and aggregation (Tsai 2003). In hemolytic–uremic syndrome, a cytotoxin released upon infection with a specific serogroup of gram-negative microorganisms (usually *E. coli* serotype O157:H7) is responsible for endothelial cell and platelet activation. In case of malignant hypertension or chemotherapy-induced thrombotic microangiopathy, direct mechanical and chemical damages to the endothelium are, respectively, presumed responsible for the enhanced endothelial cell–platelet interaction. A diagnosis of thrombotic microangiopathy relies upon the combination of thrombocytopenia, the Coombs-negative hemolytic anemia, and the presence of schistocytes in the blood smear. Additional information can be achieved by measurement of ADAMTS13; however, low levels of ADAMTS13 may occur in all forms of thrombotic microangiopathy (van den Born et al. 2008).

Drug-induced thrombocytopenia is another frequent cause of thrombocytopenia in an ICU setting (Stephan et al. 1999). It may be caused by drug-induced myelosuppression, such as that caused by cytostatic agents or by immune-mediated mechanisms. Drug-induced thrombocytopenia is a difficult diagnosis in an ICU setting as patients are often exposed to multiple agents and have numerous other potential

reasons for platelet depletion. Drug-induced thrombocytopenia is often diagnosed based upon the timing of the initiation of a new agent in relation to the development of thrombocytopenia, after exclusion of other possible causes. A rapid restoration of the platelet count observed after discontinuation of a suspected agent is highly suggestive of drug-induced thrombocytopenia.

22.5 Causes of Prolonged Global Coagulation Times

It is important to emphasize that global coagulation tests, such as PT and aPTT, are a poor reflection of in vivo hemostasis. However, these tests are a convenient method of quickly estimating the concentration of one or at times multiple coagulation factors for which each test is sensitive (Table 22.2) (Greaves and Preston 2001). In general, coagulation tests will take longer if coagulation factor levels are below 50 %. This is relevant since the coagulation factor levels needed for adequate hemostasis are somewhere between 25 and 50 % (Edmunds 2001).

Longer global coagulation tests may be due to a deficiency of one or more coagulation factors. In addition, but more rarely, the presence of an inhibiting antibody with a major in vivo relevance (such as in acquired hemophilia), but a clinically insignificant laboratory phenomenon, should be considered. The presence of lupus anticoagulant may cause a longer aPTT and can be associated with thrombocytopenia as well. Paradoxically, lupus anticoagulant may dramatically increase the risk of thrombosis. The presence of an inhibiting antibody can be confirmed using a simple mixing experiment. As a general rule, if a longer global coagulation test cannot be corrected by mixing 50 % of patient plasma with 50 % of normal plasma, then an inhibiting antibody is likely to be present.

Table 22.2 Differential diagnosis of abnormal global coagulation times

Test result	Cause
PT prolonged, normal aPTT	Factor VII deficiency Mild vitamin K deficiency Mild liver insufficiency Low doses of vitamin K antagonists
Normal PT, aPTT prolonged	Factor VIII, IX, or XI deficiency Use of unfractionated heparin Inhibiting antibody and/or antiphospholipid antibody Factor XII or prekallikrein deficiency (no relevance for in vivo coagulation)
PT and aPTT prolonged	Factor X, V, and II or fibrinogen deficiency Severe vitamin K deficiency Use of vitamin K antagonists Global clotting factor deficiency Synthesis: liver failure Loss: massive bleeding Consumption: DIC

Levi and Opal (2010)

In the vast majority of critically ill patients, deficiencies of coagulation factors are acquired, and we will not discuss the various congenital coagulation defects here. In general, deficiencies in coagulation factors may be due to impaired synthesis, massive loss, or increased turnover (consumption). Impaired synthesis is often due to liver insufficiency or vitamin K deficiency. Vitamin K deficiency may be caused by poor nutrition in combination with the use of antibiotics that affect intestinal flora and thereby bacterial vitamin K production. PT is highly sensitive to both conditions since this test is very dependent on the plasma levels of factor VII (a vitamin K-dependent coagulation factor with the shortest half-life of the clotting factors). Liver failure may be differentiated from vitamin K deficiency by measuring factor V, which is not vitamin K dependent. In fact, factor V plays an important role in various scoring systems for severe acute liver failure (Bailey et al. 2003). Uncompensated losses of coagulation factors may occur after massive bleeding, for example, in trauma patients or patients undergoing major surgical procedures. It is particularly common in patients with major blood loss where intravascular volume is rapidly replaced with crystalloids, colloids, and red blood cells without simultaneous administration of coagulation factors. The resulting depletion coagulopathy may persist and exacerbate bleeding. In addition, transfusion in these patients may lead to systemic activation of inflammatory processes and may contribute to further coagulation derangements (Vlaar et al. 2009). In hypothermic patients (e.g., trauma patients), measurements from global coagulation tests may underestimate coagulation in vivo since laboratory test-tube assays are standardized and performed at 37 °C to simulate normal body temperature. Consumption of coagulation factors may occur within the framework of disseminated intravascular coagulation (see below). In complicated cases, various causes for longer global coagulation times may exist at once, and the cause can also change over time. For example, multi-trauma patients will often present with a loss of coagulation factors due to severe bleeding, but they can later develop a consumption coagulopathy due to disseminated intravascular coagulation (DIC) that is a consequence of a systemic inflammatory response. Coagulopathy may ensue from trauma-induced liver injury and acute hepatic failure with resultant impaired coagulation factor synthesis.

Some anticoagulant agents will also lengthen global coagulation times. Unfractionated heparin lengthens aPTT, but confusingly, LMWH has no such effect (or only a very modest one). Vitamin K antagonists cause a reduction in vitamin K-dependent coagulation factors, resulting in an initial lengthening of PT, followed by lengthening of both PT and aPTT.

22.6 Disseminated Intravascular Coagulation

DIC occurs in a substantial proportion of consecutive intensive care patients. It is a syndrome caused by systemic intravascular activation of coagulation that may be secondary to various underlying conditions (Levi and ten Cate 1999). The formation of microvascular thrombi, in concert with inflammatory activation, may cause

failure of the microvasculature and thereby contribute to organ dysfunction (Wheeler and Bernard 1999). Ongoing and insufficiently compensated consumption of platelets and coagulation factors may pose a risk of bleeding, especially in perioperative patients or patients who need to undergo invasive procedures. Thrombin generation proceeds via the (extrinsic) tissue factor/factor VIIa route concomitant with depression of the inhibitory mechanisms of thrombin generation, such as the antithrombin III and protein C and S systems (Levi et al. 2008). Impaired fibrin degradation, due to high circulating levels of plasminogen activator inhibitor 1, further enhances intravascular fibrin deposition.

Patients with DIC have a low or rapidly decreasing platelet count, longer global coagulation tests, low plasma levels of coagulation factors and inhibitors, and increased markers of fibrin formation and/or degradation, such as D-dimer or fibrin degradation products (Levi et al. 2009). Coagulation proteins with a marked acute phase behavior, such as factor VIII or fibrinogen, are usually not decreased or may even increase. Thus fibrinogen, although one of the commonly advocated laboratory tests for the diagnosis of DIC, is not a very reliable marker for DIC, except in very severe cases, although sequential measurements can provide some insight. There is no single laboratory test with sufficient accuracy for the diagnosis of DIC. However, its diagnosis may be made using a simple scoring system based on a combination of routinely available coagulation tests (Taylor et al. 2001). In a number of prospective validation studies, the sensitivity and specificity of this DIC score were found to be above 95 and 98 %, respectively. Furthermore, this DIC score was found to be a strong and independent predictor of mortality in a large series of patients with severe sepsis (Dhainaut et al. 2004). Recent research points to a prominent association between activated coagulation as a result of inflammation or tissue damage and preexisting metabolic derangements, such as diabetes mellitus (Hermanides et al. 2009; Levi et al. 2008).

22.7 Management of Coagulation Abnormalities in Intensive Care Patients

The primary focus of attention in the treatment of a clinically relevant coagulopathy should clearly be directed towards the adequate management of the underlying condition. Nevertheless, in addition to a proper treatment for the underlying disorder, supportive measures for the treatment of coagulation defects are also often required.

For patients with a platelet count of $<30–50 \times 10^9$/l, accompanied by bleeding or at high risk of bleeding, and in patients with a platelet count $<10 \times 10^9$/l, regardless of the presence or absence of bleeding, most guidelines advocate a platelet transfusion. Platelet concentrates usually contain a mixture of platelets from the blood donations of 5–6 donors (equal to 5–6 units), although in some parts of the world (notably the USA), single-donor transfusion has become the usual practice due to a presumed decrease in side effects and potential for antibody formation. Platelet transfusion is particularly effective in patients with a thrombocytopenia due either to impaired platelet production or increased consumption; disorders of enhanced

platelet destruction (e.g., immune thrombocytopenia) may necessitate alternative therapies, such as steroids or human immunoglobulin. Some causes of thrombocytopenia may require specific measures. HIT (or suspected HIT) requires immediate cessation of heparin and initiation of an alternative anticoagulant treatment, e.g., with danaparoid, thrombin inhibitors, or fondaparinux (Hirsh et al. 2004). Vitamin K antagonists should be avoided in the initial treatment of HIT since these agents may cause skin necrosis. In patients with a thrombotic microangiopathy due to antibody-induced low levels of ADAMTS13, plasma exchange and immunosuppressive treatment should be initiated; in cases of congenital ADAMTS13 deficiency, plasma infusion suffices (Moake 2002).

Fresh or frozen plasma contains all the coagulation factors and may be used to make up the congenital or acquired deficiencies of these clotting factors. In most centers, the current best practice guidelines advocate the use solvent- or detergent-treated plasma, which may provide better protection against the transmission of blood-borne infections, but may also include a lower recovery of coagulation factors (Hellstern et al. 2002). Most consensus guidelines indicate that plasma should only be transfused in cases of bleeding or situations with a high risk of bleeding; it should not be based on laboratory abnormalities alone. For more specific therapy or if the transfusion of large volumes of plasma is not advisable, fractionated plasma of purified coagulation factor concentrate is available. Prothrombin complex concentrates (PCC) contain the vitamin K-dependent coagulation factors II, VII, IX, and X. Hence, these concentrates may be used if immediate reversal of vitamin K antagonist treatment is required. PCC may also be used if a replenishment of all the coagulation factors is necessary and large volumes of plasma may not be tolerated. In some cases, administration of purified coagulation factor concentrates, such as fibrinogen concentrate, may be helpful.

Pro-hemostatic treatment can be used as an adjunctive treatment in patients with significant blood loss (Mannucci and Levi 2007). De-amino-8-D-arginine vasopressin (DDAVP, desmopressin) is a vasopressin analogue that induces the release of the contents of the endothelial cell-associated Weibel–Palade bodies, including von Willebrand factor (vWF). Hence, the administration of DDAVP results in a marked increase in the plasma concentration of vWF (and associated coagulation factor VIII) and, by as yet unexplained additional mechanisms, a potentiation of primary hemostasis. DDAVP has proved to be effective in the care of patients with von Willebrand's disease and mild hemophilia A, but also of patients with uremic thrombocytopathy and other defects in primary hemostasis (Mannucci 1997).

Antifibrinolytic agents, such as lysine analogues (ε-aminocaproic acid or tranexamic acid), may also be helpful in the prevention or control of bleeding, in particular if hyperfibrinolysis is thought to be the major contributor to the hemostatic defect. Antifibrinolytic therapies may also compensate for other coagulation defects. Antifibrinolytic agents have been found effective in preventing blood loss and reducing transfusion in patients undergoing major surgical procedures, and they are relatively safe (Levi et al. 1999; Porte et al. 2000). A large, international, controlled multicenter trial recently showed that the use of the antifibrinolytic agent tranexamic acid reduced mortality in trauma patients with excessive blood loss (Shakur et al. 2010).

Recombinant factor VIIa (rFVIIa) is a pro-hemostatic agent that has been licensed for the treatment of patients with hemophilia and antibodies inhibiting factors VIII or IX. A very large number of case series have reported successful use of rFVIIa in patients with other types of coagulation defects or in patients with major bleeding due to surgery or trauma; however, the number of successful controlled clinical trials is still limited. Initial trials in patients with intracranial hemorrhage and trauma were promising; however, the benefit of rFVIIa on clinically relevant outcome parameters in these settings was not confirmed, and the incidence of thrombotic complications slightly increased (Levi 2012). A meta-analysis of all the controlled trial data on rFVIIa examined the thromboembolic event rate outside the approved label indications (Levi et al. 2010). Arterial thromboembolic rates were higher in rFVIIa-treated (5.5 %) than placebo-treated (3.2 %) patients. Venous thromboembolic rates were comparable between rFVIIa-treated (5.3 %) and placebo-treated (5.7 %) patients. In rFVIIa-treated patients, 2.9 % experienced coronary arterial thrombotic events compared to 1.1 % with placebo. Arterial thromboembolic rates were highest in patients over 65 years old (9.0 % vs 3.8 %) and particularly in patients over 75 years old (10.8 % vs 4.1 %). Therefore, until ongoing clinical trials and further safety data on critically ill patients become available, the off-label use of rFVIIa can only be justified in cases of life-threatening bleeding, when all other conventional treatments have failed (Mannucci and Levi 2007).

Supportive treatment of the coagulopathy associated with DIC is a complex issue (Levi et al. 2009). Administration of anticoagulants may theoretically be beneficial, but their efficacy has never been proved in clinical trials. Restoration of dysfunctional physiological anticoagulant pathways by administration of antithrombin concentrate or (activated) protein C has beneficial effects on laboratory parameters, but the efficacy of this approach for clinically relevant outcome parameters has yet to be confirmed. In initial trials with patients with severe sepsis, recombinant human APC (drotrecogin alpha activated) was effective (Bernard et al. 2001); however, a recently completed placebo-controlled trial in patients with severe sepsis and septic shock was prematurely stopped due to the lack of any significant benefit from APC (Ranieri et al. 2012). The manufacturer of APC subsequently decided to withdraw the product from the market, which has resulted in a revision of current guidelines for the treatment of DIC (Thachil et al. 2012). Interestingly, in all studies, the relative efficacy of APC in the subgroup of patients with DIC was higher than in those without DIC, and patients treated with APC had a more rapid resolution of DIC than placebo-treated patients (Dhainaut et al. 2004).

Soluble thrombomodulin represents a new alternative option for the treatment of DIC. In an initial phase III, randomized, double-blind clinical trial involving 234 patients with DIC, the administration of soluble thrombomodulin had a significantly better effect on bleeding manifestations and coagulation parameters than heparin, but the mortality rate at 28 days was similar in both study groups (Saito et al. 2007). DIC was resolved in 66.1 % of the thrombomodulin group, compared to 49.9 % of the heparin group (difference 16.2 %; 95 % confidence interval 3.3–29.1). Patients in the thrombomodulin group also showed a more marked improvement in the clinical course of bleeding symptoms. Soluble thrombomodulin was recently evaluated

in a phase II/III clinical study involving 750 patients with sepsis and disseminated intravascular coagulation. Twenty-eight-day mortality was 17.8 % in the thrombomodulin group and 21.6 % in the placebo group. Markers of coagulation activation were lower in the thrombomodulin group than in the placebo group. There were no differences between the groups in bleeding or thrombotic events.

Conclusions

Coagulation abnormalities occur frequently in critically ill patients and may have a significant impact on the outcome. Treatment of ICU patients should be directed primarily at their underlying condition, but an adequate explanation for the coagulation abnormalities of these critically ill patients, together with supportive therapy, may also be required. Deficiencies in platelets and coagulation factors in bleeding patients or patients at risk of bleeding can be made up by transfusion of platelet concentrate or plasma products, respectively. In addition, pro-hemostatic treatment may be beneficial in cases of severe bleeding, whereas restoring physiological anticoagulant pathways may be helpful in patients with sepsis and DIC.

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Perioperative Thromboprophylaxis

23

Marc Aldenkortt and Marc Licker

23.1 Introduction

The term "hemostasis" originally referred to a sequence of events aimed at minimizing blood loss by forming a clot at the site of vessel injury. In 1958, Astrup first alluded to the concept of "hemostatic balance," by which clot formation following tissue injury orchestrates its own destruction (Astrup 1958). Under normal blood flow conditions, endothelial cells continuously release vasodilatory and anti-aggregant substances (e.g., nitric oxide and prostacyclin) while providing a protective barrier that separates blood cells and plasma proteins from highly reactive components within the layers of the vascular wall. Vascular endothelial cells, platelets, natural inhibitors of coagulation, and the fibrinolytic system all participate in maintaining blood fluidity (Tanaka et al. 2009).

Following endothelial disruption due to trauma or surgery, local exposure of tissue factor and the activation of platelets and coagulation factors trigger a sequence of events. This involves platelet adhesion to subendothelial elements, further platelet aggregation, generation of large amounts of thrombin, and ultimately, formation of a "platelet–red cell–fibrin" thrombus that seals off the hemorrhagic vascular leak (Fig. 23.1) (Schenone et al. 2004). Under certain physiological conditions, the overwhelming thrombosis induced by excessive activation of the hemostatic process outside the traumatic area is counteracted by systemic antithrombotic activity (e.g., protein C, protein S), local activation of fibrinolysis, and the dilution effects of blood flow (Wolberg et al. 2012).

In the perioperative period, venous thrombus formation results from an imbalance between local and systemic procoagulants/anticoagulants as well as between pro- and

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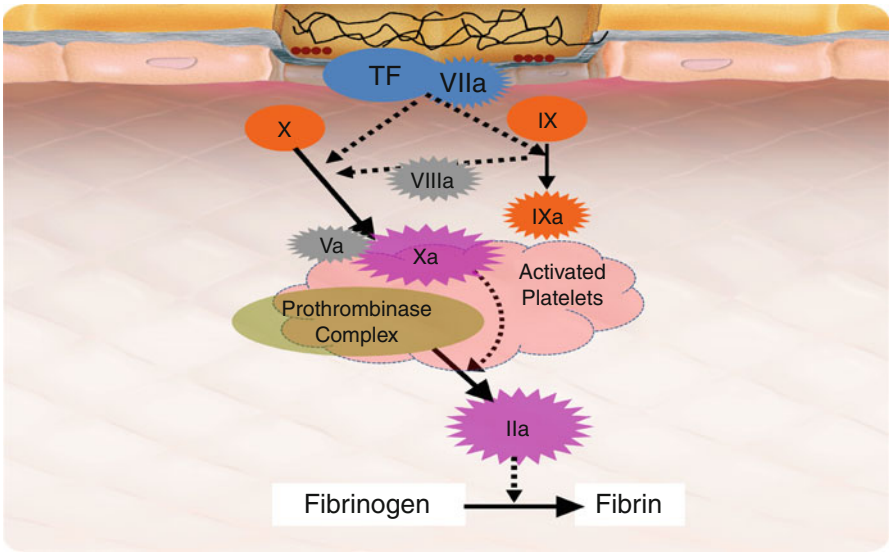

Fig. 23.1 Cell-based activation of the coagulation cascade (primary and secondary hemostasis) upon endothelial injury (*TF* tissue factor; coagulation factors and their activated forms IIa, Va, X/Xa, VIIa, and IX/IXa)

antifibrinolytic activity. According to Virchow, three key phenomena – venous stasis, vascular injury, and hemostatic abnormalities – are responsible for this imbalance (Table 23.1). Patients with cancer are particularly prone to developing venous thrombosis since tumoral cells release procoagulant substances (White et al. 2007).

23.2 Venous Thromboembolism (VTE)

23.2.1 Definition

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are considered two manifestations of the same anatomo-clinical entity, namely, venous thromboembolism (VTE). Venous thrombi are predominately composed of red blood cells, platelets, and leukocytes, all bound together by fibrin. PE is the third most common cause of hospital-related death, and it is the most common preventable cause of hospital-related death.

23.2.2 Prevalence

The highest risk of DVT occurs in the first postoperative week, but it remains important up to 3–6 weeks following major thoracoabdominal or orthopedic procedures (White et al. 2003). In the absence of antithrombotic prophylaxis and if screened by contrast venography, duplex ultrasound, or fibrinogen labeling, the prevalence of asymptomatic

Table 23.1 Pathogenic mechanisms of venous thrombosis

Venous stasis	Vascular wall injury	Hemostatic abnormalities
Impairment of blood flow	Endothelial disruption	Blood cell activation
Patient-related factors		
Pregnancy, postpartum	Inflammatory infiltration	Procoagulant tumor
Cancer	Infiltration by tumor	Polyglobulia, dehydration
Arterial aneurysm	Hyperhomocysteinemia	Hyperfibrinogenemia
Previous deep vein thrombosis	Previous deep vein thrombosis	Inherited thrombophilia[a] Myeloproliferative disorder
Obesity (>20 % ideal body weight) Congestive heart failure Varicose veins Bed rest, prolonged sitting Advanced age	Antiphospholipid/lupus-like anticoagulant antibodies	Antiphospholipid/lupus-like anticoagulant antibodies Sepsis, severe infection Post-trauma/surgical inflammation
Procedure-related factors		
Immobilization, paralysis	Surgical incision, trauma	Hormonal/chemotherapy
Mechanical ventilation	Venous puncture	Steroids
Central venous catheter Pacemaker wires Tourniquet	Heparin-induced thrombocytopenia	Heparin-induced thrombocytopenia

[a]Thrombophilic factors are found in 25–50 % of patients with VTE (factor V Leiden mutation; prothrombin 2020 mutation; deficiency of antithrombin, of protein C, or of protein S; and/or antiphospholipid syndrome)

DVT can be as high as 40–80 % following total knee arthroplasty (TKA) or total hip arthroplasty (THA) and 15–30 % following major abdominal surgery (Stringer et al. 1989; White et al. 2003). Pain or tenderness at palpation is a characteristic symptom of DVT that may be accompanied by local swelling, erythema, and increased warmth, as well as the presence of dilated veins (collaterals) on the chest wall or legs. The prevalence of symptomatic VTE has largely decreased over the last four decades because of important changes in perioperative surgical care, including less invasive surgery and earlier ambulation. Following major joint surgery, the rate of symptomatic VTE events has declined from 15 to 30 % prior to 1980 (without prophylaxis) to less than 2 % after 2000 (with prophylaxis) (Januel et al. 2012). Ethnicity, geographical location, and lifestyle may also influence the prevalence of VTE. In major orthopedic surgery, the rate of proximal DVT diagnosed by venography exceeds 20 % in Western countries but is less than 10 % in Asian countries (Kanchanabat et al. 2011).

23.2.3 Time Course and Cost Implications

Most thrombi start in the calf and have few clinical consequences if they remain confined below the knee. The probability that calf DVT will extend to involve the proximal iliofemoral and/or visceral veins, and subsequently cause PE, increases with the severity and persistence of the initiating prothrombotic stimulus. Alternatively, the fresh thrombus may dissolve by activation of the fibrinolytic

system, or the granulation tissue may invade the occlusive blood clot which can later be recanalized. Although the patency of the vessel can be restored, destruction of the venous valves results in chronic venous hypertension and secondary varices.

Studies investigating the spontaneous evolution of untreated proximal DVT are scarce, but they do suggest a risk of post-thrombotic syndrome (leg swelling, tenderness, and ulcers) in 25–50 % and of clinical PE in 10–40 % of cases (Huber et al. 1992). Importantly, about 10 % of PE are rapidly fatal as a result of acute heart failure – the right ventricle being unable to face the sudden elevation of afterload if thrombi occlude more than two thirds of the pulmonary vasculature. In patients surviving an acute PE episode, pulmonary perfusion normalizes in about two thirds of patients, while in 4–6 %, relapsing embolization of small clots from persisting DVT may lead to chronic pulmonary hypertension (Pengo et al. 2004).

From an economic standpoint, VTE increase the global burden on both the healthcare system and individuals by up to USD 1.5 billion a year in the USA and EUR 3.07 billion in the European Union (Oger 2000; Dobesh 2009). In Europe, the cost of VTE in orthopedic surgery has been estimated at EUR 8,265 per patient, thereby doubling the average cost of orthopedic inpatient care (Ollendorf et al. 2002). More recently, the risk-adjusted total healthcare cost, including the beneficiary's cost share over 1 year, was found to be USD 13,500 higher in patients with a VTE (versus without a VTE) following TKA (Baser et al. 2011).

23.3 Assessment of VTE Risk Factors

The concept of *primum non nocere* applies to VTE prophylaxis as it does to all areas of medicine. Each patient should be assessed and treated on an individual basis and balance maximal antithrombotic efficacy against minimal bleeding, while taking into account patient convenience.

Several models of VTE risk assessment have been published, namely, those developed by Caprini, Rogers, Cohen, and Kucher (Caprini et al. 2001; Cohen et al. 2005; Kucher et al. 2005; Rogers et al. 2007). Each of these models encompasses a list of exposure risk factors (presenting illness or procedure) and predisposing risk factors (genetic and clinical characteristics). The Caprini score was validated in a large retrospective study on a sample of general, vascular, plastic, and urological surgery patients (Table 23.2) (Bahl et al. 2010). Patient and surgical risk factors are summed to produce a cumulative score which falls into one of four levels of risk, with a growing incidence of VTE: low risk (VTE ~2 %) if the total score is 0–1, moderate risk (VTE ~5–10 %) if the score equals 2, high risk (VTE 20–40 %) if the score is 3–4, and very high risk (VTE ≥40 %) if the score is ≥5.

Alternatively, the American College of Chest Physicians' (ACCP) guidelines stratify the risks of VTE according to the type of procedure (orthopedic, pelvic/abdominal, cardiac, thoracic, or intracranial/spinal) and to some disease characteristics (trauma, cancer) (Falck-Ytter et al. 2012; Gould et al. 2012a). Though simple, this approach fails to provide an individualized approach to risk assessment and thromboprophylaxis.

Table 23.2 Assessment of the risk of venous thromboembolism

Risk factor	1 pt	2 pts	3 pts	5 pts
Age	41–60 years old	61–74 years old	≥75 years old	
Procedure/trauma	Minor surgery	Arthroscopy, laparoscopy (>45 min) Major surgery (>45 min) Central venous access		Elective major lower limb arthroplasty (hip, knee) Multiple trauma (<1 month) Hip, pelvis, or leg fracture Acute spinal cord injury (<1 month)
Functional status	Bed rest (medical patient)		Immobilizing plaster cast (<1 month) Confined to bed (>72 h)	
Physical status	COPD CHF or AMI Pregnancy or postpartum (<1 month) Sepsis Obesity (BMI >25) Varicose veins	Cancer		
History	DVT/PE (patient or family) Major surgery (<1 month) Inflammatory bowel disease			Stroke (<1 month)
	Recurrent abortion, unexplained stillborn infant			
Hemostasis			Facteur V Leiden Lupus anticoagulant Prothrombin 20210A Anticardiolipin antibodies Hyperhomocysteinemia HIT thrombopenia	

Modified from Caprini et al. (2001)

The risk of bleeding should be carefully balanced against the need for pharmacological VTE prophylaxis, given the dire consequences of blood loss (hemorrhagic shock) and compressive hematoma requiring homologous transfusion and/or reoperation (Chee et al. 2008). In addition to surgical characteristics (site, extent, and duration), assessing the risk of bleeding should also consider the following: the patient and family history (excessive bleeding after tooth extraction, surgery/trauma, or abortion/delivery); the presence of renal failure, liver disease, or peptic ulcer; and the concomitant use of anticoagulant/antiplatelet drugs. The average cost incurred by major bleeding averages USD 113 per patient receiving anticoagulant medication (Muntz et al. 2004).

23.4 Strategies for Perioperative Thromboprophylaxis

23.4.1 Non-pharmacological Approach

A multimodal thromboprophylaxis approach should be tailored to the patient's individual risk level. Besides the administration of antithrombotic drugs, other simple measures need to be considered, particularly in patients with a high risk of bleeding and in the early phase following surgery. These include fast-track anesthesia, early patient mobilization, and the use of mechanical methods that are deemed suitable (Table 23.3). Among patients undergoing major joint replacement, multimodal thromboprophylaxis including regional anesthesia, intermittent compression, and aspirin (in low risk patients) was associated with the lowest mortality rate – this was compared with potent anticoagulant drugs such as heparin derivatives, fondaparinux or rivaroxaban (Poultsides et al. 2012).

Table 23.3 General recommendations to minimize the risk of perioperative thromboembolism

Preoperative consultation
Assess the risk of VTE and bleeding (patient and procedure factors)
Consider discontinuation of procoagulant drugs (e.g., contraceptives, steroids)
Consider discontinuation of antiplatelet/anticoagulant drugs
Inform the patient about VTE risk, choice of thromboprophylaxis, early rehabilitation plan
Intraoperative period
Minimally invasive surgery and fast-track anesthesia protocol
Hemodynamic optimization, avoid dehydration
Transfusion protocol
Consider regional analgesic techniques
Spontaneous or assisted mode ventilation
Postoperative period
Regional anesthesia blocks, multimodal analgesia
Early extubation, patient mobilization
Early removal of indwelling catheters (arterial and central venous lines, urinary catheter) and drainage tubes

23.4.2 Anesthetic Technique and Early Ambulation

Inadequate pain management, intestinal dysfunction, and immobilization have been recognized among the main factors delaying postoperative recovery. Reducing tissue injury by minimally invasive surgical procedures, improving tissue oxygen delivery by hemodynamic optimization, and multimodal analgesic approaches are all key components of fast-track protocols that may influence Virchow's triad and reduce the risk of VTE.

Interestingly, regional anesthetic techniques, particularly continuous epidural analgesia, have been associated with a reduction in perioperative blood loss and VTE (Roderick et al. 2005; Mauermann et al. 2006). Antithrombotic effects have also been attributed to a greater inhibition of the inflammatory reaction, enhanced venous return owing to spontaneous ventilation and sympatholytic effects, and better quality analgesia allowing pain-free deambulation (Hahnenkamp et al. 2002; Delis et al. 2004).

23.4.3 Mechanical Prophylaxis

First reported in 1980, continuous passive motion (CPM) is an external motorized device that enables a joint to move passively through a preset arc of motion. Although continuous passive motion has been shown to enhance functional recovery and reduce the length of hospital stay following TKA, there are currently insufficient data supporting its effectiveness in preventing DVT (Heron et al. 2001).

British guidelines advocate a systematic use of elasticated compressive stockings (ECS) in all hospitalized surgical patients (day and night), from their admission until return to a normal level of mobility.[1] When fitted and used properly, they increase blood flow velocity, reduce the risk of venous wall dilation and intimal tear, improve venous valve function, and may reduce coagulability, all of which contribute to minimize the risk of venous thrombosis. The optimal length of ECS (thigh versus calf length) is still unresolved, but problems are more common with the thigh-length stockings and in overweight patients.

Overall, ECS can reduce the risk of VTE by as much as 50–66 % (Phillips et al. 2008; Khaw et al. 1993). The main contraindication is the presence of peripheral vascular disease. Given the fourfold increased risk (5.3 % versus 1.2 % without ECS) of local complications (breaks ulcers, blisters, and necrosis), it is recommended that ECS be removed daily for a skin inspection.

Intermittent pneumatic compression devices (IPC) comprise a pair of inflatable sleeves wrapped either around the entire leg or only below the knee and attached to a small bedside electric pump. The sleeves are inflated alternately or sequentially, first around the lower leg and then the upper, to "milk" the blood from the leg and increase venous flow. IPC is thought to facilitate mobilization and reduce the risk of venous thrombosis by enhancing microcirculatory flow, reducing soft tissue swelling, and stimulating the release of intrinsic fibrinolytic substances (Windisch et al.

[1] www.nice.org.uk/guidance/index.

2011; Urbankova et al. 2005). A recent systematic review indicated that IPC provided sufficient prophylaxis for the majority of gynecology patients undergoing benign surgery; in comparison with no prophylaxis, IPC has been shown to reduce DVT by 60 % (relative risk 0.40, 95 % CI 0.29–0.56; $p < 0.05$) (Rahn et al. 2011).

Direct comparison between ECS and IPC has failed to demonstrate a significant superiority of either method, although IPC was associated with lower DVT rates in three out of ten studies (Morris and Woodcock 2010). Since IPC and ECS are not as effective as antithrombotic drugs, these devices should be used as support to pharmacological prophylaxis, as a sole therapy in low-risk patients, or if drugs are contraindicated (e.g., early postoperative period, increased risk of bleeding) (Kakkos et al. 2008). The ACCP guidelines assign a 2A recommendation to the use of combination prophylaxis in the highest-risk group since the rate of DVT can be reduced from 19 % with pharmacological prophylaxis alone to less than 4 % with combined modalities (Kakkos et al. 2012). Unfortunately, compliance with IPC is questionable and studies on the optimal device are still lacking.

23.4.4 Pharmacological Prophylaxis

Following the success of aspirin, vitamin K antagonists (VKA), and heparin in preventing thrombotic events, several parenterally administered anticoagulants (hirudin analogues, argatroban) have been developed for patients with heparin-induced thrombocytopenia (HIT) and antithrombin deficiency (Fig. 23.2). More recently, oral

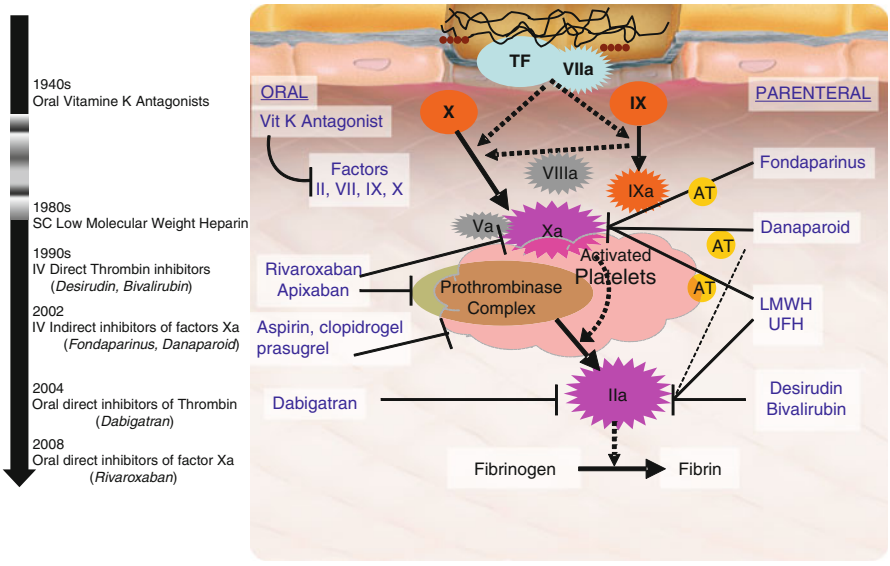

Fig. 23.2 Common antithrombotic drugs: historical development and site of action in the coagulation cascade

formulations of direct thrombin inhibitor (DTI) and anti-factor Xa have emerged; these have the advantages of a more predictable anticoagulant response, low potential of drug or dietary interaction, greater specificity (with no requirement for antithrombin binding), and no need for routine patient monitoring (Fareed et al. 2012; Bauer et al. 2011). Another advantage of novel antithrombotic drugs is the absence of rebound thrombin generation following discontinuation of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or VKA that may lead to a hypercoagulable condition. Hereafter, we present some of the key features of common antithrombotic drugs used in perioperative medicine (Table 23.4).

23.4.4.1 Aspirin

Aspirin causes an irreversible inhibition of cyclooxygenase, an essential enzyme for the production of thromboxane A2, a powerful stimulant of platelet aggregation. Thus, aspirin produces an effective anti-aggregant action for the platelet's entire lifespan. Although platelets play a role in the initiation and propagation of VTE, aspirin (even at a high dose) is less effective than heparin derivatives in preventing VTE. Current guidelines, therefore, do not recommend thromboprophylaxis by aspirin alone, except in patients at risk of bleeding. Patients receiving aspirin to prevent cardiovascular thrombotic events (atrial fibrillation, prior myocardial infarct or stroke, or vascular stent implantation), but requiring noncardiac surgery, may continue aspirin around the time of surgery, instead of stopping it 7–10 days preoperatively (Grade 2C) (Douketis et al. 2012).

23.4.4.2 Vitamin K Antagonists

23.4.4.2.1 Mechanism of Action

Coumarin derivative drugs such as warfarin (Coumadin®), acenocoumarol (Sintrom®), and phenprocoumon (Marcoumar®) act indirectly, requiring 3–5 days to reach therapeutic effectiveness. Indeed, these VKA inhibit epoxide reductase in the liver and interfere with the synthesis of coagulation factors (II, VII, IX, X, protein C, and protein S), thereby preventing new thrombus formation. Within 24 h of oral administration, prothrombin time (PT) lengthens as factor VII concentration drops rapidly, but an antithrombotic effect is not achieved until after 72–96 h because of the longer half-lives of the other vitamin K-dependent coagulation factors.

23.4.4.2.2 Pharmacokinetics

Rapidly absorbed from the gastrointestinal tract after oral intake, VKA have high bioavailability and reach maximal blood concentrations about 90 min after administration. Warfarin has a longer half-life (36–42 h), circulates highly bound to plasma proteins, and accumulates in the liver where the two isomers are metabolically transformed. Acenocoumarol has a lower degree of digestive absorption and a shorter half-life (8–12 h), with up to 36 % of the drug being retrieved inert in the stool. Phenprocoumon has 100 % bioavailability and a very long half-life (5–6 days).

The dose–response of VKA may vary up to tenfold between individuals and two- to threefold within an individual. The cytochrome P450 complex (e.g., CYP2C9, CYP3A4) has become clearly established as the predominant catalyst responsible for the metabolism of its more potent S-enantiomer and its activity may be

Table 23.4 Common antithrombotic drugs

Substance (brand name)	Hemostasis target	Route and frequency of administration	Half-life and *time* to peak concentration	Elimination	Monitoring	Reversal
Anti-vitamin K (Sintrom, Warfarin)	Factors II, VII, IX, X; protein S and C	Oral, OD	8–12 h and 1–4 h (S) 36–72 h and 1–4 h (W)	Liver, kidney	INR 2.0–3.0 (2.0–2.5 if bleeding risk)	Vitamin K PTCC, FFP
Unfractionated heparin	Factors Xa, IIa (1:1; +AT)	IV (continuous) or SC (TID)	3–4 h 30–90 min	Reticuloendothelium (kidney, liver)	(aPTT, anti-Xa, [heparin])	Protamine
Low-molecular-weight heparin	Factors Xa, IIa (2:1 or 4:1; +AT)	SC, OD, or BID[a]	5–10 h 3–4 h	Kidney	(aPTT, anti-Xa [0.5–1])	(Protamine)
Danaparoid (Orgaran)	Factor Xa (+AT)	(IV) SC, BID	25 h 4–5 h	Kidney	Not required (anti-Xa)	None (plasmapheresis)
Fondaparinux (Arixtra)	Factor Xa (+AT)	(IV) SC, OD	17–21 h 25 min	Kidney	Not required (anti-Xa)	None
Desirudin	Factor IIa	SC	1–3 h 2 h	Kidney (80–90 %)	(Ecarine CT, aPTT)	None (PTCC, HF)
Bivalirudin (Angiox)	Factor IIa	IV	25 min	Kidney	(Ecarine CT, aPTT)	(PTCC, HF)
Dabigatran (Pradaxa)	Factor IIa	Oral, BID	12–17 h 2–4 h	Kidney (80 %)	Not required (TT)	None (FFP, PTCC, Pl)
Rivaroxaban (Xarelto)	Factor Xa	Oral, OD	5–11 h 2–4 h	Kidney (65 %), liver	Not required (anti-Xa)	None (PTCC, VIIa)
Apixaban (Eliquis)	Factor Xa	Oral, OD	8–15 h 0.5–2 h	Liver, kidney (25 %)	Not required (anti-Xa)	None (PTCC, VIIa)

BID twice daily, *FFP* fresh frozen plasma, *HRA* hip replacement arthroplasty, *IV* intravenous, *KRA* knee replacement arthroplasty, *LMWH* low-molecular-weight heparin, *OD* once daily, *PTCC* prothrombinic complex concentrate, *SC* subcutaneous, *TID* three times a day

[a]Dosage adjustment (e.g., enoxaparin: 40 mg/day, if body weight <150 kg and CrCl >30 ml/min; 30 mg/day, if <150 kg and CrCl 10–29 ml/min; 30 mg twice a day, if >150 kg and CrCl >30 ml/min)

influenced by the patient's health status, genetic polymorphisms (VKORC1) and mutations, diet, and drugs (Carlquist and Anderson 2011). In the USA, Coumadin is the second most commonly mismanaged therapeutic drug, requiring more than 40,000 emergency room visits per year, resulting in about USD 40–60 million in additional medical costs per year (Budnitz et al. 2006).

23.4.4.2.3 Monitoring

Because of the large variability of plasma concentration and the unpredictability of VKA, regular monitoring of their effect on coagulation is of utmost importance. The international normalized ratio (INR) is the gold standard test for VKA monitoring, and the targeted range should be within 2.0–3.0 (or a closer range, 2.0–2.5, in patients at risk of bleeding). The INR is a mathematically transformed or calculated value converting PT in seconds to a standard ratio value. Theoretically, the INR eliminates the differences in sensitivity of various PT reagents. However, the INR may not eliminate all of the PT assay's variables, requiring adjustment to make the reagent's INR more accurate with regard to a specific local instrument in a local laboratory.

23.4.4.2.4 Reversal

In anticipation of elective surgery and to reverse a mildly elevated INR, withholding VKA for 3–4 days is indicated, perhaps complemented with the administration of oral vitamin K (Keeling et al. 2011). In patients with life-threatening bleeding, administration of vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC, including the 4 coagulation factors: II, VII, IX, and X), or even recombinant activated factor VII (rfVIIa) may be justified (Wozniak et al. 2012).

23.4.4.2.5 Indications and Contraindications

VKA are mainly indicated in vascular and major orthopedic surgery (TKA, THA). Patients undergoing arterial infra-inguinal surgery, and needing to maintain venous graft patency, are more likely to benefit from VKA treatment than from platelet inhibitors (Geraghty and Welch 2011). Compared with LMWH, treatment with VKA is less efficient in preventing DVT (RR = 1.51, 95 % CI 1.27, 1.79) and associated with a similar incidence of serious bleeding events (Mismetti et al. 2004; Muntz et al. 2004).

Treatment is initiated at relatively high doses (warfarin 5–10 mg or <5 mg in debilitated patients) in combination with UFH or LMWH (first 2 days), and thereafter, the drug dosage is tapered according to INR monitoring. The narrow therapeutic index and an unpredictable dose–response relationship may cause unexpected bleeding complications or insufficient anticoagulation. VKA should not be prescribed during pregnancy or to uncooperative patients (i.e., dementia, alcoholism).

23.4.4.3 Heparin and Its Derivatives

23.4.4.3.1 Unfractionated Heparin

Commercially available UFH preparations are derived from bovine lung or porcine intestinal mucosa; they consist of heterogeneous mixtures of branched chains of glycosaminoglycans. The molecular weights of these sulfated molecules range from 5,000 to 30,000 Da, with a mean molecular weight of 15,000 Da (~45 monosaccharide chains).

Mechanism of Action

UFH produces its major anticoagulant effect by irreversibly inactivating thrombin (IIa) and activated factor X (factor Xa) through an antithrombin-dependent mechanism with an anti-factor Xa to anti-factor IIa ratio of 1:1. Antithrombin (AT) is a native anticoagulant protein that inactivates several clotting factors (IXa, Xa, XIIa, and thrombin). Only one third of an administered dose of UFH binds to AT, while the remaining fraction has a minimal anticoagulant effect. The UFH–AT complex is 100–1,000 times more potent as an anticoagulant than AT alone (Hirsh et al. 2001).

The UFH–AT complex, through its action on thrombin, not only prevents fibrin formation but also inhibits thrombin-induced activation of factors V, VIII, and IX as well as platelets. Thereby, it prevents further growth and propagation of the thrombus, but it is unable to inactivate thrombin or factor Xa within a formed clot. In vitro, the high-molecular-weight heparin fraction also binds to platelets and von Willebrand factor; depending on the experimental settings, it can either induce or inhibit platelet aggregation.

Pharmacokinetics

After subcutaneous (s.c.) injection, bioavailability is dose dependent, ranging from 30 % at lower doses to as much as 70 % at higher doses, and its anticoagulant effect lasts around 1–2 h. Heparin is mainly cleared via internalization in endothelial cells and macrophages (heparinase and sulfatase), a small part being cleared by the kidney.

Pharmacokinetic limitations of heparin are related to its propensity to bind to positively charged surfaces (plastic tubing), macrophages, endothelial cells, osteoclasts, and circulating proteins; this results in a poorly predictable response. Heparin's half-life is prolonged with increasing dosages and in patients with renal failure, whereas it can be decreased or increased in patients with liver impairment. Importantly, acutely ill patients may require higher doses of UFH to achieve an antithrombotic effect, given increased binding to inflammatory cells and proteins as well as to deficient levels of AT (heparin resistance).

Monitoring

Anticoagulation with heparin can easily be monitored by measuring activated partial thromboplastin time (aPTT) or anti-Xa activity and, in a cardiac surgery setting or in a catheterization laboratory, by measuring activated clotting time (ACT). Monitoring is not required for the purpose of thromboprophylaxis.

Reversal

Protamine sulfate is considered the treatment of choice for patients who develop significant bleeding complications while on UFH. This basic protein 5-kDa cationic polypeptide binds to negatively charged UFH, thereby neutralizing its antithrombin effect while incompletely reversing factor Xa inhibition.

One UI of protamine neutralizes one UI of heparin. Potentially life-threatening adverse effects such as hemodynamic collapse, bronchospasm, and pulmonary hypertension may exceptionally occur in susceptible patients (prior exposure to protamine, fish allergies, and vasectomy). With high doses of protamine, increased

bleeding has been associated with dose-dependent reductions in thrombin generation.

Indications and Contraindications

Heparin was the first anticoagulant to prove its effectiveness in preventing VTE (Kakkar et al. 1972; Geerts et al. 2008; Gould et al. 2012b). Given as an s.c. fixed low dose of 5,000 U every 8 or 12 h, UFH is an effective, safe form of thromboprophylaxis, reducing the risk of VTE by 60–70 % in at-risk surgical patients. Limitations of UFH include (1) the inability of heparin to deactivate factor Xa in the prothrombinase complex or thrombin bound to fibrin, (2) HIT, and (3) osteopenia caused by heparin-induced stimulation of osteoclasts after prolonged administration (>6 months).

HIT is the most serious prothrombotic, drug-induced problem. It occurs in 0.2–0.8 % of patients as a result of antibodies directed towards platelet factor IV, leading to platelet activation with thrombin generation and ultimately vascular thrombosis (Shantsila et al. 2009). Hence, patients treated with UHF should have their platelet counts monitored every 1–2 days. A diagnosis of HIT should be considered if that count drops by more than 50 % or to <100,000/mm within the 5–10 days of treatment initiation, particularly in patients previously exposed to heparin. A benign form of thrombocytopenia occurs in 10–30 % of patients starting within the first day of heparin therapy, with the platelet count remaining stable or reversing to normal even though UFH therapy continues.

23.4.4.3.2 Low-Molecular-Weight Heparin

LMWH is derived from heparin by chemical or enzymatic depolymerization to yield fragments (>18 saccharide units) with molecular weights ranging from 1,000 to 10,000 Da (average MW of 4,500–5,000 Da). Currently, LMWH (enoxaparin, Lovenox®; dalteparin, Fragmin®; tinzaparin) has largely replaced UFH as a frontline therapy in preventing VTE following surgery; they have similar efficacy and an improved safety profile (Akl et al. 2008). Compared with UFH, the risk of developing HIT and HIT complicated by VTE can be reduced by 76 % (Junqueira et al. 2012). Moreover, the risk of major bleeding is markedly attenuated in patients receiving LMWH compared with those receiving UFH or fondaparinux (–48 %) (Muntz et al. 2004).

Mechanism of Action

Compared with UFH, LMWH has a reduced ability to deactivate thrombin as it cannot bind to AT and thrombin simultaneously. The anti-factor Xa to anti-factor IIa ratio is between 2:1 and 4:1 (Hirsh et al. 2001). Compared with UFH, LMWH has a smaller effect on platelet function and platelet adhesion, therefore interfering less with primary hemostasis.

Pharmacokinetics

Because LMWH binds less to plasma proteins and cells, they exhibit a more predictable dose–response relationship. Following a single s.c. injection of LMWH, absorption is almost complete, plasma activity peaks after 3 h, the elimination half-life approximates 4 h, whereas the mean residence time of anti-Xa activity is about 6 h,

independent of the dose (20–80 mg) (Turpie 1998). Following repeated s.c. doses, there is no evidence of accumulation or alterations in distribution and clearance.

In pregnant women, LMWH does not cross the placental barrier, as detected by anti-factor Xa activity. LMWH is weakly metabolized in the liver, and relatively small amounts are eliminated by the kidneys. The dosage of LMWH should be adjusted to body weight rather than on a fixed regimen, particularly in obese subjects.

Monitoring

Measurement of aPTT can only serve as an indicator of overdosage. Monitoring is not necessary for the prevention of VTE nor is it generally in therapeutic anticoagulation, except in three situations: renal failure, obesity, and pregnancy. In these patients, the anti-Xa level should be monitored, with a target range of 0.5–1.1 U/ml.

Reversal

Protamine sulfate can be used to reverse the effects of LMWH (1:1 ratio) although this antagonizing effect is neither complete nor predictable.

Indications and Contraindications

LMWH has become the anticoagulant of choice for the prevention of venous thrombosis following major orthopedic and thoracoabdominal surgery, as well as after major trauma. This is due to its favorable risk–benefit profile and ease of use; LMWH is at least as effective and safe as UFH.

The timing and dose of the first LMWH injection differ between Europe and North America. In Europe, 40 mg LMWH (enoxaparin) is usually given 12 h preoperatively, while in North America, 30 mg is administered twice daily, starting 12–24 h postoperatively.

23.4.4.3.3 Fondaparinux: *Arixtra*®

Mechanism of Action

Fondaparinux is a small synthetic pentasaccharide, derived from heparin. By a mechanism similar to LMWH, its high affinity for AT produces an indirect selective anti-Xa activity. Fondaparinux does not inhibit factor Xa bound to the prothrombinase complex thrombin (Petitou et al. 2009).

Pharmacokinetics

After s.c. application, fondaparinux exhibits almost 100 % bioavailability. The drug is eliminated via renal filtration, and its half-life is about 17–21 h (Nagler et al. 2012). In vitro studies show no cross-reactivity with HIT antibodies. Given its predictable antithrombotic effects and prolonged half-life, fondaparinux can be administered safely once a day (2.5 mg).

Monitoring

Monitoring fondaparinux is not routinely necessary. In certain situations, such as acute renal failure, a chromogenic anti-Xa heparin assay or a specific drug assay can be performed (pentasaccharide target 0.14–0.19 mg/l).

Reversal

Protamine sulfate and FFP fail to antagonize fondaparinux-induced antithrombotic effects, and there is limited evidence that recombinant factor VII could be used to stop fondaparinux-related bleeding, although it was found to normalize lengthened coagulation assays (Dzik 2012).

Indications and Contraindications

Fondaparinux is specifically indicated to prevent VTE following major joint surgery. Its efficacy is comparable to LMWH, and it does not cause more clinically relevant hemorrhages (Turpie et al. 2002).

Fondaparinux is contraindicated in patients with severe renal impairment (CrCl <30 ml min^{-1}), low body weight (<50 kg), or those at high risk of bleeding (Nagler et al. 2012). In patients treated with antiplatelet drugs or those receiving neuraxial anesthesia/analgesia, a safe delay should be considered before initiating thromboprophylaxis with fondaparinux (Gogarten et al. 2010).

23.4.4.3.4 Danaparoid: *Orgaran*®

Mechanism of Action

Danaparoid sodium is a mixture of partially depolymerized glycosaminoglycan. AT-mediated danaparoid catalyzes the deactivation of factor Xa (Wilde and Markham 1997). There is also an AT and heparin cofactor II-mediated inhibition of thrombin. However, the ratio of anti-Xa to anti-IIa activity is more than 22:1. Danaparoid inhibits thrombus formation with approximately the same potency as heparin but shows greater efficacy at inhibiting the expansion of preformed thrombi.

Pharmacokinetics

After s.c. administration, the absolute bioavailability of danaparoid sodium approaches 100 %, and the time to reach peak plasma anti-Xa activity levels is approximately 4–5 h (Wilde and Markham 1997). Elimination is mainly via renal filtration and biological half-life activity approximates 25 h.

Monitoring

No routine monitoring is requested. Under special circumstances (i.e., renal failure), the anti-Xa level should be determined.

Reversal

No agent can reverse the effect of danaparoid. In acute bleeding situations, plasmapheresis has been shown to effectively reduce the plasma anti-Xa levels (Dzik).

Indications and Contraindications

The substance is in clinical use for thrombosis prophylaxis in orthopedic, abdominal, and thoracic surgery. Given its low cross-reactivity with heparin–platelet factor IV, it is also a suitable alternative in patients with HIT. Danaparoid is more expensive than LMWH and is no longer marketed in the USA.

23.4.4.4 Direct Thrombin Inhibitors

23.4.4.4.1 Hirudin Analogues

Mechanism of Action

Unlike UFH and LMWH, direct thrombin inhibitors (DTI) do not require any interaction with an endogenous cofactor. The antithrombotic action results from the specific binding of free soluble and fibrin-bound thrombins. This prevents fibrin formation as well as thrombin-mediated activation of factors V, VIII, XI, and XIII and thrombin-induced platelet aggregation (Greinacher and Warkentin 2008). Since their chemical structure differs from that of heparin, hirudin analogues do not interact with HIT antibodies.

Currently, four parenteral DTI have been approved for use as anticoagulants in the USA: lepirudin, desirudin, bivalirudin, and argatroban.

Hirudin was originally isolated from the leech salivary gland and was used as the first parenteral anticoagulant for humans in 1909. Desirudin (Revasc®) and lepirudin (Refludan®) are developed by recombinant technology (65 amino acids; molecular weight, 6980 Da). Binding of desirudin to thrombin is irreversible and 10 times weaker than for hirudin.

Bivalirudin (Angiox®) is an engineered 20-amino acid, bivalent analogue of hirudin with a thrombin inhibition activity nearly 800 times weaker than that of hirudin (Van De Car et al. 2010). Its reversible binding with thrombin contributes to a decreased risk of bleeding.

Pharmacokinetics

After s.c. administration, desirudin reaches maximum plasma concentrations after 1–3 h, has a terminal half-life of 2 h, and is primarily excreted by the kidneys (80–90 %) (Graetz et al. 2011). After intravenous (i.v.) injection, bivalirudin has an immediate onset of action with therapeutic ACT achieved within 5 min and a half-life of 25 min. It is mainly cleared by proteolytic cleavage and hepatic metabolism; 20 % of the dose is eliminated by the kidneys.

Monitoring

For perioperative thromboprophylaxis, monitoring is not deemed necessary even in patients with moderate renal impairment (ClCr of 30–60 ml/min). An aPTT assay should be performed on patients with severe renal dysfunction and for therapeutic anticoagulation (target aPTT ratio between 1.5 and 2.5). An alternative to aPTT is the ecarin clotting time assay (ECT), which reflects anti-factor II activity.

Reversal

There is no specific antidote available. Hirudin-induced bleeding can be partially reversed by PCC and hemofiltration, hollow-fiber filters, and high- and low-flux polysulfone dialysers (Dzik).

Indications and Contraindications

Hirudin derivatives are mainly used in patients with HIT, as an alternative to UFH or LMWH. Desirudin (s.c.) is the only fixed dose DTI approved in Europe and North America for postoperative prevention of VTE in major orthopedic surgery. In

these patients, after 8–12 days of treatment, desirudin (15 mg/day, started preoperatively) was found superior to UFH (5,000 UI s.c. three times daily, started preoperatively) or LMWH (40 mg enoxaparin s.c. once daily), while showing a similar safety profile (Salazar et al. 2010; Eriksson et al. 1997a, b).

In 2005, the US Food and Drug Administration approved bivalirudin as an alternative anticoagulant to heparin in patients undergoing percutaneous coronary interventions. Dose adjustments of bivalirudin are necessary in patients with moderate renal insufficiency, and it is contraindicated in severe renal impairment. Because of its narrow therapeutic window and its potential for increased bleeding events, lepirudin's use as an anticoagulant is limited.

23.4.4.4.2 Dabigatran: *Pradaxa*®

Mechanism of Action

Dabigatran etexilate is an orally active, double prodrug that is rapidly converted into dabigatran by plasma esterase. It is a low-molecular-weight molecule (472 Da) that acts as a specific, potent, and reversible direct thrombin inhibitor (Schulman and Majeed 2012).

Pharmacokinetics

After oral administration, dabigatran has a low bioavailability (<10 %), independent of the dose of the prodrug. The time to maximum plasma concentration is 1.25–2.5 h, and its half-life is about 12–14 h (Schulman and Majeed 2012). The drug is neither metabolized, induced, nor inhibited by cytochrome P450 drug-metabolizing enzymes. Renal excretion is the primary elimination pathway. The remainder undergoes conjugation with glucuronic acid to form acyl glucuronides, which are excreted via the bile.

Monitoring

Given its predictable and consistent anticoagulant effects, treatment with dabigatran does not require routine coagulation monitoring or dose titration. Thrombin time (TT) is the assay most responsive to dabigatran in the clinically relevant plasma concentration range, whereas the aPTT and PT are the least so. Longer blood coagulation parameters (aPTT, PT,) occur in parallel with increasing concentrations of dabigatran.

Reversal

No specific antidote exists. Blood products (FFP, PCC, platelets) remain the mainstay of treatment in case of overdose or bleeding (Dzik). Maintaining enforced diuresis and dialysis may be attempted as the drug binds weakly to plasma proteins (Kaatz et al. 2012).

Indications and Contraindications

A cost–utility analysis from the UK National Health Service indicated that dabigatran (220 mg/day) was more effective and less expensive than enoxaparin (40 mg) in patients undergoing total knee or hip replacements (TKR or THR). In three, large, phase III RCT (RE-MODEL, RE-NOVATE, and RE-NOVATE II), oral dabigatran

(150 and 220 mg once daily) initiated postoperatively was shown to be non-inferior to s.c. enoxaparin sodium (40 mg once daily, initiated prior to surgery) with regard to the incidence of total VTE events and all-cause mortality in patients undergoing TKR or THR surgery (Burness and McKeage 2012). A meta-analysis of 14 studies indicated that DTI (ximelagatran, dabigatran, and desirudin) were equally effective to VKA and LMWH in the prevention of major VTE following major joint surgery. However, they were associated with a higher mortality and more frequent bleeding (except desirudin) (Salazar et al. 2010).

In North America and Europe, dabigatran is licensed for thromboprophylaxis in total knee and hip arthroplasty (TKA and THA), whereas in Switzerland, it is exclusively licensed for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

23.4.4.5 Oral Anti-factor Xa Agents

23.4.4.5.1 Rivaroxaban: *Xarelto*®

Mechanism of Action

Rivaroxaban is an orally active oxazolidone molecule that directly and reversibly inhibits free factor Xa, as well as clot-bound and prothrombinase complex-bound factor Xa.

Pharmacokinetics

After oral ingestion (10 mg), rivaroxaban has an 80–100 % bioavailability, with peak plasma concentrations reached in 2–4 h, and an elimination half-life of 5–9 h or 9–13 h in the elderly (Weinz et al. 2009). Rivaroxaban is extensively bound to plasma proteins, it undergoes metabolic degradation in the liver, and it is mainly eliminated through renal filtration (Eriksson et al. 2009).

Monitoring

Monitoring the antithrombotic effect of rivaroxaban is unnecessary, and no assay has yet been validated. It is of note that increasing plasma–drug concentrations correlates with longer PT and the inhibition of factor Xa activity.

Reversal

PCC were found to neutralize the anticoagulant effect of rivaroxaban in healthy volunteers. Likewise, partial reversal of longer PT and bleeding time was achieved after the administration of rfVIIa (Eerenberg et al. 2011).

Indications and Contraindications

Compared with LMWH, rivaroxaban has been shown to be slightly superior in preventing VTE in patients presenting atrial fibrillation and those undergoing major orthopedic surgery (RR 0.48, CI 0.31–0.75). It also showed significant cost savings (USD 465–533 per surgical case) (Duran et al. 2012; Gomez-Outes et al. 2012). However, the risk of clinically relevant bleeding could be higher than with LMWH

(RR 1.25, 95 % CI 1.05–1.49) (Gomez-Outes et al. 2012). Rivaroxaban has been licensed for these specific indications in North America and several European countries.

23.4.4.5.2 Apixaban: *Eliquis*®

Mechanism of Action

Apixaban is a highly selective, reversible, direct inhibitor of factor Xa. It shows moderate selectivity for clot-bound factor Xa versus free factor Xa and also inhibits thrombin generation.

Pharmacokinetics

After oral administration, apixaban has 50 % bioavailability, with peak plasma concentration reached after 0.5–3 h, and an elimination half-life of 12–15 h if it is given once daily or 8–11 h if given twice daily (Eriksson et al. 2009). The drug mainly undergoes hepatic oxidation into a phenol compound and is excreted in the bile; 25 % is eliminated via the kidneys. It has a low potential for drug–drug interaction.

The recommended dose is 2.5 mg orally, twice daily.

Monitoring

Apixaban does not interfere with platelet aggregation, while it shows a slight dose-dependent lengthening of INR and aPTT. No routine monitoring is required for thromboprophylactic purposes.

Reversal

There are no specific reversal agents. Guidelines merely recommend supportive treatment in cases of drug-associated bleeding, including the administration of blood products (FFP, PCC) and activated charcoal if drug ingestion was within the last couple of hours (Dzik) (Kaatz et al. 2012).

Indications and Contraindications

Compared with enoxaparin, apixaban was found equally effective in lowering the risk of VTE (RR 0.82, 95 % CI 0.41–1.64), while it slightly attenuated the risk of bleeding (RR 0.82, CI 0.69–0.98) (Gomez-Outes et al. 2012). In Switzerland, apixaban is licensed for the prevention of VTE in major orthopedic surgery (TKA and THA). Its main contraindication is renal failure.

To date, clinicians and patients must make trade-offs between personal convenience, risk reduction in thrombosis versus increased risk of bleeding (at higher dosage), and the higher costs of these newer agents (rivaroxaban CHF 5/day; apixaban CHF 10/day). Overall, treatment with factor Xa inhibitors is expected to prevent four instances of symptomatic DVT per 1,000 patients treated (95 % CI, 3–6 fewer events) but may increase major bleeding by two more events per 1,000 patients (95 % CI, 0–4 more events) than LMWH (Neumann et al. 2012).

23.5 Evidence-Based Guidelines for Perioperative Thromboprophylaxis

The US Agency for Healthcare Research and Policy has ranked the prevention of VTE as the most valuable patient safety practice, given its cost-effectiveness and benefit–risk ratio. In many countries, thromboprophylaxis serves as a quality indicator of hospital health care. However, there is still a large gap between official recommendations and medical practice since compliance with guidelines varies from 13.3 to 94 % (Gomez-Outes et al. 2012; Cohen et al. 2008). In addition, although many at-risk patients do not receive adequate prophylaxis, there is also evidence to suggest that low-risk patients being prescribed thromboprophylaxis comprises another important problem (Bikdeli and Sharif-Kashani 2012).

Dissemination of information through professional and social networks will enhance global awareness of the importance of VTE. Methods such as computer-based decision systems and preprinted orders have been shown to be most effective in optimizing compliance with thromboprophylactic guidelines. Finally, periodic audits focusing on outcome data and treatment adhesion, with feedback to nursing and medical teams, may reinforce consistent use of VTE prophylaxis (Galante et al. 2012).

Since 2010, guidance on VTE prophylaxis in surgical patients has been issued by a number of medical organizations: the ACCP (February 2012), the American College of Physicians (ACP, November 2011), the Scottish Intercollegiate Guideline Network (SIGN, December 2010), and the UK National Institute for Health and Clinical Excellence (NICE, January 2010). Although these recommendations are based upon data derived from large RCT, several issues deserve further clarification, including the role of screening for asymptomatic DVT, the best timing for the initiation of pharmacological prophylaxis, the optimal duration of prophylaxis in high-risk patients, and the indications for newer anticoagulant agents.

The plethora of official recommendations can be confusing, if not overwhelming. For the sake of clarity, we summarize the available effective methods of thromboprophylaxis for specific surgical categories taking into account the risk of bleeding and VTE (Table 23.5) (Darvall and Bradbury 2012; Falck-Ytter et al. 2012; Gould et al. 2012a; Muntz and Michota 2010; Deitelzweig et al. 2008).

In very-low-risk patients (expected incidence of VTE <0.5 %), early ambulation following the intervention will suffice, with no need for any specific pharmacological or mechanical prophylaxis. In low-risk patients (VTE ~1.5 %), ECS or IPC devices should be applied during the period of patient immobilization. Moderate-risk patients (VTE ~3 %) should benefit from LMWH, UFH, or mechanical prophylaxis. In high-risk patients (VTE ~6 %), dual prophylaxis should be instituted with GES or IPC combined with LMWH or UFH. If concerns are raised about the potentially devastating consequences of bleeding (e.g., hemorrhagic shock, intracranial or ocular surgery), then mechanical prophylaxis should be used alone. For instance, for every 1,000 neurosurgical patients who receive prophylactic doses of UFH or LMWH, 91 VTE events can be prevented but at the expense of 7 intracranial hemorrhagic events and 28 more cases of minor bleeding (Hamilton et al. 2011).

Table 23.5 Evidence-based guidelines for perioperative prophylaxis of venous thromboembolism

Type of surgery	Thromboprophylactic method	Grade of evidence	Duration of TP
Very-low-risk VTE <0.5%			
Caprini score 0 Same day surgery (hernia repair) Orthopedic procedure <30 min Repair of small fractures Isolated lower leg injuries + immobilization	No prophylaxis, early ambulation Mechanical prophylaxis	1B 2C	–
Low-risk VTE ~1.5%			
Caprini score 1–2 General surgery, gynecological surgery, laparoscopic surgery	Mechanical prophylaxis	2C	Hospital stay or until free ambulation
Moderate risk VTE ~3%			
Caprini score 3–4	UFH, LMWH, or fondaparinux (if low risk of major bleeding) Mechanical prophylaxis (if high risk of bleeding)	2B 2C	Start within 12–24 h postop, for 7–10 days
Bariatric surgery	One of the following options, with/without MP UFH 5,000 s.c., tid LMWH enoxaparin 40 mg s.c. od or bid (BMI <50) LMWH enoxaparin 60 mg s.c. od or bid (BMI >50) +/– mechanical prophylaxis		Start within 12–24 h postop, for 7–10 days
Cardiac surgery (no VTE risk factors) Thoracic surgery (no VTE risk factors)	Mechanical prophylaxis Or UFH or LMWH (if low risk of bleeding) Mechanical prophylaxis, if high risk of bleeding	2C 2C 2C	Start within 12–24 h postop, for 7–10 days
Neurosurgery (no VTE risk factors) Spinal surgery (no VTE risk factors) Major trauma (no VTE risk factors)	Mechanical prophylaxis Or UFH or LMWH (if low risk of bleeding)	2C 2C	Start within 12–24 h postop, for 7–10 days

(continued)

Table 23.5 (continued)

Type of surgery	Thromboprophylactic method	Grade of evidence	Duration of TP
High risk VTE ~6%			
General or abdominal, pelvic surgery Thoracic surgery + VTE risk factors	UFH or LMWH UFH or LMWH + mechanical prophylaxis (low bleeding risk)	1B 2C 2C	Start (2–12 h before or) 12–24 h postop, ≥7–10 days, 30 days if cancer (1B)
Neurosurgery + VTE risk factors Spinal surgery + VTE risk factors	Mechanical prophylaxis + LMWH or UFH (if low bleeding risk)	2C	Start 24–48 h postop, if low risk of intracranial/spinal bleeding
Major trauma + VTE risk factors (e.g., spinal/brain injury)	Mechanical prophylaxis if no lower leg injury Mechanical prophylaxis + UFH or LMWH (if low bleeding risk) If UFH and LMWH are contraindicated, choose one of following Aspirin Fondaparinux	2C 2C 2C 2C	Start 24–48 h postop, if low risk of intracranial/spinal bleeding
Total hip or knee arthroplasty (THA, TKA) Hip fracture surgery (HFS)	Consider one of the following options LMWH (UFH, adjusted-dose VKA or aspirin) Fondaparinux Apixaban, rivaroxaban, or dabigatran Mechanical prophylaxis LMWH is preferred over other drugs Dual prophylaxis, mechanical + pharmacological	 1B (2B/2C) 1B, 2B 1B, 2B 1C 2C	Start ≥12 h preop or ≥12 h postop Extend prophylaxis to 10–35 days postop or until end of rehabilitation during the hospital stay
Major orthopedic surgery (e.g., HA, TKA, HFS, spinal surgery) + patient uncooperative with injection or mechanical devices	Consider one of the following options Apixaban or dabigatran Rivaroxaban or adjusted dose of VKA	 1B 1B	
Major orthopedic surgery + risk of bleeding	Consider one of the following options Mechanical prophylaxis No prophylaxis	 2C	

Mechanical prophylaxis: intermittent pneumatic compression device or elasticated compressive stockings (>18 h/day)
LMWH low-molecular-weight heparin, *UFH* unfractionated heparin, *VKA* vitamin K antagonist, *TP* thromboprophylaxis

In bariatric surgery, PE has been reported as the most common cause of postoperative death, accounting for 30 % of all deaths in the International Bariatric Surgery Registry. Hence, the ACCP task force recommends the routine administration of UFH, LMH, or fondaparinux, in combination with optimally used IPC. Weight-adjusted doses of antithrombotic drugs should be prescribed in order to achieve a consistent VTE risk reduction, although the incidence of major bleeding increases in parallel (Becattini et al. 2012).

In major orthopedic, abdominal, or pelvic surgery, prophylaxis with UFH, LMWH, VKA, or fondaparinux should be continued beyond the hospital stay (4 weeks instead of 5–7 days) or until appropriate recovery of function (Kakkar et al. 2008; Rasmussen et al. 2009). Special attention must be given to elderly patients due to their higher prevalence of comorbidities, renal dysfunction, and impaired functional capacity. Peptic ulcer, hemophilia, or von Willebrand disease, as well as the use of antiplatelet drugs, makes thromboprophylaxis a particular challenge. Moreover, central neuraxial blockade should be performed to a dedicated time frame: a spinal or epidural needle should only be inserted 8–12 h after the last s.c. dose of UFH or 18 h after a once daily dose of LMWH (Gogarten et al. 2010; Horlocker et al. 2010a).

Conclusions

Arterial and venous thromboembolic events commonly occur after surgery and cause potentially preventable morbidity and mortality. Current evidence-based management strategies have significantly reduced the incidence of VTE, although there is room for further improvements with the administration of safer antithrombotic agents and the implementation of specific guidelines coupled with rigorous clinical audits.

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Part IV

Economic Aspects and Organization

Economic Aspects and Organization

24

Klaus Görlinger and Sibylle A. Kozek-Langenecker

24.1 Introduction: The Costs of Blood

Hospitals have limited financial resources, and transfusion and hemostasis management must compete with other diagnostic and therapeutic options for the allocation of funds. At the same time, the costs of blood transfusion continue to increase dramatically and vary widely between countries and even between hospitals within the same country (Table 24.1) (Abraham and Sun 2012; Toner et al. 2011; Glenngård et al. 2005; Varney and Guest 2003). The total cost of supplying patients with hemostatic diagnostics and therapies involves a complex bundle of activity-based costs surrounding the primary supply process, as well as secondary costs linked to transfusion-associated adverse events (Abraham and Sun 2012; Shander et al. 2010). These adverse events account for almost 35 % of transfusion-related costs (Glenngård et al. 2005). Severe bleeding and inappropriate allogeneic blood transfusion, in particular, are likely to be associated with increased morbidity, length of hospital stay, and additional secondary hospital costs (Berenson et al. 2010; Bufe et al. 2009; Christensen et al. 2009; Leahy and Mukhtar 2012; Pybus et al. 2012; Rao et al. 2008; Sarode et al. 2010; Shander et al. 2011; Stanworth et al. 2011a; Stokes et al. 2011). This chapter discusses the primary and secondary cost implications of hemostatic interventions and transfusion strategies.

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24.2 Costs of Bleeding Complications and Allogeneic Blood Transfusion

In addition to increased hospital costs, bleeding and allogeneic blood transfusion have been shown to be independently associated with increased morbidity and mortality and longer stays in intensive care units (ICU) and in hospital (Glance et al. 2011; Khan et al. 2007; Marik and Corwin 2008; Murphy et al. 2007; Pereboom et al. 2009; Sarani et al. 2008; Shander et al. 2007; Spiess et al. 2004; Watson et al. 2009). Blood transfusion costs can be separated into primary or acquisition costs for allogeneic blood products (paid by the government or the hospital itself), activity-based costs (including all processing costs, from the indication of blood transfusion to monitoring effects and for possible adverse events), and secondary costs due to any transfusion-associated adverse events (Shander 2007). Acquisition costs for allogeneic blood products vary widely between countries and are difficult to determine in those where hospitals do not pay for them directly because governments supply them "for free" (Table 24.1). However, a hospital's activity-based blood transfusion costs are usually 3.2–4.8 times higher than blood product acquisition costs (Shander et al. 2010). Shander et al.'s analysis of four hospitals showed that annual expenditures on blood and transfusion-related activities, limited to surgical patients, ranged from USD 1.62 to USD 6.03 million per hospital and were largely related to the transfusion rate. Some hospitals calculate a virtual internal transfer price which has to be "paid" by the transfusing department to the blood bank in order to compensate the blood bank for its activity-based costs (e.g., storage and crossmatching).

Transfusion-associated adverse events such as acute lung injury (ALI), transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM), nosocomial infections, and sepsis, as well as ischemic events (myocardial infarction, stroke, acute renal failure, or multiple organ failure), are all associated with increased secondary costs for hospitals, governments, health insurance companies, or patients themselves (Berenson et al. 2010; Glenngård et al. 2005; Stokes et al. 2011). However, each adverse event and each additional day with mechanical ventilation in an American ICU increase hospital costs by USD 3,800 to USD 4,000 (Dasta et al. 2005; Kaushal et al. 2007). In the UK, average "return-to-theatre costs" due to bleeding complications in cardiac surgery have been calculated as GBP 2,617 (Sharples et al. 2006). Christensen et al. analyzed data from the cardiac surgery unit of the Augsburg Clinic in Germany to determine the relationship between excessive postoperative hemorrhage in cardiac surgery, patient outcomes, and hospital costs. Excessive postoperative bleeding, defined as a drainage volume of more than 200 ml in any 1 of the first 6 h after surgery, was associated with a significantly increased incidence of adverse events (e.g., fourfold increase of strokes and doubled incidence of renal failure), doubled length of stay in ICU (3.1 ± 5.0 days versus 5.7 ± 5.3 days), fourfold increase in patient's 30-day mortality (5.5 % versus 22.4 %), and doubled total hospital costs (EUR $8{,}027 \pm 7{,}557$ versus EUR $15{,}404 \pm 8{,}986$). When adjusted for potential confounding factors, the incremental cost of excessive postoperative hemorrhage was EUR 6,251 (95 % confidence interval: EUR 4,594–7,909) (Table 24.2) (Christensen et al. 2009). Murphy et al. (2007) reported a more than

Table 24.1 Costs of allogeneic blood products and coagulation factor concentrates in the USA and Europe

Author (year)	Country	Cost calculation	PRBC	FFP	Platelets	Cryoprecipitate	Fibrinogen	PCC	rFVIIa
Varney and Guest (2003)	UK	Mean activity-based costs (NHS costs)	£635 (€1,031)	£378 (€614)	£347 (€564)	£834 (€1,354)	–	–	–
Glenngård et al. (2005)	Sweden	Societal costs	€702 for 2 filtered allogeneic PRBC units (Transfusion reactions accounted for 35 % of costs)			–	–	–	–
			€598 for 2 autologous PRBC units			–	–	–	–
			€285 for intraoperative PRBC salvage (>4 units)			–	–	–	–
Agrawal et al. (2006)	UK	Mean activity-based costs	£546.12 (€804.86) for transfusion of 2 PRBC units: Mean staff costs £37.24 (blood bank £9.68 + ward £27.56); mean costs of disposables £13.25; mean costs for blood products £287.56; mean costs of wastage £11.86; other derived cost (e.g., hospital stay) £196.21						
Murphy et al. (2007)	UK	Acquisition costs	£135.50 (€200)	£31.50 (€46)	£214 (€315)	–	–	–	–
Shander et al. (2010)	USA and Europe	Mean acquisition costs	$248.18 in Englewood Hospital Medical Center, Englewood, NJ, USA $203.47 in Rhode Island Hospital, Providence, RI, USA $193.70 in Centre Hospitalier Univers. Vaudois, Lausanne, Switzerland $153.72 in General Hospital Linz, Austria						
	USA and Europe	Mean activity-based costs	$1,183.32 in Englewood Hospital Medical Center, Englewood, NJ, USA $726.05 in Rhode Island Hospital, Providence, RI, USA $611.44 in Centre Hospitalier Univers. Vaudois, Lausanne, Switzerland $522.45 in General Hospital Linz, Austria						

(continued)

Table 24.1 (continued)

Author (year)	Country	Cost calculation	PRBC	FFP	Platelets	Cryoprecipitate	Fibrinogen	PCC	rFVIIa
Toner et al. (2011)	US	Mean acquisition costs	$210.74 ± 37.9	$60.70 ± 20	$533.90 ± 69 (apheresis)	–	–	–	–
		Median costs for mandated onsite screening	$50.00 ± 120 per unit	–	–	–	–	–	–
		Median storage and retrieval costs	$68.00 ± 81 per unit	–	–	–	–	–	–
		Mean charge to patient	$343.63 ± 135 per unit	–	–	–	–	–	–
Görlinger et al. (2011a, b) and Hanke et al. (2012)	Germany	Virtual internal transfer prices	€85	€65	€250 (pooled platelet conc.)	–	€288/g	€126 per 500 IU	€3,203 per 4.8 mg (240 KIU)
Weber et al. (2012)	Germany	Acquisition costs	€72	0.162 €/g or €40.50 per 250 ml unit	€231 (pooled platelet conc.)	–	€233 per g	€114 per 600 IU	€2,784 per 4.8 mg (240 KIU)
Abraham and Sun (2012)	Western Europe	Mean activity-based costs	€877.69 for 2 units	–	–	–	–	–	–

Table 24.2 Additional length of stay (LOS) at intensive care unit (ICU), high-dependency unit (HDU), and at hospital (HP), and incremental hospital costs due to bleeding complications in major surgery and acute coronary syndromes (ACS)

Author (year)	Clinical setting, country	Number of patients (*n*)	Patients with bleeding (%)	Additional length of stay at ICU/ hospital (HP) (days)	Incremental costs per hospitalization ($)
Murphy et al. (2007)	Cardiac surgery, UK	8,598	57.1 % transfused patients	Hazard ratio for discharge from ICU/ HDU, 0.69 (95 % CI, 0.65–0.72) and from HP, 0.63 (95 % CI, 0.60–0.67) at any postoperative time	RBC units – relative increase in costs; mean (95 % CI)
			Any: 57.1 %		Any: 1.42 (1.37–1.46)
			1 unit: 13.6 %		1: 1.11 (1.08–1.14)
			2 units: 14.5 %		2: 1.21 (1.18–1.25)
			3–4 units:15.2 %		3–4: 1.41 (1.36–1.46)
			5–9 units:10.0 %		5–9: 1.81 (1.71–1.90)
			>9 units: 3.8 %		>9: 3.35 (3.03–3.70)
Rao et al. (2008)	Non-ST-segment elevation ACS, USA	1,235	36.8 %		Unadjusted
			Mild bleeding	1.5 days	$7,392
			Moderate bleeding	9.6 days	$31,516
			Severe bleeding	11.0 days	$52,282
Bufe et al. (2009)	ACS, Germany	59	–	–	€5,415
Christensen et al. (2009)	Cardiac surgery, Germany	1,118	6.4 %	2.6 ICU days	€7,377 (unadjusted)
					€6,251 (adjusted)
Berenson et al. (2010)	ACS, USA	11,266	8.2 %	Increased	$48,114 (adjusted)
Stokes et al. (2011)	Major surgery, overall, Canada	1,608,923	29.9 % (7.5–47.4 %)	2.7 ICU/6.0 HP days (1.3–9.6) (unadjusted)	Adjusted
	Spinal surgery	107,187	15.0 %	1.4 ICU/4.5 HP days	$17,279
	Vascular surgery	216,199	31.5 %	4.8 ICU/9.3 HP days	$15,123
	Solid organ surgery	45,687	28.5 %	3.8 ICU/8.1 HP days	$13,210
	Noncardiac thoracic surgery	142,562	34.3 %	6.4 ICU/9.6 HP days	$13,473
	Cardiac surgery	103,829	47.4 %	2.8 ICU/4.8 HP days	$10,279
	General surgery	362,512	27.5 %	3.6 ICU/7.2 HP days	$4,354
	Knee/hip replacement	246,815	29.8 %	0.1 ICU/1.3 HP days	$3,005
	Reproductive organ surgery	384,132	7.5 %	0.9 ICU/3.6 HP days	$2,805

40 % increase in overall average hospitalization costs for transfused cardiac surgery patients over non-transfused patients in the UK. Bufe et al. (2009) demonstrated that costs caused by bleeding requiring transfusion of ≥2 units of blood products in an acute coronary syndrome therapy setting increased hospital costs by EUR 5,415 in Germany. Rao et al. (2008) analyzed data from the economic sub-study of the GUSTO IIb trial in 1,235 American patients with non-ST-segment elevation acute coronary syndromes to determine the relationship between bleeding, transfusion, length of hospital stay, and hospital costs. As bleeding severity increased, there was a stepwise increase in length of stay (no bleeding, 5.4 days; mild bleeding, 6.9 days; moderate bleeding, 15.0 days; and severe bleeding, 16.4 days) and unadjusted total costs (no bleeding, USD 14,282; mild, USD 21,674; moderate, USD 45,798; and severe bleeding, USD 66,564). After adjustment for baseline differences between patients, each moderate or severe bleeding event increased costs by USD 3,770, and each transfusion event increased costs by USD 2,080. Another American study reported that, after adjustment for patient characteristics, in-hospital acute coronary syndrome-related procedures, and length of stay, patients with severe bleeding incurred initial hospitalization charges of USD 48,114 higher than those of patients without bleeding (Berenson et al. 2010). Thus, clinical interventions that can effectively prevent or address severe perioperative or peri-interventional bleeding reduce transfusion requirements, and transfusion-associated adverse events are very likely to substantially improve cost-effectiveness (Kozek-Langenecker et al. 2013).

24.3 Costs of Ischemic and Thromboembolic Events

Both bleeding and allogeneic blood transfusion have been shown to be associated with an increased incidence of ischemic and thromboembolic events, as well as in-hospital and posthospital costs (Dobesh 2009; Ruppert et al. 2011; Sharples et al. 2006; Spiess et al. 2004; Vekeman et al. 2011). Therefore, hemostatic interventions that can effectively stop microvascular bleeding without increasing the incidence of ischemic and thromboembolic events are very likely to substantially improve cost-effectiveness.

24.4 Prophylactic Hemostatic Interventions with "Universal Hemostatic Agents"

In recent decades, several attempts have been made to find a universal hemostatic agent capable of ensuring hemostasis during and after major surgery and trauma, independent of the individual cause of the bleeding. Almost all the drugs studied in this context either failed to reduce bleeding and transfusion requirements if given as prophylaxis or were associated with severe adverse events, such as acute renal failure or thrombotic/thromboembolic events and even increased mortality.

24.4.1 Antifibrinolytics

Aprotinin was withdrawn from the market in November 2007 due to the reported increased incidence of renal dysfunction and mortality in cardiac surgery patients, compared to treatment with lysine analogues (Brown et al. 2007; Fergusson et al. 2008; Mangano et al. 2006). Lysine analogues (tranexamic acid or TXA, and ε-aminocaproic acid) reduce perioperative blood loss and transfusion requirements and can be highly cost-effective in major orthopedic surgery, cardiac surgery, postpartum hemorrhage, liver resection and transplantation, and trauma (CRASH-2 Trial C2010; CRASH-2 Trial Collaborators 2011; Ducloy-Bouthors et al. 2011; Fergusson et al. 2008; Ferrer et al. 2009; Goobie et al. 2011; Greiff et al. 2012; Gurusamy et al. 2009; Henry et al. 2011; Ickx et al. 2006; Martin et al. 2011; Molenaar et al. 2007; Novikova and Hofmeyer 2010; Sander et al. 2010; Sukeik et al. 2011; Rajesparan et al. 2009; Tzortzopoulou et al. 2008). Notably, in the CRASH-2 study, a reduction in mortality was only observed if TXA was administered within 3 h of a trauma. In contrast, prophylactic administration of TXA more than 3 h after trauma was associated with increased mortality (CRASH-2 Trial Collaborators 2011). The timing of TXA administration therefore seems to be crucial. During liver transplantation, a targeted therapy of hyperfibrinolysis also produced a similar reduction of transfusion requirements, which was detected using viscoelastic tests (thromboelastometry/thromboelastography) (Ickx et al. 2006; Görlinger et al. 2010). During liver transplantation, therefore, the efficacy and safety of a prophylactic administration of lysine analogues, compared to a targeted therapeutic intervention, is still being debated (Schofield et al. 2012). A large, international, prospective, randomized clinical trial looking at the outcome effects of TXA in 15,000 women with postpartum hemorrhage is ongoing (Shakur et al. 2010).

However, administration of TXA in patients undergoing major surgery has been shown to reduce transfusion requirements cost-effectively without significantly increasing the incidence of deep vein thrombosis (Rajesparan et al. 2009). Particularly in countries with limited financial resources, lysine analogues have been shown to significantly save costs and lives (Guerriero et al. 2010). Indeed, cost-effectiveness analysis based on the CRASH-2 trial data showed that an early administration of TXA to bleeding trauma patients is likely to be highly cost-effective in low, middle, and high income settings (Guerriero et al. 2011).

24.4.2 Recombinant Activated Factor VII

According to current literature, the use of recombinant activated factor VII (rFVIIa) should be restricted to its licensed indications since outside these indications its effectiveness in reducing transfusion requirements and mortality remains unproven, but the risks of arterial thromboembolic events and costs are high. All prospective randomized trials dealing with the prophylactic administration of rFVIIa have failed to show any effect on mortality (Chavez-Tapia et al. 2011; Dutton et al. 2009;

Hauser et al. 2010; Levi 2010; Kozek-Langenecker et al. 2013; Simpson et al. 2012). A reduction in the number of transfused packed red blood cells (PRBCs) by 2.6 U and a reduction in the need for massive transfusion (14 % versus 33 %) could only be demonstrated in severe blunt trauma (Boffard et al. 2005). However, a second trauma study, powered for a reduction in mortality, was terminated early since statistical significance could not be achieved (Dutton et al. 2009; Hauser et al. 2010). From a pharmacoeconomic point of view, the cost of 400 µg/kg rFVIIa (about EUR 20,000) is extremely high compared to a reduction in transfusion requirements of 2.6 U of PRBC. Indeed, a cost-effectiveness analysis of using rFVIIa as an off-label rescue treatment for critical bleeding requiring massive transfusion was recently published. The total cost per life-year gained through massive transfusion was USD 1,148,000 (95 % CI: USD 825,000–1,471,000), and the incremental cost of rFVIIa as part of that life-saving treatment was USD 736,000 (95 % CI: USD 527,000–945,000) (Ho and Litton 2012). The incremental costs of rFVIIa were much greater than the usual acceptable cost-effective limit (< USD 100,000 per life-year) for most patients with critical bleeding. Furthermore, two prospective randomized trials in patients with intracerebral hemorrhage observed a significantly increased incidence of arterial thromboembolic complications, including myocardial and cerebral infarction (7 % versus 2 % ($p=0.12$) and 10 % versus 1 % ($p=0.01$), respectively) (Mayer et al. 2005; Sugg et al. 2006). A distinct trend to more critically serious (thromboembolic) adverse events, including stroke, has also been observed in a prospective randomized study of liver transplantation (placebo 10 %; 60 µg/kg rFVIIa 19 %; 120 µg/kg rFVIIa 12 %; $p>0.05$) and cardiac surgery (placebo 7 %; 40 µg/kg rFVIIa 14 % ($p=0.25$); 80 µg/kg rFVIIa 12 % ($p=0.43$)) (Gill et al. 2009; Lodge et al. 2005). Furthermore, the risk of arterial thrombotic complications (in particular stroke and myocardial infarction) after the "off-label use" of rFVIIa has been highlighted in several other publications (Howes et al. 2009; Levi et al. 2010; O'Connell et al. 2006; Simpson et al. 2012). Finally, two recently published studies showed that rFVIIa had minimal clinical impact on outcomes for patients requiring less than 30 units of PRBCs. For patients transfused more than 30 units of PRBCs, differences in 24-h and 30-day mortality suggest that rFVIIa converted early deaths from exsanguination to late deaths from multiple organ failure (Morse et al. 2011; Nascimento et al. 2011). Therefore, in accordance with the manufacturer's recommendations, most recent guidelines recommend not to use rFVIIa in non-licensed indications (AAGBI 2010; BGMA 2009a; Kozek-Langenecker et al. 2013; Lin et al. 2012; Rossaint et al. 2010; Stürmer et al. 2011).

24.5 Cell Salvage

Cell salvage has been shown to be cost-effective in minimizing perioperative transfusion of allogeneic blood products (Carless et al. 2010; Davies et al. 2006; Wang et al. 2009). A Swedish cost study calculated intraoperative erythrocyte

salvage to be EUR 285 per transfusion (>4 units). This was comparatively much lower than the cost of a 2-unit transfusion of filtered allogeneic PRBCs, which was EUR 598. The administrative costs of preoperative autologous blood donation were found to be much higher due to the higher logistic and personnel expenses (Glenngård et al. 2005).

24.6 Implementation of Transfusion and Coagulation Management Protocols

Implementing transfusion and coagulation management protocols has the potential to reduce transfusion requirements and transfusion-associated costs in trauma and major surgery (Görlinger et al. 2013; Kozek-Langenecker et al. 2013; Rotter et al. 2010; Schöchl et al. 2013). In a study including 210 patients, Avidan et al. (2004) demonstrated that both transfusion protocols guided by routine laboratory testing and point-of-care (POC) testing were able to reduce transfusion requirements compared to transfusion and coagulation management based on clinical discretion. However, the turnaround time of conventional coagulation tests measured in a centralized laboratory is simply too long for their effective use in decision-making for severely bleeding patients (Davenport et al. 2011; Haas et al. 2012a, b; Toulon et al. 2009). Furthermore, Griffee et al. (2010) showed that massive transfusion protocols featuring an immediate availability of blood products and multidisciplinary communication reduce mortality and conserve resources. These results have been confirmed by other authors. Several before-and-after cohort studies have demonstrated that the implementation of a massive transfusion or exsanguination protocol in trauma patients resulted in a significant reduction of overall blood product consumption, post-injury complications, organ failure, mortality, and costs (Cotton et al. 2008, 2009; Dente et al. 2009; O'Keeffe et al. 2008; Riskin et al. 2009; Vogt et al. 2012). Accordingly, most recommendations and guidelines on the management of severe perioperative bleeding strongly recommend the implementation of local transfusion and coagulation management protocols (Callum and Rizoli 2012a; Dzik et al. 2011; Kozek-Langenecker et al. 2013; Rossaint et al. 2010; Stürmer et al. 2011). However, massive bleeding protocols can be based on different concepts, depending on local availability of diagnostic and therapeutic options, as well as personal experience (Cotton et al. 2008; Görlinger et al. 2011a, b; Görlinger et al. 2013; James et al. 2012; Johansson 2010, 2012; Johansson et al. 2012; Nunez et al. 2010; Schöchl et al. 2012; Schöchl et al. 2013; Solomon et al. 2012; Spinella and Holcomb 2009; Theusinger et al. 2012; Waydhas and Görlinger 2009). Large-scale randomized trials are definitely needed to compare the efficacy, safety, and cost-effectiveness of these different concepts. However, until these trials are completed, it is clear that all hospitals having to manage bleeding patients should use a severe bleeding protocol to ensure a prompt and coordinated response to hemorrhage (Callum and Rizoli 2012b).

24.6.1 Formula-Driven Transfusion Protocols (1:1:1 Ratio Concept)

Current literature does not clarify whether a formula-driven transfusion protocol reduces or increases hospital costs. Several retrospective and some prospective cohort studies – mostly performed on military trauma patients – suggest that an early transfusion of fresh frozen plasma (FFP), in an FFP to PRBC ratio between 1:2 and 1:1, results in reduced 30-day mortality (Dente et al. 2009; Holcomb et al. 2008; Maegele et al. 2008). However, the evidence for this is of low quality since there is a lack of prospective randomized clinical trials confirming these data (Cushing and Shaz 2011; Murad et al. 2010; Roback et al. 2010; Schuster et al. 2010; Zehtabchi and Nishijima 2009). Furthermore, other authors did not find a survival benefit in prospective cohort studies dealing with civilian trauma patients, nor could they identify a survival bias as the reason for the statistical significance (Ho et al. 2012; Mitra et al. 2010; Scalea et al. 2008; Snyder et al. 2009). However, a survival benefit was not demonstrated in most other transfusion populations besides massive transfusion (Murad et al. 2010; Stanworth et al. 2011b). Rather, several studies associated transfusion of FFP with a significantly increased incidence of acute lung injury, sepsis, and multiple organ failure, as well as fewer ventilator-free and ICU-free days in non-massively transfused patients (Borgman et al. 2011; Inaba et al. 2010; Johnson et al. 2010; Maegele et al. 2008; Sambasivan et al. 2011; Watson et al. 2009). Therefore, FFP transfusion should be restricted to massively transfused patients (AAGBI 2010; BGMA 2009b; Kozek-Langenecker et al. 2013; Liumbruno et al. 2009; Rossaint et al. 2010; Stürmer et al. 2011; Tavares et al. 2011).

24.6.2 Point-of-Care Testing-Driven Transfusion and Coagulation Management Protocols (POC-Driven Goal-Directed Therapy or "Theranostic" Approach)

First-line, goal-directed therapy with coagulation factor concentrates (fibrinogen and/or prothrombin complex concentrate (PCC)) guided by POC testing (thromboelastometry/thromboelastography and whole blood impedance aggregometry) has been shown to be effective in reducing transfusion-associated costs in selected patients in trauma, cardiac surgery, and liver transplantation without increasing the incidence of thromboembolic events. In principle, these functional hemostatic POC tests facilitate the optimal management of severe perioperative bleeding by guiding specific pharmacological or transfusion-based interventions and by allowing physicians to differentiate better between microvascular and surgical bleeding. Furthermore, they have the ability to reduce allogeneic blood transfusion requirements and to decrease re-exploration rates. Since re-exploration for bleeding in patients after coronary artery bypass surgery is associated with increasing perioperative mortality by 4.5 times and increased hospital costs, they have important implications for overall patient safety and health-care costs (Christensen et al. 2009; Mehta et al. 2009; Sharples et al. 2006).

24.6.2.1 Goal-Directed Therapy Guided by Point-of-Care Testing in Severe Trauma

Several cohort studies have reported decreased allogeneic blood transfusion requirements, reduced incidence of multiple organ failure, and improved survival in trauma patients with massive bleeding when treated with goal-directed hemostatic control resuscitation (HCR) guided by viscoelastic tests (thromboelastometry/thromboelastography) (Görlinger et al. 2012; Innerhofer et al. 2013; Johansson and Stensballe 2009, 2010; Nienaber et al. 2011; Schöchl et al. 2010, 2011). Indeed, some trauma centers were able to demonstrate that first-line, goal-directed therapy with fibrinogen concentrate and PCC has the potential to decrease FFP transfusion requirements by more than 90 % (Görlinger et al. 2012; Innerhofer et al. 2013; Schöchl et al. 2013). However, no data on cost-effectiveness are available in this clinical setting.

24.6.2.2 Goal-Directed Therapy Guided by Point-of-Care Testing in Liver Transplantation

Coagulopathy in patients with critical liver dysfunction is complex. In this patient population, hemostasis can quickly decompensate to either bleeding or to thrombosis, depending on concomitant risk factors (Tripodi and Mannucci 2011; Schaden et al. 2013; see Sect. 2.2). Both bleeding and thrombosis are associated with worse outcome and increased hospital costs. However, routine coagulation tests such as prothrombin time (PT) and the international normalized ration (INR) are not able to define whether a patient with critical liver dysfunction has hypo- or hypercoagulability and are not able to predict the risk of bleeding in these patients. Therefore, prophylactic transfusion of FFP and platelets, due to increased INR or low platelet count, should be avoided in this patient population. Hemostatic interventions should only be performed in cases of clinically relevant bleeding. Notably, patients with liver dysfunction and increased INR are not "auto-anticoagulated." In contrast, thrombin generation assays performed in the presence and absence of thrombomodulin, as well as viscoelastic tests (thromboelastometry/thromboelastography), indicate that patients with liver dysfunction tend to exhibit hypercoagulability with the inherent risk of thrombosis. Therefore, thromboprophylaxis should strongly be considered in patients with liver dysfunction, but in the absence of bleeding (Schaden et al. 2013).

Implementation of transfusion and coagulation management algorithms based on thromboelastometry has been shown to reduce transfusion requirements, transfusion-associated adverse events, and transfusion-associated costs in patients undergoing liver transplantation. Görlinger et al. (2010) published a retrospective study analyzing the intraoperative use of blood products and coagulation factor concentrates, as well as their respective acquisition costs, both before and after implementation of thromboelastometry-guided, goal-directed, hemostatic therapy in visceral surgery and liver transplantation. Here, transfusion requirements for PRBCs, FFP, platelets, and antithrombin concentrate decreased by 60, 89, 58, and 78 %, respectively. At the same time, use of fibrinogen concentrate and PCC increased approximately tenfold and threefold, respectively. No off-label use of rFVIIa occurred after implementation of the thromboelastometry-based algorithm. This resulted in an overall cost saving of EUR 270,167 per year (36 % reduction)

for allogeneic blood products and coagulation factor concentrates. Balanced against this were additional costs for thromboelastometry (depreciation costs of three ROTEM® devices, disposables, and reagents for 2,400 ROTEM® tests per year) amounting to EUR 16,500 (Görlinger et al. 2010). Over an observation period of ten years (covering 21,814 visceral surgeries including 1,105 liver transplantations), the total cost saving amounted to EUR 1.6 million (EUR 1,765,280 of savings on allogeneic blood products and coagulation factor concentrates and EUR 165,000 of additional costs for thromboelastometry) (Goerlinger et al. 2010). Activity-based costs and secondary costs induced by transfusion-associated adverse events were not considered in these costs analyses. Similar results have been published by other groups (Noval-Padillo et al. 2010; Trzebicki et al. 2010; Wang et al. 2010). Thromboelastometry-based, goal-directed therapy with fibrinogen concentrate and PCC was not associated with an increased incidence of thromboembolic events (Kirchner et al. 2012). This is in line with other publications reporting on the low thrombotic risk of fibrinogen concentrate and PCC, so long as an overdose is avoided (Grottke et al. 2011; Hanke et al. 2013; Kozek-Langenecker et al. 2011; Majeed et al. 2012; Manco-Johnson et al. 2009; Sørensen et al. 2011; Warmuth et al. 2012). Therefore, increased thrombosis-related costs are not to be expected.

24.6.2.3 Goal-Directed Therapy Guided by Point-of-Care Testing in Cardiovascular Surgery

Implementation of transfusion and coagulation management algorithms based on thromboelastometry/thromboelastography and whole blood impedance aggregometry have the potential to reduce transfusion requirements, transfusion-associated adverse events, thromboembolic events, and hospital costs in cardiovascular surgery.

Shore-Lesserson et al. (1999) were the first to demonstrate (using a prospective randomized clinical trial) that a POC algorithm based on viscoelastic tests (thromboelastography) reduces transfusion incidence and requirements in cardiac surgery. Since then, at least 16 clinical studies (totalizing 8,507 cardiac surgery patients) have dealt with transfusion protocols in cardiovascular surgery, comparing POC-based algorithms with algorithms based on routine laboratory testing and clinician discretion or standard of care (Görlinger et al. 2013). All 16 studies demonstrated a reduction in transfusion requirements in the POC group using viscoelastic tests (TEG® or ROTEM®). The effect size was dependent on the study population (simple coronary artery bypass graft surgery or complex cardiac/aortic surgery), the average blood loss, the extent of POC diagnostics (TEG®, ROTEM®, or ROTEM® plus Multiplate®), and the availability of specific coagulation factor concentrates such as fibrinogen concentrate, four-factor PCCs, and factor XIII concentrate for calculated, goal-directed therapy. POC diagnosis was most effective in patients undergoing complex cardiac or aortic surgery with detected abnormal bleeding (Girdauskas et al. 2010; Hanke et al. 2012; Rahe-Meyer et al. 2009a, b; Weber et al. 2012). Seven studies reported a reduction in the incidence of mediastinal re-exploration (Görlinger et al. 2011a; Nuttall et al. 2001; Spiess et al. 1995; Weber et al. 2012), massive transfusion (Girdauskas et al. 2010; Görlinger et al.

2011a; Hanke et al. 2012; Weber et al. 2012), and hospital costs (Görlinger et al. 2011a; Hanke et al. 2012; Spalding et al. 2007; Spiess et al. 1995; Weber et al. 2012). Not one study demonstrated increased hospital costs. Off-label use of rFVIIa – integrated into some algorithms as a rescue therapy if the algorithm's hemostatic therapy has failed – was almost completely eliminated in five studies (Girdauskas et al. 2010; Görlinger et al. 2011a; Hanke et al. 2012; Spalding et al. 2007; Weber et al. 2012). This was certainly important to the cost savings in these studies and potentially also for a reduction in the incidence of thrombotic/thromboembolic events. Only the four most recent studies performed, between 2010 and 2012, demonstrated an actual improvement in patient outcomes in the POC group (Girdauskas et al. 2010; Görlinger et al. 2011a; Hanke et al. 2012; Weber et al. 2012). These studies used a similar POC coagulation and transfusion management algorithm, first published in 2007, based on first-line, goal-directed therapy with fibrinogen concentrate and four-factor PCCs guided by thromboelastometry (Görlinger et al. 2007). Two studies additionally used whole blood impedance aggregometry (Görlinger et al. 2011a; Weber et al. 2012). Three of them demonstrated a reduction in thrombotic/thromboembolic events (Görlinger et al. 2011a; Hanke et al. 2012; Weber et al. 2012). Furthermore, the randomized clinical trial in coagulopathic patients undergoing complex cardiac surgery recently published by Weber et al. (2012) showed significant reductions in postoperative pulmonary dysfunction, postoperative ventilation time, stay in ICU, composite adverse events (acute renal failure, sepsis, thrombotic complications, and allergic reactions) (8 % versus 38 %; $p<0.001$), and six-month mortality (4 % versus 20 %; $p=0.013$). Since this single-center study was not set up to look at mortality and safety, the results will have to be confirmed by adequately powered multicenter RCTs and huge prospective observational studies.

24.6.2.4 Cost-Effectiveness of Goal-Directed Therapy Guided by Point-of-Care Testing in a German University Hospital

The impact of the implementation of goal-directed hemostatic therapy guided by POC testing on the acquisition costs of allogeneic blood products and coagulation factor concentrates has been analyzed for Essen University Hospital, Germany. Costs pre-implementation (in 2004) were compared to costs post-implementation (in 2007). Costs for hemostatic management of patients with hemophilia were not included. Between these dates, costs for coagulation factor concentrates (fibrinogen, PCC, antithrombin, and factor XIII concentrate) increased by EUR 810,609. At the same time, costs for allogeneic blood products (PRBCs, FFP, and pooled platelet concentrates) decreased by EUR 1,874,682, resulting in a total cost saving of EUR 1,064,073 per year for Essen University Hospital. Costs for ROTEM® analyses (disposables and reagents) amounted to EUR 24,000 per year (2.3 % of the cost saving) (Görlinger et al. 2008; Görlinger et al. 2011b). Therefore, the cost-effectiveness of implementing goal-directed therapy guided by POC testing can be assumed to be very high. It is worth noting that activity-based costs, as well as secondary costs induced by transfusion-associated adverse events and prolonged length of stay in the ICU, were not considered in this cost analysis (Table 24.3).

Table 24.3 Studies analyzing cost savings and impact of length of stay (LOS) in an ICU by point-of-care testing and goal-directed hemostatic therapy

Author (year)	Clinical setting, country	Study type, number of patients	POC device	Cost saving	Costs for POC diagnostics	ICU LOS (calculated costs)	Mean reason for cost saving
Spiess et al. (1995)	Cardiac surgery, USA	Before-and-after; 1,079 patients	TEG	Cost saving not specified	NA	NA	Decreased transfusion requirement
Spalding et al. (2007)	Cardiac surgery, Germany	Before-and-after; 1,422 patients	ROTEM	€51,000 per month (−44 %)	€1,580 per month (3.1 % of cost saving		Decreased PRBC, platelets, PCC, FXIII, and rFVIIa
Görlinger et al. (2008)	University Hospital, Germany	Before-and-after (2007 versus 2004); about 50,000	ROTEM	€1,064,073 per year	€24,000 (2.3 % of cost saving)	NA	Decrease FFP and PRBC transfusion
Goerlinger et al. (2010)	Visceral surgery and LTX, Germany	Before-and-after (2009 versus 1999); about 4,800 patients incl. 240 LTX	ROTEM	€270,167 per year (−36 %)	€16,500 (6.1 % of cost saving)	NA	Decrease FFP, PRBC, and platelet transfusion
Görlinger et al. (2010)	Visceral surgery and LTX, Germany	Before-and-after (1999–2009); 21,814 patients incl. 1,105 LTX	ROTEM	€1,765,280 in 10 years	€165,000 (9.3 % of cost saving)	NA	Decrease FFP, PRBC, and platelet transfusion
Görlinger et al. (2011a, b)	Cardiac surgery, Germany	Before-and-after (2009 versus 2005); 3,865 patients	ROTEM and Multiplate	€50,000 per year (−6.5 %)	NA	NA	Decrease FFP and PRBC transfusion
Hanke et al. (2012)	Type A aortic dissection, Germany	Before-and-after; 10 patients	ROTEM	€2,757 per case	NA	−5.8 days (×2,980 €[a] = €17,284)	Decreased FFP and PRBC transfusion
Weber et al. (2012)	Complex cardiac surgery, Germany	RCT; 100 patients	ROTEM and multiplate	€79,034 (€1,580 per patient)	€6,520 (€130.40 per patient)	−3 h (median)	Decreased FFP, PRBC, platelets, and rFVIIa
Esler et al. (2013)	Cardiac suregry, Australia	Before-and-after; 2,176 patients	ROTEM and Multiplate	AU$ 928,998 (€608,385) per year (−48.3%)	NA	NA	Decreased FFP, PRBC and platelet transfusion (−39.2%)

See Dasta et al. (2005)
NA not analyzed
[a]Costs per ICU day

24.7 Organization of Perioperative Bleeding Management

All hospitals dealing with bleeding patients should have a task force on managing severe bleeding, with the mission of continually developing and implementing standard operating procedures (SOPs) or algorithms adapted to their local patient population's needs and the diagnostic and therapeutic options available. The successful implementation of such SOPs can only be accomplished in a multi-specialty setting. Input and representation from departments such as anesthesiology, intensive care medicine, hemostaseology and hematology, transfusion medicine, laboratory medicine, trauma and emergency medicine, surgery, and obstetrics are necessary to successfully formulate and implement such protocols. Once a severe bleeding management protocol has been agreed upon, education of the entire nursing and physician staff is equally essential to its success. Once implemented, this process may lead to improved clinical outcomes and decreased overall blood use, with extremely little waste of vital blood products (Görlinger and Schlenke 2012; Levy et al. 2010; Markova et al. 2012; Milligan et al. 2011; Nunez et al. 2010). Perioperative bleeding management can be understood as a part of "patient blood management," focusing on the stabilization of perioperative hemostasis and a reduction of perioperative blood loss and transfusion requirements (Gombotz 2012; Goodnough and Shander 2012; Shander et al. 2012). Leadership in perioperative bleeding management depends on the kind of strategy hospitals use. In hospitals using formula-driven transfusion protocols with transfusion packages, clinical scores to predict the need for massive transfusion are essential to activate massive transfusion protocols (Maegele et al. 2012). A transfusion medicine department would have a central position here (Johansson 2007). In contrast, hospitals using laboratory- or POC-driven protocols focus on early detection and differentiation between coagulopathies and subsequent goal-directed therapy. Here, POC testing not only facilitates timely detection of hemostatic disorders and goal-directed therapy, but it can also be used to improve staff education and interdisciplinary communication by visualization of hemostasis as a didactic tool. In hospitals using this concept, anesthetists, intensivists, hematologists, and laboratory scientists are in central positions for the management of severe perioperative bleeding (Görlinger 2012; Kozek-Langenecker 2010; Lier et al. 2013). The optimal location for the POC device – either in the emergency room, operating room or ICU, or in the central laboratory – is dependent on the local situation, regional structure, staff education, and the hospital's requirements. If the POC device is located in the central laboratory, then a quick, effective system to transport blood samples and an electronic connection to get results back to the operating room are crucial. If the POC device is used in a mobile way, moving between the operating room and the ICU, then extensive staff education and training is necessary, as well as strict quality control management (Perry et al. 2010; Spannagl et al. 2010). If this can be done, turnaround times for POC testing and the "time-to-treat" for a bleeding patient can be minimized (Haas et al. 2012b). However, any local concept should be based on an interdisciplinary consensus and should aim for the optimal treatment of the bleeding patient concerned. In order to support physicians in hospitals in their

decision-making, the European Society of Anaesthesiology's "Task Force on Severe Bleeding Management" has developed evidence-based guidelines on the management of severe perioperative bleeding which were first presented at its autumn meeting in Prague, in November 2012. They have been published in the *European Journal of Anaesthesiology* (Kozek-Langenecker et al. 2013).

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