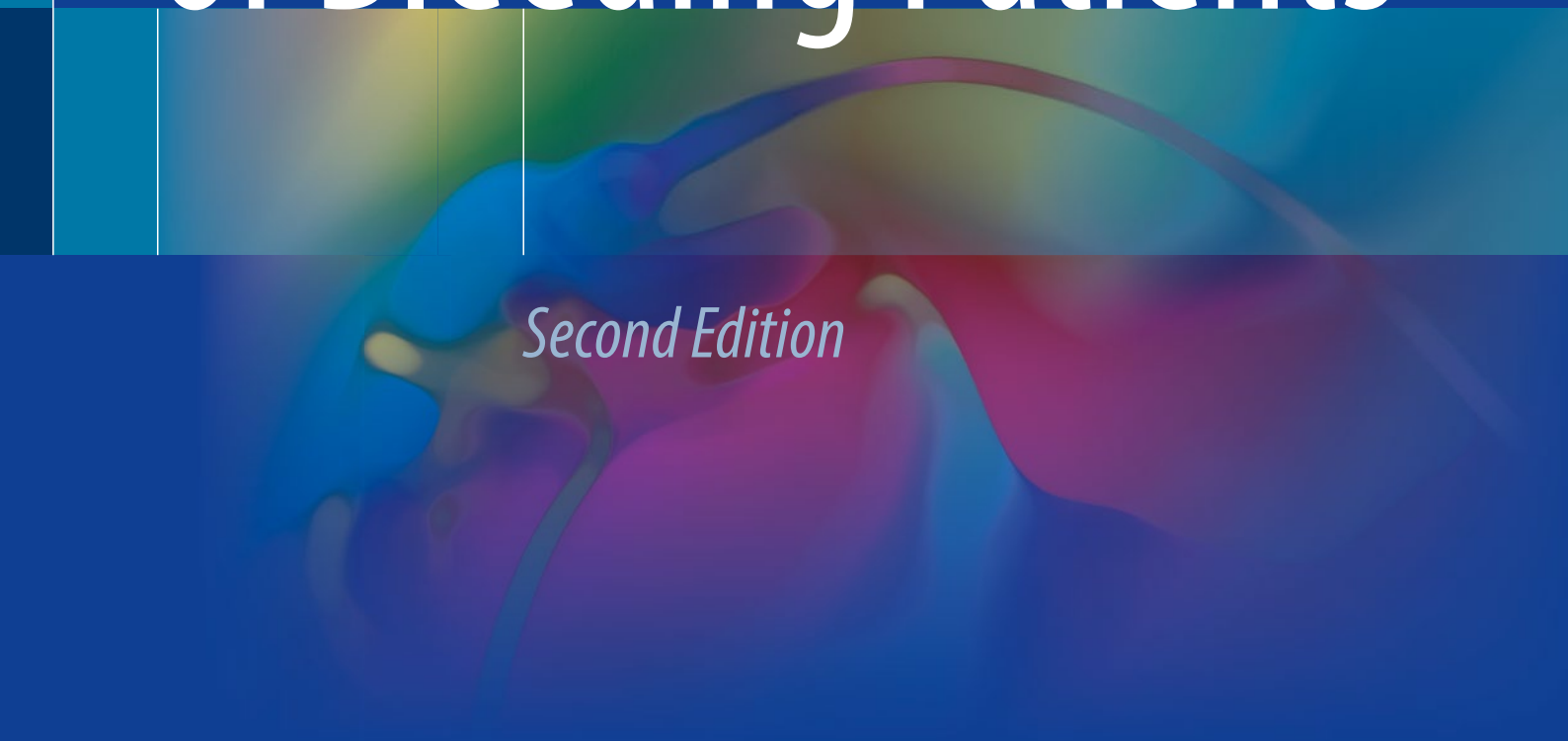
Jun Teruya
Editor

Management of Bleeding Patients



Second Edition

Springer

Management of Bleeding Patients

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Preface to the Second Edition

Since the first edition of this textbook was published in 2016, I am pleased by its success and inspired by the community's desire for a deeper understanding of the management of bleeding patients demonstrated by the many purchases and downloads. I am happy to know that this text was used by residents and fellows to enhance their hemostasis training. Our understanding of the pathophysiology of hemostasis and improvements in management are continuously evolving. In order to provide the most updated knowledge and changes in practice, I decided to publish the second edition. In the second edition, the following new chapters have been added:

- Hemostasis Basics: Figures and Facts
- Bleeding Due to Rare Coagulation Factor Deficiencies
- Bleeding Associated with Connective Tissue Disorders
- Massive Transfusion Protocol
- Management of Bleeding Associated with Durable Mechanical Circulatory Support
- Evaluation of Bleeding Risk Prior to Pediatric Invasive Procedures
- Evaluation of Bleeding Risk Prior to Invasive Procedures in Adults

I thank all the dedicated authors who contributed to this second edition.

I am hoping this edition will be more useful than the first for the management of bleeding patients.

Houston, TX, USA — Jun Teruya

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About the Editor

Jun Teruya, MD, DSc is tenured Professor and Vice Chairman for Education in the Department of Pathology and Immunology, with secondary appointments as tenured Professor in the Departments of Pediatrics and Medicine at Baylor College of Medicine, Houston, USA. He is Chief of the Division of Transfusion Medicine and Coagulation at Texas Children's Hospital.

Professor Teruya received his MD and Doctor of Science (DSc) degrees from Japan. After practicing Internal Medicine and Hematology for 10 years in Japan, he went to Massachusetts General Hospital (MGH), Harvard Medical School, for residency training in Clinical Pathology and Blood Bank fellowship. He became an Acting Assistant Director of the Blood Transfusion Service at MGH when he was a second year resident and Assistant Director the next year while he was a Blood Banking/Transfusion Medicine fellow. Since moving to his current institution in 2001, he has been engaged in managing patients with active and/or massive bleeding.

Professor Teruya has received numerous teaching awards, including Best Clinical Teacher of Clinical Pathology at MGH, Pediatric Award for Excellence in Teaching, Best Educator in Clinical Pathology (twice), and the Funniest Professor Award at Baylor College of Medicine. He was also selected as a Top Doctor in Transfusion Medicine and Coagulation by Houstonia Magazine in 2013 and Best Doctor in America since 2015.

Professor Teruya serves as the Chairman of the Plasma Coagulation Inhibitors subcommittee of the International Society of Thrombosis and Hemostasis. He also organized an International ECMO/VAD Interest group in 2017 that has 40 members worldwide. He has authored about 150 journal articles and 25 book chapters both including pending acceptance or manuscripts in preparation.

Part I

Diagnosis of Bleeding by Laboratory Testing

Hemostasis Basics: Figures and Facts

1

Jun Teruya

Introduction

In order to understand hemostatic system easily, visualization is usually more effective than text. While the details of each system are found in other chapters of this textbook, Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9 give a general overview of the hemostatic system. Explanations for each figure are included in the legend. The tables list characteristics of individual coagulation factors and von Willebrand factor. The half-life of each factor, minimum requirement for hemostasis, and choice of blood components or hemostatic drugs may be clinically useful (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9; Tables 1.1, 1.2, and 1.3).

Acknowledgment I am grateful to Lisa Hensch, MD for her review of this chapter.

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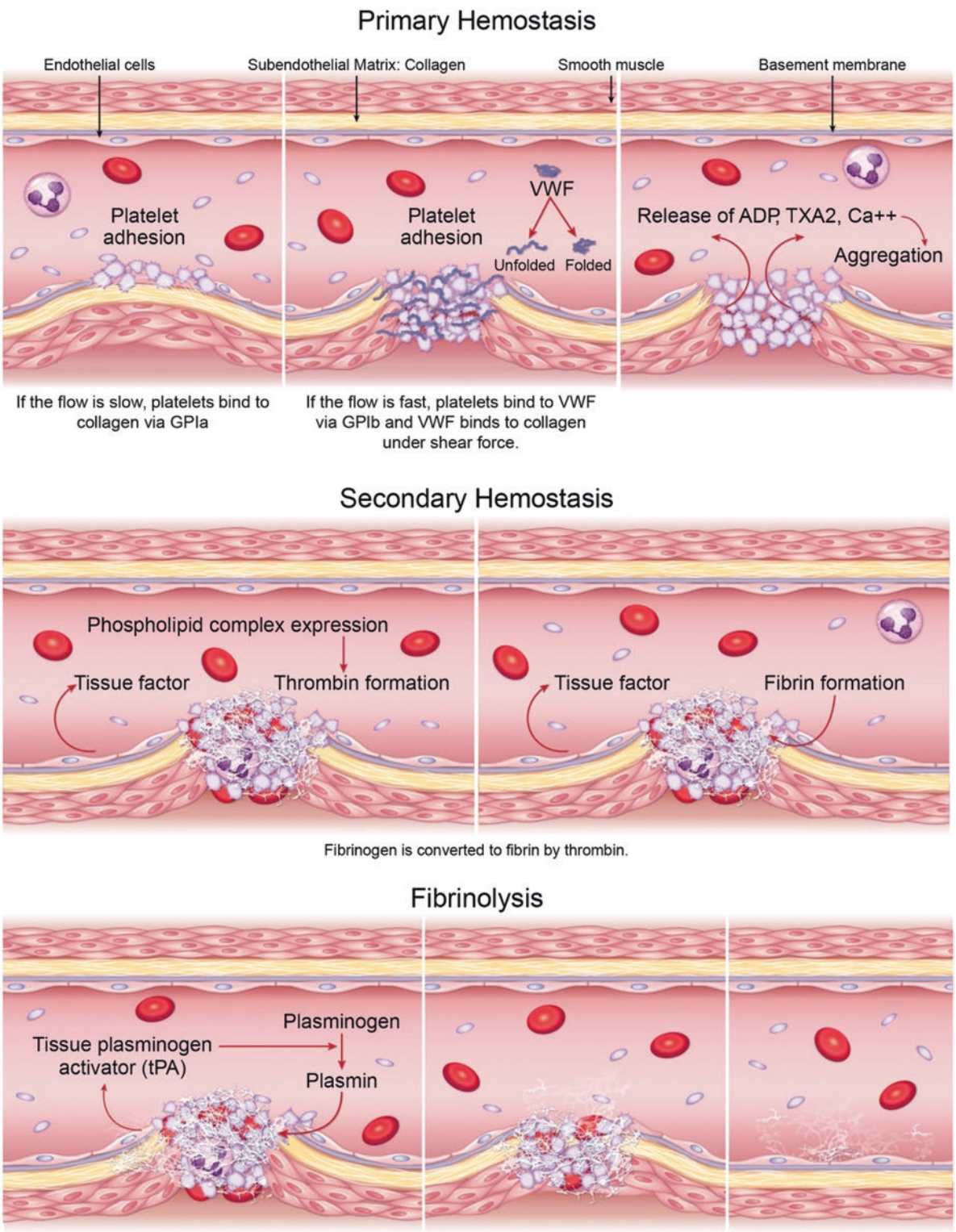

Fig. 1.1 When there is a defective vessel wall, von Willebrand factor (VWF) binds to the subendothelial matrix (composed of collagen) via the A1 and A3 domains of VWF under shear force. Platelets bind to the A1 domain of VWF via glycoprotein Ib. Platelets bound to the subendothelial matrix are activated. These activated platelets undergo shape change and degranulation, resulting in further platelet activation and the formation of platelet aggregates. This process is called primary hemostasis or platelet hemostasis. The coagulation cascade is activated by negatively charged surface and tissue factor and ultimately results in the formation of fibrin which is crosslinked via factor XIIIa. Together, crosslinked fibrin and platelet aggregates form a strong clot. This process is known as secondary hemostasis or coagulation hemostasis. Finally, once the defective vessel wall is healed, the clot is removed by the action of plasmin in a process called fibrinolysis. GPIa glycoprotein Ia, GPIb glycoprotein Ib, TXA2 thromboxane A2.

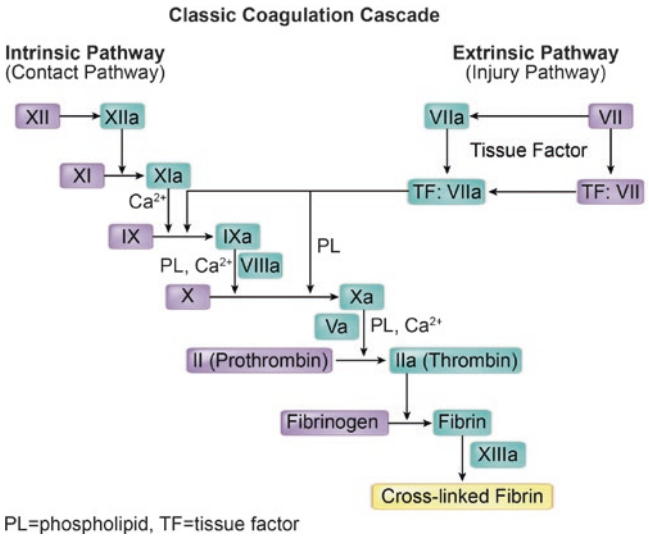

Fig. 1.2 The coagulation process was initially called "waterfall sequence for intrinsic blood clotting" in order to explain fibrin clot formation (Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood clotting. Science. 1964;145:1310–12.). Then, it was called "coagulation cascade." Now it is known that coagulation is not a one-way process. Thrombin provides positive feedback to activate various coagulation factors. See Fig. 1.3. © 2019, Texas Children's Hospital. Reproduced/used with permission

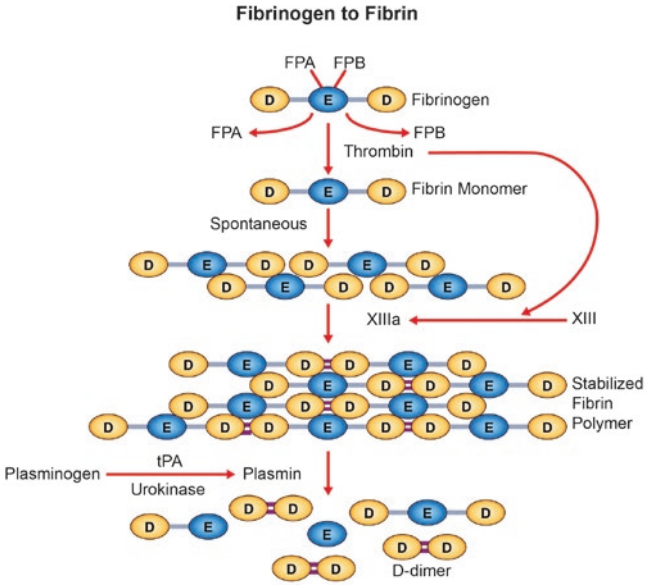

Fig. 1.4 The interaction of thrombin with fibrinogen results in the release of fibrinopeptide A (FPA) and fibrinopeptide B (FPB). A fibrin monomer is formed after releasing FPA and FPB. The fibrin monomers polymerize spontaneously. Thrombin also activates factor XIII to factor XIIIa, which crosslinks fibrin. Eventually, crosslinked fibrin will be degraded to D-dimer by plasmin. © 2019, Texas Children's Hospital. Reproduced/used with permission

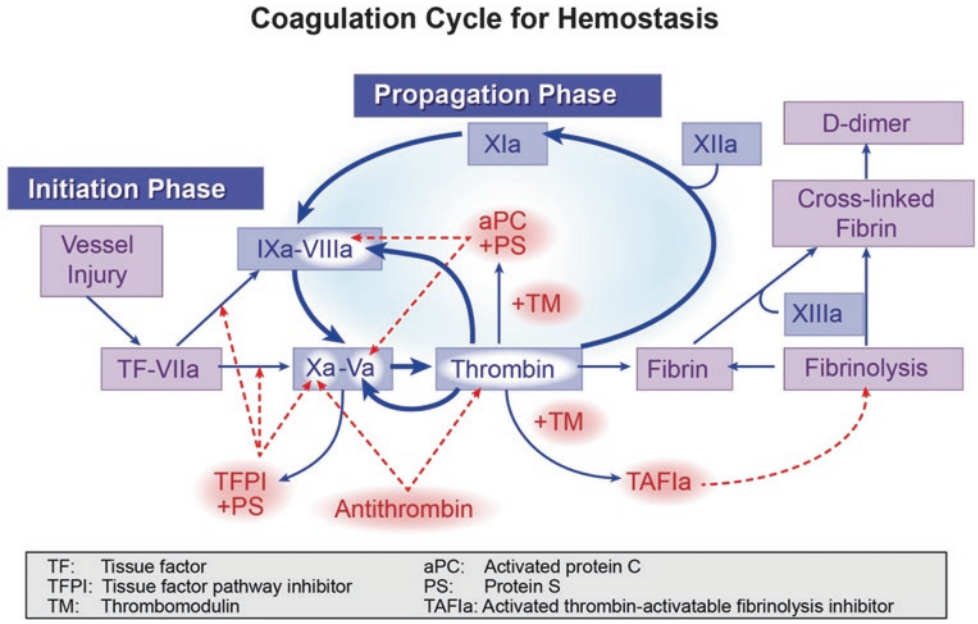

Fig. 1.3 When a vessel is injured, the factor VIIa (a small amount of activated form is circulating) and tissue factor complex activates factor IX and factor X to factor IXa and factor Xa, respectively. Tissue factor pathway inhibitor (TFPI) inhibits the activation of factor IX and factor X. Factor Xa together with factor Va, called prothrombinase, activates prothrombin to thrombin. Thrombin activates factor XI, factor VIII, factor V, and factor XIII and converts fibrinogen to fibrin. Thrombin also forms a complex with thrombomodulin on the endothelial cells. This complex then activates protein C to activated protein C and thrombin-activatable fibrinolysis inhibitor (TAFI) to TAFIa. Thrombin continues activating these factors until the process is completely inhibited by antithrombin and activated protein C. Of note, thrombin formation occurs without involvement of factor XII, which is why hemostasis is maintained in patients with factor XII deficiency. However, when factor XII is activated to factor XIIa, thrombin is formed. © 2019, Texas Children's Hospital. Reproduced/used with permission

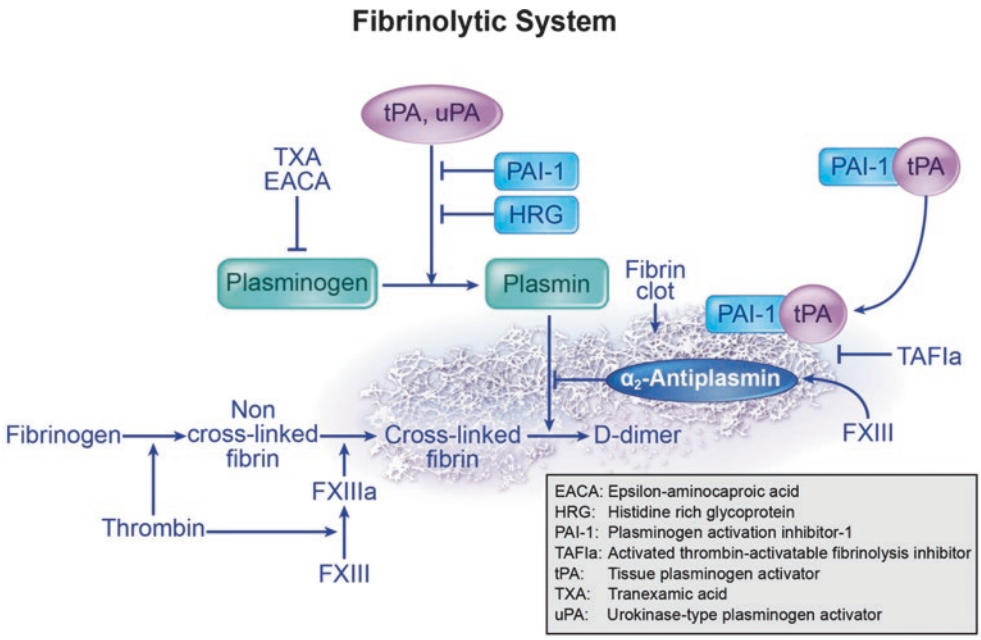

Fig. 1.5 Plasminogen is converted to plasmin by the actions of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). Plasmin cleaves fibrinogen, fibrin, fibronectin, thrombospondin, laminin, and von Willebrand factor. Plasmin is inactivated by α_2-antiplasmin and α_2-macroglobulin. Plasminogen activator inhibitor 1 (PAI-1) and histidine-rich glycoprotein inhibit the actions of tPA and uPA. © 2019, Texas Children's Hospital. Reproduced/used with permission

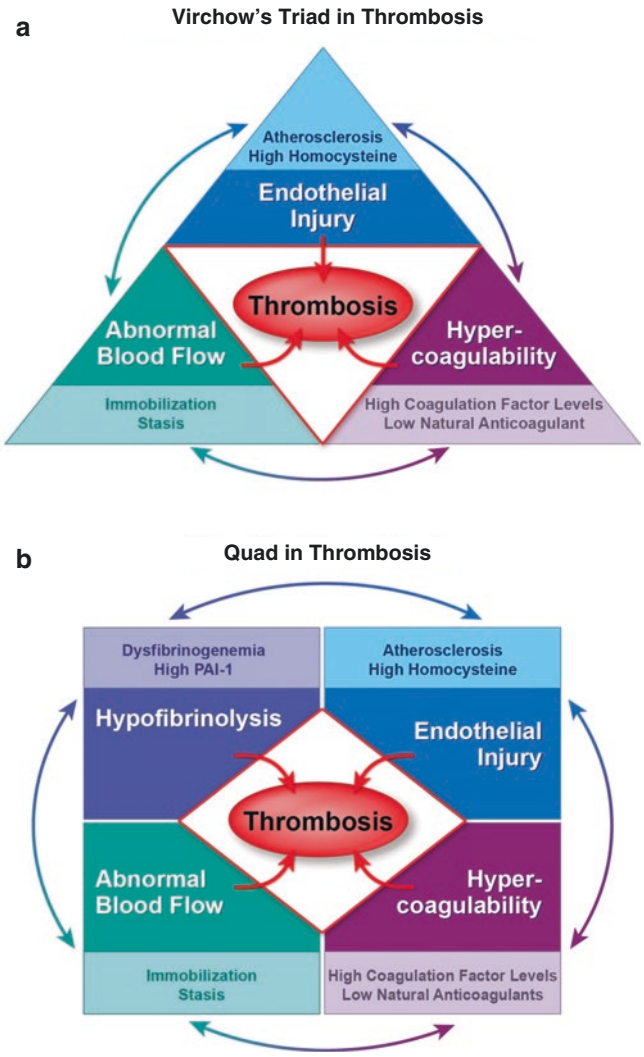

Fig. 1.6 Virchow proposed three key elements in the development of thrombosis (**a**). Hypofibrinolysis may be added to the triad (**b**). PAI-1 plasminogen activator inhibitor 1. © 2019, Texas Children's Hospital. Reproduced/used with permission

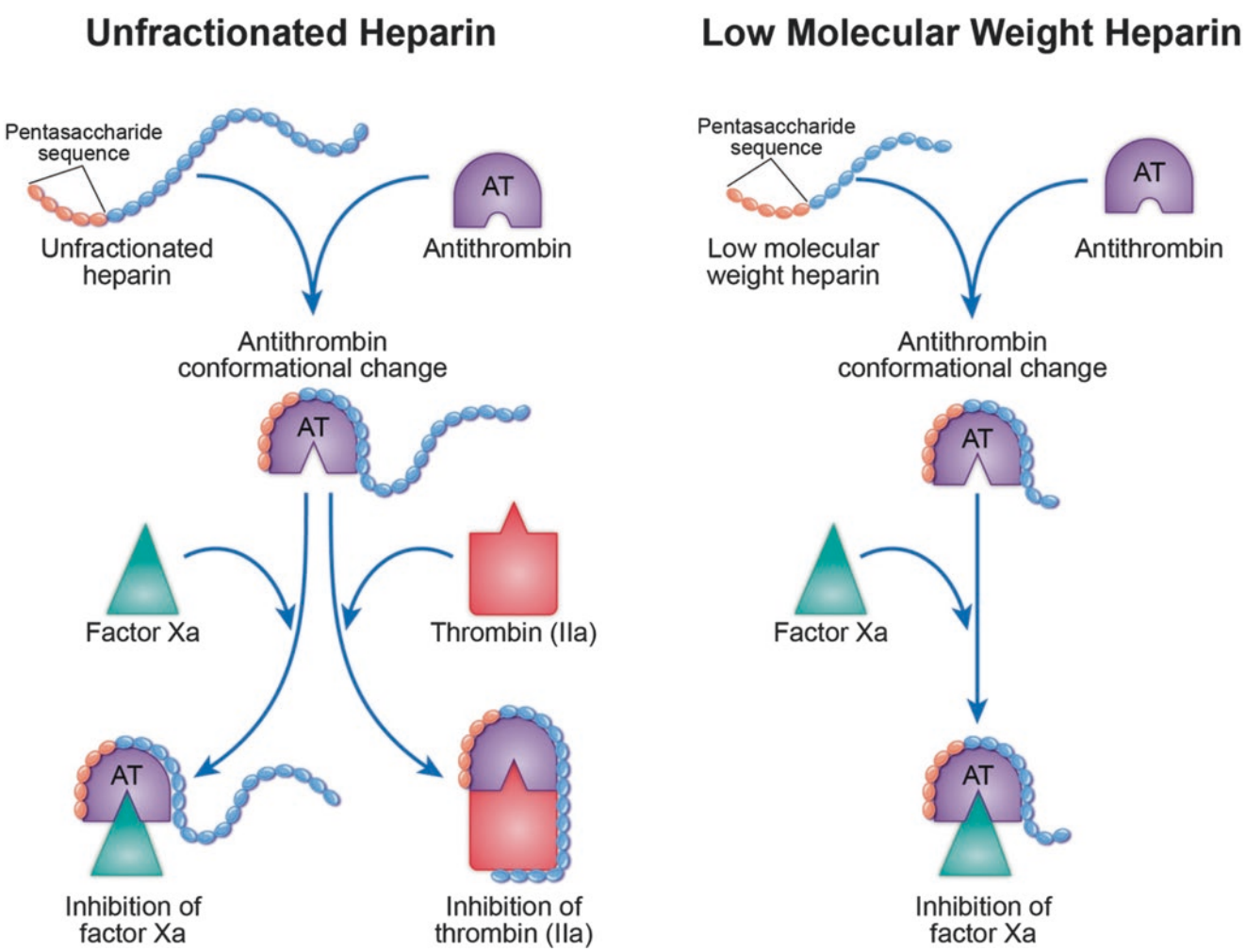

Fig. 1.7 Without heparin or heparinoids, antithrombin (AT) slowly inhibits factor Xa and thrombin. This is the "progressive form" of AT. AT also inhibits factor VIIa, factor IXa, and, to lesser extent, factor XIa. Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) forms a complex with AT resulting in a confirmational change in AT and accelerating its anticoagulant action. This is called the "immediate form" of AT. The AT and UFH complex inhibits thrombin and factor Xa immediately. Alternatively, the AT and LMWH complex inhibits primarily factor Xa immediately. Heparin also binds heparin cofactor II which inhibits only thrombin. Heparin additionally functions as an anticoagulant by causing the release of tissue factor pathway inhibitor (TFPI) from endothelial cells.

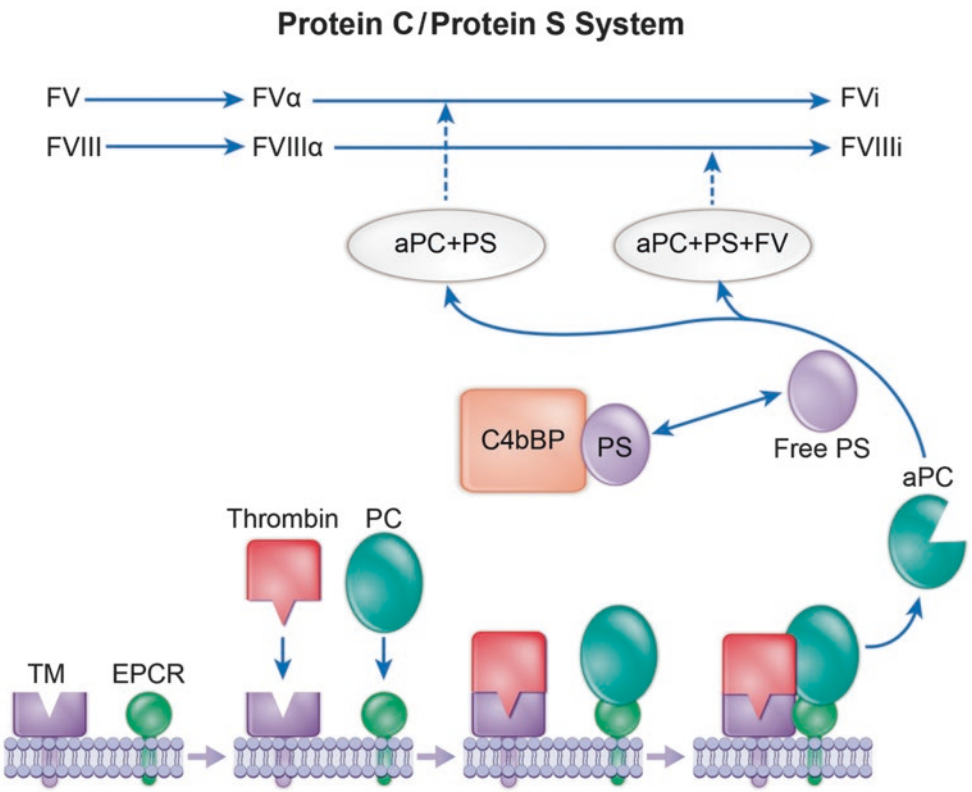

Fig. 1.8 Protein C binds to the endothelial protein C receptor (EPCR), and thrombin makes a complex with thrombomodulin (TM) on the endothelial cell surface. The thrombin thrombomodulin complex activates protein C which is bound to EPCR. Activated protein C (aPC) makes a complex with free protein S and inactivates factor Va. The aPC and protein S complex binds to factor V and inactivates factor VIIIa. This pathway inhibits procoagulant activity resulting in the prevention of excessive clot formation. C4bBP C4b binding protein, PS protein S, FV factor V, FVa activated factor V, FVi inactivated factor V, FVIII factor VIII, FVIIIa activated factor VIII, FVIIIi inactivated factor VIII, APC activated protein C, PC protein C. © 2019, Texas Children's Hospital. Reproduced/used with permission

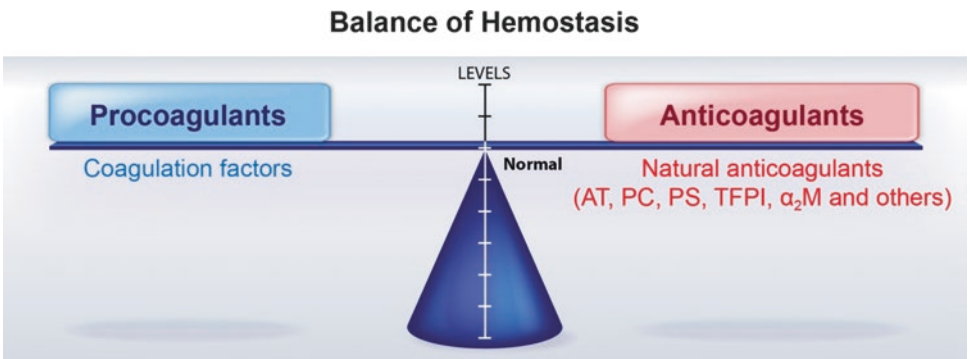

Fig. 1.9 In a normal state, procoagulants and anticoagulants are well balanced. AT antithrombin, PC protein C, PS protein S, TFPI tissue factor pathway inhibitor, α_2M α_2-macroglobulin. © 2019, Texas Children's Hospital. Reproduced/used with permission

Table 1.1 Characteristics of coagulation factors, contact factors, and von Willebrand factor

Factor	Common name	Molecular weight (Daltons) (activated form)	Concentration in 1 mL plasma	Concentration required for normal hemostasis
I	Fibrinogen	340,000 (330,000)	3 mg	100 mg/dL
II	Prothrombin	72,000 (38,000)	100 μg	20–40%
III	Tissue factor	45,000	0.02 μg	
IV	Calcium ions			
V	Proaccelerin	330,000	10 μg	>25%
VII	Proconvertin	50,000 (50,000)	0.5 μg	10–20%
VIII	Antihemophilic factor	280,000	0.1 μg	Minimum of 30% for major surgery; less for minor procedures
IX	Christmas factor	56,000 (46,000)	3–4 μg	25–30%
X	Stuart factor	55,000 (40,000)	6–8 μg	10–20%
XI	Plasma thromboplastin antecedent	160,000 (160,000)	7 μg	15–25%
XII	Hageman factor	80,000 (80,000)	30 μg	None required
XIII	Fibrin stabilizing factor	320,000 (320,000)	60 μg	>5%
	von Willebrand factor	1.2–5 million	7 μg	50%
	Prekallikrein	100,000	35–45 μg	None required
	High-molecular-weight kininogen	120,000	80 μg	None required

Table 1.2 Characteristics of coagulation factors and von Willebrand factor

Factor	In vivo half-life	Storage characteristics	Choice of components or hemostatic drug for replacement
I[a]	3–5 days	Stable in plasma at 4 °C	Cryoprecipitate, fibrinogen concentrate (RiaSTAP™, Fibryga™)
II	2–3 days	Stable in plasma at 4 °C	FFP, prothrombin complex concentrate (Kcentra™)
V	12 hours	Labile except when frozen	FFP
VII	3–6 hours	Stable in plasma at 4 °C	Recombinant activated factor VII (NovoSeven™), FFP, prothrombin complex concentrate (Kcentra™)
VIII[a]	8–12 hours	Labile except when frozen	Factor VIII concentrate, recombinant factor VIII
IX	18–24 hours	Stable in plasma at 4 °C	Factor IX concentrate, recombinant factor IX
X	30–40 hours	Stable in plasma at 4 °C	Prothrombin complex concentrate (Kcentra™, Coagadex™)
XI	52 hours	Stable in plasma at 4 °C	FFP, factor XI concentrate (not available in US)
XII	60 hours	Stable in plasma at 4 °C	Not necessary
XIII	9–10 days	Stable in plasma	Cryoprecipitate, factor XIII concentrate, recombinant factor XIII
VWF[a]	9–15 hours	Labile except when frozen	Humate-P™, Wilate™, Alphanate™, Vonvendi™ Cryoprecipitate[b]

FFP fresh frozen plasma, *VWF* von Willebrand factor
[a]Acute phase reactant
[b]If VWF concentrate or recombinant VWF is not available

Table 1.3 Natural anticoagulants

	Activation/mechanism of action	Inhibiting factors
Antithrombin	To immediate form by heparin and heparan sulfate	Thrombin, factor Xa
Protein C	Thrombin-thrombomodulin complex	Factor Va, factor VIIIa
Protein S	Cofactor of activated protein C	Factor Va, factor VIIIa
Tissue factor pathway inhibitor (TFPI)		Factor Xa, tissue factor, and factor VIIa complex
Heparin cofactor II	To immediate form by heparin and dermatan sulfate	Thrombin
α2-macroglobulin		Thrombin, factor Xa

Screening Coagulation Assays, Factor XIII and D-dimer

2

Dorothy M. Adcock and Brian F. Poirier

Physiologic Hemostasis

Hemostasis is the physiologic means by which the body both maintains circulatory flow and stops the loss of blood [1]. It is an intricate and complex process that relies on the interaction of multiple cellular components and protein pathways that serves to both maintain blood in a fluid state yet functions to develop a physical barrier to prevent excessive bleeding from injured blood vessels when needed. The system is highly regulated through a number of different mechanisms, in part being composed of proenzymes, procoagulant proteins, and anticoagulant proteins. Clot formation initiates the fibrinolytic system that functions to limit clot size and in some circumstances results in clot dissolution. The fibrinolytic system is also highly regulated containing proenzymes as well as profibrinolytic and antifibrinolytic proteins. Disorders in either clot formation or fibrinolysis can enhance bleeding potential and in some instances result in spontaneous hemorrhage.

Hemostasis progresses through three steps, beginning with (1) vasospasm which occurs nearly simultaneously with (2) platelet plug formation (referred to as primary hemostasis), followed by (3) the development of a fibrin clot (secondary hemostasis) [1–3]. Each step is triggered by injury to the blood vessel wall with resultant exposure to subendothelial matrix constituents. As vascular spasm or vasoconstriction helps limit blood loss from the vessel, primary and secondary hemostasis function together to form a fibrin clot. Primary hemostasis is described in more detail in Chapter 1.

Secondary hemostasis, also referred to as blood coagulation, is initiated by exposure of the plasma to tissue factor (TF) [1]. TF is found in the subendothelial matrix and can also be expressed by select cells in response to certain stimuli. A trace amount of procoagulant factor VII circulates in the activated rather than proenzyme form (activated factor VII [FVIIa]), and this serves to keep the hemostatic system "primed." FVIIa binds exposed TF resulting in the activation of factor X (activated FX [FXa]). This ultimately initiates the sequential activation of multiple coagulation proenzymes into functional serine proteases or functional cofactors, the activated forms of the procoagulant factors. Activated procoagulant factors bind the activated platelet and red blood cell surface, and this enables interaction with their respective cofactors and required cations, allowing the generation of highly efficient coagulation factor complexes that result in bursts of thrombin formation. Thrombin cleaves soluble fibrinogen creating fibrin polymers that polymerize electrostatically. An insoluble fibrin gel is formed when activated factor XIII covalently cross-links the fibrin polymers.

Most proteins involved in hemostasis are produced in the hepatic parenchyma with the exception of factor VIII, which is believed to be synthesized by hepatic sinusoidal endothelial cells, and a subunit of factor XIII [4]. Due to hepatic immaturity at birth, the normal reference interval for most clotting factors varies with age, a concept coined "developmental hemostasis" [5].

Laboratory Evaluation of Blood Coagulation

In the laboratory, secondary hemostasis is measured by determining the time required for a fibrin clot to form in platelet-poor plasma, when exposed to a coagulation activator and calcium. This system does not evaluate the platelet component of hemostasis, nor does it reflect the activity of the naturally occurring anticoagulants. Furthermore, lysis of the fibrin clot is evaluated using a distinct set of assays. Global screening assays that evaluate both the hemostatic and fibrinolytic systems require whole blood testing and are discussed in Chapter 5, "Hyperfibrinolysis." In addition to performing screening laboratory assays, the evaluation of a

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bleeding patient should include a complete history, physical examination, and review of medications, including prescribed and over-the-counter preparations, as well as any naturopathic remedies.

Secondary hemostasis can be evaluated using a simple battery of three assays which should be performed in all bleeding patients [1, 2]. These assays each measure the time to fibrin clot formation following the addition of different coagulation activators. The tests that evaluate secondary hemostasis include the prothrombin time (PT), activated partial thromboplastin time (aPTT), and functional fibrinogen level or a thrombin time (TT) (a surrogate fibrinogen assay when heparin is not in the specimen). In vitro, fibrin clot formation can be initiated through the intrinsic system by adding a contact activator (e.g., ellagic acid, silica, kaolin), through the extrinsic system by adding tissue factor, or it can be initiated by the addition of thrombin, each of which is added to separate aliquots of the anticoagulated plasma sample [1]. Calcium is required to reverse the anticoagulant effect of sodium citrate. Evaluation of functional fibrinogen or a thrombin time is needed in the evaluation of a bleeding patient, as the PT and aPTT are insufficiently sensitive to clinically significant decreases in fibrinogen levels. Important limitations of the PT and aPTT include the following: (1) both assays can be prolonged factitiously due to a number of different pre-analytical variables, (2) neither assay detects abnormalities of certain critical factors such as factor XIII and proteins in the fibrinolytic system nor platelet function defects, and (3) either assay may be prolonged due to conditions that do not increase bleeding risk [6]. A significant limitation of these screening assays is that in vitro fibrin clot formation does not adequately mimic the physiologic clotting process and does not evaluate the interaction of plasma factors with cellular components and the vasculature. Although the PT, aPTT, and functional fibrinogen assay are inadequate measures of in vivo hemostasis, these assays are a convenient and readily available means to provide, albeit limited, evaluation of secondary hemostasis.

Screening Coagulation Assays

Proper sample acquisition and handling is critical to obtaining accurate coagulation results [7–9]. Samples should be collected in 3.2% sodium citrate using the proper 9:1 blood to anticoagulant ratio. Incomplete filling of a sodium citrate tube, hematocrit >55%, or combining the contents of two incompletely filled sodium citrate tubes may lead to spuriously prolonged clotting times. While samples with hematocrits >55% require adjustment by reducing the amount of liquid anticoagulant in the collection tube, no adjustment is required for samples with reduced hematocrits. Samples should be collected from a peripheral vein, whenever possible, to avoid contamination from a port or intravenous infusion. Samples should be adequately mixed immediately following collection and processed in a rapid fashion. Hemolysis should be avoided as this may interfere with clot-based results.

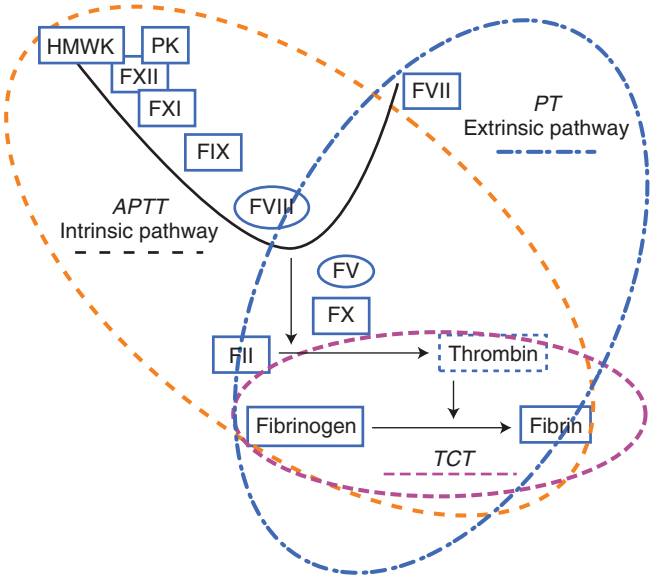

Fig. 2.1 In vitro model of secondary hemostasis

The PT evaluates factors of the extrinsic pathway (factor VII), common pathway (factors X, V, and II), and fibrinogen (Fig. 2.1) [2, 3, 10]. In the PT assay, coagulation is initiated by adding tissue factor and phospholipids (this combination is called thromboplastin) to recalcified plasma, and the time to form a fibrin clot is measured in seconds. Most PT reagents contain a heparin neutralizer, and therefore the PT does not typically elevate in the presence of heparin up to 1–2 units/mL depending on the PT reagent. The aPTT evaluates factors of the contact pathway (high molecular weight kininogen [HMWK], prekallikrein [PK], factor XII), intrinsic pathway (factors VIII, IX, and XI), and common pathway (factors X, V, and II) as well as fibrinogen [2, 3, 10]. In the aPTT, fibrin clot formation is initiated by addition of a contact activating agent, calcium, and phospholipid.

Prolongation of the aPTT or PT typically occurs when a single factor in the appropriate pathway falls below approximately 50% (a normal reference interval for factor activity is often in the range of 50–150%). An important caveat to this is that the aPTT is relatively insensitive to the clinically important intrinsic factors (factors VIII, IX, and XI), and the aPTT typically does not prolong until one of these factors falls below about 30% [3, 10]. Reagent responsiveness to factor deficiency varies between reagent manufacturers and, therefore, between laboratories. The aPTT may also elevate when multiple factors are in the lower end of the normal range, especially in a pediatric patient [11]. Neither the aPTT nor PT prolongation demonstrates a linear relationship with

decreased factor levels, and these assays prolong in an exponential fashion as functional factor concentrations decrease [12]. The thrombin time measures the time to fibrin clot formation following the addition of thrombin. The thrombin time is an indirect measure of functional fibrinogen, and in the evaluation of a bleeding patient, either a thrombin time or functional fibrinogen should be measured [13]. Functional fibrinogen is measured using a citrated plasma sample exposed to thrombin in the presence of phospholipids and calcium, which is called Clauss method. The time in seconds for fibrin clot to form is read in relationship to a standard curve of known fibrinogen concentration [1].

Once it is determined that the aPTT, PT, and/or TT are abnormal, plasma mixing studies can be performed to help determine if the prolongation of the clotting time reflects a factor deficiency or the presence of an inhibitor [2]. In the presence of a factor deficiency(ies), addition of an equal volume of normal plasma to the patient plasma typically corrects the clotting time into the normal reference interval. In the presence of a specific or non-specific factor inhibitor, addition of normal plasma typically does not lead to correction of the patient clotting time into the reference interval, although this is dependent on the reagent and type of inhibitor. Some factor inhibitors, such as specific factor VIII and factor V inhibitors, often require incubation at 37 °C for 1 to 2 hours in order to demonstrate their inhibitory effect [14]. Specific factor inhibitors are antibodies that neutralize the activity of a single coagulation factor and often lead to a bleeding diathesis. These antibodies are detected and their strength measured in the laboratory using specific coagulation factor inhibitor assays commonly referred to as a Bethesda assay [14]. Non-specific inhibitors interfere with multiple factors or can interfere with a reagent component such as phospholipid. Lupus anticoagulants and certain anticoagulant drugs including heparin, direct Xa, and direct thrombin inhibitor agents act as non-specific inhibitors in the coagulation laboratory and may lead to incomplete correction in normal plasma mixing studies [14, 15]. In order to determine the basis of aPTT, PT, and/or TT prolongation, further testing such as specific factor assays or evaluation for a lupus anticoagulant may need to be performed.

Abnormalities of the aPTT and PT are common in the critically ill as well as the trauma patient. In trauma patients, a PT and/or aPTT ratio >1.5 (compared to the control) predicts excessive bleeding [16]. However, in trauma patients, these parameters are not entirely useful within the first 1–2 hours of the trauma or until the patient stabilizes [17]. In hypothermic patients, the values of the PT and aPTT may underestimate the coagulopathy because the PT and aPTT reactions are performed on samples warmed to 37 °C [17].

A number of hemorrhagic diatheses may occur despite a normal aPTT, PT, and functional fibrinogen level (see Table 2.1). A normal aPTT does not rule out mild deficiencies of factor VIII, IX, and/or XI as these factor activities must fall to 20 to 40% or less, depending on the reagent used in the assay and how the reference range is established, before the aPTT prolongs [10]. FXIII activity, platelet dysfunction, and fibrinolytic factors are not assessed by these screening assays. The most important contributors to bleeding that are missed by the PT and aPTT are platelet dysfunction and hyperfibrinolysis [16].

Table 2.1 Bleeding with a normal APTT and PT and TT/fibrinogen

Cause	Comment
Mild factor VIII, factor IX, or factor XI deficiency	Single factors generally have to fall below approximately 30% before the aPTT is prolonged
Hereditary or acquired FXIII deficiency	Can lead to significant bleeding potential with spontaneous bleeding
Alpha 2-antiplasmin deficiency	
Abnormal platelet number or function	
Vascular or collagen abnormality	Such as Ehlers-Danlos syndrome, vasculitis
Anatomical cause	

Table 2.2 Isolated prolonged PT (normal aPTT and normal fibrinogen/TT)

Cause	Comment
Deficiency or inhibitor of factor VII	Severe deficiency may be associated with spontaneous bleeding. Factor VII is the first factor to decrease with vitamin K deficiency or antagonism and liver disease. Inhibitor is rare
Mild deficiency of factor X, factor V, or factor II	Single factor deficiencies in the 30–60% range may lead to isolated prolongation of the PT. Moderate to severe deficiency causes prolongation of aPTT as well
Anticoagulant therapy: direct Xa inhibitor anticoagulant (e.g., rivaroxaban, apixaban, edoxaban)	May cause prolongation of the aPTT depending on drug concentration. Will not affect the TT

Prolonged PT, Normal aPTT, and Normal Functional Fibrinogen

When the PT is prolonged but the aPTT and functional fibrinogen (or TT) are normal, a deficiency of factor VII should be considered (see Table 2.2) [1, 2, 18]. Mild deficiencies of factors X, V, and II may also cause isolated prolongation of the PT, as PT reagents are more sensitive to deficiencies of these common pathway factors than are aPTT reagents [19]. Certain drug therapies, such as direct Xa inhibitor anticoagulants and warfarin, can cause isolated prolongation of the PT but can also prolong the aPTT with stable warfarin therapy [15, 20].

In the presence of factor deficiency, a PT mixing study generally demonstrates correction unless the prolongation is due to vitamin K deficiency, vitamin K antagonism, or sometimes liver disease, where the PT mixing study tends to demonstrate near correction into the normal reference interval, but not completely within the normal reference interval. For example, if the normal interval of the PT is 11–14.1 seconds and a patient has a PT result of 35 seconds, a mixing study that demonstrates complete correction would have a 1:1 mix result that falls into reference interval (11–14.1 seconds), and one that demonstrates near correction may correct to a PT of 14.2–15 seconds. A PT mix that demonstrates incomplete correction would have a 1:1 mix result usually above about 18 seconds (with a normal reference interval of 11–14.1 seconds), and this occurs in the presence of a factor inhibitor such as a FVII inhibitor. This may also occur with a direct thrombin or Xa anticoagulant or can occur with a specific factor V, X, or II inhibitor, although each of these drugs and inhibitors typically also elevates the aPTT [20–22]. Select factor II (prothrombin) inhibitors, specifically those that occur in association with lupus anticoagulants, commonly function as clearing rather than neutralizing antibodies [23, 24]. See Chapter 23. These antibodies cause prolongation of the PT due to rapid clearance of the factor II-antibody complex, resulting in low factor II levels and hence factor II deficiency. A PT normal plasma mixing study demonstrates correction as these clearing coagulation factor inhibitors will not be detected with a factor inhibitor (Bethesda) assay.

Factor VII has the shortest half-life of all coagulation factors and therefore is the first factor to decrease with liver disease as well as vitamin K deficiency or vitamin K antagonists. Hereditary deficiency of factor VII is rare as is the development of acquired inhibitors to FVII [1, 25, 26]. Deficiency of factor VII prolongs the PT without affecting the aPTT or TT. A hereditary deficiency of any of the common pathway factors (factors X, V, and II) is rare [1, 25]. Heterozygous (mild) deficiencies of any of these factors may or may not be associated with bleeding. Bleeding is more typical of heterozygous factor II deficiency than heterozygous factor V, VII, or X deficiency [1, 25]. Spontaneous bleeding associated with these rare heterozygous factor deficiencies typically involves skin and mucous membranes. Heterozygous deficiency of factor V, X, or II may present with an isolated elevated PT [19]. Homozygous deficiency of any one of the common pathway factors would lead to significant factor deficiency and cause prolongation of both the PT and aPTT and may lead to a significant bleeding tendency, both spontaneous and with provocation [25]. Acquired deficiency of factor X can occur with amyloidosis and, depending on the level of deficiency, may lead to an isolated, elevated PT and increased bleeding risk [19].

Prolonged aPTT, Normal PT, and Normal Functional Fibrinogen (or Normal TT)

Prolongation of the aPTT with a normal PT and functional fibrinogen (normal TT) may reflect a deficiency or inhibitor of a contact pathway factor (factor XII, HMWK, PK), deficiency or inhibitor of an intrinsic pathway factor (factor VIII, IX, XI), or the presence of a lupus anticoagulant (see Table 2.3) [1–3, 27]. Heparin therapy or contamination, as well as direct thrombin inhibitor (DTI) anticoagulants, elevates both the aPTT and thrombin time [15]. Certain PEGylated drugs (e.g., PEG interferon) may cause prolongation of the aPTT, yet this PEG interference poses no increased bleeding risk [28]. Select lipoglycopeptide antibiotics including daptomycin and telavancin may elevate the aPTT, and in some circumstances the PT, without increasing bleeding risk [29, 30]. The degree of prolongation depends on the concentration of the antibiotic in the plasma and the reagent sensitivity to the drug. It has been reported that elevated levels of C-reactive protein may cause spurious elevation of the aPTT with commonly used aPTT reagents [3]. Severe contact factor deficiencies typically greatly prolong the aPTT, yet clinically are not associated with an increased bleeding potential. Mild deficiencies of a contact factor pathway generally will not affect the aPTT.

Table 2.3 Isolated prolonged aPTT (normal PT and TT/fibrinogen)

Cause	Comment
Intrinsic factor (factor XI, factor IX, factor VIII) deficiency or inhibitor	Severe deficiency may be associated with spontaneous bleeding; aPTT may be normal with mild single factor deficiency
Contact factor (factor XII, prekallikrein, high molecular weight kininogen) deficiency or inhibitor	Severe deficiency may lead to marked prolongation of the aPTT, but no increased bleeding risk. Heterozygous deficiency of a single contact factor will not likely affect the aPTT
Acquired factor VIII, factor IX, or factor XI inhibitors	Factor VIII inhibitor by far the most common and may lead to severe spontaneous bleeding, can occur as alloantibody (in hemophilia A) or autoantibody; inhibitors against factor IX or XI are rare
Lupus anticoagulant (LA)	Increases risk for thrombosis and obstetric complications. Leads to bleeding only when LA is associated with thrombocytopenia or deficiency of prothrombin (factor II). Factor II deficiency would cause a prolonged PT
Select PEGylated drugs	Prolongation of APTT is not associated with increased bleeding risk
Lipoglycopeptide antibiotics, select	Select agents effective against MRSA[a] such as daptomycin and telavancin. Prolongation of aPTT is not associated with increased bleeding risk. May also prolong the PT depending on plasma drug concentration and reagent used in laboratory

[a]Methicillin-resistant *Staphylococcus aureus*

Table 2.4 Causes of factor VIII deficiency

Cause	Comment
Hemophilia A	X-linked; therefore typically males affected; female carriers may bleed with provocation
von Willebrand disease (VWD)	In type 2N VWD, VWF activity and antigen may be normal and FVIII activity reduced
Acquired hemophilia A	May be associated with severe spontaneous bleeding
Acquired von Willebrand syndrome	May be associated with severe spontaneous bleeding
Spurious decrease	Can occur with some lupus anticoagulants or incorrect sample type (i.e., serum or EDTA plasma)

In a previously healthy male or female patient with a prolonged aPTT and normal PT and fibrinogen, who presents with acute, possibly catastrophic, spontaneous hemorrhage into soft tissues and muscle, acquired hemophilia (an acquired factor VIII inhibitor) or acquired von Willebrand syndrome (AVWS) should be considered (see Table 2.4) [31–34]. Factor VIII inhibitors (acquired hemophilia A) can develop in an older population for no apparent reason, or they may present in patients with underlying autoimmune disorders, underlying solid tumors, or lymphoproliferative malignancies and may also occur in association with pregnancy [31, 32]. Acquired hemophilia A should be considered early in the evaluation of abnormal bleeding in the postpartum setting [35]. FVIII inhibitors may develop 1 to 4 months and rarely as late as 1 year postpartum. Acquired factor VIII inhibitors are rare in children but have been reported [36]. In the presence of a FVIII inhibitor, the aPTT is elevated, while the PT is normal, and aPTT mixing studies may or may not demonstrate correction upon immediate mix, but typically demonstrate prolongation with incubation over time at 37 °C. Factor VIII activity and FVIII inhibitor (Bethesda) assays should be performed and also possibly von Willebrand factor activity and antigen assays (see next paragraph). Acquired inhibitors to factor VIII are the most frequent acquired factor inhibitors reported. Acquired inhibitors to factor IX or XI are rare [37, 38].

Acquired factor VIII deficiency can also occur as a feature of AVWS [34, 39, 40]. In a bleeding patient without a history of hemophilia A, who has a low factor VIII activity (<10%), von Willebrand factor antigen and activity should be measured to rule out AVWS, especially if there is no evidence of a specific FVIII inhibitor. AVWS may occur in both pediatric and adult patients [39]. There are many different underlying conditions that are associated with AVWS such as underlying lymphoproliferative disorders, certain cardiac valve disorders, ventricular septal defects, essential thrombocythemia, Wilms tumor, and hypothyroidism, to name a few. The laboratory diagnosis of AVWS is essentially the same as hereditary von Willebrand disease (VWD), and both type 1 (quantitative) and type 2 (qualitative) deficiencies may occur.

Congenital factor VIII (hemophilia A) and IX deficiencies (hemophilia B) are X-linked disorders and therefore typically present in males and rarely in females (except in specific situations, e.g., skewed lyonization, homozygosity for the hemophilia gene resulting from consanguinity, and deletions such as Turner syndrome), with an isolated prolonged aPTT and isolated deficiency of either factor VIII or factor IX [41–43]. Severe hemophilia A or B (≤1% factor VIII or IX activity, respectively) presents with spontaneous hemorrhage, while moderate (2–5% factor level) to mild (6–40% factor level) hemophilia may go undiagnosed until a patient is challenged. Hemophiliacs may develop specific factor inhibitors in response to factor replacement therapy, and when present this significantly complicates replacement therapy. Female carriers of hemophilia A and B have an increased bleeding tendency, even when factor levels are in the 40–60% range, especially when their hemophiliac relatives have a severe form of the disease [42]. Factor levels are not always a good predictor of bleeding in hemophilia carriers [44]. Recent studies have highlighted the increased incidence of postpartum hemorrhage, in the range of 20–40%, in this population [45].

Factor XI deficiency (hemophilia C) is autosomal in inheritance and affects both males and females [46, 47]. The incidence of factor XI deficiency in most populations is 1 in 1,000,000, although it is significantly greater in an Ashkenazi Jewish population occurring at a frequency of 1 in 450. Severe deficiency is defined by factor levels less than 15%. The bleeding tendency is variable and does not always correlate to factor XI activity levels, but is more likely to occur with severe deficiency and when an injury involves an area with high fibrinolytic potential, such as the oral cavity or urogenital tract. Spontaneous bleeding with hemophilia C is rare. Bleeding typically occurs only with provocation. Development of inhibitors in response to replacement therapy is unusual but reported. Acquired factor XI inhibitors are rare and may occur in those with underlying autoimmune disorders [37, 38].

VWD is the most common inherited bleeding disorder. It has an autosomal mode of inheritance and therefore affects both males and females. VWD is due to a deficiency or defect of von Willebrand factor (VWF) [1, 40, 48, 49]. VWF serves as the carrier protein for procoagulant factor VIII and also serves to bind platelets to the site of vascular injury, and therefore, VWF serves an important role in primary hemostasis. When VWF is decreased, factor VIII activity is decreased concordantly. The aPTT is not an adequate screen for VWD as the aPTT will not prolong until factor VIII levels fall below 20–30%, depending on the reagent [10]. To screen for VWD, VWF antigen and activity, as well as factor VIII activity, should be measured in plasma. Deficiencies of VWF alone do not affect the aPTT, PT, or thrombin time.

Lupus anticoagulants (LA) are a common cause of an isolated prolonged aPTT. Although historically termed an "anticoagulant," lupus anticoagulants are more commonly associated with an increased thrombotic risk and risk of certain obstetric complications, rather than increased bleeding risk [27, 50]. LA are non-specific inhibitors, and aPTT mixing studies generally demonstrate incomplete correction, although this is reagent dependent. Diagnosis of the presence of LA is made by comparing the results of phospholipid dependent assays performed in the presence of low and high phospholipid concentrations. Shortening of the clotting time in the presence of increased phospholipids is characteristic of LA [27, 50]. As PT reagents contain a greater phospholipid concentration compared to aPTT reagents, most PTs are not prolonged in the presence of LA, although certain PT reagents may demonstrate sensitivity to lupus anticoagulants. Lupus anticoagulants may interfere with the phospholipids required in factor VIII, IX, and/or XI activity assays, making the activities appear factitiously low. Assay interference should always be considered in a patient without bleeding, but with decreased factor VIII, IX, and XI activity results, especially when the values of all three factors are low. If LA interference is suspected, a chromogenic factor VIII or factor IX activity assay should be used as these assays are more accurate in the presence of LA [51]. Another option is to measure the intrinsic factors using an aPTT reagent that is not LA sensitive, and this may require sending the sample to a reference laboratory. In contrast to spurious LA interference in intrinsic factor assays where factors VIII, IX, and XI may appear decreased, severe liver disease is associated with decreased factor IX and XI activities but normal to elevated factor VIII activity. In vitamin K deficiency/antagonism, factor IX activity is low and factor VIII and XI activities are normal.

Prolonged TT, Normal PT, and Normal aPTT

In practice, this pattern of results occasionally occurs due to the presence of low molecular weight heparin or unfractionated heparin (either from low-dose therapy or contamination) or direct thrombin inhibitor (DTI) therapy (see Table 2.5) [20]. As drug concentration increases, the aPTT will elevate with heparin, and both the aPTT and PT prolong in the presence of DTI [15]. In fact, many laboratories perform a thrombin time as a quality control measure in an effort to rule out heparin therapy or contamination of a sample. In general, conditions or drugs that prolong the thrombin time that would lead to spontaneous or an enhanced bleeding diathesis would also elevate the PT and aPTT. The thrombin time is sensitive to both the amount and functionality of fibrinogen. Thus, both hypofibrinogenemia and dysfibrinogenemia may elevate the thrombin time [1, 52, 53]. Typically, the aPTT and PT will elevate when fibrinogen levels fall below around 80 to 100 mg/dL, but this depends on the reagent used in the laboratory.

Table 2.5 Isolated prolonged TT (normal aPTT and normal PT)

Cause	Comment
Deficiency of fibrinogen	Fibrinogen levels less than approximately 100 mg/dL result in prolongation of the PT and aPTT. The PT is more sensitive to low fibrinogen than the PTT
Abnormal fibrinogen (dysfibrinogen)	Tends to cause prolongation of the PT and aPTT, although the TT is the most sensitive assay. May be associated with major hemorrhage
DOAC of anti-Xa action	The PT and aPTT may be prolonged or normal
Fibrin split products at high concentration	Interferes with fibrin polymerization and may lead to prolongation of the PT and/or aPTT, although TT is most sensitive. Does not increase bleeding risk by itself
Monoclonal antibodies, select	Interferes with fibrin polymerization and may lead to prolongation of the PT and/or aPTT, although TT is most sensitive. Does not increase bleeding risk by itself

Substances that can interfere with fibrin polymerization such as fibrin(ogen) degradation products and paraproteins may elevate the TT, but are not consistently associated with an enhanced bleeding potential [54]. Interference with fibrin polymerization may also cause prolongation of the aPTT and PT, although the TT is the most sensitive of the three assays. Inhibitors of thrombin activity, such as antibodies to thrombin formed after exposure to thrombin glue, may elevate the TT but typically elevate the aPTT and PT as well [55]. Increased level of D-dimer is another cause of the prolongation of the TT.

Prolonged PT and Prolonged aPTT, Normal Functional Fibrinogen (or Normal TT)

Prolongation of the PT and aPTT with a normal functional fibrinogen (or normal TT) may reflect multiple factor deficiencies, a deficiency or inhibitor of a common pathway factor (factors X, V, and II), vitamin K deficiency, vitamin K antagonist (warfarin), superwarfarin (rat poison), or an anti-Xa inhibitor anticoagulant (see Table 2.6) [1–3, 15, 20, 56]. Some lipoglycopeptide antibiotics, such as daptomycin or telavancin, may elevate the aPTT and PT, presumably due to interference with the phospholipids required in the assay, but are not associated with an increased bleeding risk [29, 30]. aPTT and PT mixing studies demonstrate correction with factor deficiency(ies). An exception to this is factor II inhibitors that develop in association with a lupus anticoagulant as these antibodies are clearing and not neutralizing [23, 24]. Incomplete correction of both aPTT and PT mixing studies

Table 2.6 Prolonged aPTT and prolonged PT (normal fibrinogen/TT)

Cause	Comment
Vitamin K deficiency or vitamin K antagonists (warfarin or rat poison)	Can lead to significant bleeding potential with spontaneous bleeding
Factor X, factor V, or factor II deficiency	Severe deficiency may lead to spontaneous bleeding. Mild deficiency does not typically prolong the aPTT
Multiple factor deficiencies	Due to factor deficiencies involving both the intrinsic and extrinsic pathways or a single deficiency in the common pathway factors X, V, and II
Liver disease	If severe, may prolong the thrombin time due to hypofibrinogenemia or dysfibrinogenemia
Anticoagulant therapy: direct Xa inhibitor anticoagulant and warfarin	The PT is more sensitive to drug effect than is the aPTT
Dilutional coagulopathy	Associated with massive transfusion or massive fluid resuscitation
Lupus anticoagulant with hypoprothrombinemia (see Chapter xx)	May result in significant bleeding potential; the inhibitor causing decreased factor II is a clearing and not a neutralizing antibody, and therefore the PT mix typically corrects, and a factor II inhibitor titer is negative
Spurious, i.e., Hct >55% and volume of sodium citrate in collection tube not corrected, short draw, incorrect sample type (i.e., serum or EDTA plasma)	Not associated with an enhanced bleeding potential

occurs in the presence of a factor V inhibitor, factor X inhibitor, or Xa inhibitor anticoagulant therapy. While a direct thrombin inhibitor (DTI) anticoagulant can also prolong the aPTT and PT, the thrombin time would also be prolonged [20]. A lupus anticoagulant may rarely elevate both the aPTT and PT with certain PT reagents, although the PT is typically only mildly prolonged in these instances.

In a previously healthy male or female patient with a prolonged aPTT and PT and normal thrombin time or functional fibrinogen, who presents with acute, spontaneous hemorrhage, acquired vitamin K deficiency, or antagonism, should be strongly considered [15]. Vitamin K is crucial to the synthesis of functional factors II, VII, IX, and X. Infants are born naturally deficient in vitamin K, and it should be administered shortly after birth [57]. Infants who have not received vitamin K may suffer life-threatening intracranial and retroperitoneal hemorrhage occurring between days one to seven of life. Although a fat-soluble vitamin, a daily requirement exists because vitamin K is not effectively stored in the body [58]. Vitamin K is obtained through diet (e.g., leafy green vegetables) and intestinal flora. Deficiency of vitamin K should be considered particularly in patients who have experienced prolonged antibiotic use and malnourishment and in patients with biliary obstruction. Individuals with fat malabsorption disorders, including inflammatory bowel disease and cystic fibrosis, as well as individuals administered certain medication including cephalosporin, cholestyramines, anticonvulsants, and certain sulfa drugs, may be at increased risk of vitamin K deficiency [59]. Typical presenting symptoms include easy bruising and bleeding that may manifest as nosebleeds, bleeding gums, blood in the urine, blood in the stool, and tarry black stools. Bleeding may be severe and manifest as life-threatening intracranial and retroperitoneal hemorrhage. With vitamin K deficiency or warfarin, the aPTT and PT are elevated, and both may be so prolonged they yield "no clot detected." The thrombin time is normal as is fibrinogen, unless there is significant bleeding leading to consumption. Normal plasma mixing studies demonstrate correction of the aPTT into the normal range and typically near correction of the PT. Factor assays reveal decreased factor II, VII, IX, and X activities (the vitamin K-dependent factors) and normal factor XI, VIII, and V activities. In contrast, in liver disease, all factors (including functional fibrinogen) are decreased except for factor VIII, and in severe liver disease, the thrombin time tends to be elevated. In disseminated intravascular coagulation (DIC), all factors may be decreased due to consumption, including factor VIII, and fibrinogen may also be significantly decreased. A relatively efficient screen to distinguish vitamin K deficiency/warfarin from liver disease in a patient with a prolonged aPTT and PT, but normal TT, is to perform factor IX and V activities. With vitamin K deficiency/warfarin, factor IX is decreased, but factor V normal. In liver disease, both factor IX and V activities are decreased (see Table 2.7).

Anticoagulant rodenticides (rat poisons) are long-acting anticoagulants similar to warfarin [56, 60–62]. They act as vitamin K antagonists but are significantly more potent and longer-acting than warfarin. Also referred to as superwarfarins, anticoagulant rodenticides include bromadiolone, chlorophacinone, difethialone, diphacinone, and brodifacoum [61]. Brodifacoum is the agent most commonly used as a rat poison in the United States. Anticoagulant rodenticides are toxic when eaten or inhaled and when they come in contact with the skin. Clinical manifestation depends on the severity of the exposure and may result in fatal hemorrhage. Simple ingestion of a single dose, as may occur in a pediatric population, is usually asymptomatic [62]. With severe poisoning, the aPTT and PT may result in "no clot detected" while the thrombin time remains normal. Confirmation of rodenticide anticoagulant exposure requires serum determination of their presence. These agents can be measured using high-pressure liquid chromatography or mass spectrometry [63]. Serum warfarin shows no cross-reactivity with superwarfarins, and

Table 2.7 Impact of common coagulopathies on the aPTT, PT, and TT

Disorder	PT	APTT	Thrombin time	Comment
Vitamin K deficiency/ antagonism including rat poison	↑	↑	→	With rat poison, the aPTT and PT improve with administration of vitamin K but prolong with time as more rodenticide is released from the adipose tissue
FVIII deficiency	→	↑	→	FVIII deficiency can be hereditary or acquired
Liver disease	↑	↑	→ ↑	PT prolongs initially followed by aPTT and then thrombin time when severity increases
Disseminated intravascular coagulation	↑	↑	↑	

a serum warfarin assay will not detect their presence. Because these agents are lipophilic, their effect can be long-lasting. A classic feature of anticoagulant rodenticide poisoning is that the PT and aPTT are both greatly prolonged and correct with the administration of large amounts of vitamin K (ranging from 50 to 800 mg), only to prolong again with time as the rodenticide is released from the adipose tissue. Vitamin K must often be administered for prolonged periods of time on a daily or twice daily basis, sometimes up to 1 year's duration [56, 62].

Prolonged PT and Prolonged aPTT and Decreased Fibrinogen (or Prolonged TT)

This pattern may occur with a significantly decreased or abnormal fibrinogen (where the functional fibrinogen value is less than 80 to 100 mg/dL), severe liver disease, or multiple factor deficiencies as may occur with DIC. This pattern of results may also occur with DTI therapy, depending on the plasma concentration of DTI and reagent sensitivity to drug (see Table 2.8).

With liver disease, patients tend to present with bruising, epistaxis, bleeding from venipuncture sites, oral mucosa, gastrointestinal mucosa, and esophageal varices [64]. The etiology of the coagulopathy in liver disease is complex [65]. Liver disease will lead to impaired synthesis of all factors produced by the liver, as well as impaired clearance of activated factors, and increased fibrinolysis. It is important to note that both pro- and anticoagulant factors will be reduced in liver disease and thus the overall balance may not necessarily lead to anticoagulation, and in fact, thrombotic events, particularly of the mesenteric and portal veins, may occur in patients with cirrhosis [66, 67]. Further, while most coagulation factors are produced by the liver, VWF and factor VIII are not. Thus, in liver disease, all coagulation factors tend to decrease with increasing disease severity (although typically 90% of more of hepatic functionality must be lost before factor levels tend to decrease), with the exception of factor VIII, which may elevate as an acute phase protein, and this may somewhat compensate physiologically for decrease in liver-produced procoagulants. Diseases of the liver and biliary tract tend to more significantly impair production of vitamin K-dependent coagulation factors, and thus the PT will tend to be more dramatically prolonged than the aPTT (as compared to other processes such as DIC). Fibrinogen also decreases with severe liver disease and often becomes dysfunctional. Fibrinogen function may decrease over time as the fibrinogen becomes dysfunctional (even if the fibrinogen antigen levels do not) due to increased sialic acid residues, and this may, in turn, elevate the thrombin time (or decrease functional fibrinogen levels) [68]. To effectively distinguish

Table 2.8 Prolonged aPTT, prolonged PT, and prolonged TT

Cause	Comment
Severe liver disease	Can lead to significant bleeding potential with spontaneous bleeding
Disseminated intravascular coagulation	Can lead to significant bleeding potential with spontaneous bleeding; elevated D-dimer levels
Fibrinogen deficiency or dysfibrinogenemia	May result in significant bleeding potential
Anticoagulant therapy: direct thrombin inhibitor anticoagulant	May increase bleeding depending on plasma drug level
Thrombolytic therapy	May lead to significant bleeding potential with spontaneous bleeding; plasminogen is also typically decreased

liver disease from vitamin K deficiency or antagonism, factors V, VIII, and VII (or one of the other vitamin K-dependent factors) should be measured. With vitamin K deficiency, factors V and VIII will be normal and factor VII decreased, while with liver disease factors V and VII are decreased, while factor VIII is normal to elevated.

DIC may be difficult to distinguish from severe liver disease, particularly since these entities may occur together [69]. In contrast to liver disease, in DIC, fibrin degradation products and D-dimer levels tend to be more greatly elevated, both PT and aPTT are often both markedly elevated due to consumption of all factors, the platelet count is decreased to a greater degree, and signs of microangiopathic anemia may be seen on blood smear (e.g., schistocytes). Also, DIC is a more dynamic and unstable process, and thus coagulation screening tests, platelet count, and fibrin degradation products vary more over time in DIC as compared to liver disease. Fairly rapidly changing coagulation parameters over time is an important distinguishing laboratory feature.

Abnormalities of fibrinogen, either deficiency of or a dysfunctional fibrinogen protein, may lead to elevation of the aPTT, PT, and thrombin time. In patients with dysfibrinogenemia, all three screening assays are typically prolonged, while the thrombin time is the most sensitive of the three [52, 53, 69, 70]. A reptilase time, an assay similar to the thrombin time that measures the conversion of fibrinogen to fibrin, is also typically prolonged with dysfibrinogenemia [52]. A reptilase time may be used to differentiate prolongation of the thrombin time due to heparin from a fibrinogen abnormality, as the reptilase time is normal in the presence of heparin but elevated with a hypo- or dysfibrinogenemia. In dysfibrinogenemia there is a discrepancy between the concentration of fibrinogen measured by immunologic methods and its functional activity based on a clotting assay [52]. Typically with dysfibrinogenemia, fibrinogen antigen levels are normal, while fibrinogen functional activity is low, although multiple variations have been reported [69]. Congenital dysfibrinogenemia may be asymptomatic or may be associated with either a bleeding or thrombotic tendency. In those with a bleeding tendency, 11% report major bleeding and often present with bleeding following surgery or trauma. Postpartum hemorrhage is also a common presentation as is menorrhagia [71]. Patients may report easy bruising and prolonged bleeding with minor injuries. Spontaneous life-threatening bleeding is rare [71]. Acquired dysfibrinogenemia may also occur in association with cirrhosis of the liver and hepatocellular carcinoma [70].

Hypofibrinogenemia and afibrinogenemia can be hereditary or acquired and may lead to elevation of the aPTT, PT, and thrombin time. Afibrinogenemia is an autosomal recessive disorder with an incidence of 1–2 cases per million [1, 43]. Bleeding manifestations range from mild to severe, and bleeding associated with surgery or trauma is common. Most cases manifest in the neonatal period but can present at a later age. The major cause of death is intracranial hemorrhage. Another characteristic feature of afibrinogenemia is spontaneous splenic rupture [43]. In distinction, with hereditary hypofibrinogenemia, patients tend to bleed with provocation rather than suffer spontaneous bleeding, and fibrinogen levels are generally in the range of 100 mg/dL. Afibrinogenemia may also occur as an acquired condition in association with exposure to certain snake venoms, such as the Western diamondback rattlesnake [72, 73]. These patients present with greatly elevated aPTT and PT (possibly even "no clot detected") with immeasurable fibrinogen levels. Clinical bleeding in these cases is variable.

Normal PT, Prolonged aPTT, and Prolonged TT with Normal or Low Fibrinogen

This pattern of results suggests the presence of an anticoagulant including heparin or a DTI (see Table 2.9). Depending on the plasma concentration of DTI and reagent responsiveness, the PT may also elevate. As most PT reagents contain a heparin neutralizer, the PT tends not to elevate in the presence of heparin or heparin-like anticoagulants unless the anticoagulant present is so great in concentration that it overwhelms the heparin neutralizer in the PT reagent. Heparin contamination of blood samples is not uncommon when samples are collected through a port or indwelling catheter. In general, laboratory neutralization of heparin will correct the aPTT and thrombin time to normal range (in an otherwise normal specimen); however, larger concentrations of heparin may not be entirely neutralized by laboratory protocols, and thus the thrombin time or, less often, the aPTT may show residual elevation even after neutralization. Residual elevations of the aPTT and thrombin time following heparin

Table 2.9 Prolonged aPTT, normal PT, and prolonged TT with normal or low fibrinogen

Cause	Comment
Anticoagulant therapy: direct thrombin inhibitor anticoagulant (dabigatran)	The TT is exquisitely sensitive such that a normal TT can rule out significant dabigatran effect. May cause prolongation of the aPTT depending on drug concentration
Anticoagulant therapy: heparin or heparin contamination	Typically does not prolong the PT as PT reagents contain heparin neutralizers
Acquired heparin-like inhibitor (see Chapter xx)	A very rare acquired cause of bleeding, may occur with anaphylaxis or certain malignancies. Tends to prolong the aPTT as well, but not the PT as PT reagents contain heparin neutralizers. Anaphylaxis may also be associated with hyperfibrinogenolysis leading to reduced fibrinogen activity levels

neutralization may require investigation (preferably when the patient is off heparin therapy).

Heparin-like anticoagulants may develop rarely in association with certain malignancies and have been described following anaphylaxis induced by a wasp sting. See Chapter xx. This has been shown to elevate the thrombin time and greatly elevate the aPTT and may lead to measurable heparin levels in a chromogenic anti-Xa assay. Anaphylaxis is associated with mast cell activation and secretion of mediators, including heparin [74]. Secretion of tryptase from mast cells in anaphylaxis may lead to hyperfibrinogenolysis and decreased fibrinogen activity.

As mentioned in the previous section, clinically significant defects or deficiencies of fibrinogen will generally elevate the thrombin time, aPTT, and PT.

Factor XIII

Factor XIII (FXIII), also known as fibrin stabilizing factor, is necessary for the formation of a firm hemostatic plug. FXIII functions to stabilize the clot by cross-linking fibrin molecules and renders the clot resistant to fibrinolysis [75]. A deficiency of factor XIII can be hereditary or acquired. Hereditary deficiency, an autosomal condition, can be classified as severe (less than 2–5% FXIII), moderate (5–30%), and mild (30–60%). Severe factor FXIII deficiency has an estimated incidence of one in four million. Patients with severe deficiency may present with spontaneous major hemorrhage including hemarthrosis, subcutaneous hemorrhage, and intracranial bleeding, which is the leading cause of death. In women during their reproductive years, intraperitoneal bleeding may occur with ovulation. Bleeding may be delayed following surgery or trauma due to premature lysis of the hemostatic plug. Moderate deficiency may present with mild spontaneous bleeding or bleeding with provocation. Heterozygous factor XIII deficiency has an estimated frequency of 1 in 1000. Patients have plasma levels in the range of 30–60% and do not bleed spontaneously, but rather with provocation.

Acquired FXIII deficiency may reflect decreased synthesis, increased consumption, or inhibitor development [76, 77]. Consumption may occur with sepsis, trauma, or DIC and generally leads to levels in the range of 30–60%. Whether this enhances bleeding potential in these conditions must be proven. Inhibitor development is rare and can develop in deficient patients following replacement therapy but is more likely to develop de novo in association with another disease such as systemic lupus erythematosus or lymphoproliferative disorders or in response to certain medications (e.g., penicillin, ciprofloxacin, isoniazid, phenytoin). Bleeding with a FXIII inhibitor may be life-threatening and is difficult to treat. Morbidity associated with factor XIII inhibitors is high, even when treated. The presence of an inhibitor can be investigated by identifying low to undetectable FXIII activity levels and then performing FXIII activity mixing studies which demonstrate lack of correction with addition of normal plasma.

Deficiency of factor XIII does not affect the aPTT, PT, or thrombin time, which are each normal. A qualitative urea solubility test is often used to screen for FXIII deficiency, although this will only detect severe deficiency (<1–2%) and this test is no longer recommended. A quantitative FXIII activity assay is the recommended assay to evaluate functional factor XIII levels and to make a diagnosis of hereditary or acquired FXIII deficiency, though this assay may be of limited availability.

Quantitative D-Dimer

D-dimer is a terminal degradation product from the breakdown of fibrin. Unlike other fibrin degradation products, D-dimer is formed only after fibrin has been cross-linked by activated factor XIII and lysed by plasmin [78]. Quantitative D-dimer is most often used in the evaluation of venous thrombosis and DIC. There are many varied conditions, however, associated with an elevated D-dimer level [78, 79]. D-dimer will increase post-operatively and in normal pregnancy, as well as in a variety of pathologic states including venous thrombosis, DIC, consumptive coagulopathy associated with certain snakebites, visceral malignancies, and atherosclerotic vascular disease to name a few. Also, because fibrin degradation products are metabolized by the liver and secreted by the kidneys, both liver and kidney disease can affect D-dimer clearance and, hence, plasma levels. Thus, elevation of D-dimer is non-specific and must be viewed in context with other laboratory results and clinical history.

Because D-dimer represents the breakdown products of cross-linked fibrin clot, clinical conditions that cause breakdown of early fibrin formation or lysis of fibrinogen result in hypofibrinogenemia and elevated fibrin degradation products, but not elevated D-dimer levels. Examples include treatment with thrombolytic therapy and primary hyperfibrinogenolysis, as may occur with some prostate cancers [80].

The D-dimer assay is often performed in the bleeding patient, along with the clot-based coagulation screening assays, to determine the presence of in vivo clot formation and breakdown, particularly in a patient with suspected DIC. In DIC, the aPTT and PT are often prolonged, and the fibrinogen decreased, due to activation of coagulation and ongoing consumption. The platelet count is typically decreased and/or shows a decreasing trend over time. Both fibrin degradation products and D-dimer levels are elevated in the majority of cases due to fibrinolysis. Importantly, as DIC is a dynamic and unstable process, serial monitoring of

these parameters is often necessary to make the diagnosis, or to follow progression of response to treatment over time. Increasing PT, aPTT, and D-dimer levels with a decreasing platelet count are highly suggestive of DIC. In addition, the trends in PT, aPTT, and platelet count may help guide transfusion therapy in a bleeding patient or a patient undergoing an invasive procedure. DIC is discussed in more detail in Chapter 16, "Bleeding Associated with Disseminated Intravascular Coagulation."

Snakebite coagulopathies may closely mimic DIC. Snake venoms from *Agkistrodon* snakes, such as copperheads, contain thrombin-like enzymes and FX activators and lead to a venom-induced consumption coagulopathy associated with prolongation of the aPTT, PT, and thrombin time, decreased fibrinogen, and elevated D-dimer [81, 82].

Most typically, laboratories employ a latex agglutination method to quantitate D-dimer, as this type of assay provides relatively rapid and reliable results using automated instruments. The units and magnitude for D-dimer reporting are often an issue of confusion [78]. D-dimer can be reported in either D-dimer units (DU) or fibrinogen equivalent units (FEU), and there are approximately 2 FEU to 1 DU. Additionally, the magnitude for reporting may vary, with some using nanograms vs micrograms and milliliters vs liters [83]. It is advisable to pay particular attention to D-dimer units when evaluating published algorithms, or comparing results between laboratories.

Screening APTT, PT, and TT Result Combinations

(Note that reference intervals for these assays are typically validated such that approximately 2.5% of a normal healthy population will have results that fall just above reference interval.)

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Platelets

3

Kandice Kottke-Marchant

Clinical History for Patients with a Bleeding Diathesis

In the diagnostic approach to a patient for suspected platelet dysfunction, evaluation should start with a comprehensive medication and clinical history. Testing to exclude coagulation disorders, especially von Willebrand disease, is important, as the symptoms may be similar to platelet disorders. This should be followed by an assessment of platelet number and morphology, culminating with studies of platelet function.

A thorough clinical and family bleeding history should include an assessment of the duration (i.e., lifelong vs. acute), pattern, and severity of bleeding problems, including whether the bleeding is spontaneous or is associated with trauma or surgery [1, 2]. Bleeding assessment tools have been developed that may be helpful to assess whether the patient's clinical history is indicative of a bleeding disorder. The International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee Joint Working group (ISTH/SSC-BAT) has developed a tool to standardize the reporting of bleeding symptoms [2] which can be found at https://bleedingscore.certe.nl/ although this tool has not been specifically validated for platelet function disorders.

Microvascular bleeding is typical for platelet-mediated bleeding disorders, which may manifest as a mucocutaneous bleeding pattern. Common symptoms of platelet-mediated bleeding include ecchymosis, petechiae, purpura, epistaxis, and gingival bleeding. This pattern is in distinction to coagulation protein disorders, where deep tissue bleeding, such as hemarthroses and intra-cranial hemorrhage, is more common [3]. Vascular malformations may give a bleeding pattern similar to platelet disorders, but the pattern is often more focal than diffuse. Acquired purpuras, such as disseminated intravascular coagulation (DIC) or vasculitis, usually can be distinguished from platelet dysfunction [4], as platelet disorders typically cause "wet" purpura with bleeding from mucous membranes, while vascular purpura is usually confined to the skin.

Many drugs, as well as foods such as garlic or caffeine, can affect platelet function, so a complete drug and dietary history should be obtained [5]. It is important to remember that aspirin, an irreversible inhibitor of platelet function, is an ingredient of many over-the-counter and prescription medications, such as cold or flu remedies. Platelet dysfunction is a feature of many systemic disorders, such as renal disease, hepatic failure, connective tissue disorders, myeloproliferative or myelodysplastic disorders, malignancy, and cardiovascular disease. Additionally, specific clinical features, such as albinism, deafness, nephritis, and susceptibility to infections, may help in the diagnosis of the inherited platelet disorders [6].

Diagnostic Strategies for Platelet Function Disorders

Laboratory assessment for platelet function disorders should follow a thorough clinical history and exclude coagulation disorders and von Willebrand disease, through testing the prothrombin time (PT), activated partial thromboplastin time (APTT), and von Willebrand antigen and von Willebrand functional assays. The next steps in laboratory assessment of platelet testing progress from standard to specialized testing. They include platelet enumeration and morphologic assessment, screening platelet assays, and routine platelet function testing (typically aggregation), followed by specialized platelet function testing and/or genomic analysis.

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Platelet Count, Platelet Indices, and Morphology

A first step in the investigation of platelet disorders should be measurement of the platelet count, platelet indices, and review of peripheral smear morphology. This distinguishes thrombocytopenia, thrombocytosis, or normal platelet count. It also helps to exclude other pathologies such as leukemia, myeloproliferative neoplasms, myelodysplastic disorders, or microangiopathies, such as DIC or thrombotic thrombocytopenic purpura (TTP) [4].

Specimen Collection, Handling, and Processing

Blood specimens collected for platelet counting and morphology should be collected into EDTA (ethylenediaminetetraacetic acid) anticoagulant, typically a purple-capped vacutainer tube [7]. The specimen should be mixed thoroughly and gently after collection to prevent in vitro clotting. A specimen collected by venipuncture is ideal, but collection from indwelling catheters is acceptable, provided the flushing liquid is removed prior to sampling to avoid dilution. The platelet count is usually stable for up to 24 hours after collection, although mean platelet volume decreases after 3 hours. An air-dried Wright-stained smear can be made from the EDTA specimen for platelet morphologic analysis.

Test Performance and Interpretation

The platelet count and platelet size distribution are measured by automated hematology analyzers that perform complete blood counts (CBCs), usually by impedance measurement [8]. Some instruments use flow cytometry to count platelets labeled with fluorescent, platelet-specific antibodies; however the reagent cost for this method is prohibitively high for routine laboratory testing. This technique may improve the accuracy of the platelet count in patients with marked thrombocytopenia.

The platelet count is generally between 150,000 and 400,000/μL of blood in normal individuals. True thrombocytopenia must be distinguished from pseudothrombocytopenia or platelet binding to neutrophils (platelet satellitism). Pseudothrombocytopenia is a spurious in vitro platelet clumping not associated with disease, due to EDTA-dependent, cold-reacting platelet agglutinins that may be observed in patients with high immunoglobulin levels, anticardiolipin antibodies, glycoprotein IIb/IIIa (GPIIb/IIIa) antagonist drug abciximab, or infections [9]. They typically only bind platelets when calcium is chelated, such as with EDTA. In the setting of pseudothrombocytopenia, a more accurate platelet count can be established by collecting the blood specimen in either citrate or heparin anticoagulants or by collecting blood directly from a finger stick into a diluent. Giant platelets observed with macrothrombocytopenia syndromes also can give falsely low platelet counts, as the large platelets may be counted as leukocytes by automated cell counters.

In addition to platelet count, automated cell counters measure indices of platelet size and size distribution as well as immature platelet fraction (IPF) [10]. The mean platelet volume (MPV) is an indication of platelet size, with normal MPV ranges 7 to 11 fL. The platelet distribution width (PDW) is a measure of the dispersion of platelet sizes. True congenital macrothrombocytopenias usually have uniformly large platelets, with a very high MPV and normal PDW; often the platelets are at least twice normal size and may be as large as erythrocytes [11]. The MPV and PDW can detect increased platelet turnover, where MPV will be increased due to the larger size of newly produced platelets, and PDW will be increased due to a mixture of large and small platelets [12, 13]. The IPF, a measure of reticulated platelets, is typically elevated in destructive thrombocytopenias, such as immune thrombocytopenic purpura (ITP), as mRNA levels are high in newly formed platelets and decline progressively during blood circulation time [14].

Platelet morphologic analysis should accompany evaluation of the platelet count, especially if there is thrombocytopenia. It is best to assess platelet morphology in the thin part of the smear where the erythrocytes have good morphology and are present in a thin monolayer, keeping in mind that the feathered edge or the lateral sides of the smear should be scanned for platelet clumps. On a properly prepared, Wright-stained blood smear, the platelets are approximately 2 μm in diameter, with abundant purple-staining granules (Fig. 3.1)

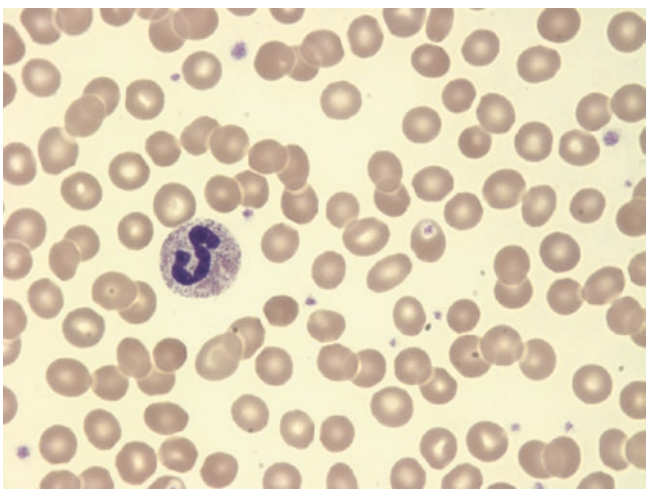


Fig. 3.1 Platelet morphology. A Wright-stained peripheral smear shows platelet as small (2 to 3 μm) diameter non-nucleated cells with a purple granular cytoplasm, reflective of the many alpha granules. (Original magnification X100)

[15]. Large platelets, dumbbell-shaped platelets, and megakaryocyte fragments are unusual. The presence of more than a few large platelets suggests increased platelet turnover, myeloproliferative neoplasm, or a congenital macrothrombocytopenia. Some platelet disorders are associated with unique platelet and/or leukocyte morphology. Giant platelets are seen in Bernard-Soulier syndrome; other macrothrombocytopenia syndromes associated with myosin heavy chain gene defects (*MYH9*) additionally may have Dohle body-like neutrophil inclusions [6, 11]. In patients with Wiskott-Aldrich syndrome, the platelets may be small. Platelets in the gray platelet syndrome, an alpha granule deficit, are characteristic for being pale, gray, and hypogranular.

Platelet Function Testing

Platelet function testing is used to detect or characterize a qualitative platelet disorder, such as a hereditary or acquired platelet dysfunction [16, 17]. Platelet function testing also has been utilized to assess and monitor the therapeutic effect of antiplatelet drugs, such as aspirin and thienopyridines, but the clinical utility of such testing is debated [18]. Caution must be exercised in interpreting platelet function testing in thrombocytopenic patients, as abnormal results are often observed due to the low platelet count; distinction of an abnormal result due to intrinsic platelet dysfunction versus thrombocytopenia alone may not be possible [11, 16].

Platelet function test types can be categorized as (1) screening, (2) routine (typically aggregation), and (3) specialized testing. Within each category, the platelet functions measured variously include adhesion, aggregation, activation, and granule release. Screening platelet tests measure global platelet function, often in whole blood, and are widely available in clinical laboratories. Platelet aggregation is the most commonly used routine platelet function test and is available in dedicated hemostasis laboratories. Specialized platelet testing includes more targeted assays for detailed diagnosis and is typically only available in reference laboratories.

Screening Assays

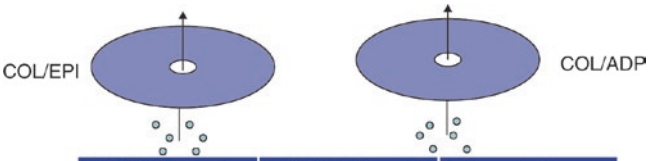
The bleeding time was the original platelet screening assay that was developed by Duke in 1910 [19]. It is fraught with variability and poor correlation with bleeding risk, and its use has largely been eliminated [20]. Whole blood platelet function assays have been developed as screening assays for platelet function that utilize small standalone devices and can be used in laboratories that otherwise could not perform platelet function studies; some can be utilized in the near-patient setting [21]; however, the recent ISTH guidance recommends proceeding directly to platelet aggregation instead of using a platelet screening assay [16]. Indeed, many of these devices are in the early stages of clinical implementation or are targeted toward monitoring of antiplatelet drugs and will not be further discussed in this chapter. These devices include the VerifyNow™ System (Accriva Diagnostics, San Diego, California) and the Plateletworks™ (Helena Laboratories, Beaumont, Texas). Thromboelastometry measures a combination of coagulation, platelet function, and fibrinolysis and is covered in Chap. 6, "Whole Blood Assay: Thromboelastometry – Basics," and Chap. 7, "Whole Blood Assay: Thromboelastometry – Bleeding Management Algorithms."

PFA-100

The PFA-100 System (Siemens Healthcare Diagnostics Inc., Tarrytown, New York) is a device that measures both platelet adhesion and aggregation in whole blood, using a high-shear testing system (Fig. 3.2) [22].

Specimen Considerations

The PFA-100 utilizes a whole blood specimen, ideally from a peripheral venipuncture, collected into a light blue top vacutainer tube containing 3.2% buffered trisodium citrate [23]. It is recommended that each laboratory establish its own reference range using blood specimens from normal indi-



COL/EPI Result	COL/ADP Result	Interpretation
NORMAL	NORMAL	NORMAL
Abnormal	NORMAL	Aspirin Effect
Abnormal	Abnormal	Platelet dysfunction, Low platelets, von Willebrand disease
NORMAL	Abnormal	Platelet dysfunction, Low platelets, von Willebrand disease

Fig. 3.2 Platelet function analyzer-100 (PFA-100). The PFA-100 measures platelet function under high shear with occlusion of an aperture by a platelet aggregate. It uses two cartridges, one with epinephrine (EPI) and collagen and the other with adenosine diphosphate (ADP) and collagen. Most patients with platelet dysfunction will have a prolonged closure time with both cartridges. However, an aspirin-like drug effect will specifically prolong the collagen/EPI closure time with a normal collagen/ADP closure time

viduals. Specimens should be kept at room temperature and transported to the laboratory, with testing completed within 4 hours of phlebotomy. Guidelines for performing PFA-100 testing have been developed by the Clinical and Laboratory Standards Institute (CLSI) and are included in the guideline for platelet function testing by aggregometry (H58-A) [24].

Test Performance and Interpretation

The disposable cartridges contain a membrane with a 147 μm diameter central aperture coated with aggregation agonists (collagen/epinephrine [EPI] or collagen/adenosine diphosphate [ADP]). A blood sample of 800–900 μL is pipetted into a sample cup. The blood is drawn out of the cup and passed through the aperture at a high shear rate (5000 to 6000 sec^{-1}), where the platelets adhere to the membrane, aggregate, and cause aperture occlusion. When the blood flow ceases, the instrument measures the "closure time," which is a reflection of platelet function.

A normal closure time indicates normal platelet function, while a shortened closure time can be seen with an elevated platelet count or increased platelet function [23, 25]. Prolonged closure times can be seen with intrinsic platelet dysfunction as well as anti-platelet drugs and von Willebrand disease; closure times may also be prolonged with thrombocytopenia or anemia (<150,000 platelets/μL or hematocrit <35%) [25, 26]. Closure times are not affected by heparin or deficiencies of coagulation factors other than fibrinogen [26]. Due to the limitations of the blood volume in the sample cup, the instrument can only measure closure times up to 300 seconds. Beyond that, the closure time is reported as >300 seconds. Duplicate testing is only recommended when the initial result shows a prolonged closure time.

Good quality control must be maintained on the instrument, including daily electronic checks and vacuum checks, as well as validation of each new cartridge lot with a fresh normal sample. External quality assurance (i.e., proficiency testing) for the PFA-100 is available; this challenge utilizes normal donor blood drawn on site into distributed specially formulated sample collection tubes [27].

The collagen/EPI cartridge is the primary screening cartridge; it detects platelet dysfunction induced by intrinsic platelet defects, von Willebrand disease, or platelet-inhibiting agents [23]. Aspirin-like drugs give a prolonged closure time with the collagen/EPI cartridge and a normal closure time with the collagen/ADP cartridge due to a high ADP concentration in the cartridge. See Fig. 3.2 for a PFA-100 interpretation algorithm. Von Willebrand disease, intrinsic platelet dysfunction, and non-aspirin drugs characteristically give an abnormal closure time with both cartridges. The PFA-100 may not be sensitive to all types of von Willebrand disease and platelet dysfunction. For example, in type 2N von Willebrand disease with decrease of only factor VIII, the PFA-100 will give normal results. Additionally, the PFA-100 may not detect platelet storage pool disorders in some patients or some macrothrombocytopenia disorders.

Routine Platelet Function Testing (Platelet Aggregation)

Platelet aggregation measures the ability of agonists to cause in vitro platelet activation and platelet-platelet binding [28]. As such, platelet aggregation is often useful to distinguish intrinsic platelet disorders involving surface glycoproteins, signal transduction, and platelet granules [16, 17].

A survey of platelet function testing techniques among North American Specialized Coagulation Laboratory Association (NASCOLA) member laboratories revealed that there was a wide variety in practice in the performance of platelet aggregation testing [29]. Subsequent standardization efforts [30, 31] have led to guidelines for performing platelet aggregation testing developed by CLSI (H58A) and the ISTH [24, 32].

Light Transmission Aggregation (LTA)

Light transmission aggregation studies are performed using a suspension of platelets in plasma, termed platelet-rich plasma (PRP), to allow optical detection of aggregation (turbidimetry).

Specimen Considerations

Ideally, blood should be obtained by peripheral venipuncture from a resting subject who refrains from smoking and caffeine intake. A record of all drugs the patient has taken in the week prior to testing should be collected, in order to assess potential drug effect [32]. If clinically feasible, drugs with known anti-platelet effects should be stopped prior to testing.

Blood for platelet aggregation studies should be drawn into an anticoagulant solution of buffered 3.2% sodium citrate, preferably with minimal or no tourniquet.

The whole blood specimen should be kept at room temperature and transported to the laboratory expeditiously. Samples should be allowed to rest at room temperature prior to centrifugation [32] with testing completed within 4 hours of phlebotomy [24, 32]. The first step in sample processing requires the production of PRP by differential centrifugation of erythrocytes and leukocytes, at a slow speed, typically 200xg, resulting in a top suspension of platelets and plasma.

Prior to testing, the platelet count in the PRP has often been normalized to 200,000 to 250,000/μL by mixing appropriate ratios of PRP and platelet poor plasma, although the recent ISTH guideline does not recommend adjusting the PRP platelet count, as the practice may impair platelet responsiveness to agonists [32]. With optical aggregation

methodologies, PRP platelet counts <150,000/μL may provide insufficiently turbid samples to provide reliable results. For such samples where the functional evaluation of patients with thrombocytopenia is desired, it may be helpful to adjust the platelet count of a normal sample to a similar low platelet count as a normal "thrombocytopenic" control [10]. The optical aggregation assay may suffer from interference from hemolyzed, lipemic, and icteric plasma.

Test Performance and Interpretation

In the optical turbidimetric platelet aggregation assay, platelet aggregation is measured spectrophotometrically by the increase in light transmission after addition of an aggregation agonist in a stirred platelet sample [16, 17, 24, 30, 32]. Agonists typically include ADP (2 μM ISTH and 5 μM CLSI), epinephrine (5 μM), collagen (2 μg/mL), and arachidonic acid (1 mM) to interrogate prostaglandin pathways/aspirin effect (Fig. 3.3). Other agonists may include thrombin receptor (PAR1)-activating peptide (PAR1-AP) or ristocetin low dose, ≤0.6 mg/mL, and ristocetin high dose, 0.8 to 1.5 mg/mL. For optical aggregation, the adequacy of the aggregation response is followed by quantifying the maximal percentage of aggregation. Other evaluation parameters may include presence of shape change, length of lag phase, the slope of the aggregation curve, or percent disaggregation [32].

With use of a subthreshold concentration of agonist, there is typically a primary wave of aggregation, with subsequent disaggregation due to lack of granule release. Optimal platelet aggregation shows a biphasic pattern for the agonists ADP and epinephrine; the initial increase in aggregation is due to primary aggregation in response to activation of the glycoprotein IIb/IIIa platelet membrane receptor, while the second wave of aggregation is the result of platelet degranulation with recruitment of additional platelet aggregates. Lack of a secondary wave suggests a platelet storage pool disorder caused either by reduced numbers of granules or defective release. Other agonists, such as arachidonic acid, thrombin receptor agonists, and collagen, usually show only a single wave of aggregation. Collagen characteristically shows an initial shape change prior to the wave of aggregation. Normal aggregation characteristically results in greater than 70% or 80% aggregation, but all laboratories should establish their own reference ranges for each agonist and agonist concentration.

Ristocetin, an agglutinating agent that facilitates the binding of vWF to the glycoprotein Ib/IX/V complex, is used to study platelet agglutination through GPIb. A normal ristocetin-induced platelet aggregation (RIPA) result requires the presence of both functional vWF *and* normal GPIb/IX/V, so RIPA can detect both von Willebrand disease and some platelet dysfunctions, such as Bernard-Soulier syndrome (Fig. 3.4).

Whole Blood Aggregometry

Platelet aggregometry studies can also be performed in whole blood by an impedance technique [33]. Agonists

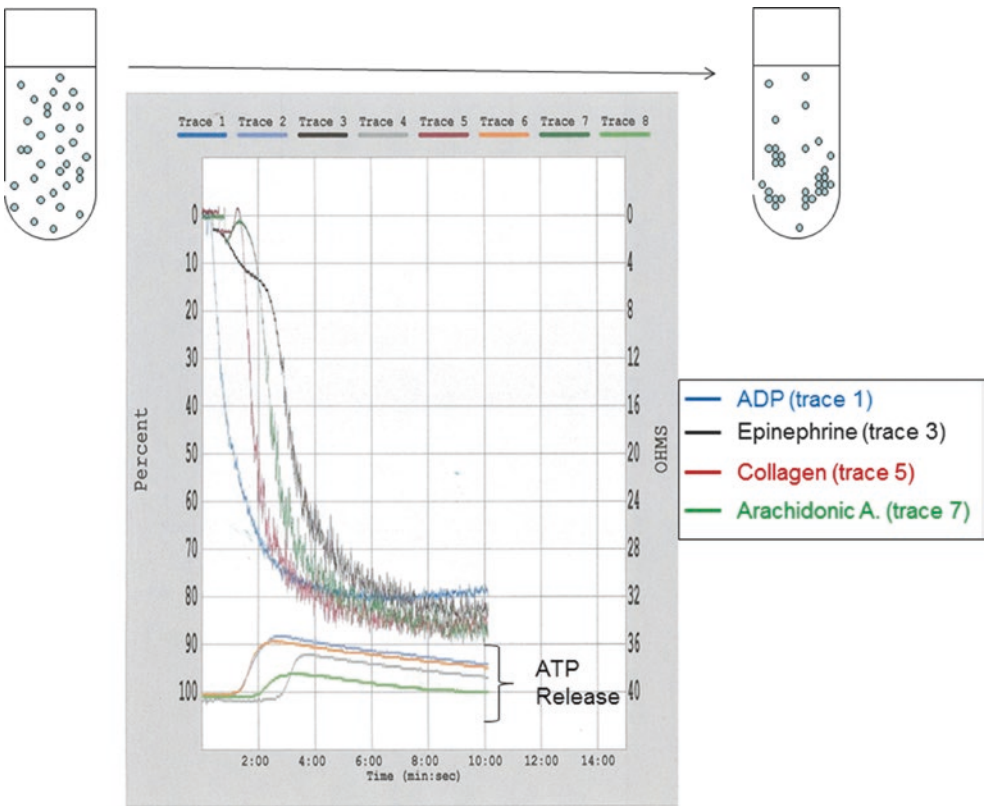


Fig. 3.3 Normal platelet aggregation. The diagram at the top of the figure shows platelet aggregation cuvettes before (turbid) and after aggregation (clear with platelet clumps). Platelet aggregation with 5 μM ADP (blue), 100 μM epinephrine (black), 2 mg/mL collagen (red), and 0.5 mg/mL arachidonic acid (green). ADP shows two waves of aggregation. Collagen aggregation characteristically shows an initial shape change (arrow). Normal aggregation for all agonists is typically >70% aggregation, but laboratories should establish their own in-house reference ranges. The tracings at the bottom show dense granule release of ATP by a luciferin/luciferase technique. (Optical platelet aggregation using a Chronolog aggregometer)

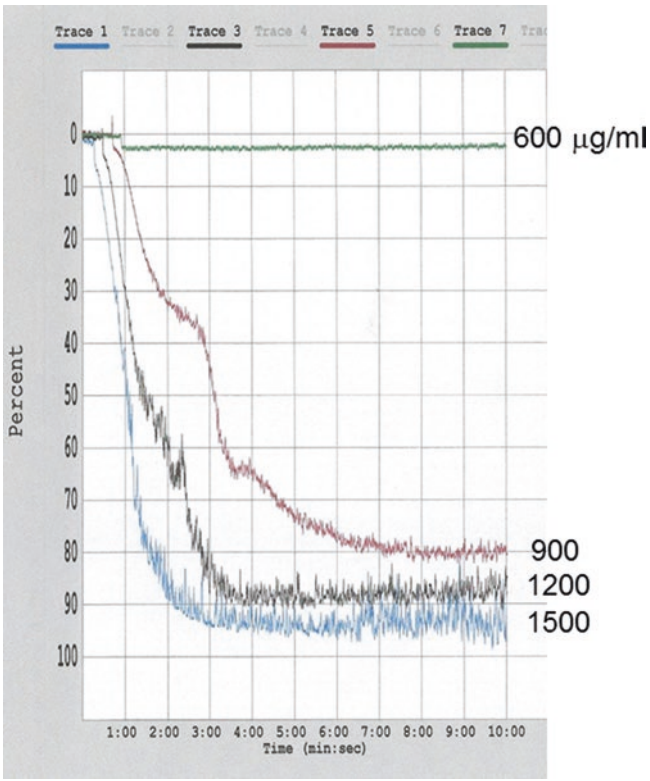


Fig. 3.4 Platelet aggregation with ristocetin. Ristocetin stimulates a conformational change in von Willebrand factor, leading to aggregation through the glycoprotein Ib/IX/V complex. Note that aggregation is virtually absent at low ristocetin concentration (600 µg/mL), becoming progressively stronger until complete aggregation is reached somewhere between 900 and 1500 µg/mL. (Optical platelet aggregation using a Chronolog aggregometer)

tested include those used in LTA, with the exception of epinephrine, since response is only seen in roughly half of patients. The extent of aggregation is determined by submerging an electrode probe assembly in blood. Impedance between two wires in the probe changes as platelets aggregate on their surfaces. Results are typically reported by maximum response with each agonist, measured in ohms. Whole blood aggregation has less specimen handling required and is performed in a more physiologic milieu than optical aggregation, with inclusion of erythrocytes and leukocytes.

Specialized Platelet Function Assays

Platelet Release Studies

Studies of granule release may be helpful to discern alpha and dense granule storage pool disorders from platelet release disorders. Platelet dense granule release can be measured by a lumiaggregation technique, whereby a luciferin-luciferase enzyme reagent that is extracted from fireflies measures dense granule ATP release during aggregation, resulting in luminescence (Fig. 3.3) [34]. Alpha granule release can be measured by the platelet-specific proteins platelet factor 4 (PF4), β-thromboglobulin (βTG), and P-selectin, but these have not been widely used clinically due to stringent sample collection and processing requirements.

Thromboxane Metabolites

Thromboxane A_2 (TXA_2) is synthesized from arachidonic acid by cyclooxygenase (COX)-1 and thromboxane synthase during platelet activation. While TXA_2 has a short half-life, stable metabolites are formed, including TBX_2 in blood and 11-dehydro-TXB_2, which is excreted in urine. Levels of these metabolites serve as an indication of COX pathway activity and may be useful in monitoring response to inhibitors of this pathway, such as aspirin.

Adhesion Assays

Many specialized experimental devices for studying platelet adhesion have been developed, but these are used largely in the research setting. A device in development is the Impact, a modified cone and plate viscometer [35]. The apparatus induces laminar flow to the sample with uniform shear stress (1800 sec^{-1}) between a disposable coverslip and a rotating polystyrene cone and measures shear-induced platelet adhesion and aggregation.

Flow Cytometry

Flow cytometry has been utilized to study platelet structure and function and is available in specialized centers [36, 37]. Flow cytometric analysis is based on the detection of cell surface proteins by laser light scatter and fluorescently labeled antibodies. With this technique, the expression of a panel of proteins can be analyzed for each platelet individually, as it flows past a laser detector in a laminar stream. Benefits of platelet flow cytometry include the ability to detect the activation state of circulating platelets, to study the reactivity of platelets to specific agonists, and to study platelet function in a very small sample with a relatively low platelet count.

Platelet flow cytometry can be used to detect the presence of typical platelet surface glycoproteins as well as decreased expression or deficiency of these glycoproteins. An ISTH-recommended panel is to test surface markers in resting platelets with antibodies against GPIIb/IIIa (CD41), GPIIIa (CD61), GPIb (CD42b), and GPIb/IX (CD42a) and on activated platelets using an antibody against a GPIIb/

IIIa activation epitope (PAC-1) [16]. Platelet flow cytometry has been used to detect the absence of GPIIb/IIIa receptors in patients with Glanzmann thrombasthenia and has been used to study deficiencies of glycoproteins Ia, Ib, IIb, IV, and IX [11, 16, 36, 37]. Platelet activation leads to a conformational change in some surface receptors, and with the use of appropriate antibodies, the percentage of activated platelets in a specimen can be determined. Measurement of platelet activation by flow cytometry has been utilized to diagnose alpha and dense granule storage pool disorders and release/signaling disorders, where measurement of activation-dependent markers, such as mepacrine and P-selectin, are measured before and after addition of a platelet agonist, such as PAR1-AP or ADP [38]. Further expanded platelet flow cytometry can be used to evaluate the glycoproteins GPIa/IIa (CD31 and CD49b), GPIV (CD36), and GPVI and to assess platelet procoagulant activity using annexin V binding to distinguish enhanced (Stormorken syndrome) or decreased (Scott syndrome) procoagulant activity [16].

Platelet Turnover (Platelet Reticulocyte Analysis)

Platelets with increased RNA content (reticulated platelets) can be measured by flow cytometry using dyes that bind to RNA and DNA, such as thiazole orange, auramine O, and coriphosphine [14]. Reticulated platelet analysis has been studied as a diagnostic tool to evaluate whether thrombocytopenia is due to increased platelet destruction or decreased platelet production, as platelets newly released from bone marrow have increased RNA content. It is now incorporated in the immature platelet fraction (IPF) on hematology analyzers, as discussed in the platelet enumeration section, where a nucleic acid-specific fluorescent dye is detected in platelets [39]. The IPF has been shown to be useful in the diagnosis of peripheral platelet consumption and as a guide to transfusion after hematopoietic stem cell transplantation [40].

Electron Microscopy

Electron microscopy (EM) may be utilized for the ultrastructural evaluation of platelets. Wholemount EM techniques have been developed for assessing storage pool disorders, while thin section EM is utilized for assessing ultrastructural morphology [41]. In patients with suspected dense granule storage pool disorders, wholemount EM shows a decrease or absence of the organelles (cytoplasmic dense bodies) storing adenine nucleotides, serotonin, and calcium.

Platelet Genetic Testing

Many platelet disorders have overlapping clinical and laboratory findings. Often, current functional assays are not able to yield a firm diagnosis. This is often the case with thrombocytopenia disorders, where patients with hereditary thrombocytopenia may be misdiagnosed as ITP by conventional laboratory testing [42, 43]. The low specificity of platelet function assays, together with establishment of the genetic basis of many inherited platelet disorders, has made genetic testing more feasible to identify inherited platelet disorders [42–44]. The increasing availability of next-generation sequencing has meant that genetic testing for diagnosis of platelet disorders is becoming available at some reference laboratories. Targeted mutation analysis and sequencing may help diagnose inherited platelet disorders, such as *ANO6* (Scott syndrome); *HPS1 to HPS6* (Hermansky-Pudlak syndrome); *FL1* (Paris-Trousseau thrombocytopenia); *GATA1* (GATA-related cytopenia); *GP1BA*, *GP1BB*, and *GP9* (Bernard-Soulier syndrome); *ITGA2B* and *ITGB3* (Glanzmann thrombasthenia); *LYST* (Chediak-Higashi syndrome); *MPL* (congenital amegakaryocytic thrombocytopenia); *NBEAL2* (gray platelet syndrome); and *WAS* (Wiskott-Aldrich syndrome, X-linked thrombocytopenia), among others [42–44]. Some disorders, such as the Quebec platelet disorder, due to a duplication of the PLAU gene, cannot be detected by sequencing and require high-density array analysis (array CGH) for detection.

Summary

Laboratory testing for platelet function is more complex than plasma-based assays for coagulation proteins because of the cellular nature of platelets. Platelet testing has traditionally included platelet enumeration and morphology with platelet aggregation. Increasingly, use of specialized testing such as flow cytometry and genomic analysis may be able to offer clinical promise for specific diagnosis of more platelet disorders.

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Von Willebrand Disease Laboratory Workup

4

Shiu-Ki Rocky Hui

Bleeding Time and Platelet Function Analysis

Bleeding time in the past has been the standard screening test for von Willebrand disease (VWD) among other bleeding disorders. However, the ability of bleeding time to distinguish patients with VWD from individuals with other bleeding disorders was poor with a sensitivity of only around 65% [1]. Bleeding time was then replaced with a laboratory-based assay, the platelet function assay (PFA) using PFA-100™ [2] and more recently PFA-200™. PFA showed superior sensitivity in distinguishing VWD patients from non-diseased individuals at 95% [3]. However, subsequent studies demonstrated that the sensitivity can be as low as 62% in distinguishing VWD from other bleeding disorders [4]. Therefore, neither PFA nor bleeding time has been validated as an effective screening test for VWD, but PFA may be a quick and useful assay in monitoring treatment response [5, 6].

Basic Coagulation Workup

Initial workup for VWD should begin with prothrombin time (PT), activated partial thromboplastin time (PTT), fibrinogen, and platelet count. These laboratory tests can rule out not only other bleeding causes and disorders but also provide useful information in diagnosing VWD. An isolated prolonged PTT with normal PT may be indicative of low factor VIII (FVIII) secondary to decreased von Willebrand factor (VWF) antigen (VWF:Ag) as in Type 1 and Type 3 VWD or defect in FVIII carrier function as in Type 2N VWD. An unexplained mild thrombocytopenia may be suggestive of Type 2B [7] or platelet-type VWD [8].

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Von Willebrand Factor Panel

Once the clinical suspicion for VWD is high, VWF laboratory workup should include VWF antigen, VWF activity (VWF:Act), FVIII activity, and a calculated VWF activity to antigen ratio (VWF:Act/Ag). It is important that the VWF panel should include all three tests as any incomplete panel can result in missed or misdiagnosis of VWD. The pattern of these initial VWF specific tests can help guide the subsequent workup toward diagnosis of specific subtype of VWD.

FVIII Activity

FVIII activity level is directly affected by the level of VWF:Ag and VWF ability to function as a carrier protein for FVIII. A low FVIII without decrease in VWF:Ag or VWF:Act may suggest Type 2N VWD. On the other hand, an increase in FVIII with normal VWF:Ag may suggest an underlying Type 1 VWD where baseline VWF:Ag is increased temporarily during acute phase reaction [9].

VWF Antigen

VWF antigen level is commonly measured by either enzyme-linked immunosorbent assay (ELISA) or latex immunoassay (LIA) method [10]. VWF:Ag is a measurement of the amount of VWF regardless of its function. A low VWF:Ag is indicative of a quantitative VWD.

VWF Activity

VWF:Act is the assessment of VWF ability to bind to platelet VWF receptor, glycoprotein Ib-V-IX complex (GPIb). Under physiological condition, this interaction requires significant shear force; however, in vitro testing the binding of VWF to platelet GPIb receptor can be triggered by addition

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of ristocetin [11]. The most common methodology is the ristocetin cofactor activity (VWF:RCo) assays where ristocetin induces VWF conformation change that facilitates the binding of VWF to platelet GPIb [12]. A platelet-free alternative has been introduced [13] and are referred to as ristocetin-triggered GPIb binding (VWF:GPIb) assays [14]. VWF:GPIb assays had shown excellent correlation with the traditional platelet-based VWF:RCo methods [15, 16]. Although there are ristocetin-independent methods to determine VWF:Act [17], VWF:RCo remains the gold standard for VWD diagnosis at this time [18]; however, more recent studies have demonstrated serious shortcomings and the potential benefits of ristocetin-independent methodology [19, 20]. Ristocetin-independent assays will be discussed later in this chapter. Of note, the coefficient of variation of VWF:RCo assay worsens as VWF:Ag decreases. It means a low VWF:Act/Ag when VWF:Ag is below 30% does not necessarily indicate Type 2 VWD [21, 22].

VWF Activity to Antigen Ratio

VWF activity to antigen ratio (VWF:Act/Ag) is calculated using the two measured VWF:Ag and VWF:RCo values. A ratio <0.5–0.7 is suggestive of Type 2 VWD with coagulation function abnormalities [23] and a normal ratio of >0.5–0.7 is expected for Type 1 VWD and Type 2N VWD. A normal ratio is also expected from individual with "low VWF level."

VWF Multimer Analysis

VWF multimer analysis (VWF:MA) is the gold standard in determination of VWF multimer distribution [24]. It is performed by electrophoresis utilizing SDS-agarose gel. VWF:MA is traditionally reported as a qualitative assay; however, newer generation VWF:MA performed via densitometry can provide a quantitative measurement of VWF multimer distribution [25, 26]. As shown in Fig. 4.1, absence of high or intermediate molecular weight multimer is indicative of Type 2A, Type 2B, platelet type, or acquired von Willebrand syndrome (AVWS). On the other hand, in Type 1 VWD, the intensity of VWF:MA is decreased, but multimer distribution should remain normal. In Type 3 VWD, which is absence of VWF, multimers are not visible.

Collagen-Binding Assay

Collagen-binding (VWF:CB) assay is used to determine the ability of VWF to bind to collagen. VWF:CB varies greatly depending on the type of collagen used in the specific assay

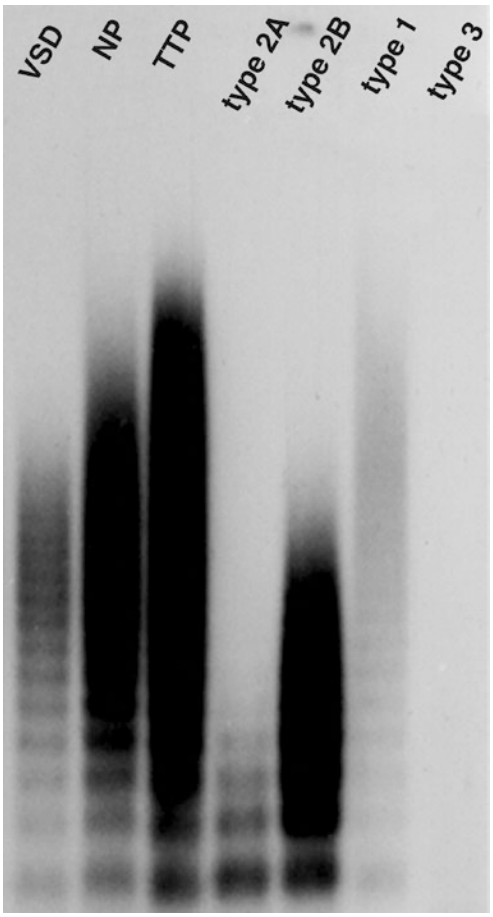

Fig. 4.1 Shows the various expected multimer analysis results of different VWD subtypes. *VSD* valvular stenotic disease, *TTP* thrombotic thrombocytopenic purpura

[27–29]. Therefore, unlike VWF:RCo, VWF:CB assay is not a standardized assay and should not be used in place of VWF:RCo for VWD diagnosis [30]. However, VWF:CB assay can be used as a supplemental test for multimer abnormalities as high molecular multimers demonstrate a higher collagen-binding affinity and increase VWF:CB [31]. Therefore, VWF:CB assay is sometimes used as a screening test for VWF:MA. Importantly, VWF:CB assay cannot detect all VWF collagen-binding abnormalities as the collagen type used for the assay is different from those in the subendothelial collagen [32].

Factor VIII Binding Assay

FVIII binding (VWF:VIIIB) assay is an ELISA test to determine patient's VWF ability to bind to extraneous FVIII [33]. VWF:VIIIB is decreased in Type 2N VWD, but it will remain normal in both hemophilia A and other VWD subtypes, including Type 1, Type 2A, Type 2B, and Type 2M VWD. Therefore, VWF:FVIIIB assay is an important and necessary laboratory workup in distinguishing hemophilia A

from Type 2N VWD. One should not forget that there are rare patients who have both hemophilia A and Type 1 VWD.

Ristocetin-Induced Platelet Aggregation

Ristocetin-induced platelet aggregation (RIPA) is used to detect potential increase interaction between patient's VWF and platelet GPIb in the presence of low-dose ristocetin. As discussed previously, ristocetin serves as a segregate for shear force. A low ristocetin concentration in non-diseased individuals will not result in platelet aggregation. However, if there is a gain-of-function mutation in either VWF or GPIb, platelet aggregation can be induced by low-dose ristocetin. A positive RIPA is indicative of Type 2B VWD or platelet Type VWD [34]. However, RIPA cannot distinguish between the two disorders, as both platelets and VWF are native from patient [35].

2B Binding Assay

2B binding assay (2B:BA) is used to detect increased binding of patient's VWF to extraneous platelets in the presence of low-dose ristocetin, and detection is via radioactively tagged anti-VWF antibodies [36]. As native platelets are not used in this assay, increase binding is only seen in Type 2B VWD and not in platelet type VWD. Therefore, 2B:BA can be considered as the confirmatory test for Type 2B VWD [37].

VWF Propeptide to Antigen Ratio

VWF propeptide to antigen ratio (VWF:pp/Ag) is to determine the clearance rate of VWF [38]. As discussed in Chapter 9, VWF propeptide dimer (VWF:pp) is packaged and released from Weibel–Palade body along with matured VWF at the time of endothelial cell activation. An increase in VWF:pp/Ag is indicative of increased clearance of mature VWF. Increased VWF:pp/Ag is seen in Type 2A VWD where there is an increased proteolysis by ADAMTS13. It is also reported in some AVWS. However, an increased VWF:pp/Ag is especially important when detected in Type 1 VWD as it is noted in Type 1C (also known as Vicenza variants) [39]. In these variants, the increased clearance makes desmopressin an ineffective treatment [40].

Ristocetin-Independent VWF Activity Assays

As discussed in previous section, VWF:RCo assay suffered from two major disadvantages (1). High coefficient of variation [41] especially when VWF:Act is moderately decreased and (2). Decreased in ristocetin binding to VWF due to genetic polymorphism which is especially common among African American [42, 43]. These two factors can result in artifactual decrease in VWF:RCo/VWF:Ag ratio and potential misdiagnosis of VWD. Due to these limitations, ristocetin-independent assays provide attractive alternatives. The two major Ristocetin-independent methodologies are the gain-of-function mutant GPIb binding (VWF:GPIbM) and the monoclonal antibody binding-based VWF activity (VWF:GPIbR) assays. Both assays have been steadily gaining supports among laboratorians and clinicians and may one day replace VWF:RCo as the gold standard for VWF:Act [14].

Molecular Analysis

As the knowledge of the various domains in the VWF molecule has increased, the ability to predict VWD phenotype based on mutation of the VWF gene also improved [44] (Fig. 4.2). Currently, the cost of a complete VWF gene analysis remains too high for wide availability. Exon 28 analysis remains the more common and cost-effective genetic study for VWD, especially in confirmation of Type 2B and 2M VWD [45]. However, exon 28 analysis alone cannot detect all diseases causing mutations as Type 2N, and some Type 2A mutations extend beyond the exon 28 [46]. Genetic study for diagnosis of Type 1 VWD remains impractical for clinical use due to high frequency of sequence variants within the VWF gene [47]. In its current state, molecular analysis should be used only as a confirmatory test for a specific VWD subtype and use of genetic analysis as a "first-line" workup is not recommended.

Algorithmic Approach of VWD Laboratory Workup

Since laboratory workup for VWD can be very complex, an algorithmic approach provides a step-wise and cost-effective method to arrive at the correct diagnosis. Workup for VWD diagnosis should begin with a basic VWF panel which should include FVIII, VWF:Ag, VWF:Act, and VWF:Act/Ag. Based on this initial panel results, the quantitative vs. qualitative VWD can be separated. If VWF:Ag and/or VWF:Act is <30% with a normal VWF:Act/Ag of >0.5–0.7, a quantitative disorder such as Type 1 or Type 3 VWD is likely (Fig. 4.3). Type 1 vs. 3 can be further determined by the severity of VWF:Ag deficiency. Type 1 VWD diagnosis should be followed by VWF:pp/Ag for consideration of Type 1C/Type 1 Vicenza VWD.

If the only abnormality in the initial VWF panel is a decreased FVIII, Type 2N VWD vs. hemophilia A should be considered. A follow-up VWF:VIIIB can differentiate the two diseases.

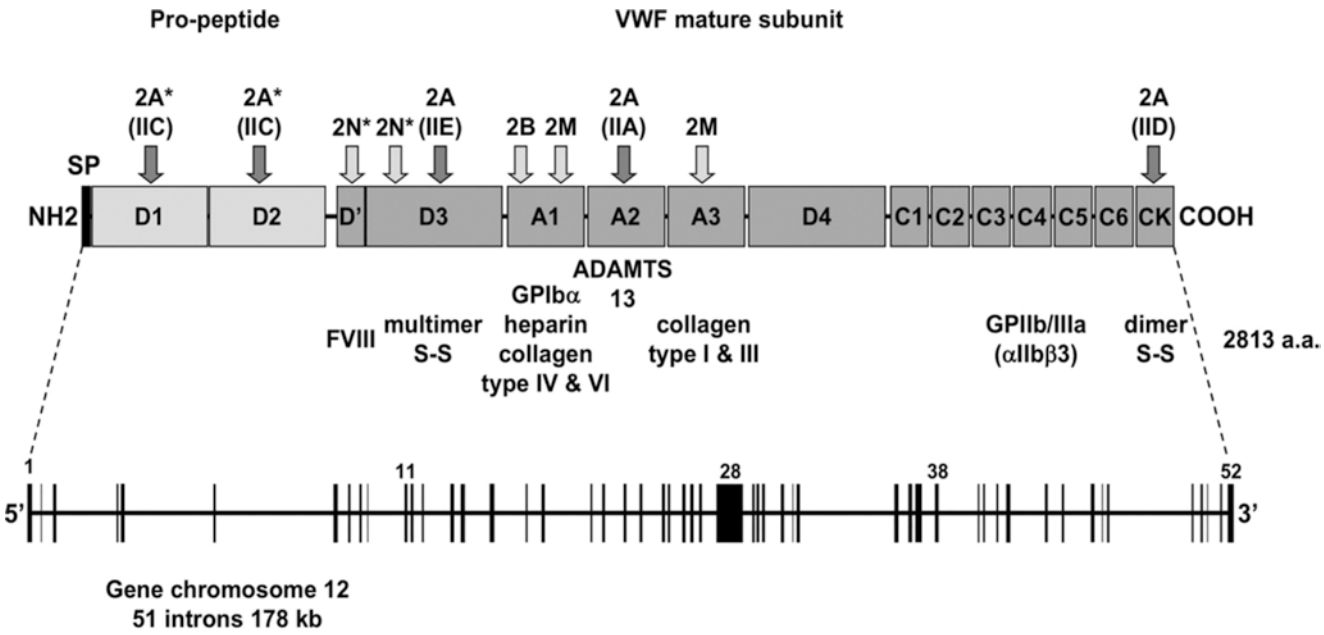

Fig. 4.2 Arrows designate position of mutations that cause Type 2 VWD. Dark arrow significant mutations that result in 2A variants with increased proteolysis (IIA) or defective multimer assembly due to mutation in pro-peptide, cysteine knot, or the D3 domain respectively (IIC, IID, IIE). * indicates recessive diseases (From Baronciani et al. [48])

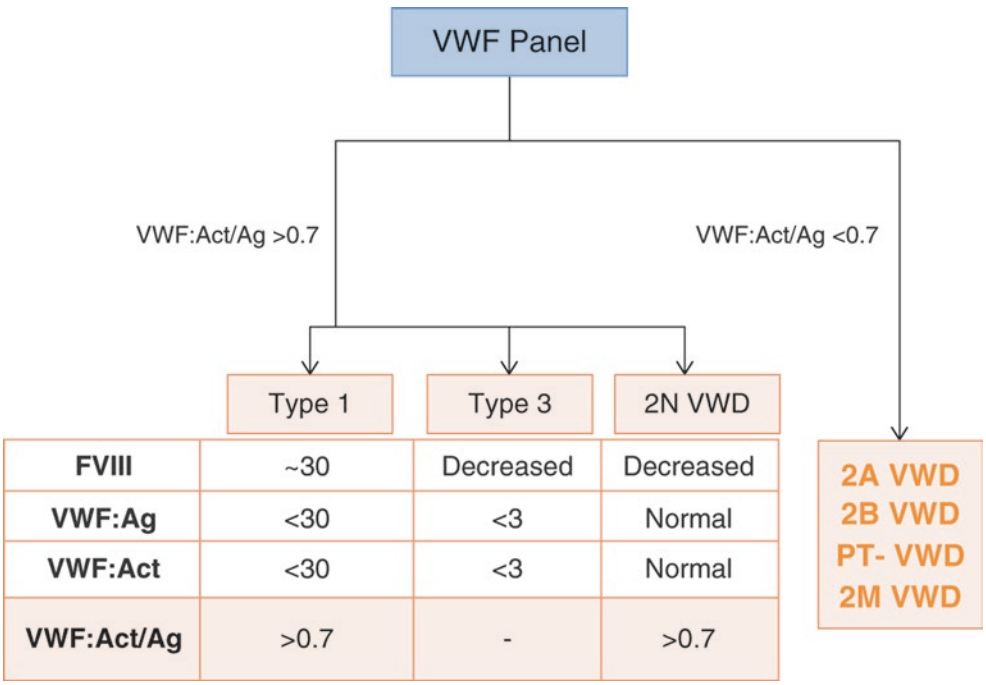

Fig. 4.3 Shows the laboratory features that distinguish Type 1, 3, and 2N VWD from other Type 2 VWD. Of note, although Type 2N is a VWF functional defect as a F8 carrier protein, the coagulation function of VWF remains normal

If there is a decreased VWF:Act/Ag of <0.5–0.7, a qualitative defect in VWF coagulation function is present (Fig. 4.4). In order to differentiate Type 2M from Type 2A/2B VWD, a VWF:MA should be performed. A normal VWF:MA with a decreased VWF:Act/Ag may indicate Type 2M VWD, which can be subsequently confirmed with exon 28 analysis.

If the decreased VWF:Act/Ag is accompanied by an abnormal VWF:MA, an abnormal RIPA study will separate Type 2A VWD from Type 2B or platelet Type VWD. To further differentiate Type 2B VWD from platelet Type VWD, a 2B:BA should be performed. An abnormal 2B:BA is indicative of 2B VWD. Lastly, if all alternative qualitative VWD has been ruled out, the diagnosis is Type 2A VWD. Of note, to confirm subtypes of Type 2 VWD, targeted VWF genetic analysis can be performed.

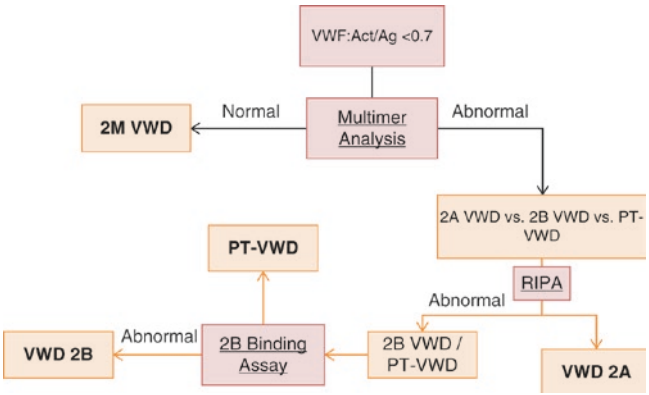

Fig. 4.4 Shows an overall algorithmic approach to subclassify the various Type 2 VWD. Of note, Type 2N is not included in this flowchart as it does not present with decreased VWF:Act/Ag ratio

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Hyperfibrinolysis

5

Wayne L. Chandler

The Fibrinolytic System

Hemostasis is a balance between procoagulant systems that work to form a hemostatic clot and anticoagulant systems that work to prevent excessive clot formation. The fibrinolytic system (Fig. 5.1) plays an important role in regulating the size of the clot [1, 2]. The conversion of fibrinogen to fibrin by thrombin leads to exposure of lysine binding sites in fibrin which promotes binding of tPA and plasminogen from blood to the fibrin surface. tPA and plasminogen also bind to the surface of endothelium where they protect the vessel from unwanted fibrin formation. Fibrin increases the activity of tPA 100-fold, acting as a catalyst for plasminogen activation to plasmin by tPA on the clot surface. Plasminogen can also be activated by urokinase plasminogen activator (uPA) and factor XIIa, but these pathways are thought to be clinically significant only in specific situations discussed in Chap. 12. Newly formed plasmin on the clot surface immediately begins lysing the fibrin releasing fibrin degradation products including D-dimer. Under normal conditions, once a hemostatic clot has formed, the rate of clot lysis by the fibrinolytic system is in balance with the rate of new clot formation leading to a stable clot size. The clot is eventually removed as it is replaced by collagen during wound repair and healing.

Fibrinolytic Proteins

tPA is a serine protease composed of an alpha-chain fibronectin finger domain, an epidermal growth factor (EGF) domain, two kringle domains and a beta-chain protease domain. tPA is continuously secreted in a single-chain active form by vascular endothelial cells. tPA can be converted to a more active two-chain form by plasmin. tPA is a specific activator of plasminogen, but it is slow at activating plasminogen in the absence of fibrin, which increases the activity of single-chain tPA 100-fold. tPA circulates in blood as both a free active enzyme and in inactive form bound to PAI-1 (tPA/PAI-1 complex). Higher levels of active PAI-1 in blood lead to lower levels of active tPA and more tPA/PAI-1 complex resulting in higher levels of total tPA antigen in blood [3]. uPA is a serine protease composed of EGF, kringle, and protease domains. uPA is produced by kidney cells, monocyte/macrophages, and other extravascular cells. It is thought to be the primary extravascular plasminogen activator important in cell migration, wound healing and metastasis. Its highest concentrations are found in urine; small amounts are also seen in blood. uPA is secreted as an inactive single-chain (scuPA) zymogen that is converted to the active two-chain form (uPA) by plasmin, factor XIIa and kallikrein. uPA has a receptor (UPAR) which is expressed on monocytes and other cells. uPA bound to UPAR is less susceptible to inhibition by PAI-1 and can be localized on cell surfaces to enhance proteolysis and cell migration. uPA levels are not important clinically.

Plasminogen is a serine protease zymogen of the active enzyme plasmin, composed of an activation peptide, five kringle domains, and a protease domain. Plasminogen is produced by the liver. Plasminogen binds to fibrin and cell surfaces through lysine binding sites. tPA and uPA activate plasminogen to plasmin through proteolytic cleavage. Active plasmin then lyses fibrin releasing fibrin degradation fragments.

Fibrinolytic activity is regulated by 3 proteins, PAI-1, antiplasmin, and TAFI. PAI-1 is a member of the SERine Protease INhibitor (SERPIN) family that includes antithrombin and antiplasmin [4, 5]. PAI-1 rapidly binds to and inhibits active tPA and uPA forming inactive tPA/PAI-1 and uPA/PAI-1 complexes. PAI-1 can bind tPA on the endothelial surface, inhibiting and releasing tPA from the surface. PAI-1 is secreted by the liver, adipose tissue, and megakaryocytes [6].

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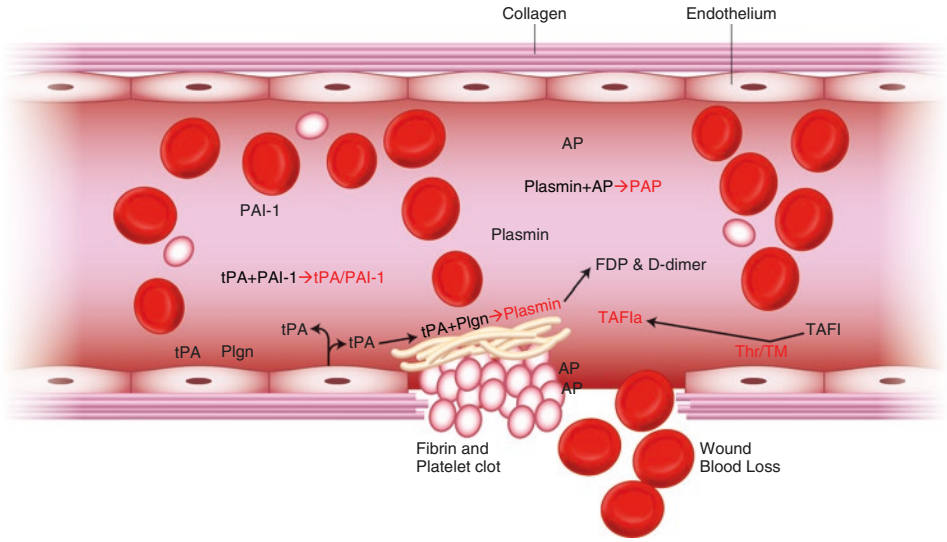

Fig. 5.1 Fibrinolytic System. Fibrinolysis begins with the secretion of tissue plasminogen activator (tPA) from endothelium. tPA along with plasminogen (Plgn) binds to fibrin where tPA converts plasminogen into plasmin which lyses fibrin releasing fibrin degradation fragments (FDP) including D-dimer. Free tPA in the blood can be inhibited by plasminogen activator inhibitor 1 (PAI-1) forming inactive tPA/PAI-1 complex (inhibitor reactions are shown in red). Free plasmin in the blood is rapidly inhibited by antiplasmin (AP) forming inactive plasmin-antiplasmin complex (PAP). Thrombin-activatable fibrinolysis inhibitor (TAFI) removes lysine binding sites from fibrin reducing the ability of tPA, plasminogen and plasmin to bind to fibrin and lyse the clot

PAI-1 is found in platelet alpha granules and is released at sites of platelet activation. PAI-1 secretion follows a circadian rhythm with peak secretion in the morning and nadir in the afternoon or evening [7]. PAI-1 is also an acute phase reactant, its level rises 5 to 50 fold during inflammation or infection. Antiplasmin (also known as α_2-antiplasmin and plasmin inhibitor) is a SERPIN that rapidly inhibits circulating plasmin forming an inactive plasmin-antiplasmin complex. Antiplasmin is produced in the liver.

TAFI is a carboxypeptidase zymogen that is activated by the thrombin-thrombomodulin complex to the active form TAFIa, which removes C-terminal lysine binding sites from fibrin, reducing the binding of tPA, plasminogen, and plasmin to fibrin, slowing the rate of plasminogen activation and fibrinolysis [8]. Platelets release TAFI when activated increasing the concentration in the vicinity of the clot. There is no known inhibitor of TAFIa, but it has a short halflife of about 10 minutes at 37 °C converting into an inactive form TAFIai. Isolated low normal TAFI levels in the absence of other problems have not been associated with hyperfibrinolytic bleeding.

The contact system (factor XII, prekallikrein, high molecular weight kininogen) may also play a limited role in fibrinolysis. Factor XIIa can activate plasminogen to plasmin, but slowly compared to tPA or uPA. In addition bradykinin stimulates the release of tPA from endothelial cells which plays a role in the hyperfibrinolysis during open heart surgery (see Chap. 12). The clinical importance of the contact system is limited, congenital deficiency of contact proteins is not associated with hypofibrinolysis.

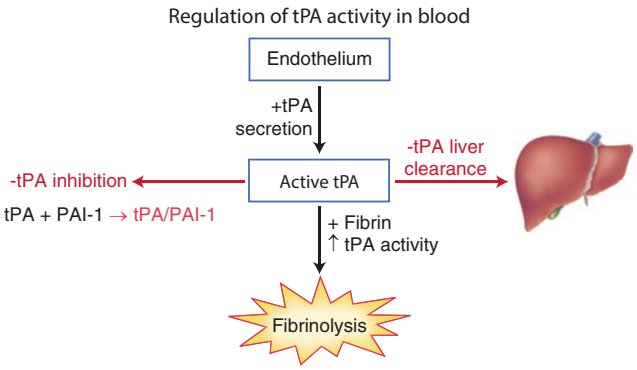

Fig. 5.2 Regulation of tPA activity. The rate of clot lysis is controlled primarily by the concentrations of active tissue plasminogen activator (tPA) in blood and intravascular fibrin. Active tPA levels are regulated by three processes: (1) the rate of tPA secretion from endothelium, (2) the rate of tPA inhibition by plasminogen activator inhibitor type 1 (PAI-1), and (3) the rate of tPA clearance by the liver. Fibrin enhances the activity of tPA

Fibrinolysis Regulation

Activation and regulation of fibrinolysis is a complex process occurring on fibrin and cellular surfaces near the clot [9]. How fast a clot is lysed is related to the level of tPA activity in blood which is affected by four processes (Fig. 5.2): (1) the rate of tPA secretion by endothelium, (2) the rate of tPA inhibition by PAI-1, (3) the rate of tPA clearance by the liver, and (4) enhancement of tPA activity by intravascular fibrin and endothelial binding proteins like

annexin A2 . Increased tPA secretion can be triggered by bradykinin, histamine, beta-adrenergic agonists, and 1-deamino-8-D-arginine vasopressin (DDAVP). Part of the tPA that is secreted by endothelium remains bound to endothelial surface proteins including annexin A2. The highest concentrations of tPA are found in venous blood downstream from capillary beds where most of the endothelium are located and on the endothelial surface. About 50% of the tPA in blood is cleared by a single pass through the liver resulting in a clearance half-life for tPA of about 2–3 minutes for active tPA and 5–6 minutes for tPA/PAI-1 complex. Liver diseases like cirrhosis that decrease liver blood flow prolong clearance of tPA resulting in higher levels in blood.

PAI-1 has both a systemic and a local inhibitory function. PAI-1 in the blood inhibits active tPA forming inactive tPA/PAI-1 complexes [3]. PAI-1 is also released from platelet alpha-granules when the platelet is activated. PAI-1 in the circulation and released from platelets binds to the surface of the clot where it inhibits tPA locally. The rate of tPA inhibition in the blood and at the clot surface is directly related to the concentration of PAI-1 in the blood and platelets. High levels of PAI-1 are seen during inflammation, low levels are typically the result of hereditary deficiency. Plasmin activity is regulated by antiplasmin which binds to and inhibits plasmin forming an inactive plasmin-antiplasmin complex. Antiplasmin is crosslinked to fibrin by activated factor XIIIa. Fibrin with antiplasmin crosslinked to it is more resistant to fibrinolysis. When plasmin is bound to fibrin, inhibition by antiplasmin is slowed, protecting plasmin activity.

In addition of activating platelets and fibrinogen to form the platelet-fibrin clot, thrombin bound to thrombomodulin activates TAFI which in turn removes C-terminal lysines from fibrin suppressing plasminogen binding and activation by tPA. While reduced levels of TAFI in a variety of disorders including cirrhosis, trauma, and leukemia theoretically may contribute to excessive fibrinolysis, acquired or hereditary deficiency of TAFI has not been conclusively linked to increased bleeding.

Procedures or disorders that increase soluble or vascular surface fibrin like cardiopulmonary bypass, severe trauma, prolonged surgery, and disseminated intravascular coagulation result in enhanced tPA activity and increased levels of plasmin in blood. Lysis at the clot surface is related to the level of tPA activity in the blood, the number of lysine binding sites present in fibrin that tPA plasminogen and plasmin can bind to and the amount of inhibitory PAI-1 and antiplasmin bound to the clot surface. Fibrin that forms on or near intact endothelium is rapidly lysed by surface plasmin generated from tPA and plasminogen on the endothelial surface. tPA activation of plasminogen can be attenuated by inflammatory proteins including fibrous components of DNA, histone, and neutrophil extracellular traps (NETs), helping to preserve the antimicrobial function of fibrin isolating the infection.

Clinical Evaluation of Fibrinolysis

The Actively Bleeding Patient

A variety of assays are available for evaluation of the fibrinolytic system (Table 5.1). For patients that are actively bleeding, where hyperfibrinolysis is suspected or other potential hemostatic causes of bleeding have been eliminated (coagulation, platelets), the only assay fast enough to provide a clinically useful evaluation of fibrinolysis is viscoelastometry [10]. Figure 5.3 shows a comparison of a normal viscoelastic curve and one showing hyperfibrinolysis. In patients with hyperfibrinolysis, the viscoelastic curve shows a progressive loss of amplitude, at times demonstrating complete lysis [11]. Because the sample is whole blood containing platelet and plasma PAI-1, only patients with severe hyperfibrinolysis will be detected using viscoelastometry [12]. Therefore if lysis is seen on viscoelastometry, it is usually clinically significant requiring treatment with a fibrinolytic inhibitor. Fibrinolysis on viscoelastometry can be confirmed by adding an antifibrinolytic agent, such as epsilon amino caproic acid (Amicar™) or tranexamic acid to the sample and demonstrating that clot lysis is eliminated. If ROTEM™ is used, FIBTEM or APTEM may confirm hyperfibrinolysis. However, while viscoelastometry can detect severe hyperfibrinolysis, it is not sensitive enough to detect all forms of clinically significant hyperfibrinolysis. Debate about the clinical utility of viscoelastic testing for hyperfibrinolysis, particularly in trauma, is due

Table 5.1 Fibrinolytic assays for evaluation of hyperfibrinolysis

Clinical assays
Tissue plasminogen activator (tPA)
tPA activity
tPA antigen
Plasminogen activator inhibitor 1 (PAI-1)
PAI-1 activity
PAI-1 antigen
Antiplasmin activity
Lysis times
Whole blood percent lysis (viscoelastometry)
Euglobulin clot lysis time (ECLT)
Research assays
tPA/PAI-1 complex antigen
Plasminogen activity
Plasmin-antiplasmin complex antigen
Urokinase plasminogen activator (uPA)
uPA activity
uPA antigen
Thrombin activatable fibrinolysis inhibitor (TAFI)
TAFI activity
TAFI antigen
Overall hemostatic potential
Global fibrinolytic capacity

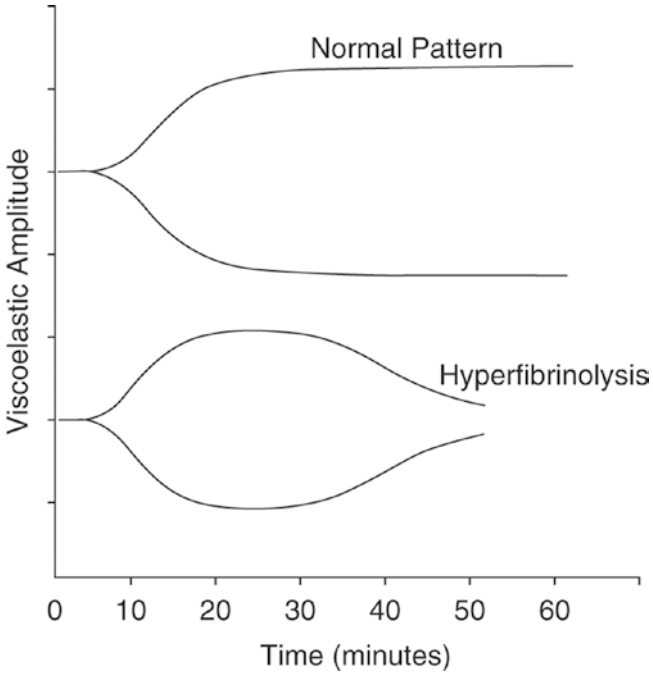

Fig. 5.3 Detection of hyperfibrinolysis using viscoelastometry. The upper curve shows a normal tracing with a stable maximum viscoelasticity. The lower curve shows a progressive loss of viscoelasticity associated with accelerated fibrinolysis and an increased risk of bleeding

to low sensitivity of the method, slow rate of detection (30–60 minutes), and lack of specificity without running a second confirmatory test [13].

Global Fibrinolytic Assays

At present there is no single assay useful for detecting clinically significant fibrinolysis that is rapid, sensitive, and specific that can be used to screen patients for abnormalities [14]. To prevent unwanted fibrinolysis, fibrinolytic inhibitors like PAI-1 and antiplasmin are in excess in blood compared to the active enzymes tPA and plasmin. Normal blood that is first clotted typically takes hours to days to lyse, too long for a practical clinical assay. In theory the best overall global assay of fibrinolysis would be a whole blood assay that includes plasma, platelets, white blood cells, and red blood cells. In reality, detecting lysis in whole blood is difficult with the principle method being the viscoelastic testing described above. Other than for detection of severe hyperfibrinolysis, it has not been shown to be a useful overall screening method for hyperfibrinolysis.

Accelerating lysis in global fibrinolytic assays requires either removing inhibitors or adding activators to the sample, which alters the balance of these factors compared to in vivo levels. A general screening test for increased fibrinolytic activity is the euglobulin clot lysis time [15]. An acid precipitate of plasma is prepared that is rich in plasminogen activators but low in antiplasmin. The precipitate is removed and reconstituted in physiologic buffer followed by activation of clotting and determination of the time required for subsequent clot lysis. The euglobulin clot lysis time is sensitive to the level of active plasminogen activators in the sample, but too slow an assay for the evaluation of actively bleeding patients, and is not available in most laboratories. Euglobulin clot lysis time measurements are limited by variable sensitivity to plasminogen activator levels and the lack of standardized methodology for preparing the euglobulin fraction and measuring the lysis time.

Other global fibrinolytic assays include the overall hemostatic potential and global fibrinolytic capacity. Overall hemostatic potential is a plasma-based assay that compares turbidity increase after activation of clotting with tissue factor, calcium, and phospholipids in one well with turbidity loss in a second well with tPA added. Coagulation potential is assessed by measuring the rate and extent of turbidity generation in the first well, while fibrinolysis potential is measured by the loss of turbidity in the second well. This assay has been studied in a number of clinical conditions acute coronary syndrome, stroke, diabetes, antiphospholipid syndrome, hemophilias, and anticoagulant usage but remains primarily a research assay.

Another global fibrinolytic assay is the global fibrinolytic capacity, an assay based on the measuring D-dimer released from a pre-formed standardized fibrin clot added with tPA to plasma. It has also been used to assess fibrinolytic potential in a variety of conditions as a research tool.

Hyperfibrinolytic Syndromes

For patients that are not actively bleeding but have a history consistent with a hyperfibrinolytic syndrome, the next step is laboratory evaluation of specific components of the fibrinolytic system. Three different assays are available to measure tPA: (1) total tPA antigen which measures active tPA and tPA/PAI-1 complex, (2) tPA activity which measures only active tPA, and (3) tPA/PAI-1 complex (usually research only) [16, 17]. tPA antigen is measured in citrate anticoagulated plasma. Measurement of active tPA requires a special acidified citrate tube to stabilize active tPA and prevent further inhibition by PAI-1 [18]. tPA is normally present in blood at a total concentration of 5 ng/mL of which about 1–2 ng/mL is active. Three assays are also available for measuring PAI-1: (1) total PAI-1 antigen which measures active PAI-1, tPA/PAI-1 complex and latent PAI-1 (a form of inactive PAI-1 released from platelets), (2) PAI-1 activity, and (3) tPA/PAI-1 complex. PAI-1 levels in blood follows a circadian rhythm with peak levels in the morning requiring separate reference ranges depending on when the sample is drawn

[7]. Evaluation of PAI-1 levels requires measurement of total tPA antigen, PAI-1 activity and PAI-1 antigen. Active tPA is cleared with a half-life of approximately 2–3 minutes, while tPA/PAI-1 complex has a longer half-life of 5–6 minutes [19]. When PAI-1 activity is increased, more tPA is converted to tPA/PAI-1 which clears slower resulting in higher total tPA but lower tPA activity [3]. When PAI-1 activity is decreased or absent, more tPA is in the active form, but is cleared faster resulting in lower total tPA antigen. Transient increases in tPA secretion will lead to high total tPA but low PAI-1 activity.

Antiplasmin activity is measured with a chromogenic back-titration assay. An excess of plasmin is added to plasma and allowed to react with antiplasmin. Residual plasmin is then measured. Antiplasmin activity is the difference between original and residual plasmin activity [20].

Lastly, genetic studies are being used to detect deficiencies and abnormalities of fibrinolytic proteins like PAI-1 and antiplasmin but often still require functional assays when variants of unknown significance are detected.

Measurements of uPA, plasminogen, TAFI, and contact system factors are available on a research basis but are seldom useful for the evaluation of bleeding patients.

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Whole Blood Assay: Thromboelastometry – Basics

6

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Thromboelastometry Devices, Assays, and Parameters

The ROTEM™ Devices

Rotational thromboelastometry (ROTEM™, Tem Innovations GmbH, Munich, Germany, and Instrumentation Laboratory, Bedford, MA, USA) is a whole blood viscoelastic hemostasis analyzer, which evolved from the original thrombelastography (TEG) system, introduced by Hellmut Hartert in 1948, in the 1990s by Andreas Calatzis to the ROTEG™ and later ROTEM™ system [1, 2]. Although the TEG™ 5000 and ROTEM™ *delta* devices still share similarities, there are several distinct differences with regard to measurement technique, assays, and measurement variables (Table 6.1).

The ROTEM™ *delta* device (Fig. 6.1a, b) consists of a compact measurement unit with four temperature-adjusted independent measurement channels, a pre-warming plate, a reagent tray, and an integrated personal computer, allowing for remote viewing and LIS (laboratory information system) connection. An attached touch screen and a software-assisted, automatic pipette are used to control the device and the specific ROTEM™ software. This makes the device very user-friendly and reduces intra- and inter-operator variability of test results [7] and allows for using the device in a multiuser environment, e.g., in the emergency room (ER), in the operating room (OR), or at the intensive care unit (ICU). Furthermore, the user is guided through the measurement process by the ROTEM™ device with instructions and pictograms, displayed on the touch screen, and a help menu can be activated if support in result interpretation is desired. Of course, this does not substitute for adequate education in hemostasis and decision-making by the attending physician.

The ROTEM™ *delta* device is complemented by the ROTEM™ *platelet* device (Fig. 6.1a, c–e), CE-marked (certification mark) in Europe since November 2013, which provides platelet function analysis based on the well-established whole blood "impedance aggregometry" or "multiple electrode aggregometry" technology (more than 600 hits in PubMed) [44–51]. Together, ROTEM™ *delta* and ROTEM™ *platelet* provide six measuring channels, four channels for viscoelastic testing and two channels for platelet function analysis.

Finally, the new fully automated ROTEM™ *sigma* device (Fig. 6.1f, g) is a cartridge-based system (with four channels), CE-marked in Europe since August 2015 (FDA validation studies are running), working with lyophilized reagent beads but still with the proven cup-and-pin technology. With the ROTEM™ *sigma* device, pipetting is no longer required, which significantly increases user-friendliness and reproducibility of the results [53].

Measurement Technique

The four independent viscoelastic measurement channels of the ROTEM™ *delta* device allow for using a panel of specific assays. This improves the diagnostic performance of the device compared to a mono-assay system activated by kaolin [13–15, 37–41]. Accordingly, the ROTEM™ *delta* device is suitable not only to detect a coagulopathy in real time but

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Table 6.1 Characteristics and performance of thrombelastography (TEG™) and thromboelastometry (ROTEM™)

Characteristics and performance	TEG™ 5000	ROTEM™ *delta*
Mechanical robustness, susceptibility to artifacts [3–6]	Cup is moving and clot firmness is detected by a torsion wire with high susceptibility to agitation and movement artifacts limiting its mobile use at the bedside; therefore, TEGs are most often located in the central laboratory	Cup is fixed and pin is moving; stabilization of the pin axis by a ball bearing and contactless optical detection of the pin movement result in low susceptibility to agitation and movement artifacts; this enables bedside testing and mobile use – even in military settings
Pipetting and reproducibility of results [7]	Manual pipetting results in higher intra- and inter-operator variability of test results	Software-assisted automatic pipette is user-friendly and results in low intra- and inter-operator variability of the results and enables a multiuser environment with bedside testing in the ER, OR, and ICU
Quality control (QC) [4, 8]	No continuous electronic QC; therefore, QC with control reagents is at least once a day (based on the local regulations in some places even every 8 h) required	Continuous electronic QC of the pin axis movement; therefore, QC with control reagents is only once a week required; this results in reduced staff workload and QC costs
Number of channels for viscoelastic testing [2–4]	2 channels per device (if TEG® platelet mapping is performed, channels are blocked for other viscoelastic testing)	4 channels per device (the ROTEM® *platelet* module provides two additional channels for impedance aggregometry)
Viscoelastic assays [9–15]	5 different assays (native TEG, kaolin-TEG, heparinase-TEG, rapid-TEG, TEG functional fibrinogen (FF)); only heparinase-TEG can be used already during cardiopulmonary bypass (CPB)	8 different assays (NATEM, NA-HEPTEM, INTEM, HEPTEM, EXTEM, FIBTEM, APTEM, ECATEM); tissue factor-activated assays (EXTEM, FIBTEM, APTEM) contain a heparin inhibitor and can – as well as HEPTEM – already be used during CPB
Preferred activation pathway [9, 16–27]	Intrinsic pathway (kaolin); poor correlation to the effect of oral vitamin K antagonists and prothrombin complex concentrate (PCC)	Extrinsic pathway (tissue factor); good correlation to the effect of oral vitamin K antagonists, direct oral anticoagulants (DOACs), and prothrombin complex concentrate (PCC)
Turnaround time [6, 11, 13, 28–35]	Reference range for r-time in kaolin-TEG 4–8 min; no early variables of clot firmness available; turnaround time 25–45 min	Reference range for EXTEM 40–80 s; early variables of clot firmness (A5 and A10) are validated and predict MCF accurately; turnaround time 10–15 min
Definition of lysis parameters [36]	LY30/LY60 (lysis 30/60) is defined as the reduction of clot firmness *30/60 min after MA* in percentage of MA	LI30/LI60 (lysis index 30/60) is defined as residual clot firmness *30/60 min after CT* in percentage of MCF
Diagnostic performance [13–15, 37–43]	Poor discrimination between fibrinogen deficiency and thrombocytopenia; most often used to predict bleeding rather than to guide hemostatic therapy	Improved diagnostic performance based on test combinations; good discrimination between fibrinogen deficiency and thrombocytopenia; enables guided therapy with allogeneic blood products and coagulation factor concentrates ("theranostic approach" in precision medicine)
Platelet function analysis [44–51]	TEG™ platelet mapping (PM); viscoelastic channels are blocked during TEG™ PM; test principle is based on the use of reptilase + FXIIIa + arachidonic acid (AA) or adenosine diphosphate (ADP); long turnaround time, high costs, and high variability of the results	ROTEM™ *platelet* module provides two additional channels for whole blood impedance aggregometry; platelet activation with AA (ARATEM), ADP (ADPTEM), or thrombin receptor-activating peptide (TRAPTEM); short turnaround time (10 min), good reproducibility of the results, and good correlation to clinical outcomes
Fully automated system [52, 53]	TEG™ 6S (CORA™ system); cartridge-based system using a new technology based on coagulation resonance analysis (CORA); interchangeability of TEG™ 5000 and TEG™ 6S (CORA™) results has to be investigated	ROTEM™ *sigma*; cartridge-based system using the proven pin-and-cup technology but lyophilized beads reagents instead of liquid reagents; ROTEM™ *sigma* beads contain a heparin inhibitor as the liquid reagents do

Courtesy of Klaus Görlinger, Essen, Germany
ER emergency room, *ICU* intensive care unit, *OR* operating room

also to differentiate between different causes of coagulopathies, e.g., between hypofibrinogenemia and thrombocytopenia, and is designed to guide hemostatic therapy in bleeding patients [32, 54–61]. Each measurement channel consists of a disposable cuvette fixed in a temperature-adjusted metal cup holder and a disposable pin attached to a moving axis, stabilized by a ball bearing. The ROTEM™ axis is alternatingly rotating forth and back by 4.75° 12 times per minute. After starting the test by re-calcifying the citrated whole blood in the cup and adding an activator (tissue factor, ellagic acid, or ecarin), clot strands between pin and cup wall are increasingly impairing the pin rotation. These changes in pin movement are detected by a LED light-mirror-light detector system, and the consequential signal is processed and transformed by the integrated computer into a thromboelastometric curve (TEMogram), finally (Fig. 6.1b). In addi-

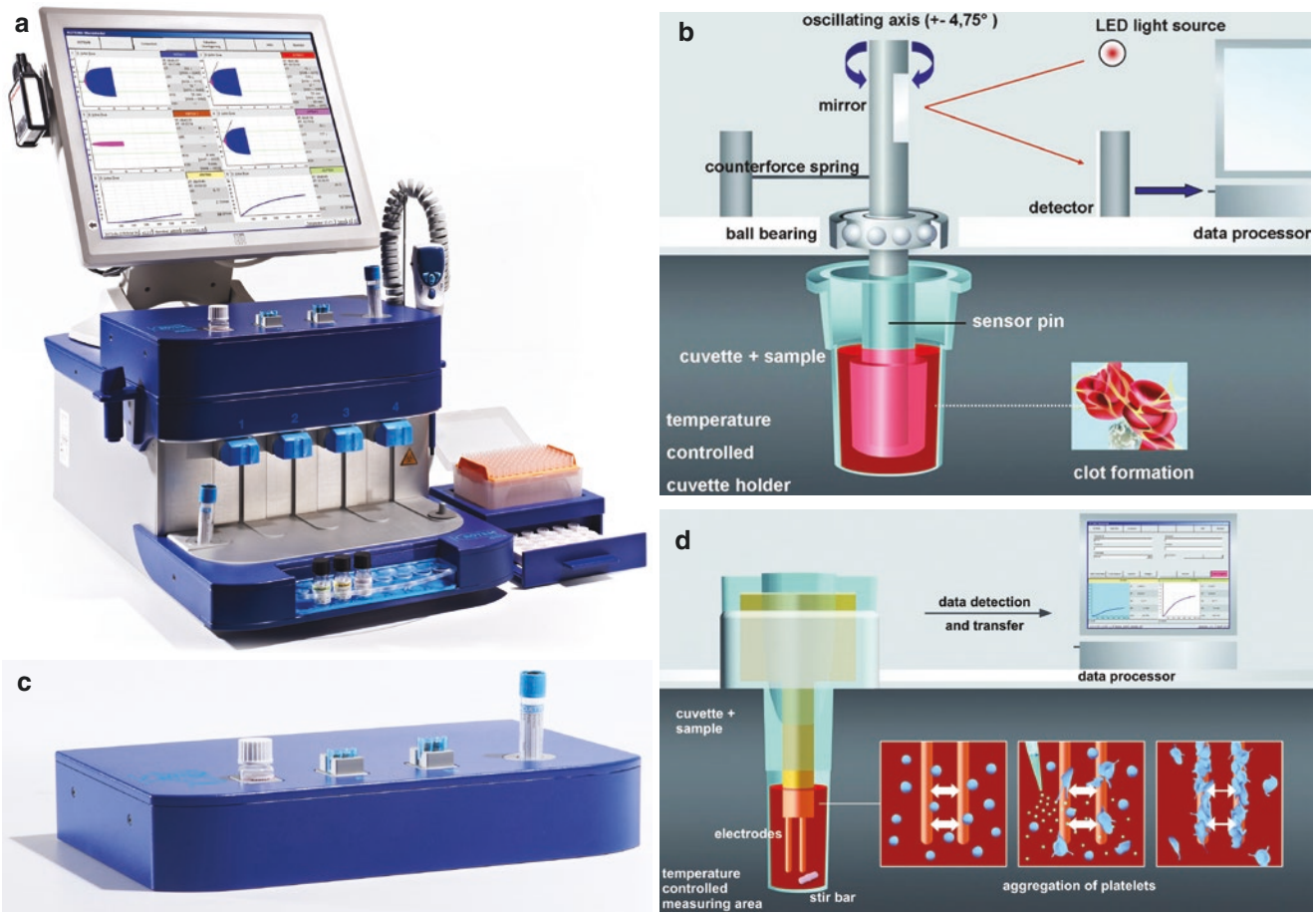


Fig. 6.1 (**a**–**g**) ROTEM™ devices. (**a**) ROTEM™ *delta* device (thromboelastometry) plus ROTEM™ *platelet* module (whole blood impedance aggregometry); (**b**) ROTEM™ *delta* measuring principle; (**c**) ROTEM™ *platelet* module; (**d**) ROTEM™ *platelet* measuring principle; (**e**) ROTEM™ *platelet* measuring curve and parameters (MS = maximum slope in Ohm/min; A6 = amplitude at 6 min in Ohm; AUC = area under the aggregation curve in Ohm*min); (**f**) ROTEM™ *sigma* fully automated device; (**g**) ROTEM™ *sigma* cartridge type 1 (C cartridge ROTEM™ assay) (Courtesy of Klaus Görlinger, Tem Innovations, Munich, Germany)

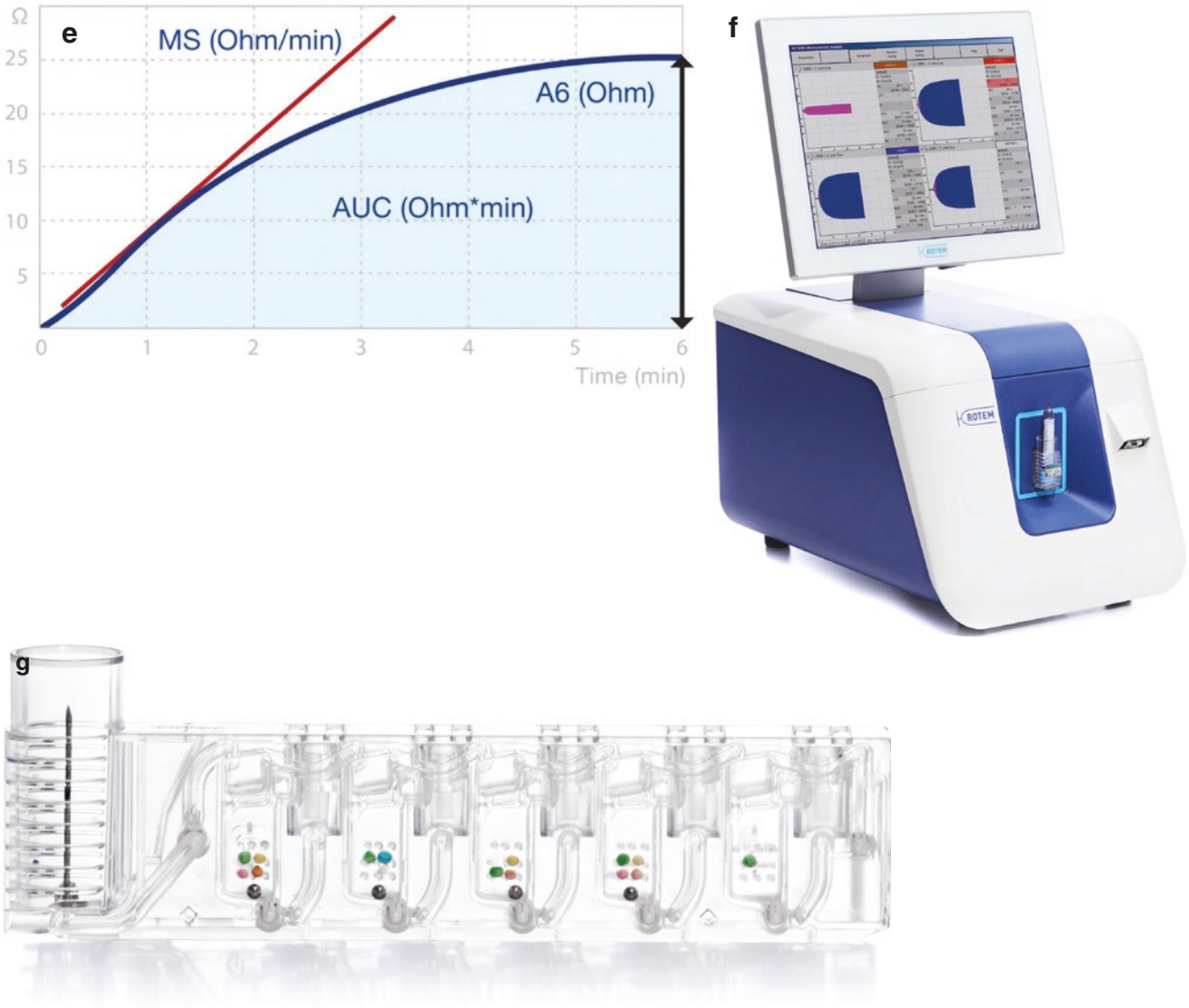


Fig. 6.1 (continued)

tion, specific ROTEM™ parameters are calculated by the computer and displayed on the touch screen in real time. These technical modifications make the ROTEM™ *delta* device on the one hand less susceptible to vibrations and movement artifacts and, on the other hand, allow for a continuous electronic quality control of the pin movement. Therefore, quality control using the reagents ROTROL™ N and P is necessary only once a week, compared to daily QCs required for other viscoelastic test devices such as the TEG™ device [4, 8]. This reduces costs and workload significantly [8]. Furthermore, the device can be used in a mobile way at the bedside (e.g., in the ER, OR, ICU, or a satellite laboratory) and can even be moved around with the patient on a customized trolley providing uninterrupted power supply (Table 6.1). Accordingly, ROTEM™ *delta* devices have successfully been used in military settings and other outdoor environments (e.g., mountaineering in the Himalaya and the Andes) [5, 6].

The ROTEM™ *sigma* device actually works with two different cartridges (Fig. 6.1g), providing four channels each (cartridge type 1, FIBTEM C, EXTEM C, INTEM C, APTEM C; cartridge type 2, FIBTEM C, EXTEM C, INTEM C, HEPTEM C; here C stands for cartridge) [53].

ROTEM™ Assays

Thromboelastometric assays use citrated whole blood (300 µL per assay), which is re-calcified and activated by tissue factor (extrinsic pathway), ellagic acid (intrinsic pathway), or ecarin (direct prothrombin activation). Some assays contain further additives (Table 6.2). In contrast to the TEG™ system, all pipetting steps are guided by the ROTEM™ software and performed using a software-driven ROTEM™ *delta* pipette. This allows for improved multiuser handling with lower intra- and inter-operator variability of the results when compared to other viscoelastic testing devices [3–5]. The ROTEM™ system provides various activated assays which in combination considerably improve the diagnostic performance of the device in comparison to a mono-assay system [37–39]. Up to four viscoelastic tests can be performed and displayed on the touch screen, simultaneously (Fig. 6.1a). Here, extrinsically activated assays (EXTEM, FIBTEM, and APTEM), intrinsically activated assays (INTEM and HEPTEM), an ecarin-activated assay (ECATEM), and two nonactivated assay (NATEM and NA-HEPTEM) are available. A new preparation of ECATEM is under development.

Similar to the prothrombin time, the *EXTEM* assay is activated by re-calcification (star-tem™ reagent, containing 0.2 mol/L calcium chloride) and addition of tissue thromboplastin (r ex-tem™ reagents, i.e., recombinant tissue factor and phospholipids). Accordingly, since coagulation is initiated through the extrinsic pathway, initial thrombin generation and hence initial clotting mainly depends on the activity of the coagulation factors VII, X, V, II, and I (fibrinogen) in EXTEM test. EXTEM CT can be used to guide FFP and PCC administration in patients suffering from bleeding due to vitamin K-dependent factor deficiency, e.g., due to warfarin therapy [17–23]. Prolonged EXTEM CT should only be used for clinical decision-making in the presence of sufficient amounts of fibrinogen (normal FIBTEM A5 or A10), since severe hypofibrinogenemia often results in prolonged EXTEM and FIBTEM CT. EXTEM and FIBTEM CT are also sensitive but

Table 6.2 ROTEM™ *delta* (*sigma*) and ROTEM™ *platelet* assays

Assay	Activators and additives	Clinical comments
ROTEM™ *delta* assays		
EXTEM	$CaCl_2$ + recombinant tissue factor + polybrene	Deficiency of factors of the extrinsic pathway; VKAs and DOACs; indication for PCC administration
FIBTEM	$CaCl_2$ + recombinant tissue factor + polybrene + cytochalasin D	Fibrin polymerization; dose calculation for fibrinogen concentrate or cryoprecipitate; hyperfibrinolysis; FXIII deficiency
APTEM	$CaCl_2$ + recombinant tissue factor + polybrene + aprotinin/ tranexamic acid	Verifying the effect of antifibrinolytic drugs; differential diagnosis to clot retraction and FXIII deficiency (in combination with EXTEM)
INTEM	$CaCl_2$ + ellagic acid	Deficiency of factors of the intrinsic pathway; unfractionated heparin (UFH) and protamine effects (in combination with HEPTEM)
HEPTEM	$CaCl_2$ + ellagic acid + heparinase	Testing in patients with very high heparin plasma concentrations; UFH and protamine effects (in combination with INTEM)
NATEM	$CaCl_2$	Tissue factor expression on circulating cells (e.g., monocytes or malignant cells); other anticoagulants (e.g., LMWH)
NA-HEPTEM	$CaCl_2$ + heparinase	Tissue factor expression on circulating cells (e.g., monocytes or malignant cells) in blood samples with heparin or HLE; other anticoagulants (e.g., LMWH) (in combination with NATEM)
ECATEM	$CaCl_2$ + ecarin	Direct thrombin inhibitors (e.g., hirudin, argatroban, bivalirudin, dabigatran); not sensitive to heparin; new preparation under development
ROTEM™ *platelet* assays		
ARATEM	Arachidonic acid (AA)	COX-1 (e.g., aspirin) and GPIIbIIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis
ADPTEM	Adenosine diphosphate (ADP)	ADP (P2Y12) (e.g., clopidogrel and prasugrel) and GPIIbIIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis
TRAPTEM	Thrombin receptor-activating peptide-6 (TRAP-6)	Thrombin (PAR-1) (e.g., vorapaxar) and GPIIbIIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis

Courtesy of Klaus Görlinger, Essen, Germany
ADP adenosine diphosphate, *COX-1* cyclooxygenase-1, *CPB* cardiopulmonary bypass, *DOACs* direct oral anticoagulants, *HLE* heparin-like effect, *LMWH* low molecular weight heparin, *PAR-1* protease-activated receptor-1, *PCC* protamine complex concentrate, *UFH* unfractionated heparin, *VKAs* vitamin K antagonists

not specific to the effect of direct oral anticoagulants (DOACs) such as dabigatran and rivaroxaban [24–27]. Furthermore, early variables of clot firmness (A5 and A10) in EXTEM can be used for early detection of fibrinolysis [33].

The *FIBTEM* assay consists of a modified EXTEM assay with addition of a potent platelet inhibitor (cytochalasin D), which blocks platelet activation, shape change, and expression and activation of glycoprotein IIb/IIIa, which is a fibrin(ogen) receptor [62]. Thereby, platelet contribution to clot formation and clot strength is eliminated in this assay [38]. Accordingly, clot strength in FIBTEM is based on fibrinogen concentration and fibrin polymerization solely, whereas clot strength in EXTEM depends on platelet count, platelet function, fibrinogen concentration, and fibrin polymerization. Therefore, the combination of EXTEM and FIBTEM allows for discrimination between thrombocytopenia or platelet dysfunction and hypofibrinogenemia [39, 58, 61]. The difference in clot strength between EXTEM and FIBTEM allows for estimation of the platelet part of clot firmness (referred as PLTEM by some authors) [13, 54, 63, 64]. FIBTEM is also sensitive to factor XIII deficiency ($r = 0.60$) [65–68]. Furthermore, recent studies have shown that FIBTEM is the most sensitive and specific assay for the detection of hyperfibrinolysis compared to kaolin-TEG and EXTEM [69, 70].

A third extrinsically activated assay – the *APTEM* test – includes an antifibrinolytic drug (in the past aprotinin and nowadays tranexamic acid (t ap-tem™)) allowing for in vitro assessment of an antifibrinolytic therapy. Furthermore, the test combination of EXTEM and APTEM allows for the discrimination between fibrinolysis and other reasons for clot instability, such as platelet-mediated clot retraction and factor XIII deficiency [71–74]. The latter ones cannot be blocked by an antifibrinolytic drug and therefore are still present in APTEM. Notably, FIBTEM can also be used for the discrimination between fibrinolysis and platelet-mediated clot retraction since platelet function is blocked in this assay. All extrinsically activated liquid assays contain polybrene, a heparin inhibitor which allows for immediate elimination of heparin effects (up to 5 units unfractionated heparin per mL). This enables the use of these tests even in heparin-treated patients, e.g., during cardiopulmonary bypass [9–15].

The *INTEM* assay is activated by re-calcification and addition of ellagic acid and phospholipids. Due to the intrinsic activation, similar to the activated partial thromboplastin time, initial thrombin generation and clot formation in INTEM mainly depends on coagulation factors XII, XI, IX, VIII, X, V, and II and I (fibrinogen) [58]. As in EXTEM, clot firmness reflects both platelet and fibrin contribution to the clot. In contrast to all extrinsically activated assays, INTEM does not contain a heparin inhibitor. However, a modified INTEM assay, containing additional heparinase (*HEPTEM*; eliminates up to 10 IU/mL), can be used in combination with INTEM in order to reveal (residual) heparinization or protamine overdose [75–77]. The INTEM/HEPTEM CT ratio correlates well with anti-Xa activity ($r = 0.72$) [78].

The *ECATEM* assay uses the viper venom ecarin as an activator. Ecarin directly converts prothrombin to meizothrombin which has already a low level of thrombin activity. Crucially, meizothrombin is inhibited by hirudin and other direct thrombin inhibitors (such as argatroban, bivalirudin, and dabigatran), but not by heparin [79–81]. Other than in prothrombin deficiency, the clotting time in ECATEM is unaffected by other enzymatic coagulation factor deficiencies, by Coumadin (warfarin), by direct factor Xa inhibitors (such as rivaroxaban, apixaban, and edoxaban), or by the presence of phospholipid-dependent anticoagulants (such as lupus anticoagulant). The eca-tem™ reagent is approved in Europe only, and a new preparation with better stability is under development [82].

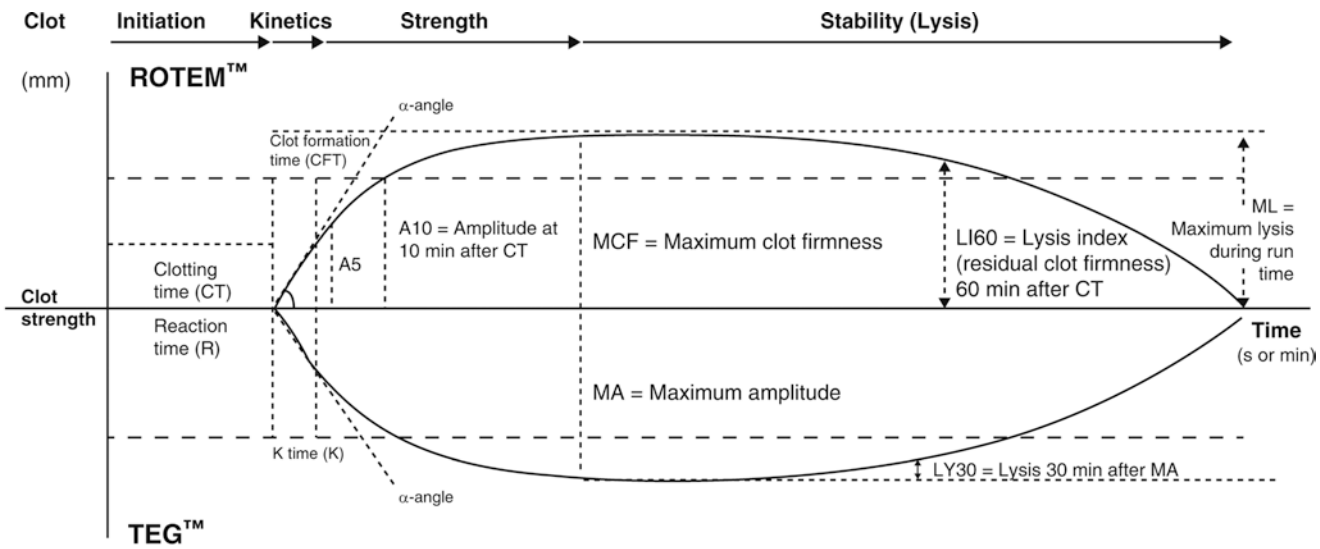
The *NATEM* assay is activated by re-calcification (star-tem® reagent) only. The test is very sensitive to any endogenous activator such as tissue factor expression on circulating monocytes in infection, sepsis, liver cirrhosis, or malignancies and in patients treated with extracorporeal assist devices [73, 83–86]. Therefore, this assay may be helpful to detect a pathophysiological change from trauma-induced coagulopathy (TIC) to disseminated intravascular coagulopathy (DIC). Finally, the *NA-HEPTEM* assay, which contains heparinase in addition to $CaCl_2$, eliminates a potential heparin effect. This avoids an interference with heparin due to prophylactic or therapeutic anticoagulation with heparin or due to an endogenous heparin-like effect (HLE) [73, 83–89], in patients in whom tissue factor expression on circulating cells should be detected. Furthermore, the NATEM/NA-HEPTEM CT ratio is very sensitive to unfractionated (UFH) and low molecular weight (LMWH) heparin [90]. Besides the standard liquid reagents, lyophilized single-potion or *single-use reagents (SURs)* are available in Europe and several other countries [91]. Since SURs contain all reagents needed for one assay, lyophilized in one vial, pipetting is minimized to adding 300 µL of citrated whole blood to the reagent vial and transferring the activated blood 5 s later to the ROTEM™ cup. SURs are labeled by the suffix S (e.g., ex-tem™ S), which is also displayed on the ROTEM™ *delta* screen when SURs have been used for the analysis. Notably, extrinsically activated SURs do not contain a heparin inhibitor and, therefore, must not be used in patients treated with UFH (e.g., in cardiac and vascular surgery or in patients with therapeutic anticoagulation with UFH) as well as in patients in which a significant endogenous liberation of heparinoids can be expected (e.g., after graft reperfusion in liver transplantation or after severe hemorrhagic shock). UFH can result in prolonged CT and CFT as well as in reduced clot firmness (A-values and MCF) by using SURs in these settings. A heparin effect can be verified by the test combination INTEM (S) and HEPTEM (S).

ROTEM™ Parameters

The ROTEM™ test results are characterized by several ROTEM™ parameters. Besides the standard ROTEM™ parameters, several other parameters are used for research only (Fig. 6.2, Table 6.3, and ROTEM™ *delta* manual) [92–95]. ROTEM™ *reference ranges* can slightly vary from country to country (e.g., between Europe and the USA) and even from hospital to hospital. Therefore, these reference ranges are for orientation only, and it is recommended to establish hospital-specific reference ranges. Here, the reference population, age, blood sampling vials and technique, sample transport, and other pre-analytic factors may affect the results. Notably, specific age-related reference ranges for *infants/children* and trimester-related reference ranges for *pregnant woman* have been published, too [53, 96–103].

Clot Initiation and Amplification Parameters (Clot Kinetics)

The thromboelastometric coagulation time (*CT*) in seconds corresponds to the reaction time (*r*) of TEG™ assays. In ROTEM™ assays, CT is defined as the time from test start until a clot firmness amplitude of 2 mm is reached. In tissue factor-activated tests, the CT is usually achieved within about 1 min. The CT reflects the speed of thrombin generation and is mainly affected by the enzymatic activity of coagulation factors (extrinsic or intrinsic, depending on the assay used), the concentration of anticoagulants and fibrin split products, as well as tissue factor expression on circulating cells (e.g., monocytes or malignant cells) [73, 83–85]. EXTEM CT is a reliable indicator of sepsis-induced DIC, diagnosed by the Japanese Association for Acute Medicine (JAAM) DIC score, and is strongly associated with severity of DIC [104]. Furthermore, EXTEM CT can be used to guide FFP and PCC administration in patients suffering from bleeding due to vitamin K-dependent factor deficiency, e.g., due to warfarin therapy, liver insufficiency, and trauma [17–23, 105]. In contrast to INTEM CT as well as kaolin-TEG and rapid-TEG R-time, EXTEM CT correlates well with INR in patients treated with vitamin K antagonists (r = 0.87) [16–18]. However, EXTEM CT is superior in predicting bleeding complications compared to international normalized ratio (INR) in several other settings such as liver cirrhosis and infection/sepsis. Thereby,



	ROTEM™	TEG™	Hemostatic factors
Clot initiation	CT (clotting time) in s	R (reaction time) in min	Enzymatic coagulation factors, anticoagulants, FDPs, tissue factor expression on monocytes
Clot kinetics	CFT (clot formation time) in s α (angle) in degrees	K (kinetic time) in min α (angle) in degrees	Enzymatic coagulation factor, anticoagulants, fibrinogen, platelets
Clot strength	(A5) A10 (amplitude (5) 10 min after CT) in mm MCF (maximum clot firmness) in mm	MA (maximum amplitude) in mm	Platelets, fibrinogen, FXIII, colloids
Clot stability (lysis)	LI60 (lysis index (residual clot firmness) 60 min after CT) in % of MCF ML (maximum lysis during run time) in % of MCF	LY30 (lysis 30 min after MA) in % of MA	Fibrinolytic enzymes, fibrinolysis inhibitors, FXIII

Fig. 6.2 ROTEM™ ("temogram") and TEG™ trace displaying the clinically most important parameters and their informative value. *FDPs* fibrin(ogen) split products (Courtesy of Klaus Görlinger, Essen, Germany)

Table 6.3 ROTEM™ *delta* (*sigma*) parameters

Acronym	Parameter	Unit	Definition
Coagulation activation and clot polymerization parameters			
CT	Coagulation time	s	Time from test start until a clot firmness amplitude of 2 mm is reached
CT-ratio	Coagulation time ratio	–	For example, INTEM CT/HEPTEM CT in order to quantify a heparin effect
CFT	Clot formation time	s	Time between 2 and 20 mm clot firmness amplitude is achieved
α	Alpha-angle	degree (°)	Angle between the baseline and a tangent to the clotting curve through the 2 mm point
Clot firmness parameters			
A5	Amplitude at 5 min	mm	Amplitude of clot firmness 5 min after CT
A10	Amplitude at 10 min	mm	Amplitude of clot firmness 10 min after CT
A20	Amplitude at 20 min	mm	Amplitude of clot firmness 520 min after CT
MCF	Maximum clot firmness	mm	Maximum amplitude of clot firmness reached during the runtime
PLTEM A5 (A10, MCF)	Platelet contribution to clot firmness	mm	EXTEM A5 (A10, MCF) – FIBTEM A5 (A10, MCF)
Clot lysis parameters			
ML	Maximum lysis	%	Maximum lysis detected during the runtime, described in % of MCF
LI30	Lysis index at 30 min	%	Residual clot firmness at 30 min after CT, described in % of MCF
LI60	Lysis index at 60 min	%	Residual clot firmness at 60 min after CT, described in % of MCF
LOT	Lysis onset time	s	Time from CT until clot firmness is decreased by 15% as compared to the MCF
ROTEM™ *delta* research parameters			
MCE	Maximum clot elasticity	–	MCE = 100 x MCF / (100 – MCF)
G	Shear elastic modulus strength	–	G = 5000 x MCF / (100 – MCF)
TPI	Thrombodynamic potential index	s^{-1}	TPI = MCE / CFT
LT	Lysis time	s	Time from CT until the clot firmness is decreased to 10% as compared to the MCF
CLR	Clot lysis rate	degree (°)	Angle between the baseline and the tangent to the declining clot firmness curve
ROTEM™ *delta* research parameters for the first derivative curve (Sørensen 2003)			
maxV	Maximum velocity	mm/min	Maximum of the first derivative of the curve
maxV-t	Time to maximum velocity	s	Time from test start until the maximum of the first derivative of the curve is reached
AUC	Area under the curve	mm × min	Area under the curve of the first derivative from test start until MCF is reached

Courtesy of Klaus Görlinger, Tem Innovations, Munich, Germany

a lot of inappropriate prophylactic interventions with FFP or PCC can be avoided without increased incidence of bleeding complications [28, 106–116]. Furthermore, EXTEM and FIBTEM CT correlate well with plasma concentrations of DOAC measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (e.g., dabigatran (r = 0.92–0.99) and rivaroxaban (r = 0.83)) [24–27]. Here, ECATEM CT prolongation is highly specific for direct thrombin inhibitors such as dabigatran, argatroban, and bivalirudin (r = 0.85–0.99) [79–81].

The clot formation time (*CFT*) in seconds indicates the time between 2 and 20 mm clot firmness amplitude is achieved. The CFT corresponds to the kinetic time (k) of TEG™ assays and reflects the kinetic of clot formation. CFT mainly depends on thrombin generation, platelet count and platelet function, as well as fibrinogen concentration and fibrin polymerization and correlates well but nonlinearly with maximum clot firmness (r = 0.89) [31]. However, CFT can also be prolonged due to anticoagulants.

The alpha angle (α) in degree (°) reflects the kinetics of clot formation, too, and is defined as the angle between the baseline and a tangent to the clotting curve through the 2 mm point. Since the alpha angle reflects the combined contribution of fibrinogen and platelets to clot strength, it cannot really be used to discriminate between fibrinogen and platelet deficits [39]. The combination of EXTEM and FIBTEM clot firmness parameters (A5, A10, or MCF) is needed for accurate discrimination [13, 14, 23, 32, 33, 37, 38, 41].

Clot Propagation (Clot Firmness) Parameters

One of the most important ROTEM™ parameters is maximum clot firmness (*MCF*) in mm which corresponds to the maximum amplitude (MA) of TEG™ assays. MCF is defined as the maximum amplitude of clot firmness reached during test runtime. Usually it takes about 30 min after CT to achieve MCF. The clot firmness amplitude reflects the mechanical strength of the clot and mainly depends on platelet count and platelet function, fibrinogen concentration and fibrin polymerization, factor XIII activity, and colloids.

In order to speed up decision-making in severe bleeding, the amplitude of clot firmness 5 or 10 min after CT (*A5* or

A10, respectively) is increasingly being used. A20 is used during quality control measurements. A5 and A10 correlate very well with the MCF (Spearman's coefficient of 0.91–0.98) and allow for decision-making within 10 to 15 min after starting the test [6, 13, 31–33, 41]. EXTEM and INTEM A5, A10, and MCF correlate with platelet count (r = 0.61–0.89) and fibrinogen concentration (r = 0.61–0.82) [13, 32, 41, 54–60, 63, 64]. FIBTEM A5, A10, and MCF correlate well with plasma fibrinogen concentration (r = 0.69–0.88) and factor XIII activity (r = 0.60) [13, 32, 41, 54–60, 63–65, 117, 118]. However, this correlation can be modified by several factors as summarized in Table 6.4 (Table 6.4). Finally, the calculated parameters PLTEM A5, A10, and MCF (EXTEM A5 (A10, MCF) – FIBTEM A5 (A10, MCF)) correlate well with platelet count (r = 0.64–0.90) [13, 63, 64, 145]. Notably, clot firmness parameters are superior in predicting bleeding compared to platelet count [146–150]. Furthermore, low clot firmness values have been demonstrated to be associated with an increased risk of hyperfibrinolysis. An EXTEM A5 ≤35 mm can identify more than 90% of patients developing hyperfibrinolysis, finally [33]. This is in line with the threshold of EXTEM A5 ≤35 mm reported by Davenport et al. to identify trauma-induced coagulopathy on arrival in the emergency room [151].

Table 6.4 Modification of the correlation between plasma fibrinogen concentration assays and FIBTEM clot firmness parameters (A5, A10, MCF)

Modification of the correlation between plasma fibrinogen concentration assays and FIBTEM clot firmness parameters (A5, A10, MCF)	
Plasma fibrinogen concentration assays in g/L (fibrinogen concentration measurement)	FIBTEM clot firmness parameter (A5, A10, MCF) in mm (fibrin polymerization measurement)
Different *measurement platforms* (intraclass correlations coefficients (ICC) for fibrinogen between 0.37 and 0.66 and for PT between 0.19 and 0.80) [119]	Differences between ROTEM *delta* and ROTEM sigma (ROTEM sigma A5 correlates better to Clauss fibrinogen (r = 0.85) compared to ROTEM *delta* (r = 0.70)) [118]
Intra-laboratory and *inter-laboratory variability* (0.02–0.04 and 0.01–0.10, resp.) [119]	Intra-operator and *inter-operator variability* (FIBTEM MCF CV = 8.3% vs. 6.9%, resp.) [7]
–	*Technical improvements in* ROTEM *sigma*: new mixer and firmware improves early availability of cytochalasin D (in FIBTEM C)
–	*Reagent improvements in* ROTEM *sigma*: FIBTEM versus FIBTEM PLUS (improved FIBTEM formulation containing cytochalasin D + albumin + GPIIbIIIa receptor antagonist) in the newest FIBTEM C version [120–122]
No effect of *hematocrit* because fibrinogen concentration is assessed in plasma after blood centrifugation	Effect of *hematocrit:* correlation between FIBTEM MCF and plasma fibrinogen is higher at lower hematocrit (<25%; r = 0.88) than at higher hematocrit (>30%; r = 0.67) [123]; in cardiac surgery with CPB: preoperative (r = 0.68) and post-protamine (r = 0.72) [124]
PT-derived versus Clauss fibrinogen: *dysfibrinogenemia* affects Clauss fibrinogen and PT-derived fibrinogen, differently [125]	FIBTEM MCF has a high sensitivity toward detection of different *congenital fibrinogen disorders* [126]
Effect of *factor XIII deficiency*: although Clauss fibrinogen was normal (at factor XIII activity of 20 ± 6 IU/dL), coagulation in FIBTEM was impaired, which FXIII administration tended to correct [127]	Effect of *factor XIII deficiency*: FIBTEM MCF is positively correlated with factor XIII activity (cirrhosis, r = 0.60; cardiac surgery, r = 0.32–0.56) [65, 68]
Effect of *colloids (HES > gelatin > albumin)*: increased turbidity results in overestimation of fibrinogen concentration in photo-optical Clauss methods [128], pronounced effect in Clauss reagents calibrated for low fibrinogen concentrations [129, 130]	Effect of *colloids (HES > gelatin > albumin)*: impaired fibrin polymerization results in low FIBTEM MCF [128]
PT-derived versus Clauss fibrinogen: effect of *heparin*; neither Clauss fibrinogen nor PT-derived fibrinogen is valid in the setting of high concentrations of heparin (on CPB) [131]; Clauss fibrinogen is significantly lower during CPB than after protamine (mean difference 1.2 g/L (95% CI, 1.03–1.4 g/L) [14]	*FIBTEM S (SUR without heparin inhibitor) versus FIBTEM (liquid) and FIBTEM C (beads in cartridge) (with heparin inhibitor; 5 IU/mL)*; FIBTEM MCF (liquid reagent) on CPB versus Clauss fibrinogen post-CPB, r = 0.78 [15]; FIBTEM S MCF correlation to plasma fibrinogen: pre-reperfusion period (LTX), r = 0.789; post-reperfusion period, r = 0.170 (contraindication for single-use reagents (SUR) according to the ROTEM instructions for use (IFUs)) [132]
Effect of *direct thrombin inhibitors* (DTIs: dabigatran, argatroban, bivalirudin): underestimation of plasmatic fibrinogen concentration with high variability between different turbidimetric assays [133]	Effect of *direct thrombin inhibitors* (DTIs: dabigatran, argatroban, bivalirudin): FIBTEM MCF is reliable even under high DTI concentrations [134–136]
Prediction of major bleeding (progress) and management of transfusion in cardiovascular surgery, liver transplantation, trauma, and PPH: plasma fibrinogen concentration is inferior to FIBTEM to predict (progress of) bleeding and massive transfusion [41, 137–139] and to guide bleeding management and improve patient outcomes in these clinical settings [9, 140–145]	*Prediction of major bleeding* (progress) and management of transfusion in cardiovascular surgery, liver transplantation, trauma, and PPH: FIBTEM (A5, A10, MCF) is superior to plasma fibrinogen concentration to predict (progress of) bleeding and massive transfusion [41, 137–139] and to guide bleeding management and improve patient outcomes in these clinical settings [9, 140–145]; e.g., FIBTEM A5 adjusted OR (95% CI; *P-value*) to predict progression of total blood loss >2500 mL in PPH, 0.85 (0.77–0.95; *P = 0.002*), versus Clauss fibrinogen, 0.93 (0.49–1.74; *P = 0.813*) [138]

Courtesy of Klaus Görlinger, Essen, Germany

A5 amplitude of clot firmness 5 min after CT, *A10* amplitude of clot firmness 10 min after CT, *CPB* cardiopulmonary bypass, *CV* coefficient of variation, *DTI* direct thrombin inhibitor, *HES* hydroxyethyl starch, *MCF* maximum clot firmness, *OR* odds ratio, *PT* prothrombin time, *r* Spearman's correlation coefficient rho, *SUR* single-use reagent

Clot Lysis Parameters

The clot lysis parameters maximum lysis (*ML*) and the lysis indices 30, 45, and 60 (*LI30, LI45*, and *LI60*) provide information about the activity of fibrinolytic enzymes, fibrinolytic inhibitors, and factor XIII [72–74, 152–154]. ML detected during runtime is described as the reduction in clot firmness after MCF was achieved in percentage of MCF. LI30, LI45, and LI60 indicate the remaining clot firmness in percentage of MCF still present 30, 45, and 60 min after CT, respectively. Notably, lysis parameters in TEG™ are defined differently regarding the time of assessment. The TEG™ lysis parameters LY30 and LY60 indicate the amount of lysis in percentage of MA, 30 and 60 min after MA is achieved. Accordingly, LY30 in TEG™ corresponds more closely to LI60 in ROTEM™ regarding runtime. The ROTEM™ lysis onset time (*LOT*) in seconds is characterized by the time period from CT until 15% of clot lysis is achieved [155, 156]. Notably, the correlation between severity of fibrinolysis and patient outcomes seems to be setting-specific. Whereas in severe trauma fibrinolysis within 1 h runtime >7.7% in rTEG and >18% in EXTEM is associated with increased mortality, even 50% fibrinolysis during the anhepatic and graft reperfusion phase of liver transplantation is not [157–160]. Notably, FIBTEM is much more sensitive and specific for the detection of hyperfibrinolysis compared to kaolin-TEG, rapid-TEG, or EXTEM [69, 70].

On the other hand, fibrinolysis shutdown (<2% fibrinolysis within 1 h runtime) can be associated with increased mortality even in trauma [157–159, 161]. Notably, fibrinolysis shutdown seems to play a major role in the pathophysiology of myocardial infarction, thrombosis, sepsis, and DIC [83, 85, 162–165].

Limitations of Viscoelastic Testing

A major limitation of standard viscoelastic testing is its insensitivity to the effects of antiplatelet drugs (e.g., cyclooxygenase-1 (COX-1) inhibitors and ADP ($P2Y_{12}$) receptor inhibitors) [93, 166]. This limitation is caused by the generation of high amounts of thrombin in viscoelastic test systems which mask the effects of antiplatelet drugs by stimulating the platelets via the thrombin receptor pathway (protease-activated receptor (PAR) 1 and 4). Since thrombin is the strongest activator of platelets, the inhibition of other pathways (e.g., arachidonic acid or ADP pathway) does not affect viscoelastic test results in the presence of high amounts of thrombin.

Furthermore, standard ROTEM™ and TEG™ assays are not sensitive to von Willebrand disease since the system does not include a collagen surface and does not induce high sheer stress [167]. However, a modification of ROTEM™ assays including a preincubation of the blood sample with ristocetin showed some promising results to improve test performance in patients with von Willebrand disease [168].

As shown in some case reports, CT in EXTEM and INTEM can be prolonged in patients with antiphospholipid syndrome (lupus anticoagulant) without increased bleeding tendency [169, 170]. However, ROTEM data in patients with antiphospholipid syndrome are sparse.

Finally, viscoelastic testing cannot detect endotheliopathy directly since endothelial cells have been included in the test system for research, only [171]. Indirectly, endotheliopathy can be detected by the presence of hyperfibrinolysis and heparin-like effects (HLE). The HLE occurs due to a damage of the endothelial glycocalyx in severe trauma/shock, infection/sepsis, and cirrhosis/liver transplantation with a subsequent endogenous heparinization [88, 172, 173]. The combination of severe hyperfibrinolysis and HLE can result in a flat-line – in particular in TEG™. In case of a flat-line in ROTEM™, an APTEM should be performed since this is actually the only viscoelastic assay available, which blocks both – hyperfibrinolysis and a HLE – and therefore allows for assessing residual hemostasis under these conditions [174].

ROTEM™ *Platelet* Module

To overcome the platelet function limitations, ROTEM™ *delta* can be combined with the ROTEM™ *platelet* module, which is CE-marked in Europe since November 2013 [46, 175]. It provides two channels for whole blood impedance aggregometry in addition to the four viscoelastic channels of ROTEM™ *delta* (Fig. 6.1a, c–e). Arachidonic acid (*ARATEM*), adenosine diphosphate (*ADPTEM*), and thrombin receptor-activating peptide-6 (*TRAPTEM*) can be used as activators in ROTEM™ *platelet*. The corresponding reagents are designed as user-friendly lyophilized single-use reagents. The main parameters of ROTEM™ platelet are the area under the curve (AUC in Ohm x min), the amplitude at 6 min (A6 in Ohm), and the maximum slope (MS in Ohm/min). AUC is the clinically most important parameter and reflects the overall platelet aggregation (Fig. 6.1e).

Platelet function analysis is much more susceptible to pre-analytic factors such as the anticoagulant used (citrate, lithium heparin, or hirudin), the size of the blood sampling vial, transportation with a pneumatic system, and resting time of the blood sample before analysis [176–179]. Therefore, these pre-analytic factors have to be standardized and validated, and hospital-specific reference ranges and cut-off values for therapeutic interventions should be established.

Whole blood impedance aggregometry has been shown to detect the effect of COX-1 inhibitors and ADP receptor inhibitors, effectively, and to predict stent thrombosis/ischemic events and bleeding/platelet transfusion in interventional cardiology and cardiac surgery [45–48, 51, 93, 180–184]. Furthermore, the effects of drugs, such as desmopressin, tranexamic acid, and protamine, on platelet function can be assessed by whole blood impedance aggregometry [185–189]. Beyond drug monitoring, the effect of cardiopulmonary bypass, extracorporeal life support such as extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD), liver transplantation, trauma, and sepsis can be assessed with whole blood impedance aggregometry [49, 50, 189–194].

Predictive Value of Thromboelastometry and Impedance Aggregometry

The positive predictive value of thromboelastometry and impedance aggregometry to predict bleeding in elective surgery is low (15–50%), but the negative predictive value is very high (80–97%) [50, 139, 195, 196]. Therefore, pathologic thromboelastometry or impedance aggregometry results do not mean that the patient has to bleed. This is not a surprise since hemostasis provides several compensatory mechanisms such as high factor VIII levels in patients with low levels of vitamin K-dependent coagulation factors due to cirrhosis and high fibrinogen levels in patients with thrombocytopenia. Accordingly, pathologic thromboelastometry or impedance aggregometry results should only be treated in the presence of clinically relevant bleeding requiring a hemostatic intervention (*Don't treat numbers!*). In contrast to patients scheduled for elective surgery, in patients with preexisting hemostatic disorders, such as liver cirrhosis, trauma, sepsis, or specific drug effects, thromboelastometry and impedance aggregometry provide a positive predictive value, too [41, 49, 139, 193, 194, 197–200].

However, it is rather the question "Why does this patient bleed?" than "Will this patient bleed?" which can be answered by thromboelastometry and impedance aggregometry in the perioperative setting. Accordingly, the main advantage of thromboelastometry and impedance aggregometry is to identify or exclude a specific hemostatic disorder as the reason for bleeding in a timely manner, and ROTEM™ algorithms have to be understood as "*not-to-do algorithms*" by step-by-step exclusion of different coagulopathic reasons for bleeding. If both thromboelastometry and impedance aggregometry show normal results, the probability of coagulopathic bleeding is very low (<5%), and the patient should be rechecked for surgical reasons for bleeding (Fig. 6.3).

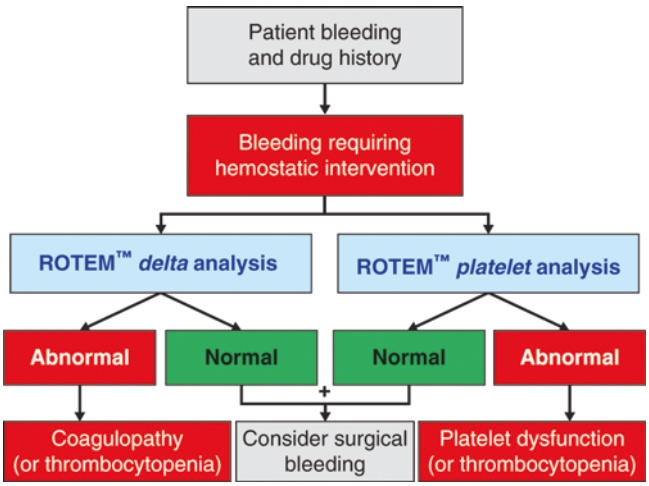


Fig. 6.3 ROTEM™ diagnostics flowchart (improved diagnostic performance by combining thromboelastometry (ROTEM™ *delta*) with whole blood impedance aggregometry (ROTEM™ *platelet*)) (Courtesy of Klaus Görlinger, Essen, Germany)

Prediction of Progress of Bleeding and (Massive) Transfusion

Plasma transfusion may improve outcome in patients requiring massive transfusion, whereas plasma transfusion in patients not requiring massive transfusion only shows an increase in complication rates, such as transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM), nosocomial infection, and sepsis [108, 116, 200–202]. However, prophylactic or inappropriate platelet transfusion might even be more harmful in several clinical settings [116, 203–208]. Thus, early prediction of massive transfusion is crucial for decision-making to start plasma transfusion in severe trauma, postpartum hemorrhage (PPH), and major surgery [138, 209, 210]. On the one hand, the need for massive transfusion can be predicted based on clinical scoring systems and, on the other hand, based on thromboelastometry (A5, A10, or MCF in INTEM, EXTEM, or FIBTEM) or impedance aggregometry results (AUC in TRAPTEM or ADPTEM) on arrival in the ER [41, 49, 151, 198, 211–213]. In these trauma studies, the optimum cut-off value to predict massive transfusion has been identified as EXTEM A5 ≤35 mm, INTEM A10 ≤44 mm, and FIBTEM A10 (MCF) ≤7 (9) mm [151, 198, 212]. None of the patients with a FIBTEM A10 ≥12 mm on admission received a massive transfusion finally [198]. EXTEM A5 (≤35 mm) was more accurate in predicting massive transfusion than INR (>1.2) [151]. These findings have been confirmed by an international prospective validation study in 808 trauma patients, identifying an optimum threshold for EXTEM A5 ≤40 mm and for FIBTEM A5 ≤9 mm (plasma fibrinogen

concentration ≤1.9 g/L) as a valid marker for TIC and predictor for massive transfusion [41]. Accordingly, the panel of the "2014 consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation" and the authors of the Lancet Neurology paper about the management of coagulopathy in traumatic brain injury recommend thresholds for EXTEM A5 (A10, MCF) <35 (45, 55) mm and for FIBTEM A5 (A10, MCF) <9 (10, 12) mm to consider platelet or fibrinogen administration in bleeding trauma patients, respectively [23, 214]. This is in line with the results of the prospective observational multicenter TACTIC trial, recommending a threshold of FIBTEM A5 <10 mm for fibrinogen replacement and a threshold of PLTEM A5 (EXTEM A5 – FIBTEM A5) <30 mm for platelet transfusion in bleeding trauma patients [215]. Chapman et al. could identify an optimum threshold for TRAPTEM of <53 Ohm x min (ROC AUC, 0.97) and for ADPTEM of <43 Ohm x min (ROC AUC, 0.95) in citrated blood samples at hospital admission for prediction of massive transfusion by impedance aggregometry using ROTEM™ platelet [49].

Similar cut-off values have been published to predict bleeding and transfusion in other perioperative settings. In postpartum hemorrhage (PPH), on multivariate analysis FIBTEM A5, but not plasma fibrinogen concentration, was independently associated with progression to bleeds >2500 mL and transfusion of at least 8 units of blood products [138]. Here, women with progression had a median (IQR) FIBTEM A5 and Clauss fibrinogen of 12 (7–17) mm and 210 (180–340) mg/dL, respectively, compared with 19 (17–23) mm and 390 (320–450) mg/dL for those not progressing. FIBTEM A5 was available about 10 min and Clauss fibrinogen about 65 min after venipuncture in this study. The higher fibrinogen requirements in PPH fits well with the increased reference ranges for FIBTEM and Clauss fibrinogen at the end of pregnancy [99–101, 103, 118]. A threshold of FIBTEM A5 <12 mm for fibrinogen replacement could also be confirmed by a randomized controlled trial assessing the effect of FIBTEM-guided fibrinogen concentrate administration versus placebo for treatment of postpartum hemorrhage as well as in an implementation study in Wales [145, 216, 217].

The best predictive value for bleeding in patients undergoing cardiac surgery with cardiopulmonary bypass has been identified as FIBTEM MCF <8 mm (plasma fibrinogen concentration <1.8 g/L) [137]. In patients preoperatively treated with thienopyridines (ADP receptor antagonists), the best cut-off value to predict bleeding for ADPtest (impedance aggregometry performed with Multiplate™, Roche Diagnostics, Mannheim, Germany) was 31 U (with a negative predictive value of 92% and a positive predictive value of 29%) [195]. If TRAPtest was ≥75 U, even ADPtest <22 U was not associated with severe bleeding (negative predictive value, 100%) [196]. A comparative study between the two impedance aggregometry devices Multiplate™ and the ROTEM™ *platelet* device identified the best cut-off value to predict bleeding at 5–10 min after heparin reversal with protamine as ASPItest ≤26 U, ARATEM ≤15 Ohm x min, ADPtest ≤33 U, ADPTEM ≤36 Ohm x min, TRAPtest ≤78 U, and TRAPTEM ≤78 Ohm x min. Transfusion requirements correlated significantly with the degree of inhibition and the number of platelet activation pathways inhibited [50]. This is in line with the results of other authors [195, 196].

In liver transplantation, the cut-off values that best predict bleeding and transfusion have been determined as EXTEM A10 (MCF) ≤35 (44) mm and FIBTEM A10 (MCF) ≤8 (9) mm [139, 197, 218].

Prediction of Thrombotic/Thromboembolic Events

Three important mechanisms are involved in the pathophysiology of DIC, microvascular thrombosis, and multiple organ failure: hypercoagulability, characterized by an increased clot firmness in EXTEM, INTEM (MCF >68 mm), and FIBTEM (MCF >22 mm); tissue factor (TF) expression on circulating monocytes and microparticles, characterized by a shortening of CT in NA-HEPTEM despite prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT); and fibrinolysis shutdown, characterized by less than 3% fibrinolysis within 1 h in NA-HEPTEM [73, 83–85, 104, 170]. This triad results in delocalization/dissemination of clot formation and microthrombosis and a simultaneous shutdown of the physiologic fibrinolytic cleaning system. Accordingly, it seems to be important to detect the time point when TIC shifts to DIC in trauma patients. This may also be one reason why tranexamic acid increased mortality in the CRASH-2 and WOMAN trial when given later than 3 h after injury [219–221] and why a fibrinolysis shutdown (here defined as LI60 >98% in EXTEM (<2% lysis in EXTEM within 60 min after CT) or LY30 <0.6% in rapid-TEG™ (<0.6% lysis within 30 min after MA)) detected in trauma patients at hospital admission was associated with increased mortality due to multiple organ failure [157–159].

By avoiding overtreatment and consecutive thrombotic/thromboembolic events, thromboelastometry is not only effective in stopping bleeding timely by guide therapy but is also a step forward to safer patient care [9, 140–145, 222–225].

Clot Firmness in EXTEM, INTEM, and FIBTEM

In a prospective observational study in 69 patients with cardiovascular diseases, Dimitrova-Karamfilova et al. assessed the ability of routine coagulation tests (PT, aPTT, fibrinogen, and platelet count) and ROTEM™ tests to identify patients with hypercoagulability and thrombotic complications [226]. No statistically significant difference could be found for routine coagulation tests. In contrast, significant difference in ROTEM™ parameters could be observed in the 35 patients with thrombotic complications compared to the 34 healthy controls. In particular, EXTEM and INTEM CFT and MCF were able to identify patients with thrombotic complications using a MCF cut-off value of >68 mm with a sensitivity and specificity of 94%. FIBTEM MCF, with a cut-off of >24 mm, achieved only a sensitivity and specificity of 77% and 88%, respectively. This suggests that an elevated fibrinogen level which compensates for a low platelet count seems not to increase the thrombotic risk. The EXTEM and INTEM thrombodynamic potential index (TPI = (100 × MCF/100 – MCF)/CFT), with a cut-off value of >3.5, provided even a sensitivity and specificity of 100% and 92%, respectively. In conclusion, ROTEM™ analysis was definitively superior to routine coagulation tests in identifying patients with thrombotic complications.

These results could be confirmed by another recently published prospective observational study in 318 noncardiac surgery patients. Hincker et al. evaluated preoperative routine coagulation tests (aPTT, INR, and platelet count) and ROTEM™ tests to identify patients at increased risk for postoperative thromboembolic complications [227]. Twenty-nine percent of the included patient population has been recruited from the orthopedic and spine department. Again, none of the routine coagulation tests has been useful in predicting thromboembolic events, but preoperative EXTEM and INTEM CFT, alpha angle, A10, and MCF were predictive for thromboembolic complications. INTEM and EXTEM A10 were the best predictors with a cut-off value of 61.5 mm and a ROC AUC of 0.75 and 0.72, respectively. None of the FIBTEM parameters predicted thromboembolic complications, confirming that elevated fibrinogen levels alone seem not to be an independent risk factor for thrombosis. However, increased FIBTEM MCF values (>19 mm) may play a role in non-cirrhotic and cirrhotic patients with portal vein thrombosis [170, 228–230] and in patients with increased flap loss rate (EXTEM MCF >72 mm and FIBTEM MCF >25 mm) in patients undergoing reconstructive microsurgery [231].

In obese patients, hypercoagulability (increased MCF in INTEM, EXTEM, and FIBTEM) and hyperaggregability (increased AUC in impedance aggregometry) can be detected, too. Here, hypercoagulability correlates with body mass index (BMI) and inflammatory markers [232].

Tissue Factor Expression on Monocytes, Microparticles, and Malignant Cells

Stimulation with bacterial toxins, activation of purinergic (ADP) receptors ($P2X_7$), stimulation by activated platelets, contact with surfaces of extracorporeal assist devices (e.g., cardiopulmonary bypass, ECMO, VAD, dialysis), and ischemia/reperfusion lead to tissue factor (TF) expression on circulating monocytes [73, 83–86, 104]. This TF expression in the intravascular space results in delocalization/dissemination of coagulation and is an early and important pathomechanism of DIC and thrombosis. Similar effects have been observed in patients with malignancies [229, 230, 233, 234]. TF expression on circulating cells can be detected very sensitively (in picomolar concentrations) but not specifically by a reduction in CT in NA-HEPTEM [83–86]. Since heparinoids (e.g., by glycocalyx degradation or therapeutic administration) can mask this effect, NA-HEPTEM – and not just NATEM – should be used in order to eliminate any interference by a potential heparin effect [83].

Notably, TF-expressing monocytes inhibit fibrinolysis through a thrombin-activatable fibrinolytic inhibitor (TAFI)-mediated mechanism, which is the next step to microthrombosis and multiple organ failure [235].

Hypofibrinolysis (Fibrinolysis Shutdown)

In contrast to TIC, physiologic fibrinolysis is shut down in the early phase of infection, sepsis, and thrombosis due to an upregulation of plasmin activator inhibitor type-1 (PAI-1) and activation of TAFI [85, 235–237]. Notably, whether the thrombin-thrombomodulin complex results in activation of protein C, with subsequent downregulation of PAI-1 and activation of fibrinolysis, or activation of TAFI – with subsequent shutdown of fibrinolysis – is regulated by platelet factor 4 (PF4) and dependent on the consumption of protein C as well as genetic polymorphisms [238, 239].

However, Chapman et al. could demonstrate that not only increased fibrinolysis but also a fibrinolysis shutdown at hospital admission is associated with increased mortality in trauma patients due to multiple organ failure [157–159]. Accordingly, Adamzik et al. showed that the ROTEM™ LI60 in NA-HEPTEM can discriminate between intensive care patients suffering from severe bacterial sepsis (NA-HEPTEM LI60 >96.5% corresponding to a ML <3.5% within 1 h after CT) and postoperative patients with just systemic inflammatory response syndrome (SIRS) or healthy volunteers [83]. Furthermore, the LI60 (ROC AUC, 0.901; $P < 0.001$) proved to be more accurate in detection of bacterial sepsis than classical laboratory parameters such as procalcitonin (ROC AUC, 0.75; $P < 0.001$). Interleukin-6 and C-reactive protein were not able to differentiate between sep-

tic and postoperative patients. The same research group also found that ROTEM™ findings were a better predictor of 30-day survival in septic patients than established risk scores (SAPS II, SOFA) [199].

In conclusion, both hyper- and hypofibrinolyis seem to play an important role in the pathophysiology of TIC and DIC, and viscoelastic testing may be helpful in differentiating between both pathophysiologic entities and right decision-making regarding the appropriate use and timing of antifibrinolytic therapy.

Prediction of Mortality

Viscoelastic testing has been shown to be a good predictor of mortality in trauma in a recently published systematic review of the literature [40, 217]. Levrat et al. included 87 trauma patients in a prospective observational trial. Patients with hyperfibrinolysis were more severely injured, had greater coagulation abnormalities, and had a higher mortality rate (100% vs. 11%) [240]. Schöchl et al. identified in their database 33 patients with hyperfibrinolysis at hospital admission retrospectively. They found hyperfibrinolysis to be a strong predictor for mortality (88%). Furthermore, it appeared that the earlier fibrinolysis could be detected by viscoelastic testing, the earlier the patient died, irrespective of appropriate treatment [241]. Theusinger et al. showed that in their patient population mortality in the trauma hyperfibrinolysis group (77%), as diagnosed by ROTEM™, was significantly higher than in the non-trauma hyperfibrinolysis group (41%) and the matched trauma non-hyperfibrinolytic group (33%). Accordingly, hyperfibrinolysis was significantly ($p = 0.017$) associated with increased mortality in trauma [242]. In contrast, even 50% fibrinolysis during liver transplantation is not associated with increased mortality [160].

In a prospective cohort study including 517 trauma patients, Rourke et al. found admission fibrinogen level to be an independent predictor of mortality at 24 h and 28 days. Hypofibrinogenemia could be detected early by FIBTEM A5 (A10), and administration of cryoprecipitate or fibrinogen concentrate could correct coagulopathy and improved survival [146]. Similar results were shown in a prospective cohort study in 334 blunt trauma patients performed by Tauber et al. They identified cut-off values of FIBTEM MCF <7 mm and EXTEM MCF <45 mm as predictors for increased mortality. EXTEM MCF was independently associated with early mortality, and hyperfibrinolysis increased fatality rates, too [212].

Furthermore, early platelet dysfunction after trauma and in sepsis is associated with increased mortality [49, 193, 194].

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Whole Blood Assay: Thromboelastometry – Bleeding Management Algorithms

7

Klaus Görlinger, James Iqbal, Daniel Dirkmann, and Kenichi A. Tanaka

Pathophysiology of Perioperative Hemostasis

In contrast to hereditary bleeding disorders, pathophysiology of posttraumatic or perioperatively acquired bleeding is most often multifactorial [1–5]. For example, trauma-induced coagulopathy (TIC), disseminated intravascular coagulation (DIC), and coagulopathy in liver cirrhosis are different pathophysiological entities requiring different treatment strategies [2, 5–11]. Notably, patients can be at risk of bleeding and thrombosis at the same time [12, 13].

One common issue in perioperative bleeding is that bleeding, coagulopathy, and transfusion are independent risk factors for poor outcomes and can build up each other in a vicious circle [14]. Furthermore, preexisting issues such as anemia, coagulopathy, drug effects, genetic factors, trauma, inflammation, and surgical bleeding can aggravate the vicious circle of perioperative bleeding. Other amplification factors can be shock, hypoperfusion, acidosis, hypothermia, hemodilution, inappropriate transfusion, transfusion-associated adverse events, nosocomial infection, and sepsis [15]. Finally, this can result in single or multiple organ failure.

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The best way to avoid this vicious circle is to identify the specific hemostatic deficits, to stop bleeding as soon as possible, and to avoid any inappropriate or unnecessary blood transfusion. This was addressed in the "STOP the Bleeding Campaign" initiated by the authors of the updated European trauma guidelines in 2013 [16]. Here the acronym "*STOP*" comprises the following elements: *Search* for patients at risk of coagulopathic bleeding; *Treat* bleeding and coagulopathy as soon as they develop; *Observe* the response to interventions; *Prevent* secondary bleeding and coagulopathy. However, overtreatment should be avoided to prevent thrombotic or thromboembolic events in the postoperative phase [17–19]. Here, a "therapeutic window" concept may address this issue most appropriate [20, 21]. Due to the multifactorial pathophysiology of perioperative bleeding, a systematic diagnostic approach is needed to identify the underlying hemostatic disorder and to guide hemostatic therapy in a specific and timely manner. This approach is addressed in the terms "precision medicine," "personalized medicine," "goal-directed therapy," "targeted therapy," and "theranostic approach" [2, 6–8, 10, 11, 21–26].

Thromboelastometry-Guided Hemostatic Therapy

Development of Thromboelastometry-Guided Algorithms

Pathophysiology of posttraumatic and perioperative bleeding is complex and cannot always be addressed adequately by hemostatic resuscitation (1:1:1 concept) only [7, 27, 28]. In order to guide hemostatic therapy in bleeding patients, algorithms have been developed as a link between ROTEM™ diagnostics and hemostatic therapy ("theranostic approach") [6, 11, 20, 23, 29–33]. Due to the increasing number of publications and data available – the number of ROTEM™ publications nearly doubled in the last 3 years since the first edition of this textbook in 2016 – these algorithms changed

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from experience-based algorithms to evidence-based algorithms. Furthermore, these algorithms have been validated in big cohort studies and randomized controlled trials (RCTs) showing that the implementation of these algorithms is able to reduce transfusion requirements, complication rates, patient's morbidity and mortality, and health care costs, in particular in cardiovascular surgery [10, 17, 18, 34–46]. Several cohort studies reported similar results in liver transplantation, trauma, and postpartum hemorrhage (PPH), but only four RCTs have been published in the setting of trauma, burns, and pediatric orthopedic surgery [10, 11, 29, 37, 44, 47–62]. The RETIC trial randomized patients with TIC to a group treated with fresh frozen plasma (FFP) or to a group treated with coagulation factor concentrates guided by ROTEM™ [62]. The study had to be stopped early since the FFP group failed after two rounds of FFP (2 × 15 mL/kg body weight) in 52% to stop bleeding and to correct coagulopathy. In contrast, the ROTEM™-guided administration of coagulation factor concentrates failed only in 4%. Furthermore, massive transfusion (12% vs. 30%, $P = 0.042$) and days on hemofiltration (11 vs. 27 days; $P = 0.038$) could be reduced significantly in the ROTEM™-guided group. In addition, there was a strong trend to reduce the incidence of multiple organ failure (50% vs. 66%; $P = 0.15$) and venous thrombosis (8% vs. 18%; $P = 0.22$) in the ROTEM™-guided group. Further RCTs have just been finalized or are still running [63–66].

Evidence-based ROTEM™-guided algorithms for bleeding management in severe trauma/major surgery, obstetric/postpartum hemorrhage, and cardiovascular surgery are presented in Fig. 7.1a–c and characteristic thromboelastometric traces in Fig. 7.2a–j.

Since the ROTEM™ parameter A5 is not yet FDA-approved (as of December 2019), ROTEM™-algorithms for the USA actually have to use A10, whereas A5 is used as clot firmness parameter in the rest of the world in order to speed up decision-making. Due to the good correlation and fixed bias between A5, A10, and MCF, ROTEM™ MCF, A10, and A5 algorithms can be converted to each other easily. The difference between A10 and A5 for FIBTEM is usually 1 mm and for EXTEM, APTEM, INTEM, and HEPTEM 8–10 mm [67–70]. The bias between early clot values (A5 and A10) and MCF is displayed in Table 7.1.

Clinical Assessment

Hemostatic interventions should be performed only in patients with diffuse bleeding and if blood transfusion is considered. Severity of trauma (ISS ≥25), clinical bleeding scores (e.g., TASH score ≥15), hemodynamic instability (e.g., hemorrhagic shock), hypothermia (core temperature <35 °C), and results of blood gas analysis (e.g., pH <7.2, BE <–6 mmol/L, Hb <10 g/dL, Ca_i^{++} <1 mmol/L) should be considered, too, since they may be associated with an increased risk of hyperfibrinolysis, hypofibrinogenemia, and decreased thrombin generation [30, 71, 72]. Accordingly, decision-making for hemostatic interventions should not be based on ROTEM™ results solely, in the absence of clinically relevant bleeding.

Furthermore, the concept behind an *evidence-based ROTEM™-guided bleeding management algorithm* is to administer the *right hemostastic drug/intervention*, in the *right dose*, at the right time, and in the *right sequence*. Accordingly, *vertical algorithms* with a clear sequence of diagnostic steps and interventions (Fig. 7.1a–c) should be preferred to horizontal algorithms which don't provide a ranking of pathologic ROTEM™ results [20]. Due to the low positive and high negative predictive value of ROTEM™ results for bleeding, ROTEM™ algorithms have to be understood as *"not-to do" algorithms*, which means:

- *Avoid inappropriate blood transfusion/hemostatic interventions* (high negative predictive value of 16–23%) [73].
- *Don't treat numbers (pathologic results) in the absence of clinically relevant bleeding* (low positive predictive value of 90–97%) [73].

Management of Fibrinolysis

Hyperfibrinolysis (≥18% within 60 min after CT) as well as fibrinolysis shutdown (≤2% within 60 min after CT) is associated with increased mortality in severe trauma due to bleeding on the one hand or multiple organ failure on the other hand [74]. Therefore, exogenous inhibition of the fibrinolysis system in severely injured patients requires careful selection, as it may have an adverse effect on survival, in particular if tranexamic acid is given later than 3 hours after injury [74–79]. In contrast to trauma and postpartum hemorrhage, even 50% fibrinolysis during liver transplantation is not associated with increased mortality but may be associated with an increased incidence of thrombotic events [76]. Therefore, it is still under discussion, whether antifibrinolytic drugs should be given prophylactically to every bleeding patients or not. The answer of this question seems to be dependent on the clinical setting, timing, application (bolus and/or continuous infusion), and dosing.

In order to enable quick decision-making, early thromboelastometric variables of clot firmness in EXTEM (A5 and A10) can be used to identify patients at risk for fibrinolysis. An EXTEM A5 threshold of ≤35 mm (EXTEM A10 ≤45 mm) detects more than 90% of patients which will develop hyperfibrinolysis, finally [80]. Notably, FIBTEM is more sensitive to fibrinolysis compared to EXTEM and kaolin-TEG [81, 82]. A flat-line in FIBTEM characterized

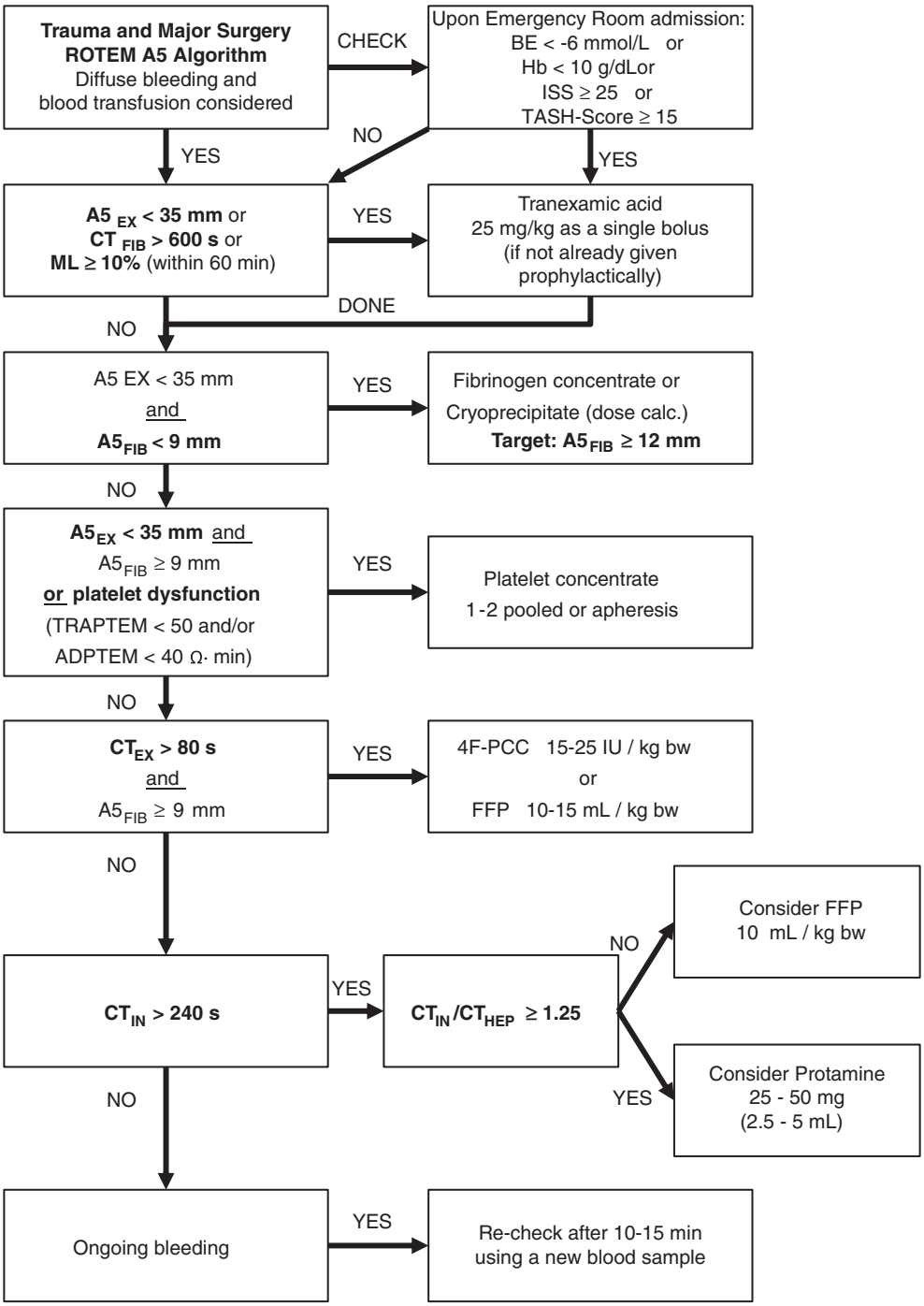


Fig. 7.1 (**a–c**) (**a**) Evidence-based ROTEM™ A5 bleeding management algorithm for severe trauma and major surgery. (**b**) Evidence-based ROTEM™ A5 bleeding management algorithm for obstetric/postpartum hemorrhage. (**c**) Evidence-based ROTEM™ A5 bleeding management algorithm for cardiovascular surgery. $A5_{EX}$, amplitude of clot firmness 5 min after CT in EXTEM; $A5_{FIB}$, amplitude of clot firmness 5 min after CT in FIBTEM; ACT, activated clotting time; BE, base excess; bw, body weight in kg; CT_{EX}, coagulation time in EXTEM; CT_{FIB}, coagulation time in FIBTEM (CT_{FIB} >600 s reflects a flat-line in FIBTEM); CT_{HEP}, coagulation time in HEPTEM; CT_{IN}, coagulation time in INTEM; FFP, fresh frozen plasma; Hb, hemoglobin concentration; ISS, injury severity score; IU, international units; ML, maximum lysis (within 1 hour run time); 4F-PCC, four-factor prothrombin complex concentrate; TASH score, trauma-associated severe hemorrhage score (Courtesy of Klaus Görlinger, Essen, Germany)

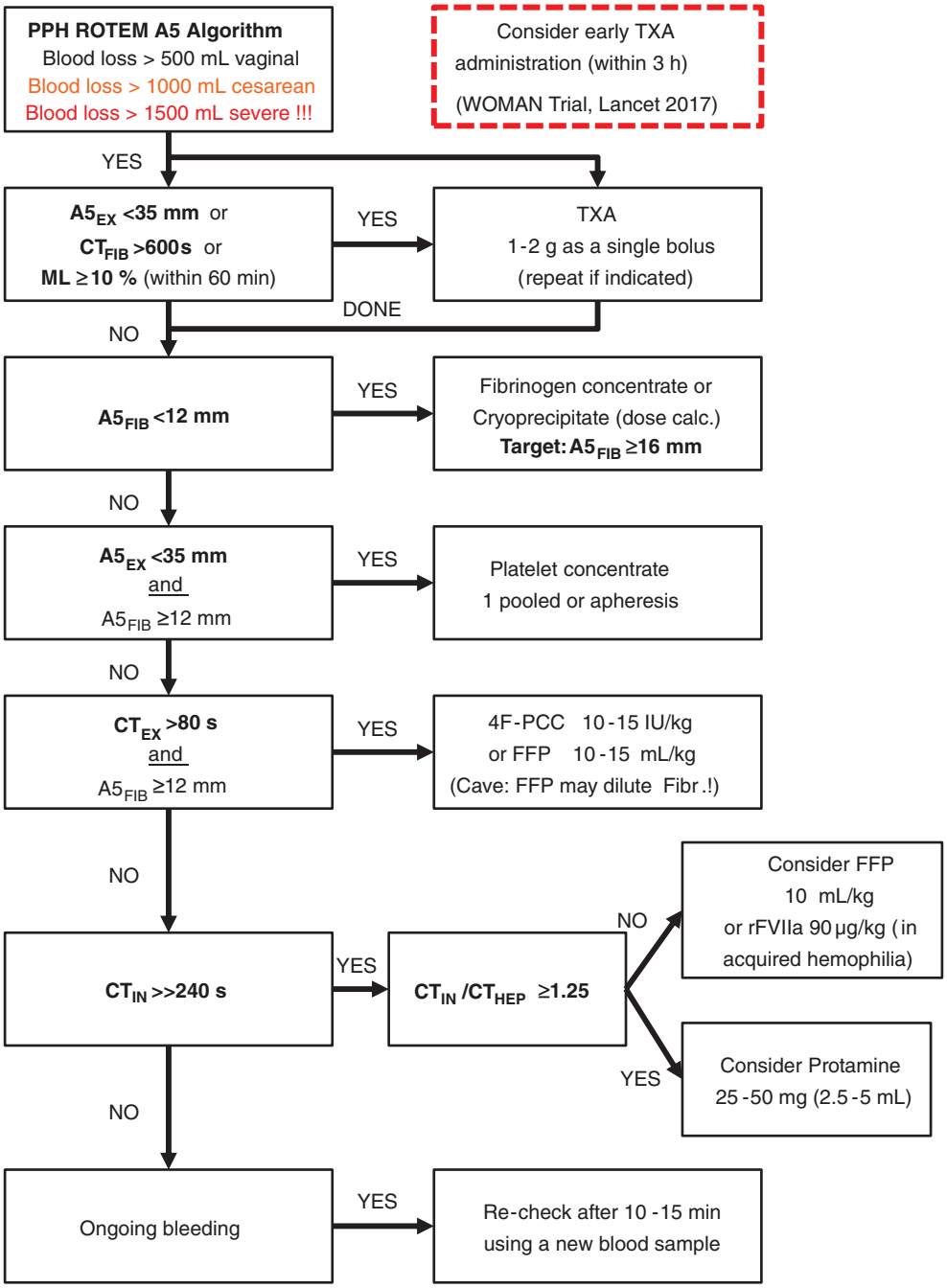


Fig. 7.1 (continued)

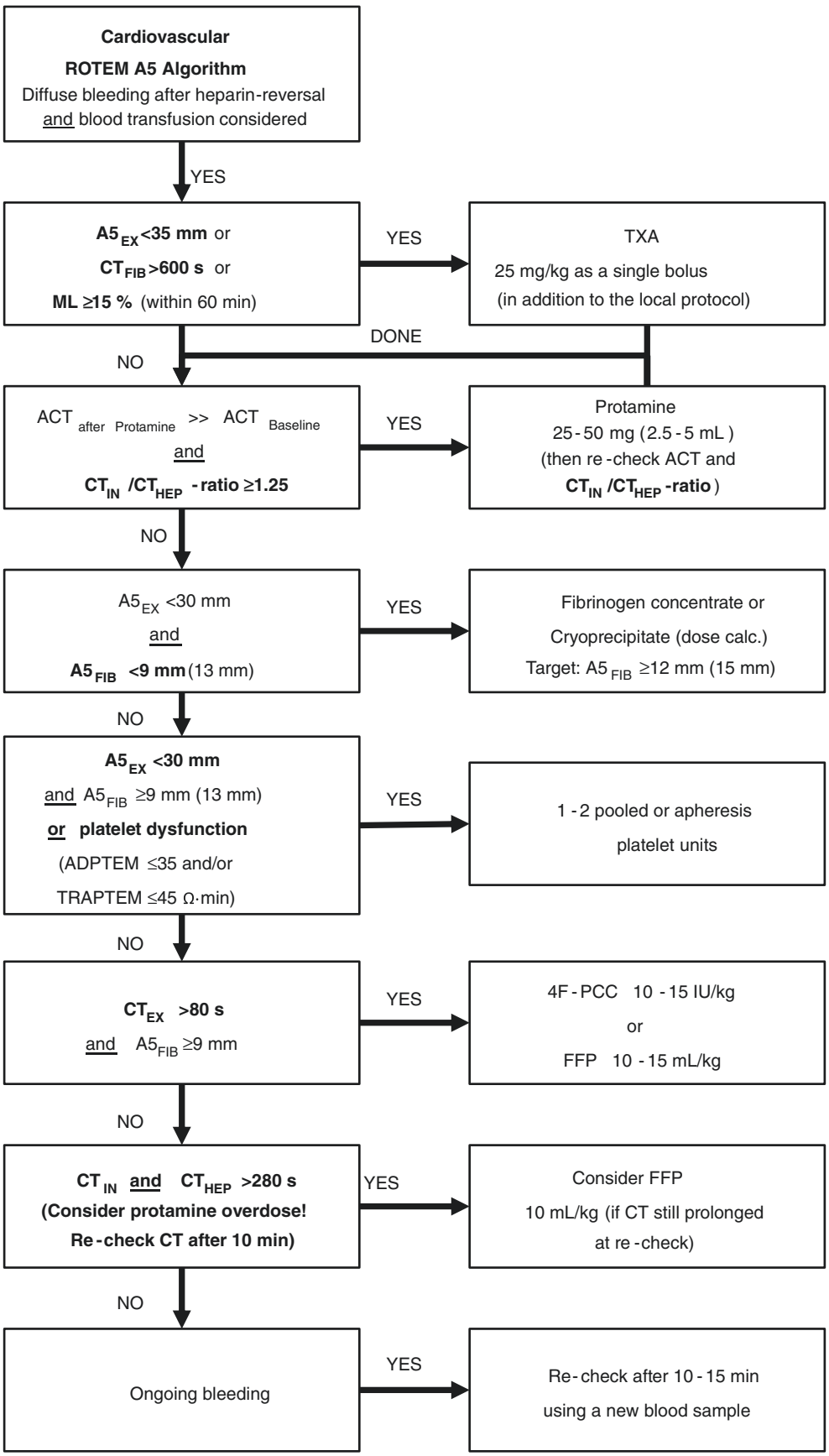


Fig. 7.1 (continued)

by a FIBTEM CT >600 s seems to be associated with hyperfibrinolysis, too. Furthermore, colloid infusion (HES > gelatin > albumin) results in reduced resistance of polymerized fibrin to plasmin degradation [83]. In contrast, high factor XIII levels attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood [84].

Management of Clot Firmness

TIC is functionally characterized by a reduced clot firmness in EXTEM with an A5 <35 mm (A10 <45 mm) and predicts the need for massive transfusion [2, 7, 85–87]. Reduced clot firmness can be based on hypofibrinogenemia, fibrin polym-

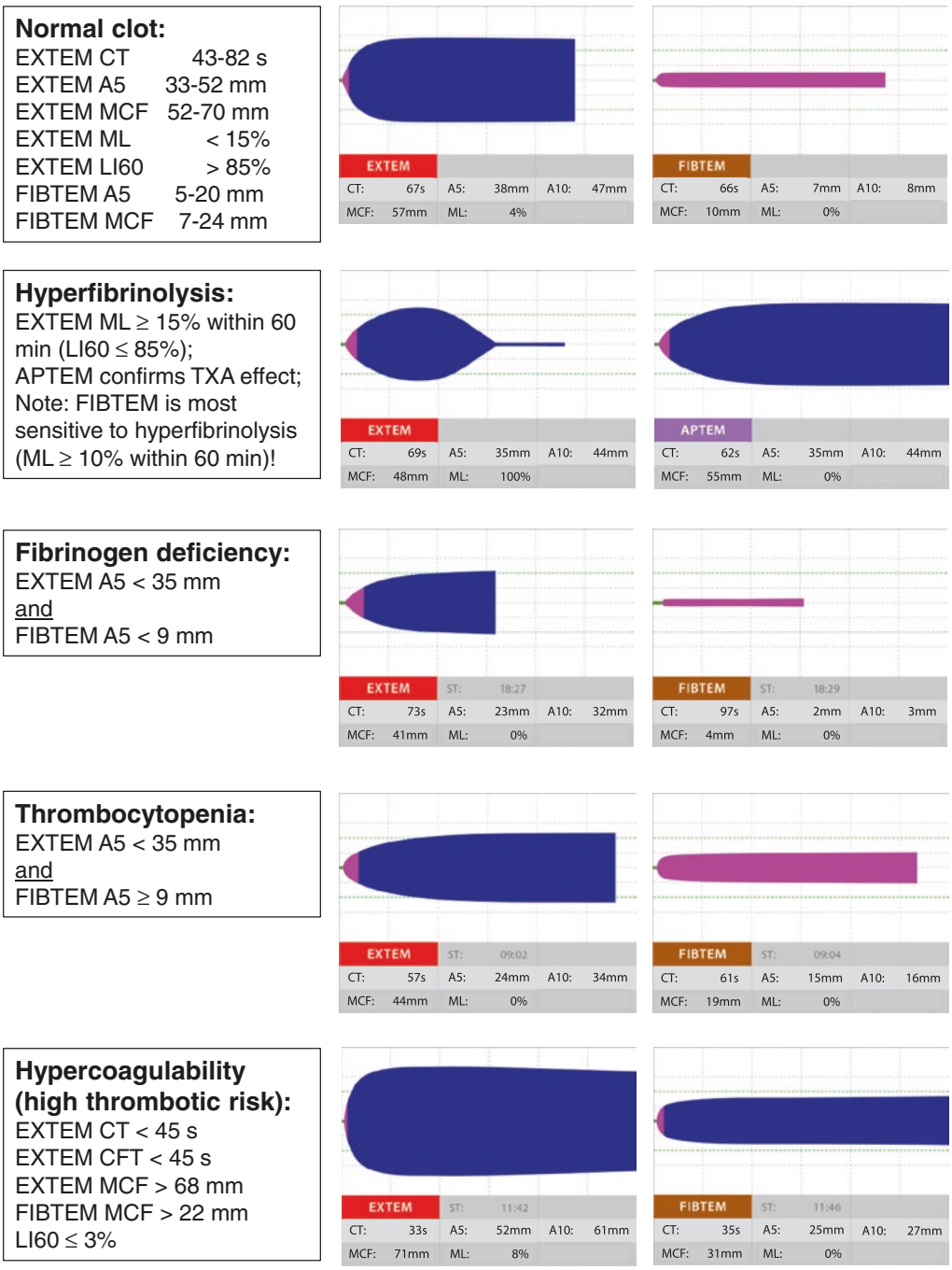
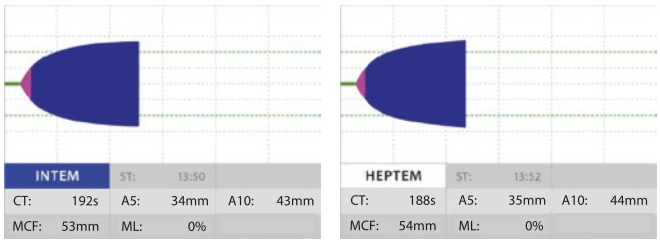
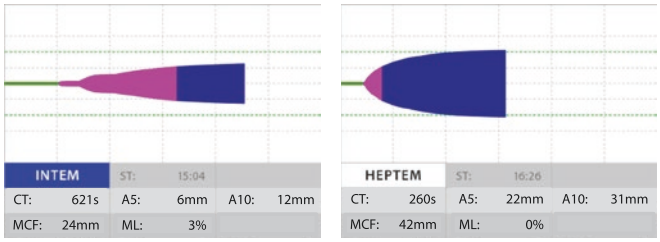


Fig. 7.2 (**a–j**) Characteristic thromboelastometry traces. The diagnostic performance is increased by test combinations, e.g., EXTEM and FIBTEM, EXTEM and APTEM, or INTEM and HEPTEM. 4F-PCC, four factor prothrombin complex concentrate; A10, amplitude of clot firmness 10 min after CT; CFT, clot formation time; CPB, cardiopulmonary bypass; CT, coagulation time; LI60, lysis index 60 min after CT; MCF, maximum clot firmness; ML maximum lysis during runtime; OLT, orthotopic liver transplantation; TXA, tranexamic acid (or other antifibrinolytic drug) (Courtesy of Klaus Görlinger, Essen, Germany)

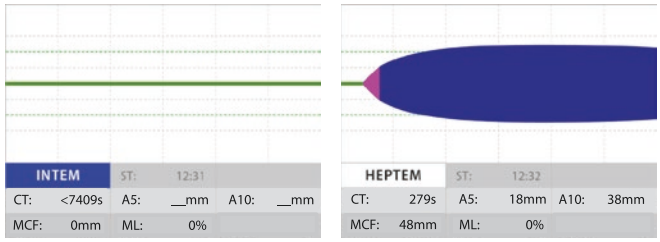
Normal clot (adequate heparin - reversal with protamine after CPB):
INTEM CT 122-208 s
INTEM A5 33-52 mm
INTEM MCF 51-72 mm
INTEM/HEPTEM CT-ratio 0.9-1.1



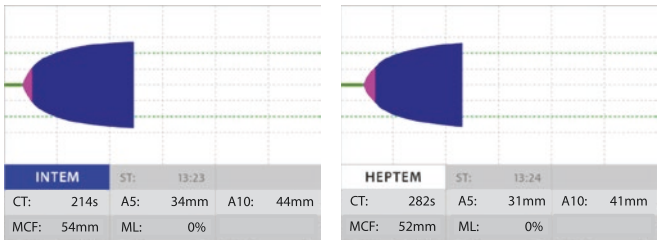
Heparin, low dose (e.g., endogenous heparin-like effect during OLT, sepsis or severe shock):
INTEM/HEPTEM CT-ratio 1.1-2.5 (significant ≥ 1.25)



Heparin, high dose (e.g., during CPB):
INTEM flat-line (CT > 1200s)
and
HEPTEM CT < 280 s



Protamine overdose (after heparin-reversal):
HEPTEM CT prolonged and
INTEM/HEPTEM CT-ratio < 1.1



Deficiency of vitamin K-dependent factors (warfarin or cirrhosis):
EXTEM CT > 80 s
(here, EXTEM CT decreased to 70 s after 4F-PCC administration; right graph)

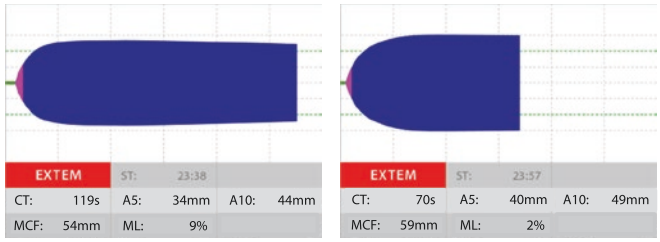


Fig. 7.2 (continued)

erization disorders (e.g., due to colloids or factor XIII deficiency), thrombocytopenia, and severe thrombocytopathy (reduced platelet aggregation due to inactivation of platelets' ADP and thrombin (PAR-1) receptors) [88–92].

FIBTEM A5 (A10) can be used for rapid and correct discrimination between hypofibrinogenemia and thrombocytopenia [50, 69, 70, 93, 94]. A FIBTEM A5 <8 mm (A10 <9 mm) is associated with an increased risk of massive bleeding in severe trauma and major surgery and can be used as a trigger value for fibrinogen substitution in these settings [2, 7, 51, 94, 95]. Here, the targeted FIBTEM A5 value is usually ≥12 mm (A10 ≥13 mm). However, some patients may even need a higher FIBTEM A5 trigger value of 12 mm (with a targeted value of 16 mm) – in particular in patients with severe bleeding due to obstetric hemorrhage/PPH, unstable pelvic fractures, traumatic brain injury (TBI), or

Table 7.1 Bias between early clot firmness values (A5 and A10) and maximum clot firmness (MCF) for all assays as obtained from Bland-Altman analyses. Data are presented in number of ROTEM™ analyses (*N*), mean differences (bias; ΔMCF-A5 and ΔMCF-A10 in mm), and Spearman's correlation coefficient rho (*r*) from linear regression analyses. The good correlation and fixed bias allows for easy conversion between ROTEM™ MCF-, A10- and A5-based algorithms [67–70]

Assay	*N*	Δ MCF-A5	*r*	Δ MCF-A10	*r*
INTEM, HEPTEM	3654	19 mm	0.94	10 mm	0.96
EXTEM, APTEM	7226	19 mm	0.94	10 mm	0.96
FIBTEM	3287	2–4 mm	0.95	1–3 mm	0.96

Courtesy of Klaus Görlinger, Essen, Germany

major aortic surgery [38, 96, 97]. The required fibrinogen dose can be calculated based on the targeted increase in FIBTEM A5 (A10):

$$\text{Fibrinogen dose}\left(\text{g}\right) = \text{targeted increase in FIBTEM A5 (or A10)}\left(\text{mm}\right) \times \text{body weight}\left(\text{kg}\right)/160\left(\text{mm}\bullet\text{kg}\bullet\text{g}^{-1}\right)$$

Here, the correction factor (140–160 mm·kg·g^{-1}) depends on the actual plasma volume [22, 29, 30, 38]. In case of high plasma volume (e.g., in pregnancy), hemodilution (in particular with colloids), transfusion-associated circulatory overload (TACO), factor XIII deficiency or in severe bleeding, the achieved increase in FIBTEM A5 (A10) may be lower than the calculated increase. Fibrinogen substitution can be done by fibrinogen concentrate administration or cryoprecipitate transfusion, dependent on the local approval and availability. As a rule of thumb, 10 units cryoprecipitate contain about 2 g fibrinogen. Table 7.2 provides a quick overview about the fibrinogen concentrate or cryoprecipitate dose needed to achieve the targeted increase in FIBTEM A5 (A10) [21, 29, 30].

If clot firmness in EXTEM is reduced (A5 <35 mm or A10 <45 mm), but FIBTEM clot firmness is above the trigger value (A5 ≥8 mm or A10 ≥9 mm), platelet transfusion has to be considered in severe bleeding. Notably, ROTEM™ analysis has been shown to be superior to platelet count in predicting bleeding in patients with severe thrombocytopenia [98, 99]. The expected increase in EXTEM A5 (A10) per transfused pooled or apheresis platelets is 5–10 mm in adult patients [100–102]. Therefore, the number of transfused platelets can be calculated based on the targeted increase in EXTEM A5 (A10). At least one pooled or one apheresis platelet unit is needed per targeted increase of 10 mm. In case of very low EXTEM A5 (<15 mm or A10 <25 mm), a combined administration of fibrinogen and platelets should be considered.

Notably, standard viscoelastic assays are not sensitive to the effects of antiplatelet drugs such as COX-inhibitors (e.g., aspirin) and ADP-receptor antagonists (e.g., clopidogrel, prasugrel, and ticagrelor) since high amounts of thrombin are generated in the test system which overcomes the effects of antiplatelet drugs. Therefore, platelet function analysis should be performed in patients with suspected platelet dysfunction [15, 103]. In the ROTEM™ system, this is realized by the ROTEM™ *platelet* module, which provides two channels of whole blood impedance aggregometry in addition to the four viscoelastic channels of the ROTEM™ *delta* device. Characteristic ROTEM™ *platelet* traces are displayed in Fig. 7.3a–f. Besides detection of the effects of antiplatelet drugs and other drugs with antiplatelet effects (e.g., analgetics, antidepressants, antibiotics, cardiovascular drugs and protamine), whole blood impedance aggregometry has been shown to detect early direct effects of trauma and sepsis on platelet function which is associated with increased mortality [21, 95, 104–111]. However, actually it is not yet clear whether early trauma- or sepsis-induced platelet dysfunction should be treated with platelet transfusion or not [112, 113]. In liver transplantation, platelet transfusion is associated with increased mortality, independent from the platelet count prior to transfusion [85, 87, 114, 115]. Therefore, decision-making for platelet transfusion should be done carefully and alternatives (e.g., desmopressin, tranexamic acid, fibrinogen concentrate, or cryoprecipitate) may be considered [38, 97, 116–119].

Table 7.2 FIBTEM-guided fibrinogen substitution. Here, fibrinogen dose calculation is based on the targeted increase in FIBTEM A5 (A10) in mm [22, 29, 30, 89]. In case of severe bleeding, high plasma volume (e.g., in pregnancy, significant hemodilution or TACO) and/or factor XIII deficiency, the achieved increase in FIBTEM A5 (A10) may be lower than the calculated increase

Targeted increase in FIBTEM A5 (A10) (mm)	Fibrinogen dose (mg/kg bw)	Fibrinogen concentrate (mL/kg bw)	Cryoprecipitate (mL/kg bw)
2	12.5	0.6 [1 g per 80 kg]	1 [5 U per 80 kg]
4	25	1.2 [2 g per 80 kg]	2 [10 U per 80 kg]
6	37.5	1.9 [3 g per 80 kg]	3 [15 U per 80 kg]
8	50	2.5 [4 g per 80 kg]	4 [20 U per 80 kg]
10	62.5	3.1 [5 g per 80 kg]	5 [25 U per 80 kg]
12	75	3.8 [6 g per 80 kg]	6 [30 U per 80 kg]

Courtesy of Klaus Görlinger, Essen, Germany
TACO transfusion-associated circulatory overload

Management of Coagulation Time (Thrombin Generation)

Coagulation times (CT) can be prolonged due to a deficiency of enzymatic coagulation factors, a low plasma fibrinogen concentration, or the presence of an anticoagulant, e.g., war-

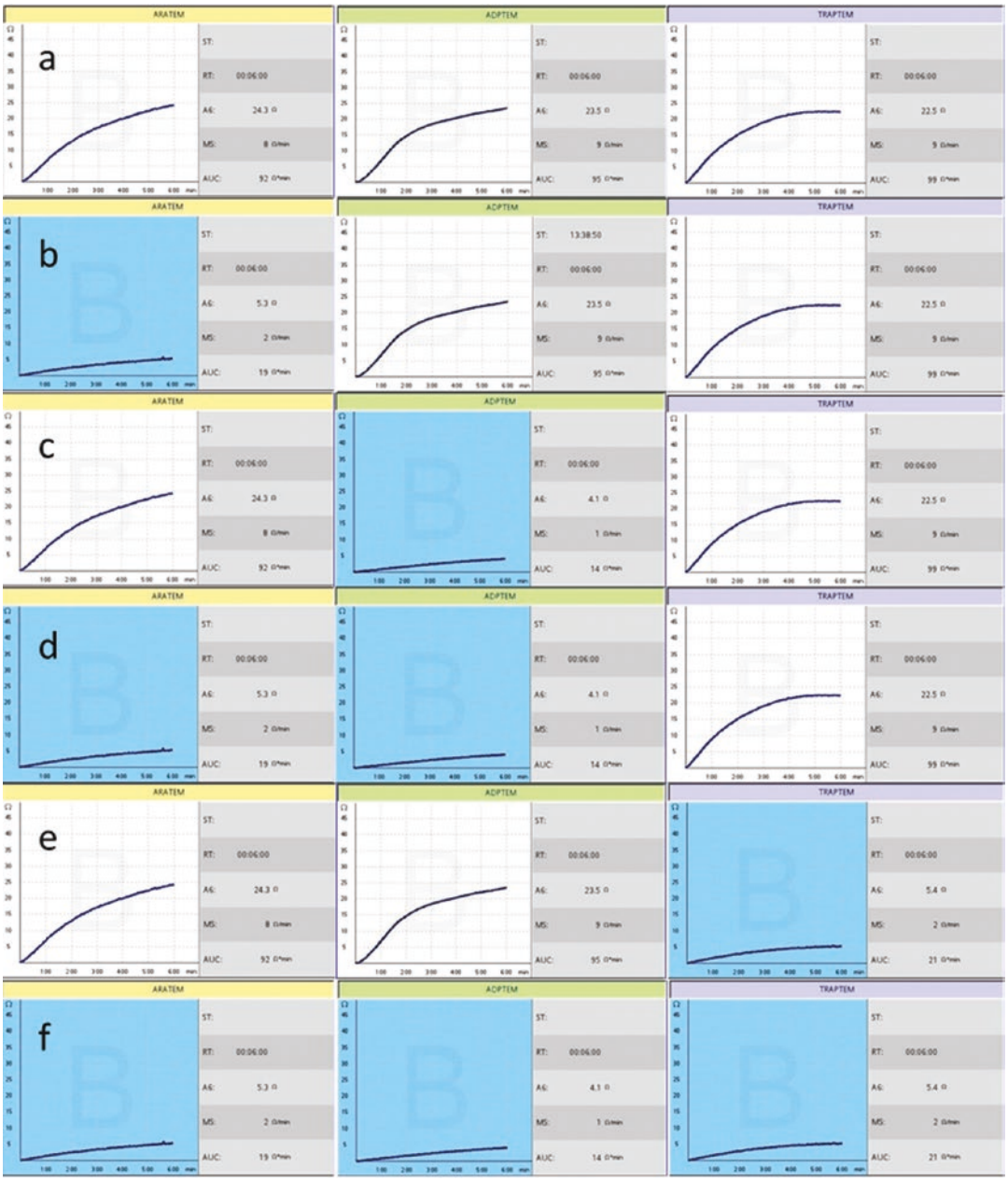


Fig. 7.3 (**a–f**) Characteristic whole blood impedance aggregometry traces (ROTEM® *platelet*) achieved by activation with arachidonic acid (ARATEM; left column), ADP (ADPTEM; middle column), and TRAP-6 (TRAPTEM; right column). (**a**) Normal platelet function; (**b**) Selective inhibition of the arachidonic acid pathway (e.g., by aspirin); (**c**) selective inhibition of the ADP-receptor pathway (e.g., by clopidogrel or prasugrel); (**d**) inhibition of the arachidonic acid and ADP-receptor pathway (e.g., dual antiplatelet therapy with aspirin and clopidogrel); (**e**) selective inhibition of the thrombin-receptor pathway (e.g., by vorapaxar); (**f**) general platelet dysfunction due to triple antiplatelet therapy, GPIIbIIIa-receptor antagonists (e.g., abciximab, eptifibatide, or tirofiban), platelet receptor destruction (e.g., due to cardiopulmonary bypass, severe trauma, or sepsis), or severe thrombocytopenia (Courtesy of Klaus Görlinger, Essen, Germany)

farin, heparin, direct thrombin inhibitors (e.g., hirudin, argatroban, or bivalirudin), or direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, or edoxaban (Fig. 7.4a) [34, 120–133]. Notably, a protamine overdose can prolong CT, too (Fig. 7.4b) [134–136].

Usually a CT prolongation in EXTEM indicates a deficiency of coagulation factor from the extrinsic or common pathway (factors VII, X, V, II, and I). A deficiency of vitamin K-dependent coagulation factors (factors X, IX, VII, and II) can be based on a therapy with vitamin K-antagonists (warfarin), liver cirrhosis, or hemodilution/consumption during sever bleeding. Since the vitamin K-dependent inhibitors proteins C and S in these situations are low, too, the coagulation system can be re-balanced at a low unstable

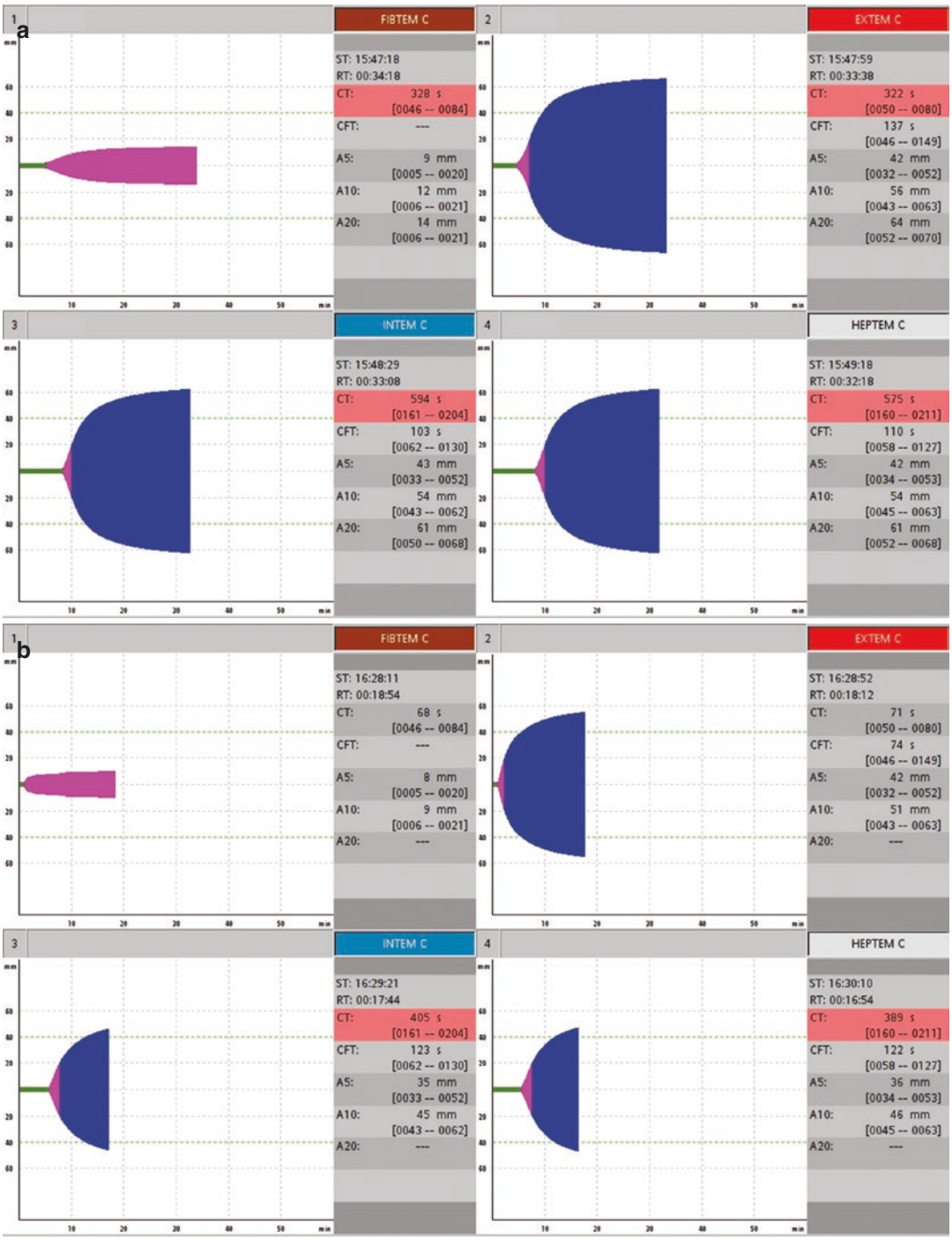


Fig. 7.4 (**a–c**) Characteristic ROTEM™ patterns for (**a**) *direct thrombin inhibitors* (argatroban, bivalirudin or dabigatran; dabigatran concentration (ng/mL) = 1.59 × EXTEM CT - 64; e.g., an EXTEM CT of 322 s corresponds to a dabigatran concentration of 448 ng/mL [124]), characterized by a prolonged CT in extrinsic and intrinsic ROTEM™ assays, (**b**) *protamine overdose* within 15–20 min after excess protamine administration (here 0.5 IU/mL), characterized by prolonged CT in INTEM and HEPTEM and an INTEM/HEPTEM CT-ratio <1.1) and (**c**) *acquired hemophilia A* characterized by short CT in EXTEM and FIBTEM and marked prolongation of CT in INTEM and HEPTEM; rare disease occurring most often during or after pregnancy, in patients with malignancies and in older patients (Courtesy of Klaus Görlinger, Essen, Germany)

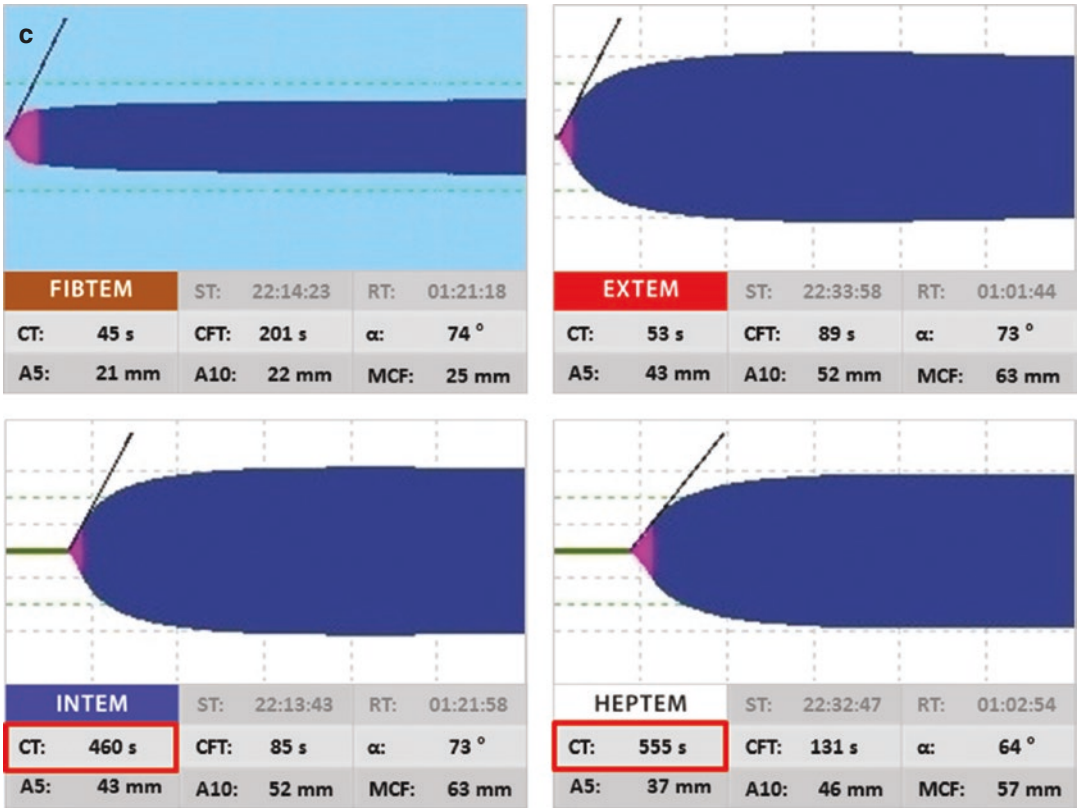


Fig. 7.4 (continued)

level – associated with a high risk of bleeding and thrombosis [12, 13]. EXTEM CT correlates well with international normalized ratio (INR) in patients treated with warfarin [120, 121]. However, the activity of the vitamin K-dependent coagulation factors usually is decreased below 30% of their normal activity if CT in EXTEM exceeds 80s [29]. Notably, a severe fibrinogen deficiency can prolong CT in EXTEM, too. Therefore, EXTEM CT can be used for guiding therapy with prothrombin concentrate complex (PCC) or FFP only in case of a normal A5 (A10) in FIBTEM [2, 6, 7, 17, 29, 31]. Accordingly, management of clot firmness precedes management of coagulation time in ROTEM™ algorithms. Usually, a dose of 15–25 units/kg body weight of PCC is sufficient to normalize EXTEM CT, to reduce INR below 1.5, and to stop coagulopathic bleeding [6, 17, 18, 29, 67, 70, 120, 121, 137, 138].

The use of three- or four-factor PCCs or FFP is dependent on the local approval and availability in the respective countries. Notably, four-factor PCCs (Beriplex™ and Octaplex™) are approved in Europe for prophylaxis and therapy of bleeding in patients with hereditary and acquired deficiencies of vitamin K-dependent factors, whereas four-factor PCC (Kcentra™) in the USA is FDA-approved for urgent reversal of vitamin-K antagonists only [139–141]. In patients with warfarin-induced bleeding complications, four-factor PCCs have been proven to be superior to FFP transfusion regarding efficacy and safety [142–145]. Even though they are not yet FDA-approved for other indications, PCCs are increasingly recommended and used as a therapeutic option in patients with severe bleeding and a proven deficit in thrombin generation (e.g., by EXTEM CT prolongation) [6, 7, 17, 29, 52, 53, 56, 61, 137, 143, 146–149]. Here, four-factor PCCs enable a rapid and calculated increase in coagulation factor activity and, at the same time, avoid the typical and serious adverse events associated with FFP transfusion, such as transfusion-related acute lung injury (TRALI), TACO and transfusion-related immunomodulation (TRIM) [139–145, 150–152]. Administered in a targeted way, the risk of thrombotic events by using four-factor PCCs seems to be low [153–155]. However, further studies are needed for final risk assessment.

Notably, direct thrombin inhibitors such as dabigatran can result in a marked increase in EXTEM, INTEM CT and ECATEM CT (Fig. 7.4a) [123, 124, 126, 127, 129]. The ecarin-based ROTEM™ assay ECATEM is specific for direct thrombin inhibitors such as hirudin, argatroban, bivalirudin, and dabigatran [127–129, 146].

Activated PCCs (factor eight inhibitor bypassing agent = FEIBA) and recombinant activated factor VII (rFVIIa) are only indicated in acquired hemophilia with inhibitors [156–159]. The typical ROTEM™ pattern of an

acquired hemophilia is shown in Fig. 7.4c. Due to the high risk of arterial thromboembolic events, the off-label administration rFVIIa should be restricted to bleeding not responding to comprehensive coagulation therapy [15, 156, 160, 161]. The implementation of thromboelastometry-guided bleeding management algorithms usually eliminates the need for rFVIIa administration as a rescue therapy [17, 18, 40, 41, 60, 61].

INTEM CT can be prolonged due to a heparin or heparin-like effect or a deficiency of coagulation factors of the intrinsic pathway and common pathway (factors XII, XI, IX, VIII, X, V, II, and I). A heparin-like effect, e.g., due to endothelial glycocalyx degradation, reperfusion of a liver graft during liver transplantation, or re-transfusion of heparin by using a cell-saver in the emergency modus, can be confirmed by the normalization of CT in HEPTEM resulting in an INTEM/HEPTEM CT-ratio ≥1.25 which corresponds to an anti-Xa activity of about 0.2 IU/mL [31, 122, 126, 162, 163]. Protamine administration can be considered – in particular in cardiovascular surgery when heparin-reversal is intended. In other settings, such as liver transplantation and hemorrhagic shock, protamine administration should considered carefully and only be done in severe bleeding because a heparin-like effect in these settings is most often self-limiting after hemodynamic stabilization [164]. Notably, protamine overdose can also prolong CT in INTEM and HEPTEM (Fig. 7.4b) and in severe cases even in EXTEM and FIBTEM. Protamine overdose results in an INTEM/HEPTEM CT-ratio <1.1 [163] and disappears most often within 15–20 min after protamine administration by binding of excess protamine to the endothelial glycocalyx. However, protamine overdose is associated with increased transfusion requirements and an increased incidence of resurgery and should therefore strictly be avoided [134, 136]. Protamine-induced platelet dysfunction might be causative, here [106]. In case of CT prolongation in INTEM and HEPTEM – not due to a protamine overdose – FFP transfusion can be considered in bleeding patients. In pregnant women and patients with malignancies, the possibility of an acquired hemophilia should not be forgotten (Fig. 7.4c) [157–159].

Clinical and ROTEM™ Reassessment

Finally, clinical bleeding has to be reassessed after running the algorithm and performing hemostatic interventions. In case of ongoing bleeding, ROTEM™ should be reassessed 10–15 minutes after the hemostatic intervention with a new blood sample and running the algorithm again.

In case of normal results in both thromboelastometry and whole blood impedance aggregometry, surgical bleeding should be considered and the patient should be re-examined surgically.

Thromboelastometry-Guided Bleeding Management Algorithms: Impact on Patient Outcomes

Implementation of ROTEM™-guided bleeding management algorithms reduced bleeding and transfusion requirements in several clinical settings, including cardiovascular surgery, severe trauma, liver transplantation, PPH, and major adult and pediatric surgery [10, 11, 17, 18, 20, 35–44, 49–62, 165, 166]. Görlinger, Fries, and Schöchl reported in their retrospective analysis that implementation of a ROTEM™-guided algorithm in their institutions reduced transfusion requirements for FFP, red blood cells (RBC), and platelets by 70–90%, 10–60%, and 20–70%, respectively. At the same time, the incidence of intraoperative massive transfusion (≥10 units of RBCs) could be more than halved (1% vs. 2.5%; $p < 0.001$) [29]. These results could be confirmed by several other cohort studies and RCTs [17, 18, 32, 37, 39–44, 47–62, 167, 168].

Furthermore, efficacy of viscoelastic testing can be increased by a combination with point-of-care platelet function analysis such as whole blood impedance aggregometry (e.g., ROTEM™ *platelet* or Multiplate™) [1, 17, 18, 40, 41, 60].

Besides reduction of transfusion requirements, the need for large volume (≥4 units of RBC), or massive transfusion (≥10 units of RBC), for surgical re-exploration for bleeding or for postoperative hysterectomy [17, 18, 35–37, 40, 41, 47, 48, 60], several studies could show improved patient outcomes, such as reduced incidence of pulmonary complications/postoperative ventilation time [18, 37, 47, 48], acute kidney injury/need for renal replacement therapy [18, 35, 73], thrombotic/thromboembolic events [17, 18, 35, 61, 62, 169], nosocomial infections/sepsis [18, 41], multiple organ failure (MOF) [55, 62, 168], stay at intensive care unit (ICU) [37, 39, 41, 47, 48], and mortality [18, 50, 52, 55, 61]. Notably, postoperative acute kidney injury is associated with increased short- and long-term mortality in cardiac surgery, liver transplantation, and trauma [170–174]. Furthermore, health-care costs could be reduced significantly, first by reduction of transfusion-associated costs, and second – and may be even more important – by reduction of complication-related costs, reduced ICU and hospital length of stay, and increased number of cases performed in the study period [17, 18, 29, 31, 40–42, 45, 46, 57, 61, 168, 175–181].

Therapeutic Window Concept

The algorithms presented in Fig. 7.1a–c are based on the "therapeutic window concept." This concept has been developed for guiding antiplatelet therapy in patients undergoing percutaneous coronary interventions (PCIs) in order to mini-

mize the risk of ischemia (stent thrombosis) and bleeding [20, 21, 182–184]. Accordingly, bleeding management algorithms guided by thromboelastometry and whole blood impedance aggregometry are designed to minimize the risk of both bleeding and thrombosis, by a personalized therapy according to the concept of precision medicine [2, 6–8, 10, 21–26]. Here, the right therapeutic intervention, in the right dose, at the right time, and in the right sequence is defining the framework of the therapeutic window, e.g.:

- EXTEM A5: 35–50 mm (A10: 45–60 mm)
- FIBTEM A5: 8–18 mm (A10: 9–19 mm)
- EXTEM CT: 40–80 s
- ADPTEM: 35–45 Ω x min (in patients with drug-eluting stents)

Using this concept in cardiovascular surgery, it was possible to reduce both transfusion requirements and thrombotic/thromboembolic complications, significantly [17, 18, 35, 169, 182–184].

Guidelines, Health Technology Assessments, Knowledge Translation, and Implementation

Based on the actually available evidence, the implementation of ROTEM™-guided algorithms is highly recommended (Grade 1B-1C) by the guidelines for the management of severe perioperative bleeding from the European Society of Anesthesiology (ESA), the updated European guideline for the management of bleeding and coagulopathy following major trauma, and the updated practice guidelines for perioperative blood management by the American Society of Anesthesiologists (ASA) Task Force on Perioperative Blood Management (A1-B evidence) [15, 103, 141]. Viscoelastic testing is an essential part of multimodal protocols/algorithms in patient blood management, which typically consist of a predeterminated bundles of diagnostics and interventions intended to reduce blood loss and transfusion requirements [141, 185–188]. In particular, therapeutic interventions with highly effective coagulation factor concentrates, such as fibrinogen concentrate and PCC, should be guided by thromboelastometry (Grade 1B-1C). Furthermore, it is stated that the implementation of transfusion and coagulation management algorithms (based on ROTEM™/TEG™) can reduce transfusion-associated costs in trauma, cardiac surgery, and liver transplantation (Grade C) and that targeted therapy with fibrinogen and/or PCC guided by ROTEM™/TEG™ is not associated with an increased incidence of thromboembolic events (Grade C) [103]. The importance of viscoelastic testing supported by bleeding management algorithms has been pointed out by several other national (AAGBI, American College of Surgeons, AWMF/DGU/DGAI/DIVI, AWMF/DGGG/OEGGG/SGGG/DGAI/GTH, BSH, NBA Australia, SEDAR/SEHH/SEFH/SEMICYUC/SETH/SETS, SFAR, SNG Portugal) and international guidelines (EACTS/EACTA, ISTH), too [7, 189–201].

The cost-effectiveness of ROTEM™-guided bleeding management has also been proven by several health technology assessments and pharmaco-economic analyses [45, 46, 177, 180, 202–204]. However, guidelines and health technology assessments can only change practice and improve patients' outcomes in combination with knowledge translation and implementation. Therefore, the "STOP the Bleeding Campaign" was initiated in 2013, the NHS/NBTC "Recommendation for the implementation of PBM (patient blood management)" has been published by the UK National Blood Transfusion Committee (NBTC) in 2014, the "National Patient Blood Management Implementation Strategy 2017–2021" has been published by the Australian National Blood Authority in 2017, the "PBM Implementation Guides" for health authorities and for hospitals have been published by the European Commission in April 2017, and the "National STOP the Bleed Month" has been initiated in the USA in May 2019 [16, 205–208].

Thromboelastometry as an Integral Part of a Patient Blood Management (PBM) and Patient Safety Program

PBM is the timely application of a multidisciplinary, evidence-based medical concept, which helps to optimize the patient's own blood volume, minimize blood loss, and thereby significantly reduce or even avoid allogeneic blood transfusion [209, 210]. The patient blood management concept was highlighted in 2010 by the World Health Assembly as an important concept to improve patient safety. Accordingly, all WHO member states were requested to implement this concept in a timely manner. Perioperative thromboelastometry-guided bleeding management is an essential part of PBM and patient safety [57, 167, 169, 200, 211–215]. Accordingly, all NHS hospitals in the UK have been requested by the NHS Blood and Transplant, the UK Department of Health and the UK National Blood Transfusion Committee (NBTC) to establish a PBM program, including point-of-care (POC) testing and implementation of bleeding management protocols [205]. In 2014, a German PBM network has been founded, and a prospective multicenter trial enrolling 129,719 patients has been performed to assess safety, efficiency, and cost-effectiveness of implementing a PBM program. Besides a significant relative reduction in blood transfusion by 17% ($P < 0.001$), the incidence of acute renal failure could be decreased by 30% (1.67% vs. 2.39%; $P < 0.001$) without any safety issues [216]. Notably, the

decrease in acute renal failure is of high clinical importance since postoperative acute renal failure is associated with increased short- and long-term mortality [170–174]. Accordingly, blood transfusion was reduced by 41% ($P < 0.001$), hospital acquired infections by 21% (OR, 0.79; $P < 0.001$), acute myocardial infarction and stroke by 31% (OR, 0.69; $P < 0.001$), and hospital mortality by 28% (OR, 0.72; $P < 0.001$) in a Western Australian patient blood management implementation study recruiting 605,046 patients. This was also associated with a significant reduction in hospital length of stay and cost savings (US$ 18,078,258 over 6 years) [215, 217]. A recently published meta-analysis confirmed that implementing a comprehensive PBM program addressing all three PBM pillars (e.g., viscoelastic testing in pillar two) is associated with reduced transfusion needs, lower complication and mortality rates, and thereby improving clinical outcome [218]. Thus this first meta-analysis investigating a multimodal approach should motivate all executives and health-care providers to support further PBM activities and by doing so decrease health-care costs [46, 175, 215–218].

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Part II

Bleeding Associated with Disease Condition

Known Bleeding Disorders for Surgery

8

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Introduction

Management of a bleeding disorder in the perioperative setting involves achieving and maintaining a desired (missing) factor level for hemostasis. Choice of hemostatic agent varies per country regarding availability, approval, and indication. Recombinant or plasma-derived factor concentrates remain the treatment of choice where available. However, use of human blood-derived products, such as fresh frozen plasma (FFP) and cryoprecipitate can be used to prevent bleeding complications during and after surgery and are considered primary agents in areas of the world where recombinant or plasma-derived factor concentrate products are not available. In less common congenital disorders, commercial concentrates for replacement therapy are often not available, regardless of geographical location. In this instance, FFP or cryoprecipitate may be used. FFP contains all coagulation factors, as opposed to cryoprecipitate which contains factors I (fibrinogen), VIII, and XIII and von Willebrand factor (VWF). On average, 1 mL of FFP contains 1 unit of each coagulation factor. However, the volume of a "unit" of FFP, the concentration of the citrate anticoagulant, and the concentration of individual donor coagulation factors are variable, depending on the donor blood composition, the method of collection, and the anticoagulant solution used [1]. Unfortunately, human blood-derived products typically require large volumes to achieve a desired factor level. Therefore, circulatory overload becomes a concern, especially in fluid volume-sensitive populations, such as cardiac failure patients.

Adjunctive measures toward hemostasis include antifibrinolytics such as ε-aminocaproic acid or trans-*p*-aminomethylcyclohexane carboxylic acid (tranexamic acid), which may be given topically, orally or intravenously, especially in surgeries involving the gastrointestinal tract (nasal, oral, intestinal) where fibrinolytic activity is high. In general the ε-aminocaproic acid dose is 50–100 mg/kg, max 3 g dose (30 g/day) every 6 hours orally or 4–5 g (initial dose) intravenous with 1 g per hour for 6–8 hours (pediatric dosing 100–200 mg/kg IV/PO x1, then 100 mg/kg IV/PO every 4 to 6 hours). Tranexamic acid dose is 1300 mg (pediatric 25 mg/kg) orally every 8 hours or 10 mg/kg intravenous every 6–8 hours [2]. Fibrinolytic inhibitors should not be used when hematuria is present due to associated risk of urinary flow obstruction. Topical agents such as fibrin glue, fibrin sealants, and oxidized cellulose also provide local hemostatic success in external wounds and dental procedures.

1-Deamino 8-D-arginine vasopressin (DDAVP) is a vasopressin analogue that causes vasoconstriction of the endothelial cells lining the blood vessels, releasing VWF and factor VIII (FVIII) from the Weibel–Palade bodies by an indirect mechanism. Prior to surgery, a DDAVP challenge should be undertaken to determine if there is an appropriate response—typically a two- to sixfold increase in VWF ristocetin cofactor (VWF:RCo) and FVIII activity (FVIII:C) from baseline. DDAVP is available for intravenous (IV), subcutaneous (SQ), or intranasal (IN) administration. Dosing of the intranasal DDAVP which comes as a 1.5 mg/mL solution is weight-based: one spray in one nostril per day in persons

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<50 kg (150 μg/day) or one spray per nostril per day in persons >50 kg (300 μg/day). Intravenous or subcutaneous dosing is 0.3 μg/kg body weight every 12–24 hours (for intravenous administration DDAVP is diluted in 50–100 mL saline and infused over 30 minutes) [2]. The IV route is the preferred route in surgical prophylaxis [3, 4]; however, intranasal dosing has been used with success. Adverse effects include tachyphylaxis, fluid retention, hyponatremia, and seizures, among others. Therefore, use should be limited to no more than three consecutive days.

The success of perioperative management not only relies on achieving and maintaining hemostasis but includes the coordination of a multidisciplinary approach. The procedure itself should be performed in a facility that has experience in caring for individuals with bleeding disorders, and the surgeon should have experience performing operations in this unique population. A laboratory well versed in monitoring of factor levels and testing for inhibitors is necessary. Ample supply of factor should be available for the duration of the surgery as well as the postoperative period for wound healing as well as rehabilitation. Where factor concentrates or recombinant factor is not available, blood bank support is imperative to provide FFP, cryoprecipitate, and red blood cells [4].

Von Willebrand Disease

Replacement therapy for von Willebrand disease (VWD) includes several commercially available plasma-derived concentrates of von Willebrand factor (VWF/FVIII) and recent addition of a recombinant von Willebrand concentrate product, VONVENDI™ (Baxalta Inc.). For VWD patients that have a baseline FVIII level below 40% or unknown, the concomitant administration of a single dose of recombinant (non-von Willebrand factor containing) FVIII (rFVIII) is recommended in order to quickly normalize levels. Once this is achieved, repeat dosing of rFVIII is not required. If rFVIII is not infused initially, plasma FVIII levels will normalize by 12 hours [2, 5]. The VWF:RCo to FVIII:C ratio ranges from 1:1 to 2:1 for plasma-derived concentrates. Each unit/kg body weight of von Willebrand factor increases the VWF:RCo by approximately 1% regardless of product used [6].

VWD: Minor Surgeries

For minor surgeries, a dose of VWF concentrate of 30–60 IU/kg is recommended to increase VWF:RCo and FVIII:C above 30–50% [3, 7]. Depending on the procedure, a single dose may be sufficient; however, some surgeries may require an additional dose of 20–40 IU/kg in 12–48 hours after the first dose to keep VWF:RCo and FVIII:C above 50% [3, 7] (see Table 8.1). Daily monitoring of VWF:RCo and FVIII:C to maintain troughs greater than 50% for 1–5 days until wound healing may be necessary for some procedures. It is prudent to monitor VWF:RCo and FVIII:C peak and trough daily to avoid over-treating as levels of VWF:RCo over 200 IU/dL or FVIII over 250–300 IU/dL are associated with an increased risk of thromboembolism [3]. If recombinant von Willebrand factor (rVWF) is used, a preoperative dose may be administered 12–24 hours prior to surgery to allow the endogenous FVIII levels to increase to at least 30 IU/dL for minor surgeries. FVIII:C levels should be reassessed within 3 hours prior to procedure and if the FVIII:C levels are at or above the recommended minimum target levels, a loading dose of rVWF alone should be administered within 1 hour prior to the procedure. If the FVIII:C is below the recommended minimum target level, administration of rFVIII in addition to rVWF is recommended to raise VWF:RCo and FVIII:C [2, 5].

Table 8.1 Goal VWF:RCo in the perioperative period

Category	Procedure	VWD
Major surgery	Neurosurgery Cardiovascular surgery Cesarean section Hysterectomy Abdominal surgery Orthopedic surgery (hip arthroplasty, knee arthroplasty, arthrodesis) Limb amputation Tonsillectomy/adenoidectomy	Goal VWF:RCo and FVIII:C Load to goal of 100% then maintain >50%
Minor surgery	Cataract surgery Cardiac catheterization Endoscopy with/without biopsy Liver biopsy Gingival surgery CVC placement Orthopedic surgery (i.e., isotopic synovectomy)	Goal VWF:RCo and FVIII:C >30–50%
Dental	Uncomplicated/complicated dental extractions	Goal VWF:RCo and FVIII:C >30–50%

Supportive measures such as topical hemostatic agents and antifibrinolytics may be used in surgical locations where fibrinolytic activity is high, avoiding its use in bleeds from the genitourinary tract due to the formation of clots in the ureters and bladder.

Sample Case

- A 16-year-old female with type I VWD is scheduled for wisdom teeth extraction. She weighs 50 kg with VWF:RCo measured at 18 IU/dL and FVIII:C at 30 IU/dL. Prior challenge showed a poor response to DDAVP. In

this case, a loading dose of 40 IU/kg would be expected to increase both VWF:RCo and FVIII:C to >50%. The calculated VWF concentrate dose for this patient: 40 IU/kg × 50 kg = 2000 IU of a VWF product with VWF:RCo to FVIII:C ratio of 1:1. Monitoring closely for adequate hemostasis is important and a repeat dose of factor may be administered as necessary. Aminocaproic acid 3 g swish and spit (or swallow) for 7 days should be started in the preoperative period and continued every 6 hours. Tranexamic acid 1300 mg po every 8 hours for 5 days is another option for this individual. Topical sealants should also be considered during surgery to achieve hemostasis.

In this case if rVWF were to be used, a loading dose of rVWF alone (without factor VIII treatment) within 1 hour prior to procedure would be sufficient given a baseline FVIII:C of 30 IU/dL (minimum target level for minor surgeries).

Persons with von Willebrand disease (VWD) who are known responders may use DDAVP as monotherapy or adjunctive therapy for surgical prophylaxis if levels are known to rise above the minimum goal VWF:RCo and FVIII:C. In the sample case above, if prior DDAVP challenge had revealed a post-DDAVP VWF:RCo and FVIII:C levels of >90%, she could have received DDAVP every 24 hours starting in the preoperative period then continued for another 48 hours.

Major Surgeries

An initial loading dose of 40–60 IU/kg VWF concentrate to increase VWF:RCo and FVIII:C to 100% is recommended for major surgeries. This is followed by 20–40 IU/kg every 8–24 hours to maintain a goal trough VWF:RCo and FVIII:C >50% for 7–14 days until wound healing has completed [3, 7] (see Table 8.1). If rVWF is utilized administration recommendations are similar to that of minor surgeries. A dose of rVWF may be given 12–24 hours prior to procedure to allow for the endogenous factor VIII levels to increase to at least 60 IU/dL. Assessment of baseline VWF:RCo and FVIII:C levels should be performed within 3 hours prior to surgery. If the FVIII:C level is below the recommended minimum target level, administration of rVWF followed by recombinant FVIII within 10 minutes to raise VWF:RCo and FVIII:C is recommended [5]. DDAVP monotherapy is not adequate for major surgeries; however, DDAVP and antifibrinolytics may be utilized as adjunctive therapy.

Sample Case

- A 45-year-old woman with type 2 VWD is scheduled for hysterectomy. She weighs 60 kg. Her VWF:RCo measured is 28 IU/dL and FVIII activity is 36 IU/dL. Prior challenge showed a poor response to DDAVP. In this case, a loading dose of 60 IU/kg is expected to increase both VWF:RCo and FVIII:C to >100%. Calculated dose for her: 60 IU/kg × 60 kg = 3600 IU of a VWF product with VWF:RCo to FVIII:C ratio of 1:1. Subsequent daily dosing will be based on follow-up VWF:RCo and FVIII:C in 12–24 hours. Antifibrinolytics can be used to provide additional hemostasis.

In this case, if rVWF were to be used a preoperative dose would be indicated 12–24 hours prior to surgery to allow the endogenous FVIII levels to increase to at least 60 IU/dL, before the loading dose (1 hour preoperative dose) of rVWF. FVIII:C reassessment 3 hours prior to procedure will determine if the addition of recombinant FVIII is indicated.

Hemophilia A

The dose of factor needed to achieve hemostasis is variable, and the choice of dose needs to be calculated based on three parameters: severity of bleeding episode; pharmacologic properties of the clotting factors, which include the half-life; and the in vivo recovery based on the volume of distribution within the vascular compartments [8]. Factor replacement can be administered by either continuous infusion or boluses. Bleeding complications associated with surgery in hemophilia can be seen in up to 20% of the cases, usually occurring during the postoperative period rather than during the surgical procedure. There are many recombinant and plasma-derived concentrates of FVIII commercially available, with the recent addition of several recombinant extended half-life (EHL) FVIII products. For individuals that undergo major surgical procedures, a in vivo recovery and half-life study should be performed in the non-bleeding state with a 3–5 day washout period. Each IU/kg body weight of FVIII increases the FVIII:C by 2% or 2 IU/dL. The following formula can be used to calculate FVIII dosing: Dosage Required (IU) = Body Weight (kg) × Desired FVIII level minus baseline (FVIII:C % or IU/dL) × 0.5 (IU/kg per IU/dL).

In mild hemophilia patients who are known responders, DDAVP may be utilized as monotherapy or adjunctive therapy, depending on the procedure and dose response.

Minor Surgery

In patients with hemophilia, minor procedures have the potential for life-threatening bleeding complications requiring a multidisciplinary team and an adequate hemostasis plan. Minor surgical procedures include skin biopsy, prostate biopsy, endoscopy with biopsy, lymph node biopsy, and dental procedures, among others. For minor surgeries in per-

Table 8.2 Goal FVIII:C and FIX:C in the perioperative period

Category	Procedure	Hemophilia A & B	Hemophilia A & B with inhibitor
Major surgery	Neurosurgery Cardiovascular surgery Cesarean section Hysterectomy Abdominal surgery Orthopedic surgery (hip arthroplasty, knee arthroplasty, arthrodesis) Limb amputation Tonsillectomy/adenoidectomy	Goal FVIII:C Load to goal of 100% then >60–80% Goal FIX:C Load to goal of 100% then >40–60%	rFVIIa: initial dose of 90–180 μg/kg body weight, then every 2 h intra and post-op period with slow decrease in frequency every 48–72 h as long as hemostasis is adequate
Minor surgery	Cataract surgery Cardiac catheterization Endoscopy with/without biopsy Liver biopsy Gingival surgery CVC placement Orthopedic surgery (i.e. isotopic synovectomy)	Goal FVIII:C & FIX:C Load to goal of 50–80% then 30–80%	rFVIIa: initial dose of 90 μg/kg body weight + additional doses as necessary depending on procedure
Dental	Uncomplicated/complicated dental extractions	Goal FVIII:C & FIX:C >30–50%	rFVIIa: initial dose of 90 μg/kg body weight + additional doses as necessary depending on procedure

sons with hemophilia A, a pre-op FVIII:C of 50–80% is recommended. In the postoperative period, a goal FVIII:C of 30–50% for 1–5 days may be necessary depending on the surgery [4, 8]. A daily dose of 30–40 IU/kg should achieve these goals [9], and daily monitoring of FVIII:C levels are recommended if treatment extends beyond 3 days (Table 8.2).

Sample Case

- A 50-year-old man with moderate hemophilia A (baseline FVIII:C 3%) weighing 85 kg is scheduled for a laparoscopic hernia repair. Calculated FVIII dose: 85 kg × 80 IU/dL × 0.5 = 3400 IU to be given 30 minutes to 1 hour prior to procedure. Additional lower daily doses may be necessary until adequate healing is achieved.

DDAVP can be used for dental procedures in known responders. FVIII products should be given to increase FVIII:C to goal 30–50% preoperative with postoperative dosing based on the procedure performed and level of hemostasis achieved. Local sealants such as fibrin glue and systemic antifibrinolytics are essential supportive therapies.

Major Surgery

Goal FVIII:C for major surgeries is 80–100%. In the post-op period, a goal FVIII:C of 60–80% is desirable for the first 72 hours followed by FVIII:C of 40–60% on days 4–6 and 30–50% until day 14 [8, 10]. For severe and moderate hemophilia, a loading dose of 50 IU/kg FVIII followed by maintenance dosing to goal 60% for the first week is usually adequate. Additional doses to goal ~30% FVIII:C can be given daily until healing is achieved. For rehabilitation 20–30 IU/kg can be administered before each session for 8–10 weeks.

Sample Case

- A 60-year-old man with severe hemophilia A is scheduled for knee replacement. He weighs 70 kg. Loading dose FVIII: 70 kg × 100 IU/dL × 0.5 = 3500 IU. In the postoperative period, maintenance dose calculated would be 70 kg × 80 IU/dL × 0.5 = 2800 IU to maintain levels of FVIII: C at 60–80%. Since the half-life of FVIII products is typically between 8–12 hours, this dose can be administered every 12 hours for the first 48 hours. Daily monitoring of levels and adjusting dose and frequency is advisable (Table 8.2).

Dosing recommendations remain similar whether a standard half-life or a recombinant EHL FVIII product is used. Dosing frequency is expected to be extended with the use of an EHL product, with repeat dosing typically administered after 24 hours if necessary following minor surgical procedures and every 8 to 24 hours if necessary following major surgical procedures [11, 12]. Factor product choice may ultimately be decided by surgical center availability.

Continuous Infusion

Use of a continuous factor infusion to maintain hemostasis during surgical procedures may be considered. Some advantages of continuous infusion include reaching a

steady state in plasma faster, maintenance of a constant therapeutic factor avoiding peaks and troughs, and decrease in the total factor use in up to 30% [8]. Batorova et al. report using continuous infusions for surgical prophylaxis with an initial factor bolus dose of 50 IU/kg to goal 100% [13]. This is followed by the calculated rate of infusion (IU/kg/h) = Clearance (mL/kg/h) × Desired Level (IU/mL). Clearance was determined prior to surgery via PK studies. Daily monitoring of FVIII:C was used to adjust the rate of infusion to goal FVIII:C ≥50 % for the first 4 days, followed by FVIII:C of ~40% on days 5–7, and FVIII:C ~ 30% on days 8–12 [13, 14].

Hemophilia B

The overall management for surgery is similar to individuals with hemophilia A. As with FVIII, there are many recombinant and plasma-derived concentrates of factor IX (FIX) commercially available, with the recent addition of several recombinant extended half-life (EHL) FIX products. However, dosing between FVIII and FIX products differs in that each IU/kg body weight of FIX increases the FXI activity (FIX:C) by approximately 1% or 1 IU/dL. For plasma-derived and recombinant EHL FIX dosing, the formula is: Dosage Required (IU) = Body Weight (kg) × Desired FIX level minus baseline level (FIX:C % or IU/dL) × 1 or Recovery (IU/kg per IU/dL) [15–17]. Recombinant standard half-life FIX products have a lower recovery than plasma-derived or rEHL FIX, such that one IU/kg rFIX increases FIX:C by 0.8 IU/dL in adults and 0.7 IU/dL in children (less than 15 years old). Recombinant FIX dose is calculated by: Dosage Required (IU) = Body Weight (kg) × Desired FIX level minus baseline level (FIX:C % or IU/dL) ÷ 0.8 IU/dL (Adults) or 0.7 IU/dL (<15 years of age). EHL FIX post operative dosing should be administered less frequently given the half life of these products (90–115 hours).

Sample Case

- A 70 kg man with severe hemophilia B is scheduled for thyroidectomy. Desired FIX:C is ~100%. Recombinant FIX product will be used. Calculated dose rFIX: 70 kg × 100 IU/dL ÷ 0.8 IU/dL = 8750 IU.
- If this was a 35 kg child scheduled for surgery, rFIX dose would be: 35 kg × 100 IU/dL ÷ 0.7 IU/dL = 5000 IU.

Antifibrinolytics and topical hemostasis agents are also utilized in persons with hemophilia B undergoing surgery. DDAVP has no role in hemophilia B. In areas where plasma-derived single FIX and rFIX products are not available, prothrombin complex concentrates (PCCs) containing FIX may be used. In this case, however, tranexamic acid should be avoided due to increased risk of thrombosis.

Minor Surgery

For minor surgeries in persons with hemophilia B, goal FIX:C are similar to individuals with hemophilia A, a pre-op FIX:C of 50–80% recommended. Postoperative, a goal FIX:C of 30–80% should be maintained for 1–5 days, depending on the surgery [4, 10] (see Table 8.2).

Major Surgery

Pre-op FIX activity of 80–100% is recommended for major surgery in individuals with hemophilia B [17]. In the postoperative period, a goal FIX:C of 60–80% is desirable for days 1–3, followed by 40–60% on days 4–6, and 30–50% for a total of 7–14 days [4] (see Table 8.2).

Hemophilia A and B with Inhibitors

Inhibitory antibodies to FVIII or FIX pose a challenge in the management of patients with hemophilia A or B with regard to achieving hemostasis and require careful consideration when faced with the prospect of surgical intervention. The use of a bypassing agent is necessary to ensure adequate hemostasis, as factor replacement, whether standard or extended half-life products, are not likely to be effective. However, the challenge remains as bypassing agents are not 100% effective and response can vary among individuals. The development of an individualized hemostatic management plan, including the pre-, intra-, and postoperative periods, is imperative and should involve all participating specialties [18]. There are currently two bypassing products approved by the FDA to treat patients with hemophilia and inhibitors: recombinant activated factor VII (rFVIIa), NovoSeven™ (Novo Nordisk, Bagsvaerd, Denmark), and FVIII inhibitor bypassing activity, FEIBA™ (Baxter, Vienna, Austria). The latter is a plasma-derived activated prothrombin complex concentrate (aPCC) rich in activated factor VII and mainly non-activated factors II, IX, and X. Both products are used for the treatment of bleeding episodes as well as perioperative management. There are currently no studies suggesting one product is superior to the other, and as such, personal physician preference guided by experience and availability of product may dictate which bypassing agent is utilized for surgical prophylaxis. Thromboembolic events have been documented with the use of rFVIIa, as well as with the use of FEIBA™. Surgical experience regarding this

specific population has grown in the last 15 years providing less morbidity and improving quality of life. Although these procedures require thorough planning and aggressive management, good control of hemostasis can be achieved with the use of a bypassing agent, and therefore patients with inhibitors should not be denied indicated procedures, unless the risks outweigh the benefit.

The FDA has recently approved the use of HEMLIBRA™ [emicizumab] (Genentech Inc., Chugai Pharmaceutical Co., Tokyo, Japan), a bispecific FIXa- and FX-directed antibody, for routine prophylaxis in adult and pediatric patients ages newborn and older with hemophilia A with or without FVIII inhibitors [19]. HEMLIBRA™ is not currently labeled for surgical use, and although it has demonstrated improved hemostasis, it does not normalize hemostasis. Therefore the use of FVIII replacement products or bypassing agent (NovoSeven™) may be indicated in the surgical setting. Surgical studies are currently underway.

Minor Surgery

The recommended dose for rFVIIa in persons with hemophilia A or B with an inhibitor is 90 μg/kg body weight immediately prior to surgery followed by repeat dosing every 2 hours given its short half-life. As hemostasis is maintained, the interval between doses may be slowly increased (see Table 8.2).

Sample Case

- A 3-year-old boy with severe hemophilia B has poor venous access and is a candidate for a central venous catheter. He has history of high-titer inhibitor, last titer 8.54 B.U. and weighs 14 kg. Pre-op dose rFVIIa: 90 μg/kg × 14 kg = 1260 μg per dose. A dose should be given immediately prior to the procedure, and patient should be monitored for post-op bleeding and additional doses administered every 2–3 hours as necessary.
- If FEIBA™ was used, then the dose calculated: 50 IU × 14 kg = 700 IU given once prior to the procedure followed by additional doses every 8–12 hours if needed.

Major Surgery

For major surgeries, a loading dose of rFVIIa 90 μg/kg body weight is recommended, with repeat dosing every 2 hours during procedure and postoperative period with an even slower taper in dosing interval following procedure until wound healing occurs [20, 21] (see Table 8.2). A higher preoperative rFVIIa dose of 120–180 μg/kg body weight has been suggested in Giangrande et al. [22] proposed protocol for elective orthopedic surgery (major surgery) in hemophilia patients with inhibitors. In the postoperative period, rFVIIa 90 μg/kg body weight remains scheduled every 2 hours for the first 48 hours. If hemostasis is maintained, the frequency may then be decreased to 90 μg/kg every 3 hours for the next 48 hours. On days 5–8, the frequency may be further reduced to every 4 hours, and if adequate hemostasis persists, dosing may be decreased to 6 hours for another 48–96 hours with possibility of discharge at day 12 [22]. The protocol utilized by our hemophilia treatment center is depicted in Fig. 8.1a, b. We prefer to start surgery with rFVIIa due to the flexibility in dosing and frequency; however many procedures have been performed satisfactorily with the use of FEIBA™.

Sample Case

- A 35-year-old with severe FVIII deficiency and high-titer inhibitor is scheduled for right knee replacement. He weighs 80 kg. Dosing of rFVIIa based on our protocol:
- Pre-op dose: 200 μg/kg × 80 kg = 16 mg. The post-op dose: 90 μg × 80 kg = 7200 μg every 2 hours × 48 hours. On days 3–5, administer rFVIIa 7200 μg every 3 hours × 48 hours, followed by 7200 μg q4 hours × 72 hours, and then 7200 μg q 6 hours. If hemostasis is maintained, he may be discharged home by day 10–12. Doses may need to be adjusted if bleeding complications arise (see Fig. 8.1a, b).

Continuous Infusion

Use of continuous infusion of bypassing agents for surgical prophylaxis has been studied; however, this practice is not common and would defer this regimen until more data is available [21].

Rare Bleeding Disorders

For the rare bleeding disorders, there is limited data from which general recommendations are proposed. Generally levels between 15–40% are recommended pre-op for adequate hemostasis. However, in persons with factor II, VII, and XI deficiencies, the individual factor level may not correlate with bleeding tendencies. As such, a bleeding history is necessary to guide therapy, especially for surgical procedures. Available therapies to facilitate and correct hemostasis in less common congenital bleeding disorders are limited and often have no commercially available concentrate for replacement therapy. Therefore, FFP or cryoprecipi-

a

Day 1-2	• 200 μg/kg 5 minutes before incision • 90-120 μg/kg every 2 hours during surgery • 90-120 μg/kg every 2 hours in recovery room • 90-120 μg/kg every 2 hours for the next 48 hours

- Blood draw for CBC every 8 hours in day 1 and then once a day
- Drainage quantification
- Periodic Thromboelastrography (15 min, 1 hour, 2 hours after a dose)

Day 3-4	• 90-120 μg/kg every 3 hours for the next 48 hours
Day 5-6	• 90-120 μg/kg every 4 hours for the next 48 hours
Day 7-8	• 90-120 μg/kg every 6 hours for the next 48 hours
Day 8-10	• 90-120 μg/kg every 6-8 hours for the next 48 hours
Day > 10	• 90-120 μg/kg every 8 hours until discharge

For drainage or suture removal administer a bolus of 90 μg/kg

Start physical therapy by day 3-5 post-op. Every session of PT should be done under coverage of a bypassing agent

b

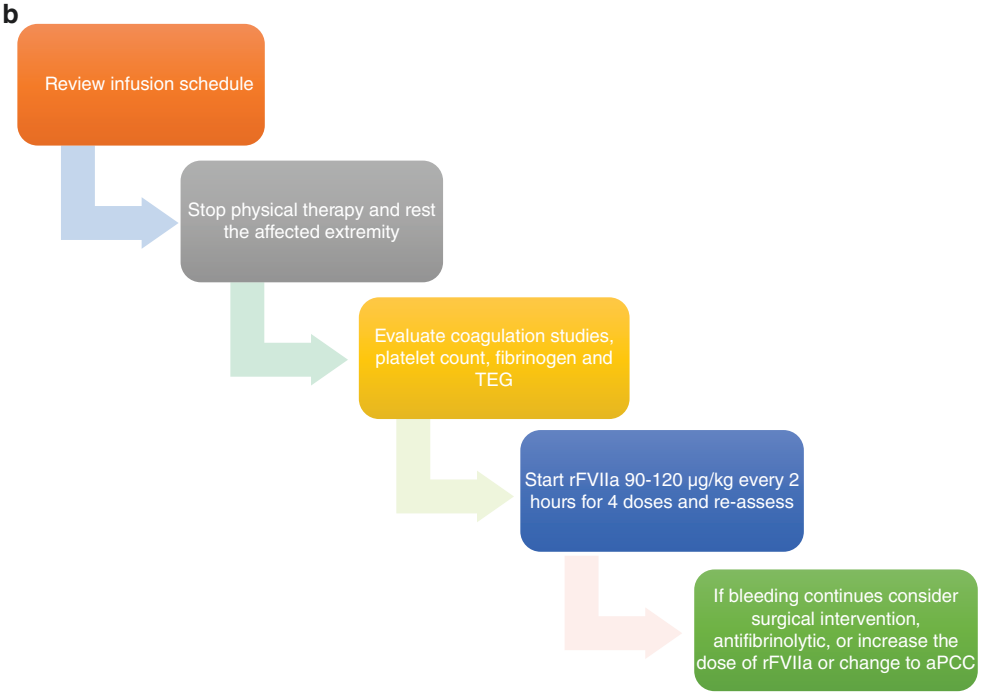

Fig. 8.1 (**a**) Surgical protocol for patients with inhibitors using rFVIIa. (**b**) Post-operative bleeding

tate is primarily used to maintain hemostasis. However, recombinant products or plasma-derived factor concentrates are considered to be first-line therapy over FFP or cryoprecipitate for factor replacement, when and where available. In deficiencies where there is a specific replacement, it is advisable to have a recovery study performed prior to surgery to help aid in dosing and frequency of factor replacement. For surgeries involving the nose, mouth, gastrointestinal tract, and gynecological systems, supportive care including topical hemostatic agents and antifibrinolytics is often utilized as adjunctive therapy or even monotherapy with/without factor replacement.

Fibrinogen (Factor I)

There are several purified and virally inactivated plasma-derived fibrinogen concentrates available in different countries. In the USA, plasma-derived fibrinogen concentrates RiaSTAP™ (CSL Behring, Marburg, Germany) and FIBRYGA™ (Octapharma, Vienna, Austria) have been approved for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. There is data suggesting the use of a plasma-derived fibrinogen concentrate in the perioperative setting is successful in achieving hemostasis during and after surgery [23]; however, FIBRYGA™ is currently the only product indicated for perioperative prophylaxis. Median single dose administered for surgery studies has ranged from 63.5 to 70 mg/kg. Goal fibrinogen preoperative is 100–150 mg/dL with levels at least above 50 mg/dL maintained until wound healing is complete. Mannucci et al. [24] suggests dosing of at least 20–30 mg/kg body weight for major surgeries with a target fibrinogen of greater than 50 mg/dL. The below dosing formula may be used. For unknown fibrinogen levels, a dose of 70 mg/kg body weight is recommended (Eq. 8.1).

$$\left[\frac{\text{Target level}\left(\text{mg/dL}\right)-\text{measured level}\left(\text{mg/dL}\right)}{1.7\left(\text{mg/dL per mg/kg body weight}\right)}\right] \quad (8.1)$$

Where fibrinogen concentrates are not available, cryoprecipitate can be used, as it contains a rich source of fibrinogen. Each bag of cryoprecipitate contains approximately 300 mg of fibrinogen, raising fibrinogen levels by about 10 mg/dL. In the pediatric population, 1–2 units/10 kg child increases fibrinogen by 60–100 mg/dL [25]. An adult dose of approximately ten single bags of cryoprecipitate increases fibrinogen by 60–100 mg/dL [26]. For major surgical procedures or severe trauma, the duration of daily treatment may be 2 to 3 weeks.

Antifibrinolytics may be used as an adjunct to hemostasis but should be avoided in individuals with personal or family history of thrombosis.

Factor II (Prothrombin)

There are currently no available plasma-derived or recombinant factor II concentrates at this time. FFP is the recommended treatment of choice with a loading dose of 15–20 mL/kg of body weight, followed by 3 mL/kg every 12–24 hours. In patients requiring extensive surgery, the use of plasma exchange with FFP may be performed prior to the operation, thereby avoiding the use of prothrombin complex concentrates (PCCs) [27]. There are two PCCs that are commercially available in the US market—Kcentra™ (CSL Behring, Marburg, Germany) and Profilnine™ SD (Grifols Biologicals, Los Angeles, CA); however, none of these products have been approved for congenital prothrombin deficiency. PCCs may be used to manage prothrombin deficiencies; however, they contain significant quantities of other vitamin K-dependent factors. Thromboembolic complications have been reported with the use of PCCs. Prothrombin levels of 20–40% are typically adequate to maintain hemostasis [28]. General dosing recommendations range from 20 to 30 IU/kg of prothrombin complex concentrate followed by 5 IU/kg every 24 hours [24, 29]. Laboratory monitoring for disseminated intravascular coagulation during and after PCC use is recommended.

Factor V

There are currently no commercially available factor V (FV) concentrates for replacement therapy. FFP is currently the only factor replacement option. Therefore, FFP is the treatment of choice for major surgery at a dose of 15–20 mL/kg body weight, followed by 3–6 mL/kg every 24 hours to attain levels of approximately 25% of normal [30]. Levels should be monitored during and after surgery to prevent bleeding complications [30, 31]. Minor surgeries (i.e., dental extractions) may be treated with local measures and the use of antifibrinolytics.

Combined Factors V and VIII Deficiency

Individuals with combined FV and FVIII deficiency may be treated with FFP to increase both FV and FVIII levels. As the half-life of FVIII is approximately 1/3 that of FV (10–14 versus 36 hours), DDAVP or even FVIII products may be used to help maintain FVIII levels [24]. Bolton-Maggs et al.

[29] suggest administering FVIII products along with FFP every 12 hours each to maintain FVIII above 50% and FV >25%. Levels of both FV and FVIII should be monitored during the surgical procedure as well as in the postoperative period.

Factor VII

Bleeding manifestations vary widely among individuals with congenital factor VII (FVII) deficiency. Severe bleeding is typically seen in individuals with levels less than 1%, although individuals with higher levels may also bleed significantly or none at all. rFVIIa is FDA approved for use in congenital FVII deficiency. For surgical procedures, a rFVIIa dose of 15–30 μg/kg body weight immediately pre-op to achieve a FVII activity of greater than 15–20% is recommended [24, 30, 32]. Dosing should be repeated every 4–6 hours for the duration of surgery. Additional doses may be necessary to maintain hemostasis based on individual response to therapy as well as type of surgery [32]. Due to clinical bleeding variability, it is imperative to consider higher levels of FVII be maintained in persons with congenital FVII deficiency with history of significant bleeding despite their baseline levels being above the targeted goal of greater than 15–20% [33].

Plasma-derived FVII concentrates are available in Europe. PCCs as well as FFP are also other sources of FVII when rFVIIa or plasma-derived FVII concentrates are not available.

Factor X

Until recently FFP was the treatment of choice for replacement of factor X (FX). In 2015, Coagadex™ (Bio Products Laboratory, Hertfordshire, UK), a plasma-derived FX concentrate, was approved in the USA for the treatment of bleeding episodes and for perioperative management of patients with congenital FX deficiency. For surgery, plasma FX level should be approximately 70–90 IU/dL followed by 50 IU/dL in the postoperative period. Dosing may be calculated every 24 hours using the following formula: Dosage Required (IU) = Body Weight (kg) × Desired FX Increase (FX:C % or IU/dL) × 0.5 [34, 35]. When FX concentrate is not available, FFP may be used with a loading dose of 10–20 mL/kg followed by 3–6 mL/kg every 12 hours to achieve a FX level of greater than 10–20% [36]. PCCs containing FX with 1:1 ratio of FX to IX will increase FX activity by 1.5% per IU/mL. Dosing of PCCs is recommended at 20–30 U/kg every 24 hours [24]. Due to concomitant increases in other factors (FII, FVII, and FIX) present in PCCs, monitoring of these factor levels in the post-op period is necessary to avoid supratherapeutic levels, thereby increasing the risk of thrombosis [28].

Factor XI

There are no commercially available factor XI (FXI) concentrates for use in the USA at this time. FFP may be used at a loading dose of 15–20 mL/kg body weight, followed by 3–6 mL/kg every 12 hours. For minor and major surgery, a minimum level of 30% and 45% of normal, respectively, is recommended [28]. Mannucci et al. [24] recommend maintaining FXI greater than 20% for major or minor surgeries. It is important to note that individuals with FXI deficiency have bleeding manifestations not directly correlated with their factor level; therefore, consideration for higher levels of FXI in individuals with a more significant bleeding history irrespective of their baseline FXI levels is warranted [30]. Conversely, antifibrinolytic agents can be used alone or in combination with FFP to control bleeding. Tranexamic acid monotherapy for dental procedures in individuals with severely low FXI without reported bleeding sequela have been described [37].

Circumcision should be held at birth if cord blood reveals FXI activity <10%. A repeat FXI level should be measured at 6 months of life, and if it remains <10%, it is recommended the infant be covered with factor to the above recommended dosing to avoid bleeding. If follow-up levels at 6 months old is >10%, monotherapy with tranexamic acid is recommended for the circumcision. It is preferable the procedure will be performed in a hospital setting [29]. In the case of a tonsillectomy/adenoidectomy with FXI level below 30%, replacement with FPP and an antifibrinolytic is recommended.

Factor XIII

Factor XIII (FXIII) deficiency results from lack of either the A or B subunit of FXIII. Usually homozygous mutation of the FXIII gene results in severely reduced levels, <1%, and these individuals have clinical bleeding manifestations. Heterozygotes for FXIII mutations have higher levels and generally do not experience bleeding complications. For severe FXIII deficiency, <1%, prophylaxis with FXIII concentrate every 4 weeks is recommended to maintain FXIII activity between 5% and 20% [38].

Corifact™ is a plasma-derived dual-subunit FXIII concentrate (CSL Behring, Marburg, Germany) available in the USA currently approved for routine prophylaxis and perioperative management. In individuals with known FXIII A-subunit deficiency, there is also a recombinant FXIII A-subunit product, Tretten™ (Novo Nordisk, Bagsvaerd,

Denmark) that may be used, although current indications are limited to routine prophylaxis of bleeding.

For surgical prophylaxis, replacement with FXIII is recommended to maintain FXIII levels between 5% and 20% for both minor and major surgeries [24, 38].

A pre-op level is necessary to determine if a dose prior to surgery is warranted. Monitoring FXIII level during and after surgery is recommended. Where recombinant FXIII or plasma-derived FXIII concentrates are not available, FFP and cryoprecipitate are options.

East Texas Bleeding Disorder (ETBD) and Factor V Amsterdam

This novel autosomal dominant bleeding disorder was initially described in 2001 in a family of four generations from east Texas. Later in 2015 similar findings were described in a Dutch family. Two mutations have been identified (A2440G-ETBD and C2588G- FV Amsterdam) in the FV gene causing a bleeding disorder through an indirect gain-of-function mechanism. This is the first known bleeding disorder resulting from increased plasma levels of tissue factor pathway inhibitor alpha (α). There are no current treatment standards for individuals with ETBD or FV Amsterdam. From personal experience, use of aPCC at low doses (30 IU/kg IV every 8–24 hours) in individuals with ETBD has been successful in preventing bleeding during surgical procedures. Treatment may be guided with the use of thromboelastography/thromboelastometry or thrombin generation assay [28].

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9 Hemophilia A, Hemophilia B, Congenital von Willebrand Disease, and Acquired von Willebrand Syndrome

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Hemophilia A

Hemophilia A is an X-linked disorder due to congenital deficiency of factor VIII (FVIII). The frequency of hemophilia A is estimated to be approximately 1/5000 male births across all ethnic groups. The degree of bleeding severity, with rare exception, is directly related to patient's baseline FVIII level and can range from mild to life-threatening [1]. Although hemophilia A affects mostly males, infrequently the disease can manifest in female patients via chromosome lionization [2–4]. In addition, approximately 30% of hemophilia A can present secondary to de novo mutations. Therefore, the diagnosis of hemophilia A should be considered even in the absence of a strong family history [5–7].

Factor VIII Protein

Unlike most other plasma coagulation proteins, which are produced by hepatocytes, FVIII is mainly produced by liver endothelial cells [8, 9]. This is likely the reason for elevated FVIII even in the setting of liver failure.

The FVIII protein is produced as a six-domain protein, A1-A2-B-A3-C1-C2 [10–12]. In the Golgi compartment, FVIII is cleaved within the B domain to form the mature FVIII heterodimer that consists of the 200 kDa A1-A2-B heavy chain and the 80 kDa A3-C1-C2 light chain [13]. Once FVIII is released into circulation, it binds to von Willebrand factor (VWF) which serves to increase FVIII half-life and regulate FVIII activity. Upon activation by thrombin, FVIIIa functions as a co-factor for factor IXa (FIXa) in the activation of factor X (FX) to factor Xa (FXa) and ultimately generates thrombin [13–16]. Hemophilia A has been linked to a variety of well-known molecular mutations including inversion, large deletion, frameshift, nonsense, and missense defects [17, 18]. The severity of the disease can often be predicted by the site and type of mutation in the FVIII gene [19–22].

Diagnosis of Hemophilia A

The diagnosis of hemophilia A begins with recognition of an X-linked inheritance pattern of an unexplained and isolated prolongation of activated partial thromboplastin time (aPTT) that is corrected in a mixing study [23]. Subsequent laboratory workup using FVIII assay should identify a FVIII deficiency. However, it is important to note that an initial finding of an isolated prolonged aPTT with mixing study correction does not immediately imply hemophilia A [24]. Other aPTT pathway factor deficiencies, such as factor IX (FIX) or factor XI (FXI) deficiency, or even non-clinically significant factor XII deficiency will present with the same initial laboratory finding [25]. Therefore, it is important to order FIX and FXI along with FVIII to rule out other potential congenital bleeding disorders. Furthermore, it is important to consider von Willebrand disease (VWD) when considering the diagnosis of hemophilia A, as carrier defect (Type 2N) or deficiency (Type 1 and Type 3) of VWF will result in decrease of FVIII. The diagnosis of these specific types of VWD will be discussed later in this chapter.

The severity of hemophilia A is directly related to the degree of deficiency of FVIII activity as measured by one-stage assay. Mild hemophilia A is defined by FVIII activity between 5% and 40%, moderate disease is activity 1–5%, and severe hemophilia A is below 1%. Although FVIII activity via one-stage assay can generally predict bleeding phenotype, in very rare situations, there can be discrepant clinical bleeding symptoms with FVIII activity via this method. In such a scenario, a two-stage or chromogenic FVIII assay may be used to better define the patient's disease [26, 27].

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Hemophilia B

Like hemophilia A, hemophilia B is also a X-linked bleeding disorder affecting around 1 in 25,000 male births. In hemophilia B, FIX is deficient which results in lifelong bleeding symptoms. The severity of bleeding is directly related to the degree of FIX deficiency. Approximately one third of all cases arise from spontaneous mutations [28]. Therefore, like hemophilia A, a lack of family history does not exclude the diagnosis.

Factor IX Protein

FIX protein is a 57 kDa multi-domain protein produced in the liver by hepatocytes. FIX is a vitamin K-dependent protein, requiring gamma-carboxylation to be fully functional. FIX can be activated into FIXa via the intrinsic pathway by FXIa or in the extrinsic pathway by tissue factor and factor VIIa (FVIIa) [29]. FIXa in the presence of calcium, FVIIIa, and phospholipids in turn activates FX to FXa and ultimately into thrombin. Hemophilia B has been linked to a number of mutations, especially frameshift, missense, or nonsense mutations within the CpG dinucleotide mutation hotspot. Large and short deletions and insertions complete the genetic mutation profile for hemophilia B [28].

Diagnosis

A deficiency in FIX may indicate vitamin K deficiency instead of hemophilia B, especially in neonates [30]. Since FVII is also a vitamin K-dependent factor, an isolated prolonged aPTT without prolongation of PT makes hemophilia B more likely as half-life of FVII is shorter than FIX. Like FVIII in hemophilia A, the severity of hemophilia B is directly related to the degree of deficiency of FIX activity. Mild hemophilia B is defined by FIX activity between 5% and 40%, and moderate disease is activity 1–5%, while severe hemophilia B is below 1%.

Hemophilia Carriers

It has been long thought that women as hemophilia carriers are not clinically affected. However, more recent studies have shown that hemophilia carriers have lower factor activity than non-carriers and significantly lower overall quality of life especially in terms of greater menstrual blood loss [31–39]. Therefore, women who are known hemophilia carriers should be assessed carefully in terms of personal bleeding history and baseline factor level. If factor level is consistent with diagnosis of hemophilia, these carriers should be treated with factor replacement like their male counterparts [32].

Congenital von Willebrand Disease

VWD remains the most common congenital bleeding disease worldwide across all ethnic groups. Unlike hemophilia, VWD is an autosomal disorder; therefore it affects both sexes equally, and this inheritance pattern helps to distinguish it from hemophilia A. Bleeding characteristics and severity are greatly affected by its subtypes and can range from joint and muscle bleeding (Type 3) to menorrhagia to mild oral and mucosal bleeding [40, 41]. Due to variation in clinical presentations, a complete and accurate laboratory workup is important for the subtyping of VWD [42]. The laboratory workup for VWD is discussed in detail in Chapter 4, "von Willebrand Disease Laboratory Workup."

von Willebrand Factor

Unlike most other coagulation proteins, VWF is not produced by the liver. This helps to explain elevated FVIII and increased thrombotic risk in the setting of liver dysfunction. VWF is produced by both megakaryocytes and endothelial cells (Fig. 9.1) as a 2813 amino acid long pre-propeptide (Fig. 9.2) in the endoplasmic reticulum, which is then dimerized into 800 kDa dimers. These dimers are then polymerized into mature VWF multimers up to 20,000 kDa in length, and VWF propeptide (VWF:pp) dimers are cleaved from the mature multimers as they travel through the Golgi. Finally, both the mature VWF and VWF:pp are packaged and stored in Weibel-Palade bodies in endothelial cells or alpha granules in platelets. Upon activation, mature VWF and VWF:pp are released from storage into circulation; once released, VWF multimers are cleaved at a specific site in the A2 domain into multimers of variable sizes by a metalloprotease, ADAMTS13 [43–45]. Under normal physiological condition, VWF exists as large, intermediate, and low molecular weight multimers in a balanced distribution. However, when this normal size distribution is disturbed, it will result in disease conditions such as thrombotic thrombocytopenic purpura when there are ultra large multimers [46] or bleeding when there is absence or decrease in large multimers [47].

Circulating VWF plays an important role in both primary and secondary hemostasis. In primary hemostasis, VWF serves to support platelet adhesion to the site of vascular injury via binding to sub-endothelial collagen and to the glycoprotein Ib-V-IX complex (GPIb) on platelet surface. This interaction is important in recruiting and activating platelets at the site of vascular injury [48]. In terms of secondary hemostasis, VWF serves as a carrier protein for FVIII, which both protects FVIII from proteolysis and localizes FVIII to platelet surface [49, 50].

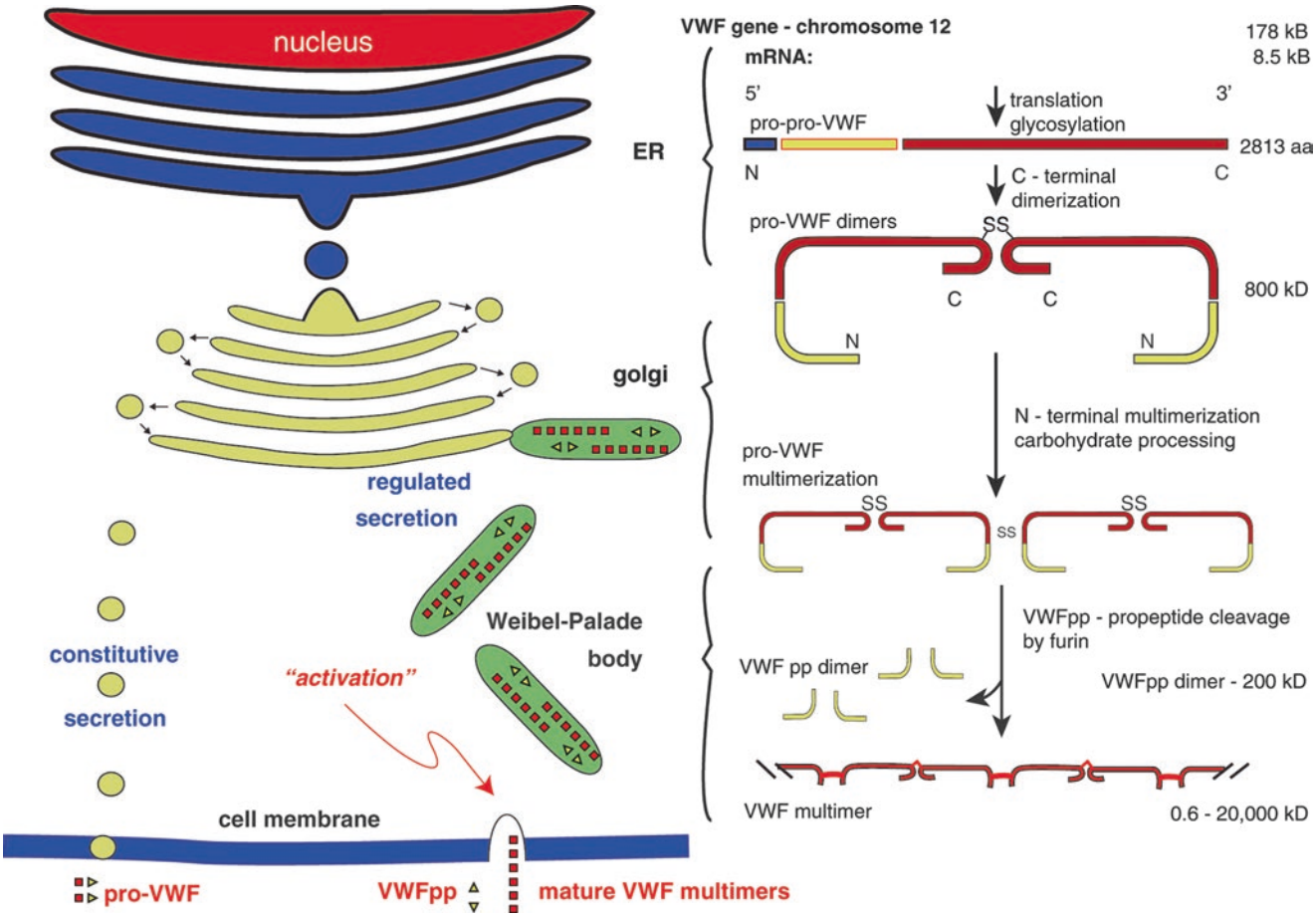

Fig. 9.1 Demonstrates the production of VWF multimers in endothelial cells. Matured VWF and propeptide are stored within Weibel-Palade bodies ready for release upon activation (From Haberichter [87])

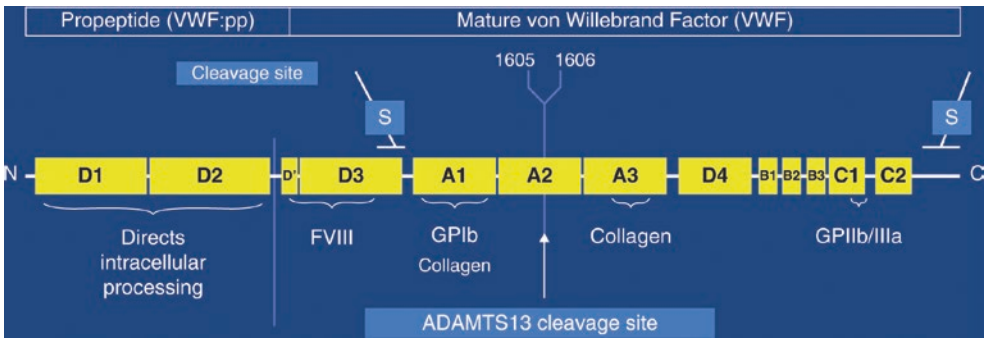

Fig. 9.2 Showed the various known VWF domains and their respective contributions to VWF function

von Willebrand Disease

As discussed previously, VWD can present with widely different bleeding phenotypes depending on the underlying pathophysiology. In general, VWD (Table 9.1) can be broadly divided into two types of VWF defects, quantitative (Type 1 and Type 3) and qualitative (Type 2). It is important to distinguish the various subtypes of VWD via an algorithmic laboratory approach, as it can greatly impact the management of the patient. Various laboratory workups and an algorithm are described in details in Chapter 4 "von Willebrand Disease Laboratory Workup."

Type 1 von Willebrand Disease (VWD)

Type 1 VWD accounts for the majority of VWD (80%). It is a quantitative defect defined as either VWF antigen (VWF:Ag) or VWF activity (VWF:Act) between 1% and

Table 9.1 Various VWD subtypes and their expected laboratory findings

Condition	VWF:Act	VWF:Ag	FVIII	VWF:Act/Ag	VWF multimer analysis
Type 1	<30	<30	Low to normal	>0.7	Normal but low intensity
Type 2A	<30	<30–200	Low to normal	<0.7	Missing large multimer
Type 2B/PT-VWD	<30	<30–200	Low to normal	<0.7	
Type 2M	<30	<30–200	Low to normal	<0.7	Normal
Type 2N	30–200	30–200	Significantly lower than VWF antigen	>0.7	Normal
Type 3	<3	<3	<10	–	–
"Low VWF"	30–50	30–50	Normal	>0.7	Normal
Normal	50–200	50–200	Normal	>0.7	Normal

30% without any observable VWF function defects. VWF activity-to-antigen ratio (VWF:Act/VWF:Ag) should be normal at >0.5–0.7 [51]. In addition, VWF multimer analysis (VWF:MA) should show a normal size distribution with decreased intensity. The mechanism for Type 1 VWD is a decreased synthesis of VWF; however, Type 1 variant (Type 1C or Type 1 Vicenza) has been shown to have increased clearance and decreased VWF half-life. It is important to rule out such Type 1 variant as 1-deamino-8-D-arginine vasopressin (DDAVP) administration will not be an effective treatment as the therapy yields only short-lasting effect [52]. In Type 1C VWD or Type 1 Vicenza, DDAVP challenge is expected to show good 1 h post-administration response with a decreased 4 h post-administration response [53]. Compared to other Type 1 VWD, VWF:pp/VWF:Ag is increased, which is the defining characteristic of this Type 1 variant [54]. It is important to note that FVIII in Type 1 VWD is proportionally decreased as VWF is a carrier protein for FVIII; thus, VWD workup should be performed in initial diagnosis of hemophilia A. Furthermore, hemophilia A can coexist with other subtypes of VWD. Lastly, laboratory diagnosis of VWD has proven to be challenging as VWF is an acute phase protein. Since the level can be increased several fold from baseline, a one-time normal VWF:Ag and VWF:Act cannot definitively rule out Type 1 VWD [55]. Furthermore, FVIII is not an effective marker for acute phase as its level is directly affected by VWF:Ag level. Concurrent fibrinogen level or C reactive protein level may be used as potential acute phase markers, but neither has been universally validated. Until a better marker can be established, the most effective method to distinguish acute phase from baseline study remains repeat testing.

Low von Willebrand Factor (VWF)

It is important to discuss "low VWF" in the discussion of quantitative Type 1 and Type 3 VWD. As normal VWF:Ag and VWF:Act level is usually defined as >50% and Type 1 VWD is <30%, the gray zone area between 30 and 50% can be difficult to define [51]. This "in-between" VWF:Ag and VWF:Act can fall within Type 1 VWD in European region as Type 1 VWD is defined as <45% [56]; others have also proposed defining Type 1 VWD based on a cutoff of <2.5 percentile [57]. However, in the United States, Type 1 VWD is strictly reserved for patient with VWF:Ag or VWF:Act <30% without functional defects. Hence, individuals with repeat VWF level between 30% and 50% should be considered as having "low VWF" and not VWD. Of note, blood group O individuals are more likely to have "low VWF" than other blood groups [58], which may be related to post-translational modification [59]. Individuals with "low VWF" by current criteria in the United States are not classified as VWD. However, it is important to note that more recent studies have demonstrated that some individuals with "low VWF" report high bleeding scores, particularly for dental bleeding and menorrhagia [60]. However, unlike patients with VWD, the correlation of VWF level and bleeding score was poor [61], suggesting that a complete and comprehensive bleeding history may be more effective in identifying these higher-risk individuals than antigen and activity alone [62]. Unfortunately, there are no guidelines on identifying these higher-risk "low VWF" individuals. Therefore the decision to treat should be personalized to the specific patient based on bleeding history and ongoing symptoms [63].

Type 3 von Willebrand Disease

Type 3 VWD accounts for less than 1% of VWD. It is a severe quantitative defect defined as absence (<1%) of both VWF:Ag and VWF:Act [51]. As FVIII level can fall within moderate hemophilia A range, it is important to rule out Type 3 VWD.

Type 2A von Willebrand Disease

Type 2A VWD accounts for approximately 10% of all VWD. It is characterized by the absence of both high and intermediate molecular weight VWF secondary to decreased synthesis or increased proteolysis by ADAMTS13 [51]. Therefore, the laboratory workup demonstrates a qualitative defect of decreased VWF:Act but relatively normal VWF:Ag,

which results in decreased VWF:Act/VWF:Ag ratio at <0.5–0.7. Of note, unlike Type 2B VWD, mild thrombocytopenia is not an expected finding. Type 2A VWD is often considered as a diagnosis of exclusion.

Type 2B von Willebrand Disease

Type 2B VWD accounts for approximately 3–5% of all VWD. Although its laboratory findings are similar to Type 2A VWD with decreased VWF:Act/Ag ratio and loss of high molecular weight multimers, the mechanism for this disease is entirely different [51]. Type 2B VWD is due to a gain-of-function mutation in the platelet GPIb binding to A1 domain of the VWF protein, which results in increased and spontaneous binding of VWF to platelets without shear stress [64]. This abnormal interaction results in loss of both high molecular weight VWF and platelets, which explains the pathognomonic findings of thrombocytopenia in Type 2B VWD. This gain-of-function mutation makes desmopressin a contraindication for Type 2B VWD as it may result in thrombotic complications. Therefore, it is important to distinguish Type 2B from other Type 2 VWD; ristocetin-induced platelet aggregation study (RIPA) is only abnormal in gain-of-function VWD which includes Type 2B VWD.

Pseudo-von Willebrand Disease/Platelet-Type von Willebrand Disease

As in Type 2B VWD, the pathogenesis of platelet-type VWD (PT-VWD) is due to abnormal spontaneous interaction between platelet GPIb and VWF [51]. However, in contrast to Type 2B VWD, the gain-of-function mutation is in the platelet GPIb receptor [65]. Overall, initial laboratory workup is indistinguishable from Type 2B VWD, including decreased VWF:Act/VWF:Ag, loss of high molecular weight VWF multimers, thrombocytopenia, and even abnormal RIPA. A specialized laboratory test, the 2B binding assay, can be used to differentiate PT-VWD from Type 2B VWD. As in Type 2B VWD, desmopressin is contraindicated for the treatment of PT-VWD.

Type 2M von Willebrand Disease

Type 2M VWD accounts for only 1–2% of VWD. The initial laboratory workup, similar to Type 2A, 2B, or PT-VWD, shows decreased VWF:Act/VWF:Ag [51]. Like Type 2B VWD, pathogenesis for Type 2M VWD also lies in the A1 domain of VWF, but it is a loss-of-function mutation where the interaction between platelet GPIb receptor and VWF is decreased [66]. Therefore, multimer analysis for Type 2M VWD is normal and does not demonstrate loss of high or intermediate molecular weight VWF. The presence of normal multimer distribution with decreased VWF:Act/VWF:Ag are the defining laboratory characteristics of Type 2M VWD.

Type 2N von Willebrand Disease

Type 2N VWD is qualitative VWF disorder that accounts for 1–2% of all VWD [51]. However, its functional defect lies not in VWF function as a coagulation protein, but its FVIII carrier function. Mutations within the D' and D3 domain of VWF molecule render the binding of VWF to FVIII defective [67]. As the coagulation function of VWF is unaffected, the VWF laboratory workup is unremarkable at first glance: normal VWF:Ag, VWF:Act, and VWF:Act/VWF:Ag and even normal multimer analysis. However, FVIII activity can be decreased to as low as 5–15%, making Type 2N VWD sometimes difficult to differentiate from hemophilia A [68, 69]. The inheritance pattern of Type 2N VWD is autosomal recessive in contrast to X-linked in hemophilia A. FVIII binding assay (discussed in Chapter 4, "von Willebrand Disease Laboratory Workup") can be used to distinguish Type 2N VWD from hemophilia A. It is important to note that, like other VWD subtypes, Type 2N VWD can coexist in patients with hemophilia A. Therefore, concurrent Type 2N VWD should always be considered and ruled out as it can affect patient's response to recombinant FVIII infusion.

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AVWS) is a collection of acquired bleeding disorders (Table 9.2), secondary to loss of VWF quantitative or qualitative functions [70]. Dozens of diseases have been associated with AVWS; nonetheless, laboratory findings often mimic subtypes of congenital VWD, especially Type 2A VWD with decreased VWF:Act/VWF:Ag and loss of high to intermediate molecular weight VWF multimers. The loss of high molecular weight VWF multimers can be secondary to either pathological high shear stress such as in aortic stenosis [71], presence of autoantibodies against VWF [72], or even direct absorption by tumor cells [73]. Less commonly, AVWS may result from decreased overall VWF production as opposed to selective loss of high molecular weight VWF multimers. This can occur in the setting of hypothyroidism [74]. The bleeding diathesis of AVWS may vary, but bleeding symptoms and VWF laboratory abnormalities usually resolve upon resolution of the underlying disorders.

Table 9.2 Various disorders that have been reported to be associated with AVWS

Underlying disorders	Previous literature, ISTH-SSC and German registry 1968–2011 (n = 1292)	
Cardiovascular	*414*	*32%*
Aortic stenosis	201	16%
Cardiac assist device	110	9%
AV septal defects	21	2%
Myeloproliferative	*350*	*27%*
Essential thrombocythemia	212	16%
Polycythemia vera	88	7%
CML and myelofibrosis	64	5%
Lymphoproliferative	*321*	*25%*
MGUS	193	15%
MM and WMg	80	6%
NHL, HCL, and ALCL	28	2%
Systemic diseases (hepatitis C, cirrhosis, hypo-thyroid, hemoglobinopathies, uremia, diabetes)	*87*	*7%*
Drugs (valproate, hydroxystarch, etc.)	*40*	*3%*
Neoplasia	*32*	*2%*
Immune	*21*	*2%*

AV atrioventricular, *CML* chronic myelogenous leukemia, *MGUS* monoclonal gammopathy of undetermined significance, *MM* multiple myeloma, *WMg* Waldenstrom macroglobulinemia, *NHL* non-Hodgkin lymphoma, *HCL* Hodgkin lymphoma, *ALCL* anaplastic large cell lymphoma

Table 9.3 Published recommendations for peri-operative management of hemophilia A, hemophilia B, and VWD patients

	Hemophilia A [75, 84]	Hemophilia B [75, 84]	von Willebrand disease [84]
Dental procedure	50–100% prior + antifibrinolytic × 7–10 days post	50–100% prior + antifibrinolytic × 7–10 days post	60% prior
Surgery (minor)	80–100% prior + >50% × 5–7 days	80–100% prior + >50% × 5–7 days	60% prior + >30% × 2–4 days
Surgery (major)	80–100% prior +	80–100% prior +	100% prior + >50% × 5–10 days
	80–100% × 1–3 days	80–100% × 1–3 days	
	60–80% × 4–6 days	60–80% × 4–6 days	
	+40–60% × 7–14 days	+40–60% × 7–14 days	
Delivery	>50% prior [86] × 3–4 days [85]	>50% prior [86] × 3–4 days [85]	80–100% prior + >30–50% × 3–4 days, up to 2 weeks [85]

Management of Hemophilia A, Hemophilia B, and von Willebrand Disease for Invasive Procedure, Surgery, and Pregnancy

The management of patients with hemophilia A, B, and VWD can be complex; however, there have been established recommended guidelines (Table 9.3) that can provide some important standard of care guidance in managing these patients around time of procedures, surgeries, or deliveries. It is important to note that factor concentrates or recombinant factors should be used in place of plasma or cryoprecipitate as the replacement of choice since the concentration is much higher and infectious risk is significantly less. DDAVP may be used in patients with mild hemophilia A, mild VWD, or hemophilia A carrier in place of factor replacements; however, a trial should be performed to ensure effectiveness prior to use in surgical settings. Antifibrinolytic therapy may be used in conjunction with standard factor replacement [75]; however, this practice has not been well-standardized beyond dental procedure, but should be considered if risk is high or if replacement therapy alone is ineffective.

Enhanced half-life FVIII and FIX, with 1.5 [76] and 5 times [77] half-life of traditional recombinant factors, respectively, are becoming more prevalent in the treatment of hemophilia [78]. These agents have been shown to be particularly effective in providing hemostatic support for surgery [79, 80, 81]. However, they can be challenging to monitor, as routinely available one-stage clotting factor assays can underestimate or overestimate the factor level depending on the agent and assay used [82, 83]. Accurate monitoring of enhanced half-life FVIII and FIX requires chromogenic factor assays, which may not be available at all institutions. Therefore, prior to utilizing these agents, the availability of chromogenic factor assays for monitoring responses must first be confirmed.

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Bleeding Associated with Coagulation Factor Inhibitors

10

Charles Eby

Abbreviations

aPTT	Activated partial thromboplastin time
FEIBA	Factor eight inhibitor bypass activity
INR	International normalized ratio
LA	Lupus anticoagulant
NPP	Normal pooled plasma
PT	Prothrombin time
rFVIIa	Recombinant factor VIIa
TT	Thrombin time

Presentation

Patients with clinically important coagulation factor inhibitors usually present with excessive hemorrhage and bruising exceeding the patient's typical spontaneous or traumatic bleeding patterns. The symptoms may be subtle and localized at first, gradually exacerbating to life-threatening hemorrhage from multiple sites, or the first bleeding complication may compel the patient to seek medical attention. Healthcare providers may search for, identify, and treat an anatomic cause for bleeding, often via invasive procedures, before considering the possibility of a systemic bleeding condition or reviewing screening coagulation test results. For example, gross hematuria or rectal bleeding may lead to detection of a bleeding tumor. However, to biopsy or resect the tumor in the patient with an acquired factor deficiency can result in uncontrolled bleeding. While at least one screening coagulation test will be abnormal in almost all patients with a clinically important inhibitor, there are some exceptions. For example, an acquired factor XIII (FXIII, hereafter all factors are abbreviated to F) deficiency will not prolong aPTT or PT, but would make a patient vulnerable to spontaneous and post-invasive procedure bleeding. Finally, some patients with neutralizing coagulation factor autoantibodies can be asymptomatic, and the first clue is an unexplained prolonged aPTT, PT, or both.

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Laboratory Detection and Confirmation of Coagulation Factor Autoantibodies

Bleeding complications are unlikely unless the reduction of the target factor activity is low enough to prolong screening clotting tests, aPTT, PT, or both, depending upon the inhibited factor. Figure 10.1 shows the coagulation cascade and the factors included in PT and aPTT screening tests. Figure 10.2 provides an algorithmic approach to evaluate a patient suspected of having an acquired inhibitor. Indirect evidence of a neutralizing autoantibody is incomplete correction of a 50:50 mixing study performed by repeating the prolonged screening clotting test using a mixture of equal volumes of patient plasma and normal pooled plasma (NPP). Acquired FVIII inhibitors are notorious for delayed inhibition of FVIII molecules in NPP [1]. An aPTT performed immediately after mixing plasma containing a FVIII inhibiting antibody and NPP may show considerable, or even complete, correction which could be interpreted as a simple factor deficiency. Therefore, it is a standard laboratory practice when evaluating an unexplained prolonged aPTT (and in some laboratories, PT as well) to perform both an immediate 50:50 aPTT and a second aPTT after incubating the 50:50 mixture of patient plasma and NPP for at least 60 min at 37 °C in order to observe the maximal inhibitory effect and prolongation of the aPTT. However, a delayed in vitro inhibition pattern in an aPTT 50:50 mixing study is not specific for a FVIII inhibitor or an acquired inhibitor of one of the other coagulation factors in the intrinsic pathway since a lupus anticoagulant autoantibody may occasionally mimic this pattern [2]. When the 50:50 mix results show incomplete correction, the next step is to perform additional coagulation testing (Fig. 10.2).

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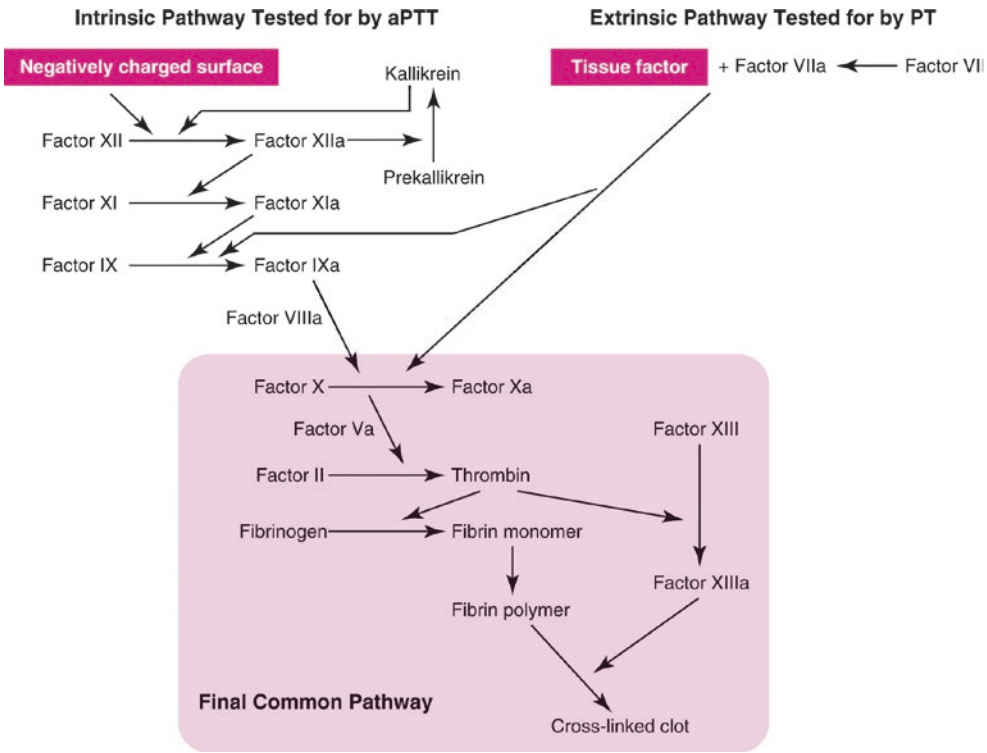

Fig. 10.1 Model of the classic coagulation cascade and screening coagulation tests. aPTT reagent activates FXII to initiate the intrinsic pathway. PT reagent activates FVII to initiate the extrinsic pathway. Factor deficiencies or inhibitors of the intrinsic pathway prolong the aPTT and of the extrinsic pathway prolong the PT. Factor deficiencies or inhibitors of the common pathway prolong both the aPTT and PT. The exception is FXIII deficiency or inhibition, which will not prolong the aPTT or PT. From Lefkowitz JB. Coagulation pathway and physiology (From Kottke-Marchant [41]. Reproduced with permission)

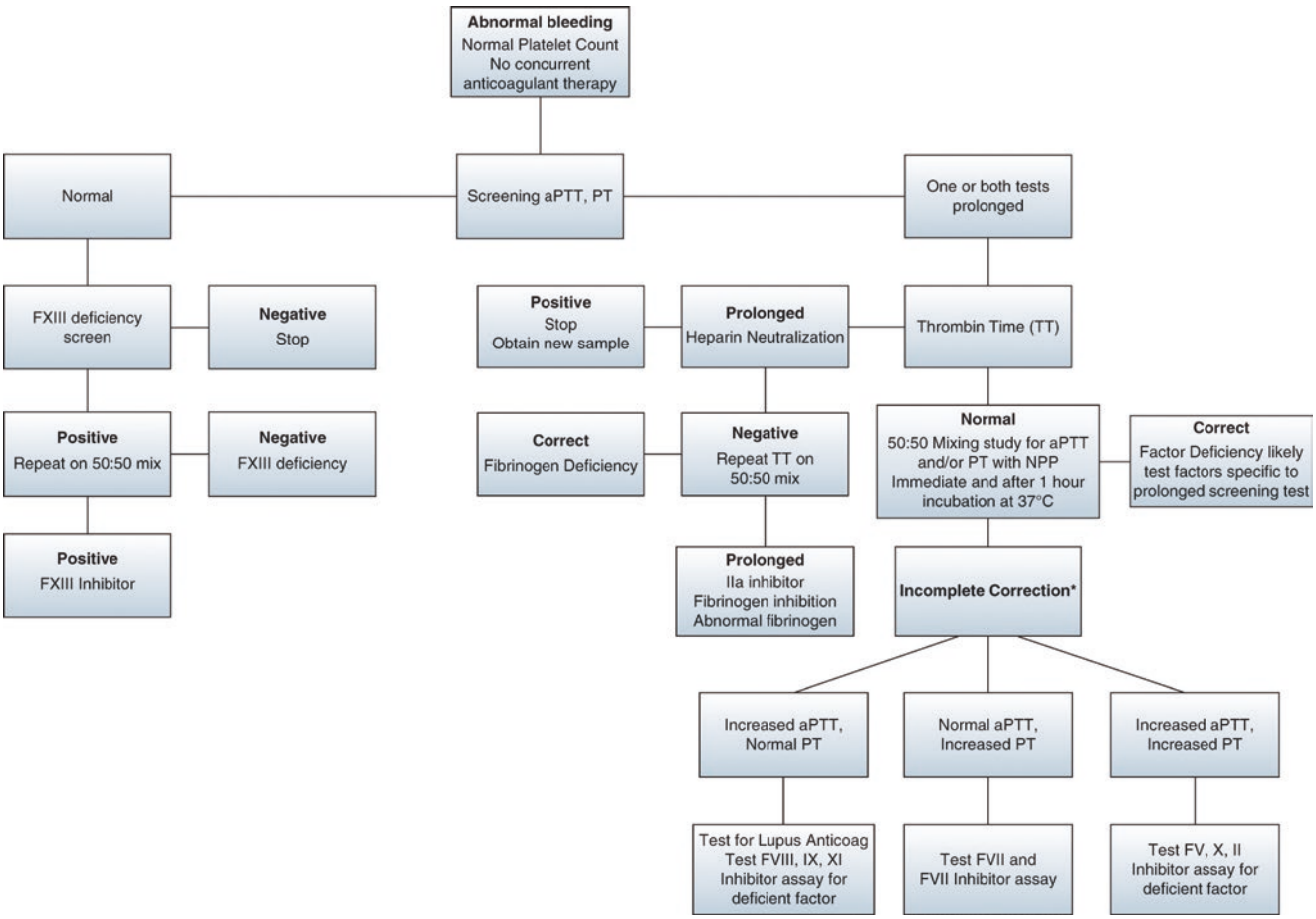

Fig. 10.2 A diagnostic algorithm for laboratory evaluation of a suspected acquired bleeding disorder

Table 10.1 Apparent activity of intrinsic factor pathway coagulation factors in plasma containing a FVIII inhibitor. Recovered factor activities corrected for serial dilutions

Plasma dilution	FVIII (%)	FIX (%)	FXI (%)
1:10	1	24	11
1:20	1	45	23
1:40	1	67	54

A specific neutralizing antibody will result in a moderate-to-severe in vitro deficiency of its target factor. However, neighboring factor assays may show inhibition due to partial interference of the specific inhibitor in these assays (Table 10.1). Having confirmed the specificity of the inhibitory antibody, its potency is measured by performing either a Bethesda or Nijmegen inhibiter titer assay [1]. Serial dilutions of the patient's plasma are mixed with NPP (50:50 mix) and incubated for 2 h at 37 °C followed by measurement of the residual activity of the inhibited factor. Results are expressed as the reciprocal of the patient's plasma dilution which neutralized 50% of the target factor activity in the diluted NPP. This method was originally developed to measure FVIII inhibitors in hemophilia A patients who developed alloantibodies to infused FVIII. The in vitro behavior of FVIII alloantibodies typically shows simple, irreversible inhibition of FVIII, and interpretation of the inhibitor assay results is straightforward, while acquired FVIII autoantibodies may show a more complex pattern of inhibition [1]. The Bethesda or Nijmegen assay can be adapted to measure the potency of other coagulation factor inhibitors by measuring the recovery of the factor of interest.

Acquired Hemophilia A

The most common coagulation factor target for neutralizing autoantibodies is FVIII with an estimated incidence of 1.4/million [3]. The results of several large prospective registries or population-based cohorts show similar findings for clinical presentations [3–6] (Table 10.2). Affected patients are typically elderly, slightly biased toward men. About half of acquired FVIII inhibitor patients have an underlying autoimmune disorder, malignancy, or other condition (suspected medication [7], infection, dermatologic disease), which may be causally related to inhibitor development, while the other 50% of patients' inhibitors are idiopathic. One unique FVIII inhibitor population is post-partum women representing 2–3% of all cases. The median onset of bleeding is 2.5 months post-partum. They have excellent responses to hemostatic and immunosuppression treatment with >85% complete remissions and much lower mortality rates compared to older patients [8].

Table 10.2 Presentation and clinical outcome of 154 patients with acquired hemophilia A in the United Kingdom 2001–2003 [3]

Median age (years)	78
FVIII activity on presentation	
<1%	30%
1–5%	36%
>5–50%	34%
Initial inhibitor titer (unit)	
1–10	6%
11–100	81%
>100	11%
Underlying disorders	
None	63%
Malignancy	16%
Autoimmune disease	15%
Dermatologic disease	3%
Pregnancy post-partum	2%
Other	1%
Clinical outcomes	
Required hemostatic treatment	66%
Death due to bleeding	9%
Death due to sepsis	11%
Complete remission (CR)	71%
Median time to CR (days)	57
Relapse rate	24%

Symptoms at Presentation

Patients typically present with new onset of spontaneous bruising and bleeding at one or more sites, while intracranial and joint hemorrhages are uncommon. Bleeding can be spontaneous, post-traumatic, or post-invasive procedures and is usually severe. However, up to a third of patients are asymptomatic when an inhibitor is discovered based on an incidentally prolonged aPTT [3, 4].

Laboratory Findings

FVIII activities range from <1 to ~50% and most inhibitor results are >10 units (Table 10.2). Other coagulation factor activities based on aPTT testing may show varying degrees of inhibition due to the partial neutralization of the factor VIII during the 3–5 min incubation stage of an aPTT-based FXII, FXI, or FIX (Table 10.1). The inhibitor behavior is diminished when the factor assay is performed on serial dilutions of the patients' plasma. Patients with FVIII inhibitors may also have positive lupus anticoagulant (LA) results using an aPTT-based method [9]. While it is possible for a patient to have both a non-specific LA and a specific FVIII inhibitor, most often the positive LA is an artifact due to interference from the factor VIII neutralizing antibody rather than evidence for an additional autoantibody since the DRVVT-based LA test, which activates FX and FV of the common pathway (Fig. 10.1), is negative in most patients with FVIII inhibitors.

Immediate Management: Stop Severe Bleeding

Neither the severity of FVIII deficiency nor the potency of the inhibitor predicts bleeding severity [3]. Most symptomatic acquired FVIII inhibitor patients require infusions of hemostatic products to stop acute hemorrhaging (Table 10.3). Rarely, weak inhibitors (inhibitor titer <5 unit) may be overwhelmed with larger doses of FVIII concentrate or stimulation of endogenous FVIII release by vasopressin analog DDAVP (Desmopressin™). An effective alternate strategy to generate sufficient fibrin clot to stop bleeding is to bypass the inhibited function of FVIII by infusing recombinant factor VIIa (rFVIIa) or an anti-inhibitor plasma concentrate containing FVIIa and mainly nonactivated FII, FIX, and FX: FVIII inhibitor bypass activity (FEIBA) [10]. While no study has directly compared these two approaches to stop bleeding, findings from case series and registries show they are very similar in efficacy and safety [5, 10]. For both bypass therapies, effectiveness is based on clinical monitoring of bleeding and not based on correction of in vitro coagulation tests. Most FVIII autoantibodies do not avidly inhibit porcine FVIII, at least upon initial exposure, and porcine FVIII is a suitable substitute for human FVIII in patients with inhibitors [11]. However, concern for transmission of porcine parvovirus leads to its discontinuation around 2000. In 2015, the US FDA approved recombinant porcine FVIII (rPFVIII) for the treatment of life-threatening bleeding in patients with acquired FVIII inhibitors [12]. Unlike rFVIIa and FEIBA, rPFVIII can be monitored by FVIII activity testing to permit dose adjustments to obtain desired peak and trough levels in addition to clinical monitoring of bleeding sites. These three hemostatic products are expensive and could be associated with thrombotic events in elderly patients. Therefore, the goal of hemostatic treatment is to stop life-threatening bleeding. Persistent minor bleeding and bruising is not an indication for continued bypass therapy. FVIII acquired inhibitor patients experiencing mucosal bleeding may also benefit from antifibrinolytic treatment with tranexamic acid or epsilon aminocaproic acid. In the setting of life-threatening bleeding not responding to hemostatic therapies, extracorporeal immunoabsorption [13], which in not available in the United States, and plasma exchange [14] may be effective interventions to reduce inhibitor titers. In 2019, the US FDA approved emicizumab, a bispecific antibody which binds FIXa and FX, for subcutaneous injection to prevent bleeding in hemophilia A patients with or without inhibitors [15]. One can anticipate clinical studies will be performed to evaluate emicizumab treatment for bleeding complications in non-hemophiliacs with acquired FVIII inhibitors.

Table 10.3 Hemostatic and immunosuppression regimens for acquired hemophilia A

Hemostatic treatment options	Immunosuppression treatment options
FVIII concentrate	Prednisone
DDAVP	Prednisone + cyclophosphamide
Recombinant factor VIIa (NovoSeven™)	Rituximab +/− prednisone
FEIBA™	Other cytotoxics
Recombinant porcine FVIII (Obizur™)	Cyclosporine
Plasma exchange, immunoabsorption	Mycophenolate

Concurrent Management: Immunosuppressant Therapy to Eliminate Factor VIII Inhibitor

While acquired FVIII inhibitors occasionally spontaneously remit, immunosuppression therapy should be started once laboratory testing confirms the diagnosis to reduce the risk of future bleeding complications. Clinical remission (CR) is defined as FVIII activity >50–70% and no inhibitor activity detected in plasma following withdrawal of immunosuppression treatment. Experts agree all patients should initially receive prednisone (typically 1 mg/kg/day). But there is no consensus on whether cytotoxic immunosuppression with oral cyclophosphamide 1–2 mg/day should be started with prednisone or reserved for patients who do not respond to several weeks of prednisone monotherapy [4, 5, 16].

Due to the rarity of acquired FVIII inhibitors, an adequately powered prospective randomized trial comparing first-line prednisone and cyclophosphamide to prednisone is not feasible. Comparing outcomes for different treatment regimens from registry databases may be skewed by confounding variables and clinician biases as well. However, there are several consistent observations: (1) Initial prednisone + cyclophosphamide produces inhibitor remission faster than prednisone alone [16], but does not affect long-term outcomes of clinical remission (CR) and survival [3, 16]. (2) Intravenous immunoglobulin (IVIG) is not effective as a monotherapy or in combination with prednisone and cyclophosphamide [3, 16]. (3) Rituximab is not an effective first-line monotherapy [16]. (4) Patients with initial severe FVIII deficiency and high inhibitor titers have lower CR rates and poorer survival [5, 16, 17]. (5) Relapses do occur, ranging from 15% to 24% during the first year of follow-up [3, 16]. Therefore, initial immunosuppression treatment decisions require assessing the likely risks and benefits of the alternative approaches specific to each patient. If prednisone monotherapy is chosen, median time to CR is about 5 weeks [17].

For the minority of patients who do not respond to prednisone or prednisone + cyclophosphamide, there are alterna-

tive immunosuppression therapies to consider including cyclosporine, azathioprine, and mycophenolate [18]. Rituximab has grown in popularity as a second-line treatment [19].

Acquired Inhibitors of Other Coagulation Factors

FVIII is by far the most immunogenic coagulation factor and yet the incidence of FVIII inhibitors is <2.0/million/year. Information on the presentation, management, and outcomes for acquired inhibitors to other coagulation factors is limited to sporadic case reports or small case series, which makes it difficult to provide definitive descriptions of their presentations and prognoses, or recommendations for management [20, 21]. In addition, reporting bias may affect the accuracy of the information. However, experience gained from diagnosis and treatment of acquired hemophilia A patients can generally be applied to these much rarer inhibitors. Since screening coagulation test results are a crucial first step toward diagnosis of an acquired inhibitor, it is appropriate to organize a review around the different patterns which can occur (Fig. 10.1).

Acquired Inhibitors Other Than Factor VIII Which Prolong the aPTT: Factor IX, Factor XI, and Factor XII

Information about inhibitory autoantibodies to FIX (acquired hemophilia B) consists of a handful of case reports. Bleeding sites, association with autoimmune disorders or malignancies, response to rFVIIa or FEIBA to control bleeding, and immunosuppressive therapy to eliminate the inhibitor are similar to findings from acquired FVIII case series [22]. The aPTT is prolonged and only partially corrects with immediate 50:50 mixing, and there is no progressive inhibition with prolonged incubation as is typically seen with FVIII inhibitors. The FIX inhibitor potency can be measured with the Bethesda or Nijmegen method technique by measuring residual FIX activity with shorter incubation times [1].

To date, most, but not all, reports of acquired FXI inhibitory antibodies have occurred in patient with systemic lupus erythematosus [20]. In a review of 14 cases 9 presented with spontaneous or trauma-induced bleeding and 4 with thrombotic events, and 1 was asymptomatic. Immunosuppression therapy resolved all inhibitors [23].

Reports of acquired inhibitors to FXII usually are in the context of antiphospholipid syndrome or liver disease [20]. Since congenital FXII deficiency does not cause excessive bleeding, it is not surprising that case reports of acquired FXII deficiency have not been associated with bleeding either.

Acquired Inhibitors Which Prolong the PT: Factor VII

While inherited FVII deficiency is estimated to have a prevalence of 1 per 500,000, acquired, isolated FVII deficiencies are extremely rare and associated with underlying malignancies, infections, and hematopoietic stem cell transplants; and inhibitory antibodies are identified in a minority of cases [24, 25]. Bleeding complications range from mild to severe [26]. One patient's plasma demonstrated a time-dependent in vitro inhibition of FVII in NPP, similar to acquired FVIII inhibitors [27]. Given the rarity of acquired FVII inhibitors, management of immune suppression strategy would be empiric, borrowing from the experience with acquired FVIII inhibitors.

Bleeding complications have been managed with fFVIIa, fresh frozen plasma, and prothrombin complex concentrates [25]. However, there is insufficient evidence to determine if there is superior treatment.

Acquired Inhibitors Which Prolong Both aPTT and PT: Factor V, Factor X, Factor II, and Fibrinogen

Historically, factor V (FV) was a relatively frequent target of acquired inhibitory autoantibodies, due to iatrogenic exposure to bovine FV. An effective surgical hemostasis technique was to apply an aerosol mixture of bovine thrombin and fibrinogen to produce a fibrin sealant on a diffusely oozing surface. However, bovine thrombin contains bovine FV, and some patients would produce neutralizing antibodies which would cross-react with human FV. The presentation could be delayed, post-operative prolongation of PT and aPTT with or without bleeding complications [28]. Some patients suffered major complications or death. Fortunately, the incidence of acquired FV inhibitors has dramatically declined following replacement of bovine thrombin with either human plasma-derived or recombinant human thrombin. Acquired FV inhibitors are associated with additional triggering factors including surgery without exposure to thrombin glue; a wide range of antibiotics, including beta lactams; malignancies; autoimmune disorders; and infections [29]. Laboratory findings include a prolonged aPTT and PT, which do not completely correct with 50:50 mixing and do not demonstrate time-dependent neutralization; selected deficiency of FV; and an inhibitor based on a Bethesda or Nijmegen methods [30]. In addition to the interventions used to stop bleeding in acquired hemophilia A patients, platelet transfusions are probably effective in patients with FV inhibitors by delivering FV released from activated platelet alpha granules at the site of vascular injury. Frequently, FV inhibitors spontaneously remit, especially

when a suspected antibiotic is discontinued, and not all patients required immunosuppression [29].

Acquired factor X (FX) deficiency is most commonly due to absorption of the coagulation protein to amyloid deposits in patients with amyloidosis [31]. Management of bleeding due to acquired FX deficiency associated with amyloidosis includes infusions of prothrombin complex concentrates [32] and plasma-derived FX concentrate [33], which is approved for the treatment of congenital FX deficiency (Coagadex™).

Neutralizing FX autoantibodies are extremely rare [34]. A literature review identified 34 case reports, but only 26% provided convincing laboratory evidence of a FX inhibitor [35]. Cases were associated with malignancies and infectious and inflammatory diseases or considered idiopathic. Interestingly, 38% of cases were preceded by a non-specific respiratory viral illness. Bleeding complications varied from none to life-threatening with multiple interventions to stop bleeding. All patients survived and their inhibitors resolved including 16% with spontaneous remissions.

Prothrombin (FII) autoantibodies are a common laboratory finding in patients with lupus anticoagulants, and they have been associated with increased thrombosis risk. They are typically non-neutralizing and do not affect aPTT or PT, but if antibody-mediated clearance of prothrombin is greatly enhanced, patients may experience bleeding complications with laboratory findings of prolonged aPTT and PT and very low factor II activity (see Chapter 23 Lupus anticoagulant hypoprothrombinemia syndrome).

Acquired inhibitors of thrombin are very rare and, when described, are usually associated with exposure to bovine thrombin glue and less often with underlying autoimmune disorders or monoclonal gammopathies [20]. In addition to prolonging aPTT and PT, thrombin inhibitors prolong the thrombin time (TT), which is performed by adding purified thrombin to patient plasma and monitoring the time to fibrin clot formation. A TT mixing study would show incomplete correction. Management of bleeding complications due to a thrombin inhibitor is empiric, but plasma exchange may be an important therapeutic intervention to reduce antibody potency acutely since bypass coagulation products may not be as effective as they are for "upstream" factor inhibitors.

Hypofibrinogenemia due to dilution or consumption is common, but acquired inhibitors of fibrinogen are very rare. They may interfere with fibrin monomer formation or fibrin polymerization. Bleeding symptoms may be as severe as seen in patients with congenital afibrinogenemia. Typical laboratory findings include prolonged aPTT, PT, and TT, which do not correct with 50:50 mixing. A reptilase time would distinguish a fibrinogen inhibitor from a thrombin inhibitory autoantibody. Reptilase time uses the batroxobin snake venom to activate fibrinogen instead of thrombin, and it would be prolonged in the presence of a fibrinogen inhibitor but not a thrombin inhibitor [36].

Acquired Inhibitors Which Do Not Prolong aPTT or PT: Factor XIII

Both inherited and acquired severe deficiencies of FXIII are extremely rare. Presenting symptoms include spontaneous bleeding, including intracranial hemorrhage, delayed bleeding after trauma, and impaired wound healing. FXIII circulates as a pair of alpha and beta chain heterodimers. Thrombin activates the alpha chain, which stabilizes fibrin monomers via formation of multiple covalent cross-linking bonds (Fig. 10.1). Clot-based coagulation methods such as PT and aPTT detect initial polymerization of fibrin and are insensitive to FXIII deficiency. Therefore, testing for acquired FXIII inhibitor is appropriate in a patient who presents with an abrupt onset of severe unprovoked hemorrhage, normal platelet number and function, and normal PT and aPTT, fibrinogen, and thrombin time. Many laboratories screen for FXIII deficiency with the urea clot solubility test. A fibrin clot is produced from a patient's plasma by adding thrombin. Then the visible clot is placed in a 5 M solution of urea. If fibrin is not cross-linked by FXIIIa, it will dissolve in the urea. However qualitative assays are insensitive and may yield false negative results for a clinically important FXIII deficiency. The preferred initial screening test is a sensitive, qualitative assay for FXIIIa transglutaminase activity [37, 38]. Confirmatory studies to demonstrate inhibitor activity and to measure FXIII antigen concentration are provided by a few reference laboratories. Notable findings from a systematic literature review of 28 cases of FXIII inhibitors included as follows: median age 65.5; 70% associated with a medication, specifically isoniazid in 30%; and 30% were idiopathic [39]. There were five fatal intracranial bleeds and overall mortality rate was 29%. Various strategies were employed to stop bleeding (FXIII concentrate, cryoprecipitate, FFP, plasma exchange) and suppress inhibitors (steroids, cyclophosphamide, rituximab, IVIG). A majority of patients obtained a remission, of which 25% were spontaneous after withdrawing a suspected medication.

Summary

Coagulation factor inhibitory antibodies are fortunately uncommon. However, when patients present with abnormal bleeding and bruising due to acquired inhibitors, their rarity can lead to incorrect or delayed diagnoses, greater morbidity, and fatalities. The first step is to rapidly perform laboratory investigations similar to the algorithm outlined in Fig. 10.2. Once an inhibitor is identified, interventions to restore hemo-

stasis and initiate immunosuppression are indicated for most patients (Table 10.3). The majority of inhibitor management experience is derived from patients with acquired hemophilia A, which may be empirically applied to most other acquired inhibitors. A search for an underlying cause should be done concurrently with hemostatic treatment, but about 50% of acquired coagulation inhibitors are idiopathic. If diagnosed promptly and treated effectively, most patients will achieve a clinical remission. However, since many patients with acquired inhibitors are elderly, deaths from bleeding, treatment-related sepsis, and other comorbidities are fairly common [40].

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Bleeding Due to Rare Coagulation Factor Deficiencies

11

Nicola Curry

Background

Disorders that cause bleeding may be inherited or acquired. The inherited conditions include haemophilia and von Willebrand disease as well as the rare coagulation factor deficiency (RCD) disorders. RCD is a term that encompasses multiple conditions including fibrinogen deficiency and deficiencies of single coagulation factors, including factors II, V, VII, X, XI and XIII, and a combined clotting factor deficiency – known as combined factor V and VIII deficiency (F5F8D). RCD disorders, as the name suggests, are rare causes of bleeding, and although RCD encompasses multiple conditions, each condition differs in its severity of bleeding and the attendant risks of bleeding at certain sites (e.g. intracranial, joint or mucocutaneous sites) [1].

Intuitively, it would make sense to imagine that the severity of bleeding a patient experiences should closely correlate with the degree of factor deficiency, i.e. the lower their clotting factor level, the greater the amount of bleeding. This is the case for most of the RCD conditions, but is not the case for all (e.g. dysfibrinogenemia and deficiencies of factors VII and XI). Furthermore, some conditions are associated with clinical sequelae unrelated to bleeding, such as pregnancy loss, poor wound healing and paradoxically, in fibrinogen conditions at least, thrombosis.

The majority of RCD can be detected in the laboratory by prolongation of one or both of the standard coagulation screens, e.g. activated partial thromboplastin time (APTT) or the prothrombin time (PT). However, this does not apply to all RCD, and therefore a high degree of clinical suspicion is important for patients presenting with unexplained spontaneous bleeding or bleeding deemed to be in excess of the norm after a traumatic or surgical insult.

This chapter will describe the presentation, diagnosis and management of patients with RCD. For ease of presentation, the chapter will be set out with a general approach to management of bleeding in this group of patients, and then specifics will be given for each of the separate factor deficiencies.

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General Approach to a Patient with an Inherited Bleeding Condition

Bleeding History

The most important part of the assessment of a patient who presents with bleeding is an accurate bleeding history. The salient points of a bleeding history are summarised in Table 11.1. It is important to try to get a feel for whether the patient is likely to have an isolated bleeding problem or whether their symptoms are a manifestation of a wider problem. Remember to ask about accompanying fatigue (anaemia), increased infection (leucopenia), lymphadenopathy

Table 11.1 The clinical bleeding history

Points in a clinical bleeding history
Age at first bleeding event
Inherited/acquired
Family history (autosomal dominant/recessive, X-linked inheritance)
Spontaneous or traumatic bleeding
Post-operative bleeding – excessive bleeding due to platelet dysfunction or thrombocytopenia tends to occur immediately, whereas bleeding due to coagulation abnormalities may be delayed
Related to childbirth – need for transfusions, dilatation and curettage, iron therapy, hysterectomy
Tooth extraction – this is often the first and only significant haemostatic challenge a person faces. The need for packing, suturing or even transfusions may be significant
Frequency of bleeding
Severity of bleeding
Requirement for transfusion
Requirement for intervention (cautery/packing)
Drugs

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and joint pains which, for example, may all point towards a systemic condition. Be guided by the history.

Some of the most important parts of the history suggesting an inherited bleeding disorder include (a) a lifelong history of bleeding and (b) for some of the RCD conditions, a family history of bleeding. It should be noted that many of the RCD are autosomal recessive conditions, meaning that there will not be a clear family history of bleeding. In these settings, it may therefore be important to ask whether the patient's parents are related by marriage.

As a general rule, the more severe the symptom, the more severe the bleeding disorder. Below is a list of situations that are suggestive of a bleeding disorder that requires further investigation:

- Recurrent bleeding, i.e. bleeding more than three times at one site of the body
- More than two sites of the body affected at one time
- Unusual bleeding following a routine operation/childbirth; particularly if it requires a blood transfusion
- Iron deficiency anaemia secondary to blood loss
- Bleeding lasting more than 30 minutes and requiring intervention (such as nasal packing)

Laboratory Diagnosis

There are a few tests which should be performed as a screen for all patients with bleeding symptoms. However, the patient's history and the severity of their symptoms should be taken into account.

Patients should have the following initial tests performed:

- Full blood count and blood film
- Coagulation profile: PT, APTT, fibrinogen

Any abnormality that arises in these tests can then guide you to your next investigation. As mentioned above, factor XIII (FXIII) deficiency will not prolong standard laboratory clotting screens, and further testing is warranted if there is a high level of clinical suspicion.

If there is a patient with a suspected bleeding disorder, it is often best to refer them to a haematologist with a special interest in haemostasis. Many of the bleeding disorders are diagnosed using specialised testing that is only available in haemophilia centres. The specifics for testing are noted under each individual coagulation disorder, set out below. DNA analysis can also be employed for every inherited bleeding condition, the results of which can then be used to test extended members of each family, particularly for carrier status in autosomal recessive conditions. Genetic counselling should be offered to all families with inherited bleeding conditions.

As RCD are very rare, it is important that large international collaborations collect data on patients to further scientific understanding. One such collaboration, named the Prospective Rare Bleeding Disorders Database (PRO-RBDD), was set up in 2016 across Europe. PRO-RBDD is an international collaborating network that has developed a web database designed to prospectively collect clinical and laboratory data of patients with coagulation factor deficiencies in order to evaluate prevalence, bleeding frequency and management, as well as consumption of treatment products and related complications [2].

General Management for Patients with Bleeding Disorders

Whatever the cause of the bleeding, simple instructions can be given to a patient to reduce their risk of further bleeding [3]. These include:

- Avoidance of intra-muscular injections
- Avoidance of anti-platelet/anti-inflammatory/anti-coagulant drugs if possible
- Avoidance of contact sports in severe bleeding disorders
- Informing any physician/dentist prior to an invasive procedure of their bleeding history and if possible seeking advice from a haematologist

Tranexamic acid (TXA) is a very useful drug for reduction of bleeding in patients with RCD and is recommended alone as treatment for minor bleeding such as gum bleeding and minor nose bleeds or for some less invasive dental procedures. It is also used as an adjunct to factor concentrate/plasma replacement therapy in more significant bleeding conditions or for major surgery. A standard dose of TXA is 15–20 mg/kg (max. 1 g) three or four times a day. TXA should be avoided for urinary tract bleeding (due to the risk of clot colic).

Several of the RCD are treated using fresh frozen plasma or plasma-derived factor concentrates which confer a small but finite risk of viral infection. All patients who may potentially be exposed to these products should be vaccinated against hepatitis A and B and should be tested for hepatitis C and HIV after exposure to these treatments.

Table 11.2 The rare coagulation factor deficiency disorders

Disorder	Inheritance pattern	Haemostatic level	First-line treatment for major bleeding
Fibrinogen deficiency	AR and AD	0.5–1.0 g/L	Fibrinogen concentrate (20–30 mg/kg)
Prothrombin deficiency	AR	0.2–0.3 IU/mL	PCC (20–30 units/kg)
Factor V deficiency	AR	0.15 IU/mL	SD-FFP (15 mL/kg)
Factor VII deficiency	AR	0.15–0.20 IU/mL	rFVIIa (15–30 μg/kg)
Factor X deficiency	AR	0.15–0.20 IU/mL	PCC (20–30 units/kg)
Factor XI deficiency	AR and AD	Minor: 0.20–0.30 IU/mL Major: 0.30–0.45 IU/mL (aim for 0.70 IU/mL peak)	Variable: SD-FFP (15 mL/kg), FXI concentrate (20–30 units/kg)
Factor XIII deficiency	AR	0.10 IU/mL	FXIII concentrate (10–20 units/kg)

Key: *AD* autosomal dominant, *AR* autosomal recessive, *PCC* prothrombin complex concentrate, *rFVIIa* recombinant activated factor seven, *SD-FFP* solvent detergent fresh frozen plasma

Specific Factor Deficiencies (Table 11.2)

Fibrinogen Deficiency

There are several distinct types of fibrinogen deficiency which are caused by defects in one of the three fibrinogen chains (Aα, Bβ, γ) which in turn leads to a reduction in functional fibrinogen. Defects in fibrinogen can be due to (a) quantitative defects – such that there is normal fibrinogen circulating but it is at reduced levels (afibrinogenaemia or hypofibrinogenaemia) – or (b) qualitative defects, such that normal or even increased levels of fibrinogen is formed but it does not work normally (dysfibrinogenaemia). Afibrinogenaemia has a prevalence of one in one million individuals [4] and is inherited as an autosomal recessive condition. The prevalence of dysfibrinogenaemia is not known and it is an autosomal dominant condition.

Pathogenesis

Fibrinogen is made from three peptide chains: Aα, Bβ and γ. It is a large glycoprotein that is essential for the formation of a stable clot. Fibrinogen is the major ligand for the platelet αIIBβ3 integrin and stabilises platelets into a developing clot. It is also cleaved by thrombin to form individual fibrin strands which then polymerise into an insoluble fibrin mesh. The fibrin strands are then cross-linked by factor XIIIa to form an extensive interconnected fibrin network that is the basis of a mature, stable fibrin clot. The haemostatic level for fibrinogen is generally deemed to be between 0.5 and 1.0 g/L [4].

Afibrinogenaemia is due to a homozygous mutation or a combination of two heterozygous (compound heterozygous) mutations in the *FGA*, *FGB* or *FGG* genes (these code for Aα, Bβ and γ chains, respectively). Hypofibrinogenaemia is usually found in patients with a heterozygous mutation, i.e. in only one of the fibrinogen genes. Dysfibrinogenaemia can occur with a mutation in any one of the three fibrinogen genes, although there appear to be functional 'hotspots' within which many of the patients are found to have variants.

A- and Hypofibrinogenaemia

Symptoms of patients are widely variable, and spontaneous as well as trauma-induced bleeding can occur. The severity of bleeding correlates well with blood fibrinogen levels. More severe conditions will therefore present at an earlier age, including in the perinatal period.

Typical presentations of a fibrinogen disorder include mucocutaneous, soft tissue, joint, genitourinary, traumatic and surgical bleeding. Heavy menstrual bleeding is also commonly seen in affected women. In around 5% of affected cases, more severe bleeding can be seen and typically takes the form of intracranial bleeding. Umbilical stump bleeding is also a recognised symptom in neonates with very low fibrinogen levels.

Laboratory Diagnosis

A diagnosis of afibrinogenaemia is made when the fibrinogen blood level, using a functional assay, such as Clauss fibrinogen, is found to be <0.1 g/L (normal range 1.5–4.0 g/L). Hypofibrinogenaemia is diagnosed when a Clauss fibrinogen level measures <1.0 g/L. Standard clotting screens will be abnormal – the APTT, PT and thrombin time (TT) will be prolonged, as the end point for completion of these assays is the formation of fibrin. Extended laboratory testing for investigation of a patient with a fibrinogen defect includes a fibrinogen antigen measurement. In a- and hypofibrinogenaemia, there is a similar reduction in Clauss levels (activity assay – how well it works) and fibrinogen antigen levels (quantitative assay – how much is present).

Management

The mainstay of treatment for patients with low fibrinogen levels is with a plasma-derived fibrinogen concentrate (or cryoprecipitate in countries where factor concentrate is unavailable). Fibrinogen concentrate therapy can be given

either as treatment, for an acute bleeding event, or as prophylaxis to prevent future bleeding events. Typically, patients who present with more severe bleeding episodes, such as intracranial haemorrhage, will be treated using a prophylactic regimen to prevent future bleeds and treatment regimens aim to treat patients weekly and maintain trough levels (blood fibrinogen levels prior to the next dose) between 0.5–1.0 g/L.

A 4.0–6.0 g dose of fibrinogen concentrate is expected to raise the blood fibrinogen level by 1.0–1.5 g/L in a 70 kg man. The half-life of fibrinogen in the non-bleeding state is reported as 3–4 days. Standard treatment schedule for treatment of bleeding, and indeed for prevention of bleeding perioperatively, is 50–100 mg/kg every 2–4 days. More frequent dosing (i.e. daily) is often required in children, as well as for replacement therapy during major surgery, and in severe bleeding episodes [4].

There are two potential risks from the infusion of fibrinogen concentrate: (a) thromboembolic disease and (b) viral transmission. A large pharmacosurveillance programme spanning 22 years, during which fibrinogen concentrate was administered in more than 250,000 doses of 4 g across 21 countries, reported 9 spontaneous thrombotic adverse events, an incidence of 3.48 events per 105 treatment episodes, suggesting a low risk associated with treatment [5]. There were no data presented in the review to be able to determine whether the thrombotic events related to a high fibrinogen level [5].

Fibrinogen concentrate is a plasma product. To limit viral transmission, all plasma donations used in the manufacture of fibrinogen concentrate undergo extensive viral screening, and during production it is subjected to a viral inactivation step; pasteurisation-heat treatment at +60 °C for 20 hours. There remains a higher risk of Parvovirus B19 transmission than for other viruses [6]. Patients should be counselled about the risks of receiving plasma-derived products prior to use, where possible.

Obstetric Management

Women with a- and hypofibrinogenaemia are at risk of pregnancy loss, ante-partum haemorrhage (APH) and post-partum haemorrhage (PPH). Fibrinogen therapy has been shown to reduce these risks and management typically involves regular therapy to maintain a trough level above 0.5 g/L during pregnancy and around 1.0–1.5 g/L at delivery [4]. The frequency of therapy, and doses required, often increases as gestation progresses, such that by term a woman is likely to be receiving fibrinogen concentrate every 2–4 days [7]. Central neuraxial anaesthesia should generally be avoided for women with severe fibrinogen deficiency, or a personal or family history of bleeding, due to the difficulty in assuring correction with factor concentrate. They may be used after individual assessment if adequate replacement therapy is confirmed.

Dysfibrinogenaemia

Patients with dysfibrinogenaemia have very variable clinical phenotypes [8]. As many as 50% of patients are asymptomatic and will have received their diagnosis following investigation of an abnormal clotting screen, taken for another reason. Around one quarter have bleeding problems (typically mucosal, surgical or traumatic bleeding), and the remaining one quarter have thrombotic problems. In some patients, bleeding and thrombosis can co-exist.

Laboratory Diagnosis

As dysfibrinogenaemia is due to the release of functionally poorly active fibrinogen, laboratory tests that look at activity show low values – i.e. Clauss fibrinogen levels will be low, and therefore APTT, PT and TT will commonly be prolonged. Unlike quantitative defects, with dysfibrinogenaemia the fibrinogen antigen will not be low – and the diagnosis of dysfibrinogenaemia can be confirmed by a discrepancy between Clauss fibrinogen levels and fibrinogen antigen levels. It should be noted that the PT-derived fibrinogen assay is not suitable for diagnosis of this condition.

There is no correlation with blood levels and severity of the condition in dysfibrinogenaemia, although it is increasingly shown that certain genotypes are associated with either thrombotic or bleeding phenotypes [8, 9].

Management

The management of patients with dysfibrinogenaemia is more complex than for a- or hypofibrinogenaemia. Firstly, many patients – even when challenged with surgery – may not bleed, and secondly some patients may be at risk of thrombosis both from their underlying condition, as well as the surgery they are about to have [10].

In patients with no history of bleeding, it is reasonable to approach surgery with a conservative management plan, using TXA (15–20 mg/kg up to 4 times a day) and have fibrinogen concentrate on standby (at a dose of 4.0–6.0 g according to weight) to be used in theatre if bleeding is noted. TXA may be given either as an intravenous bolus or orally. Patients who have previously developed bleeding with surgical or other haemostatic challenges can reasonably be treated pre-operatively, in the anaesthetic room. Care should be taken when considering thromboprophylaxis and patients should be managed on an individual basis and with the advice of an experienced haematologist.

Obstetric Management

Women with dysfibrinogenaemia are at risk of pregnancy loss, ante-partum haemorrhage (APH) and post-partum haemorrhage (PPH). Fibrinogen therapy may reduce these risks in some patients. The genotype strongly influences the clinical phenotype and for some patients no therapy is required antenatally. Treatment is often required for delivery, aiming for a

fibrinogen level of 1.5 g/L at delivery and for 3–5 days post-delivery [7]. Thromboprophylaxis must be considered [10]. Central neuraxial anaesthesia should be avoided.

Factor II (Prothrombin) Deficiency

Pathogenesis

Factor II (FII) deficiency is a very rare autosomal recessive bleeding condition caused by a quantitative (hypoprothrombinaemia) or qualitative (dysprothrombinaemia) defect in the FII gene. The prevalence is in the order of one in two million [4].

Prothrombin is activated by FX, as well as the prothrombinase complex, during the clotting process, into the active form thrombin. Thrombin is the central procoagulant serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalysing many other coagulation-related reactions and activating platelets. The haemostatic level for prothrombin is between 0.20–0.30 IU/ML (20–30%).

Clinical Diagnosis

The most common bleeding symptoms include mucocutaneous, soft tissue, joint and surgical bleeding. Heavy menstrual bleeding is a symptom reported by affected women. Intracranial and umbilical stump bleeding are also presenting symptoms in more severely affected children. Intracranial haemorrhage (ICH) has been reported in up to 7% of cases.

More severe bleeding tends to be seen in patients with FII activity <0.1 IU/ML (10%) when compared to affected patients with levels greater than 0.1 IU/mL (who report only mild mucocutaneous symptoms).

Laboratory Diagnosis

Both the APTT and PT are prolonged in FII deficiency. Diagnosis is confirmed by testing a FII assay.

Management

Prothrombin complex concentrates (PCC) such as Kcentra™ are the standard method of treatment for FII deficiency. A typical dose is 20–30 units/kg and this increases the FII level by 0.4–0.6 IU/Ml (40–60%). FII has a plasma half-life of approximately 60 hours and where repeated dosing may be required is commonly given every 2–3 days.

If PCC is unavailable, pathogen-reduced fresh frozen plasma (FFP) such as solvent detergent FFP (SD-FFP) is acceptable, and 15–20 mL/kg FFP is expected to raise the blood FII level by approximately 0.3–0.4 IU/mL (30–40%).

Obstetric Management

FII levels do not rise during pregnancy and patients with severe FII deficiency are at risk of APH, pregnancy loss and PPH. It is recommended that in women with FII levels below 0.2 IU/mL, PCC 20–40 units/kg is given for delivery (aiming for a FII level of 0.2–0.4 IU/mL). FII levels should be maintained above 0.2 IU/Ml (20%) for at least 3 days after vaginal delivery (doses commonly given every 48 h) [7].

Factor V Deficiency

Pathogenesis

Factor V (FV) deficiency is an autosomal recessive condition caused by a quantitative (and very occasionally a qualitative) defect in the FV protein, caused by variants in the *FV* gene. It has a prevalence of one in one million [4].

FV is activated by thrombin and/or FXa and becomes a cofactor for FXa in the prothrombinase complex which has a main effect of activating thrombin. The haemostatic level for FV is 0.15 IU/Ml (15%).

Clinical Diagnosis

Patients most commonly present with mucocutaneous, soft-tissue, surgical and traumatic bleeding. Heavy menstrual bleeding does affect women. ICH has been reported in children (approximately 8% of cases), and seems to occur in those more severely affected, i.e. with FV levels less than 0.10 IU/mL (10%). Patients with FV levels greater than 0.10 IU/mL (10%) generally are asymptomatic or have mild mucocutaneous bleeding symptoms only.

Laboratory Diagnosis

Both the APTT and PT will be prolonged, since FV acts within the common pathway of the clotting cascade. FV assays will confirm a low FV level.

Management

There is no specific FV concentrate, and therefore the mainstay of therapy lies with solvent detergent (SD) treated FFP (SD-FFP). 15 ml/kg SD-FFP increases FV blood levels by 0.15 IU/mL, and therefore is a good treatment for acute bleeding or prevention of bleeding for surgical procedures. The half-life of FV is 16–36 hours and retreatment for severe bleeding or major surgery may be required on daily/twice daily schedules (according to blood levels).

FV is not only found in the plasma but is also found in the α-granules of platelets. Platelet concentrates have therefore been used therapeutically to treat FV-deficient patients when SD-FFP is not effective. SD-FFP prophylaxis (20–30 mL/kg twice a week) can be used for patients with ICH although

long-term use is difficult due to fluid overload concerns, as well as allergy concerns.

Obstetric Management

FV deficiency is associated with PPH, if not treated. FV levels do not rise significantly during pregnancy and women with severe FV deficiency will need therapy with SD-FFP for delivery, aiming for a FV level of 0.2–0.4 IU/Ml (20–40%). Dosing often involves 15–25 mL/kg SD-FFP administered once a woman is in established labour (or just before caesarean section). Further dosing of SD-FFP, at doses of 10 mL/kg at 12-hour intervals to maintain factor V activity more than 0.2 IU/mL (20%), is likely to be required for at least 3 days [7].

Factor VII Deficiency

Pathogenesis

Factor VII (FVII) deficiency is an autosomal recessive condition that is caused by reduced plasma FVII activity due to either quantitative or qualitative defects in the FVII protein. The prevalence is estimated at one in half a million [4].

Activated FVII (FVIIa) binds to tissue factor at sites of blood vessel injury and the resulting complex – TF-FVIIa – generates more FVIIa and ultimately activates FX and FIX facilitating low levels of thrombin generation in the initiation phase of coagulation. The haemostatic level for FVII is 0.15–0.20 IU/mL (15–20%).

Clinical Diagnosis

The most common symptoms associated with FVII deficiency include: mucocutaneous, soft tissue, joint and gastrointestinal bleeding. Heavy menstrual bleeding is also reported in affected women. ICH (reported to affect 3–17% cases) and umbilical bleeding occurs in neonates and may be the presenting feature of the condition.

Severe bleeding is more likely to be seen in patients with FVII levels less than 0.10 IU/mL (10%) compared to patients with levels more than 0.10 IU/mL (10%). However, there seems to be a weak association with blood level and bleeding phenotype.

Laboratory Diagnosis

Coagulation screens will show a prolonged PT with a normal APTT. The FVII activity will be reduced using a one-stage PT-based assay.

Management

Haemostatic levels of FVII are quoted as between 0.15–0.20 IU/mL (15–20%). Recombinant factor VIIa (rFVIIa) is the first-line therapy for patients with FVII deficiency. Treatment is usually recommended for patients undergoing surgery if the FVII level is below 0.10 IU/mL (10%). Treatment doses are much lower than those given for traumatic coagulopathy – between 15 and 30 mcg/kg – and should be given just prior to surgery and repeated every 4–6 hours, as required. A minimum of three doses is recommended for surgery. The duration of therapy for FVII replacement will depend on the bleeding risk and site of the surgery, so, for example, surgery that carries minor bleeding risks such as tooth extraction may be simply treated with three doses of rFVIIa, whereas as joint replacement surgery would need considerably longer. Prophylaxis is not commonly given for severe FVII deficient patients (FVII levels <0.01 IU/mL) but can be given using a schedule of dosing of 20–40 mcg/kg three times a week, adjusted to clinical response.

Obstetric Management

Women with mild FVII deficiency may see a sufficient rise in their FVII levels throughout pregnancy such that no treatment is required for delivery [7]. Patients with more severe disease should be treated on an individual basis, such that if a woman has a FVII level at term <0.20 IU/mL (20%) and requires a caesarean section or has a history of bleeding, then rFVIIa, 15–30 mcg/kg, should be given at delivery and up to 3 days afterwards, every 4–6 hours. Those women with low FVII levels and no history of bleeding should be given rFVIIa only in the face of untoward bleeding [1].

Factor X Deficiency

Pathogenesis

Factor X (FX) deficiency is an autosomal recessive condition caused by either a quantitative or qualitative reduction in FX activity. One in one million people are estimated to have FX deficiency [4].

FX is a key coagulation factor that is activated by TF-FVIIa during the initiation phase and then the tenase complex during the amplification phase of the clotting process. FXa, with the cofactor FVa, make up the prothrombinase complex which activates FII into thrombin (FIIa). The haemostatic level of FX is 0.15–0.20 IU/Ml (15–20%).

Clinical Diagnosis

The most common symptoms related to FX deficiency include mucocutaneous (including gastrointestinal and menstrual bleeding), joint and soft tissue bleeding. ICH occurs in just over one-fifth of reported cases and umbilical bleeding is also a presenting feature of this condition.

More severe bleeding is seen in patients with FX levels <0.10 IU/mL (10%), and intracranial, joint and GI bleeding seem to only occur in patients with levels less than 0.02 IU/mL (=2%).

Laboratory Diagnosis

Since FX makes up part of the common pathway, FX deficiency is picked up with standard clotting tests showing a prolongation of the APTT and PT. A confirmatory FX PT based one stage assay will confirm the diagnosis.

Management

FX replacement can be achieved by use of either PCC or FX concentrate which is currently available on trial and on a named patient basis for children in the UK. PCC should be given at a dose of 20–30 units/kg which will raise the blood level by 0.4–0.6 IU/mL. The half-life of FX is around 30 hours, and therapy is typically given every 24–48 hours depending on the duration and severity of the bleeding/surgery. FX concentrate is an alternative treatment, but there is limited access to this product in the clinic.

Obstetric Management

Women with severe FX deficiency will frequently require replacement therapy at the time of delivery, and they are at risk of APH, pregnancy loss and PPH. For delivery in women with factor X activity less than 0.3 IU/mL (30%) in the third trimester who have a history of bleeding and all those who require caesarean section, use PCC 20–40 units/kg (or factor X concentrate if available) to achieve factor X activity more than 0.4 IU/mL (40%). Consider further PCC 10–20 units/kg once daily to maintain factor X activity more than 0.3 IU/mL (30%) for at least 3 days. Antenatal prophylaxis may be considered in women with a history of recurrent bleeding or adverse pregnancy outcome using PCC 20–30 units/kg two or three times a week to maintain trough factor X more than 0.01 IU/mL (1%) [7].

Factor XI Deficiency

Pathogenesis

Factor XI (FXI) deficiency is an autosomal recessive and an autosomal dominant disorder in which low levels of FXI is caused by a quantitative (or rarely qualitative) defect in the FXI protein, caused by variants in the *F11* gene. Prevalence of autosomal recessive FXI deficiency is quoted as one in one million, whereas autosomal dominant FXI deficiency is estimated at 1 in 30,000 individuals. The prevalence of FXI deficiency is higher in the Jewish population. Some of the FXI genetic variants are classed as dominant negative variants – as they cause intracellular retention of FXI.

FXI is activated on the platelet surface by thrombin during the initiation phase of coagulation. Activated FXI then activates FIX, causing a positive feedback loop and maintenance of thrombin generation, as well as activation of thrombin-activatable fibrinolysis inhibitor (TAFI). A haemostatic level for minor procedures is quoted at 0.20–0.30 IU/mL (20–30%) and for major surgery as 0.30–0.45 IU/mL (30–45%) [11].

Clinical Diagnosis

The most common symptom for patients with FXI deficiency is bleeding after surgery (particularly mucosal surgery such as dental procedures) or trauma. Heavy menstrual bleeding and PPH are common in women. Bleeding is more likely to occur after surgery if the FXI level is below 0.2 IU/mL (20%). However, up to 65% of patients report no bleeding symptoms at all. FXI blood levels have a very weak correlation with clinical symptoms [12].

Laboratory Diagnosis

FXI deficiency will typically cause a prolonged APTT and a confirmatory test, using a FXI assay based on the one stage APTT, can be used. Importantly, some laboratory APTT assays may be insensitive to mildly low FXI levels (i.e. between 0.5 and 0.7 IU/mL), which can still be associated with bleeding in some patients, and therefore if a patient presents with a bleeding history, it is important to check a FXI level, even if the APTT is normal [12].

Management

Treatment usually involves treatment of traumatic bleeds or prevention of surgical bleeds using SD-FFP or FXI concentrates in more severely affected patients. There are two unlicensed FXI concentrates available for use, although they are usually only available on a named patient basis and concentrate stocks are often low. A typical therapeutic dose of FXI concentrate is 10–20 units/kg which will raise the blood level by 0.2–0.4 IU/mL (20–40%). The half-life of FXI is 50 hours. Due to the variable clinical picture for FXI-deficient patients, it is common practice to give patients TXA prior to surgical procedures and only give more definitive haemostasis therapy such as FXI concentrate or SD-FFP, if there are signs of clinical bleeding peri-operatively.

Thrombosis is a well-known side effect of FXI concentrate and strict dosing of patients is important [13]. Clinicians must ensure that peak FXI activity levels do not exceed 0.70 IU/Ml (70%). SD-FFP is an alternative source of FXI and may not carry the thrombotic risk. TXA should not be co-administered to patients when they are in receipt of FXI concentrate [13].

Obstetric Management

Women with low FXI levels are at risk of PPH. The risk is highest in those with a bleeding phenotype and of blood group O and least in non-O blood groups with a nonbleeding phenotype. Obstetric bleeding correlates poorly with FXI levels; however, in general terms, women with FXI levels <0.15 IU/mL (15%) are at the highest risk of bleeding, and treatment of these women at delivery with either FXI con-

centrate or SD-FFP should be considered. Central neuraxial anaesthesia should not be given to women with low factor XI levels with a known bleeding phenotype, where the phenotype is not clear or when there is a severe reduction in level. In those with a nonbleeding phenotype, discussion and counselling should be given regarding the risks and benefits of allowing neuraxial anaesthesia with or without factor replacement [7].

Factor XIII Deficiency

Pathogenesis

Factor XIII (FXIII) deficiency is an autosomal recessive condition which is caused by a quantitative (or rarely qualitative) defect in the FXIII A-subunit protein. Much less frequently, FXIII deficiency is caused by a quantitative defect in the FXIII B-subunit. FXIII deficiency is estimated to affect one in two million people [4].

FXIII circulates in plasma as a protein made up of four subunits: two catalytic A-subunits and two carrier B-subunits. It is found as A-subunit dimers in platelets and monocytes. FXIII is activated by thrombin to form activated A-subunits that covalently link fibrin chains to one another (stabilising a forming clot), as well as crosslinking alpha-2 antiplasmin to fibrin (increasing resistance to clot breakdown). The haemostatic level of FXIII is 0.10 IU/mL (10%) [1].

Clinical Diagnosis

FXIII deficiency is one of the more severe bleeding disorders and commonly cited symptoms include soft tissue, umbilical, surgical, joint and intracranial bleeding (in 34% cases). Poor wound healing is another common symptom. Heavy menstrual bleeding and intra-abdominal bleeding can occur with ovulation in affected women. Severe bleeding is most commonly encountered with blood levels between 0.00 and 0.11 iu/mL.

Laboratory Diagnosis

FXIII deficiency cannot be detected using standard coagulation screens, and patients will have normal APTT, PT and TT. Plasma FXIII activity can be directly measured, or an immunoassay looking at both subunit-A and subunit-B can be employed.

Management

ICH is a significant problem in FXIII deficiency and up to one-third of patients are affected [1]. As such, most patients with severe FXIII deficiency (i.e. those with FXIII levels <0.10 IU/mL), and all patients with low levels and a bleeding history, will receive prophylaxis [1]. A plasma-derived FXIII concentrate is most commonly used and has a plasma half-life of 7 days. Dosing usually starts at 20–40 units/kg and is given monthly, and is adjusted according to trough levels, aiming to maintain a 28 day trough of between 0.10–0.20 IU/Ml (10–20%).

Obstetric Management

FXIII deficiency is known to lead to high rates of pregnancy loss, if untreated. FXIII levels decrease with pregnancy and successful pregnancy outcomes in women with severe FXIII deficiency have only been possible more recently with FXIII concentrate prophylaxis [7]. Prophylaxis frequency is likely to increase throughout gestation, such that by term FXIII concentrate may be given every 14–21 days to maintain a trough of >0.2 IU/mL (20%).

Combined Factor V and Factor VIII Deficiency

Pathogenesis

Combined FV and FVIII deficiency (F5F8D) is a rare autosomal recessive condition that is due to reduced levels of both clotting factors in the plasma, in turn due to a genetic variant in the lectin mannose-binding protein 1 (*LMAN1*) gene or the multiple coagulation factor deficiency protein 2 (*MCFD2*) gene. F5F8D has an estimated prevalence of one in two million.

LMAN1 and MCFD2 proteins both form a vesicular receptor which aids the intracellular transport of FV and FVIII. Variants in the *LMAN1* or *MCFD2* genes lead to variable protein levels and therefore reduced intracellular transportation of FV and FVIII. *MCFD2* variants appear to cause lower FV and FVIII levels than *LMAN1* variants, although clinical phenotypes are similar.

Clinical Diagnosis

F5F8D is a mild to moderate bleeding condition and symptoms include mucocutaneous bleeding, including heavy menstrual bleeding and surgical and traumatic bleeding. Unlike haemophilia, spontaneous muscle or joint bleeds are rare [1]. More severe bleeding such as ICH is extremely rare and bleeding in neonates is uncommon. There is a poor correlation between blood factor levels and clinical phenotype [1].

Laboratory Diagnosis

F5F8D causes a prolongation of both the APTT and PT, with similar reductions in FV and FVIII levels (most commonly found between 0.05–0.20 IU/mL).

Management

Treatment is usually only required for traumatic bleeding or to prevent bleeding peri-operatively or at the time of delivery. Approaches can include SD-FFP to replace both FVIII and FV, although it should be noted that the FV half-life is

considerably longer than FVIII and an additional source of FVIII (such as a recombinant FVIII concentrate) may be necessary for prolonged treatments. 15–25 mL/kg SD-FFP is likely to be sufficient to replace FV levels.

Obstetric Management

FV levels do not rise during pregnancy, although FVIII levels do. Therefore therapy focuses often on replacement of FV at delivery, with recommendations suggesting SD-FFP at a dose of 15–25 mL/kg to achieve levels of 0.2–0.4 IU/mL (20–40%) FV.

Conclusion

RCD conditions are rare and present with a varied clinical picture. Patients are at risk of spontaneous bleeding for some conditions, as well as increased bleeding following trauma or surgery in the majority of conditions. Clinical management involves both general principles (providing broad advice to patients about how to reduce their risk of bleeding) and specific management for each individual condition. Care of patients with RCD is best conducted under the auspices of a comprehensive haemophilia centre by haemostasis specialists.

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Pregnancy-Associated Bleeding

12

Karin A. Fox

Introduction and Background

Bleeding is a leading cause of maternal mortality worldwide, second only to preexisting medical conditions such as cardiovascular disease or chronic hypertension [1]. In the United States, approximately 11% of maternal deaths are due to obstetrical hemorrhage [2], and although the number of deaths in developed countries has declined in the last two decades [3], hemorrhage remains a leading *preventable* cause of maternal mortality worldwide. Lack of adequate postpartum monitoring and lack of early, appropriate response to signs and symptoms of hypovolemia have been cited in 66–73% of deaths due to pregnancy-associated bleeding [3, 4]. For every woman who dies due to bleeding, nearly ten others suffer serious major morbidity [1], underscoring both the risks inherent in pregnancy and the need for improved planning and multidisciplinary response for women when bleeding occurs.

Physiologic Changes in Pregnancy

With the exception of fetal and neonatal growth and development, there is no other time during a woman's life in which such marked physiologic changes occur as during pregnancy and the postpartum period. Virtually every major organ system adapts to allow the female body to host a semi-allogenic fetus (or fetuses in the case of multiple gestations) and to meet the demands of providing nutrients and oxygen necessary for fetal growth, of providing respiration and removal of metabolic waste from the fetus, and of preparing the mother for childbirth. Those changes that directly affect obstetrical hemorrhage are discussed below.

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Cardiovascular System, Red Blood Cells, and Circulating Blood Volume

Significant remodeling of the maternal cardiovascular system begins as early as the first trimester. The left ventricular mass increases slightly, mainly due to increased wall thickness, with only little or no change in the ventricular cavity size [5]. Cardiac output (CO) begins to increase as early as 8–11 weeks of pregnancy, from approximately 6.7 ± 0.9 L/min to 8.7 ± 1.4 L/min at 36–39 weeks of gestation, and returns to pre-pregnancy levels by 12 weeks postpartum [5]. This occurs with only up to 21% decrease in systemic vascular resistance (SVR) [5, 6], primarily through a progressive increase in heart rate (HR) and stroke volume (SV). Recall that:

$$CO = SV \times HR \qquad (12.1)$$

It is common for a woman's heart rate to approach 95–100 beats per minute (bpm) in a normal pregnancy. A heart rate of 120 or above is almost always abnormal and warrants investigation for a pathologic cause of tachycardia [7].

Blood Volume

Circulating white and red blood cell volumes both gradually increase, due to increased hematopoiesis and erythropoietin activity [8]. Although red blood cell volume increases by approximately 32%, total blood volume increases by approximately 48% [9]. This relatively greater increase in plasma leads to a physiologic anemia and mild decrease in platelets at term and also results in decreased blood viscosity, which may permit improved perfusion. The total blood volume increases from 3250 mL to 4820 mL [9], which provides sufficient reserve to allow a woman to lose a physiologic volume of blood at delivery without cardiovascular compromise. Higher volumes of blood loss at delivery are required before signs of advanced hemorrhagic shock are evident, compared to a woman in the non-pregnant state. Should decompensation occur, however, it may occur more precipitously. While

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sudden, rapid bleeding may alert the clinician and care team to the risk of hemorrhagic shock, slow, steady, or intermittent bleeding can be equally hazardous should large cumulative losses occur that go unnoticed until vital signs show clear evidence of hemodynamic compromise.

Uterine Blood Supply

The growing fetus requires an ample, consistent supply of oxygen and nutrients, and the maternal circulation acts as the waste removal system for the fetus. As pregnancy progresses, blood flow to the uterus comprises an increasing percentage of total cardiac output, with up to 500–700 mL/min of blood flowing through the uterine arteries at term [10]. Rich collateral blood supply from cervical branches of the uterine arteries and ovarian vessels ensures adequate perfusion and can also be a source of profound bleeding. This can occur whenever the uterus fails to adequately contract after delivery, leaving venous sinuses open to ooze. Postpartum hemorrhage may result from significant lacerations of the uterus, cervix, or vagina or if uterine vessels become injured at the time of cesarean or vaginal delivery. During a normal vaginal delivery, blood loss is approximately 500–700 mL, and up to 1000 mL with cesarean delivery, but can be significantly higher when complications arise.

Respiratory System

During pregnancy, functional residual capacity decreases due to upward displacement of the diaphragm by the growing fetus. The respiratory rate remains constant, but under the influence of circulating progesterone, minute ventilation increases by 30–50% due to an increase in tidal volume [11]. This leads to a mild physiologic respiratory alkalosis [12], with a normal arterial pH of 7.44 in pregnancy, compared to 7.40 in the non-pregnant state. The kidney partially compensates by increasing excretion of bicarbonate ions, which then results in a serum bicarbonate concentration closer to 18–22 mEq/L during pregnancy [13]. These changes facilitate gas exchange between mother and fetus and are important to recognize when treating hemorrhagic shock. Arterial blood gases in a pregnant patient may appear relatively normal in a pregnant patient in the early stages of acidosis, if the physiologic norms in pregnancy are not considered. In other words, if maternal arterial blood gas values are consistent with acidosis using non-pregnant values, the pregnant or newly delivered patient is most certainly acidotic.

Coagulation Factors

Bleeding after delivery of the placenta is universal; the increase in maternal blood volume and red cell expansion buffer losses from normal postpartum bleeding. Additionally, there are significant alterations in circulating coagulation factors during pregnancy that further mitigate the risk of postpartum hemorrhage. Specifically, there are marked increases (20–1000%) in circulating levels of factors VII, VIII, IX, X, and XII and von Willebrand factor [14]. Fibrinogen levels increase throughout pregnancy and particularly just prior to delivery [15]. In addition to increased hypercoagulability, fibrinolytic activity decreases due to increases in plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) [14, 15].

Any underlying inherited or acquired deficiency in coagulation factors and von Willebrand factor predisposes the pregnant patient to an increased risk of peripartum hemorrhage. Conversely, obstetrical hemorrhage alone can quickly lead to disseminated intravascular coagulopathy (DIC), particularly in the setting of massive hemorrhage, when blood loss is sufficient to cause hypofibrinogenemia. This may occur in the setting of moderate bleeding in which intravascular resuscitation is limited to the use of large volumes of crystalloid or red blood cells only, leading to a dilutional effect of factors essential to coagulation. Erez and colleagues [15] illustrated this phenomenon in their efforts to modify the International Society on Thrombosis and Hemostasis DIC score to account for changes in pregnancy. Within their cohort of 19,889 women with 24,693 deliveries, the authors found a rate of DIC of 0.35%. They found that prolongation of the prothrombin time (PT), low platelet count, and low fibrinogen significantly increased a patient's risk of progression to DIC and a fibrinogen level of <3.0 g/L conferred the highest relative risk (59.0) [15]. Low fibrinogen levels are one of the earliest identifiable laboratory changes in the setting of obstetrical hemorrhage, with a drop in fibrinogen often preceding PT prolongation, making this a clinically useful parameter for evaluation of and monitoring for treatment of DIC.

Special Considerations

Preeclampsia is characterized by hypertension (defined as systolic blood pressure of 140 mmHg or greater, diastolic of 110 mmHg or greater) developing after 20 weeks of gestation and is variably associated with multi-organ dysfunction, including renal dysfunction resulting in proteinuria or oliguria; liver dysfunction or injury; and capillary leakage, resulting in peripheral, pulmonary, and/or cerebral edema [16]. In women who develop preeclampsia, the physiologic expansion of blood volume may not occur, and even in the presence of marked edema, the intravascular volume is relatively diminished, making women with preeclampsia particularly susceptible to hemorrhagic shock.

Deterioration may occur at lower volumes of blood loss, relative hypotension resulting from hemorrhage may appear to be in the normotensive range, and it may be difficult to

determine whether oliguria is due to ongoing preeclampsia or blood loss. Women with preeclampsia should be monitored closely for signs and symptoms of occult blood loss whenever hypertension resolves rapidly, especially if an operative delivery is performed. Paradoxically, women with preeclampsia may be more susceptible to volume overload, pulmonary edema, and acute lung injury secondary to resuscitation and transfusion due to capillary endothelial cell injury.

HELLP syndrome is defined as hemolysis, elevated liver enzymes, and low platelets. A hallmark of HELLP is thrombocytopenia (platelet count less than 100,000/mm^3). Accompanying liver dysfunction can result in coagulopathy due to lack of synthesis of coagulation factors. Liver capsule hematoma formation can add to the risk for morbidity and mortality. Frequent laboratory evaluation, including coagulation factors and fibrinogen, is recommended whenever HELLP is suspected.

Bleeding in the Antenatal Period

Conditions in pregnancy associated with bleeding are listed in Table 12.1, but the most common will be discussed below.

First and Early Second Trimester Bleeding

Ectopic Pregnancy

Bleeding from ectopic pregnancy is a leading direct cause of pregnancy-related death during the first trimester [2]. Ectopic pregnancies, defined as embryo implantation outside the intrauterine cavity, occur in 1.2–1.4% of all pregnancies and develop 95.5% of the time within the ampulla of the fallopian tube [17]. Ectopic pregnancy may also present in the cervix, cesarean scar, uterine cornua, or outside the uterine cavity, implanted on intraabdominal structures. The risks of death from ruptured ectopic pregnancy appear to be declining in developed countries due to improvements in early diagnosis and management [18, 19], but still account for up to 80% of deaths in early pregnancy [17].

In ectopic pregnancy, the growing embryo may outgrow the confines of the tissue into which it implants, causing rupture of the structure and bleeding [20]. This may occur after attempts at conservative or medical management. In some cases, bleeding consists of slow, consistent oozing which may present with no or relatively mild symptoms such as non-specific abdominal pain with only a mild drop in hemoglobin and lack of visible intrauterine pregnancy on ultrasound, despite a serum β-hCG level above the discriminatory zone at which an intrauterine pregnancy should be readily seen (usually 1000–2000 IU/L) [20]. Left untreated this can progress to frank rupture with profound blood loss, hypovolemic shock, and DIC. In other cases, rupture is more rapid and may lead to a more pronounced presentation of symptoms when blood loss occurs acutely.

Medical management with methotrexate is a reasonable first-line option in women without evidence of active bleeding and low serum β-hCG level. In cases in which significant bleeding has occurred or is ongoing, surgery – laparoscopic or open – is required [21]. The intraabdominal cavity can hold up to 1–2 liters of blood and clot, and preparation for adequate blood and blood product replacement to prevent the development or worsening of DIC is essential.

Molar Pregnancy

A molar pregnancy arises when a triploid zygote implants and develops. The pregnancy is considered a *complete mole* when there are no embryo and no normal placental tissue and all three sets of chromosomes are parental in origin. A *partial mole* may contain an embryo/fetus and some normal

Table 12.1 Pregnancy-specific conditions associated with postpartum hemorrhage

First trimester	Special considerations
Ectopic pregnancy	May rupture after medical management Surgery definitive treatment
Spontaneous (especially septic) abortion	
Hemorrhagic cyst	
Spontaneous hemoperitoneum	Rare-associated with endometriosis, abdominal vessel aneurysms
Second/third trimesters	
Abruption	More common in 2nd trimester than 3rd, usually associated with pain and/or contractions
Trauma	With or without abruption
Placenta previa	Usually painless
Placenta accreta/increta/percreta	
Intra-/primary postpartum	
Abruption	May present acutely
Placenta previa	
Placenta accreta/increta/percreta	Massive blood loss frequent
Uterine atony	Approx. 80% of postpartum hemorrhage
Genital tract lacerations	
Uterine inversion	Associated with bleeding and vasovagal shock
Uterine rupture	Associated with vaginal birth after cesarean, rarely occurs spontaneously
Amniotic fluid embolism	Catastrophic
Delayed postpartum	
Retained products of conception	Required dilatation and curettage
Subinvolution of the placental bed	May present 3–4 weeks postpartum

placental tissue combined with abnormal placental tissue, and the tissue consists of one set of maternal chromosomes and two paternal sets of chromosomes. Fetal growth restriction and a thick, hydropic placenta are seen later in pregnancy, and women pregnant with a partial mole may develop symptoms that mimic preeclampsia or hyperthyroidism. Bleeding is the most common presentation [22]. Treatment often consists of dilatation and curettage. At the time of uterine evacuation, heavy bleeding may ensue, and preparations should be made for appropriate blood product replacement.

Second and Third Trimesters

Bleeding occurs far less frequently in the second trimester than in the first or third trimesters. Once in the second trimester, the risk of spontaneous abortion or likelihood that an ectopic pregnancy is ongoing is markedly lower than in the first. The overall rate of preterm birth has declined from 12.8% of all births in the United States in 2006 to 11.4% in 2013 with evidence-based interventions [23]; therefore, bleeding associated with preterm labor and delivery may occur in the second trimester which comprises a far smaller proportion of cases compared to those that occur later in the third trimester. The most common etiologies of bleeding in the second and third trimesters are discussed below.

Placental Abruption and Placenta Previa

Placental abruption, when part or all of the placenta separates from the uterine wall prior to delivery of the fetus, occurs in approximately 0.6–1% of all pregnancies [24]. The incidence of abruption is highest at 24–26 weeks of gestation and declines slowly as pregnancy advances [24]. Dozens of risk factors for abruption have been identified. Hypertension – whether due to chronic disease, preeclampsia, or substance abuse, particularly smoking and amphetamine and cocaine use – is associated with a 1.5- to 5-fold increased odds of abruption. Perturbations of amniotic fluid levels, including oligohydramnios, polyhydramnios, and preterm premature rupture of membranes (PPROM), increase the risk of placental separation, as does inflammation caused by chorioamnionitis.

Trauma is among the leading causes of placental abruption. Abruption complicates up to 50% of major trauma and 1–5% of minor injuries such as a fall not involving the abdomen. Both a direct "shearing" stress between utero-placental interface and subsequent tensile or "countercoup" effect may occur. Forward displacement of the uterus creates negative pressure due to differential elasticity of the uterus and placenta, further increasing the risk of placental separation and bleeding [25, 26]. Pregnant women of 20 weeks of gestation or later should be monitored for a minimum of 4 h after trauma or for 24–48 h or more, if contractions, vaginal bleeding, maternal tachycardia, or fetal heart rate decelerations occur [27]. Continuous fetal heart rate monitoring and tocodynamometry of uterine activity are more sensitive than use of ultrasound [28].

Fetomaternal hemorrhage occurs 4–5 times more frequently when a woman suffers a traumatic injury; therefore, any Rh-negative woman should have Kleihauer-Betke testing and Rh immunoglobulin administered as needed to prevent isoimmunization [28].

Abruption may present subtly with chronic, slow amounts of bleeding that do not cause immediate maternal or fetal compromise, but may remain stable and manageable with close monitoring. In other cases, abruption presents acutely, sometimes catastrophically. Significant abruption may be *concealed*, if retro-placental bleeding occurs, but does not cause separation of the placental edges, from which blood can be allowed to escape vaginally, especially if accompanied by pain, contractions, or fetal heart decelerations. Coagulopathy, particularly hypofibrinogenemia, is common in cases in which a mother presents with intrauterine fetal demise due to complete abruption or when slow, steady bleeding accumulates. In these cases, early utilization of fibrinogen-containing products including fresh frozen plasma (FFP) and cryoprecipitate in addition to red blood cells (RBCs) is essential.

Placenta previa complicates approximately 1 in 200 births, and occurs when all or part of the placenta covers the internal cervical os [29], and is associated with an approximate 10-fold risk of antepartum bleeding [30]. Planned cesarean delivery is recommended in cases of placenta previa, but in cases in which the placental edge is low-lying, defined as <20 mm from the internal os, vaginal delivery may be considered, but an increased risk of bleeding remains. In 1 study of 98 pregnancies with low-lying placenta, defined as placental distance within 20 mm of the os, bleeding necessitating cesarean delivery occurred in 25% of patients, and 43% of women developed postpartum hemorrhage [31]. Even among women undergoing elective cesarean delivery, presence of placenta previa significantly increased the risks of postpartum hemorrhage (OR 1.91, 95% CI 1.74 to 2.09), blood transfusion (OR 4.39, 95% CI 3.76 to 5.12), and hysterectomy (OR 39.7, 95% CI 22.42 to 70.3) [32]. Additionally, placenta previa is one of the major risk factors for placenta accreta spectrum disorders, including placenta accreta, increta, and percreta, especially in women with prior cesarean deliveries (see Sect. 11.4.3) [33].

Postpartum Hemorrhage

Postpartum hemorrhage is classified as *primary*, when it occurs within the first 24 h after delivery and is most commonly due to uterine atony, reproductive tract injury such as

lacerations, hematoma formation, uterine inversion, or coagulopathy. *Secondary* postpartum hemorrhage occurs between 24 h and 6–12 weeks postpartum and is more commonly associated with retained products of conception, subinvolution of the placental site, infection, or inherited coagulation disorders such as von Willebrand disease [34]. During active bleeding, anticipation of the next steps in management is essential. Transfusion and identification/control of the source(s) of bleeding often must occur concomitantly. Although estimated blood loss of 500 mL for vaginal delivery and 1000 mL for cesarean delivery have been used to define postpartum hemorrhage and are practical guidelines, in actuality, some women may have blood loss up to 700 mL after vaginal delivery and up to 1200 ml after cesarean without significant physiologic detriment. For this reason, the American College of Obstetricians and Gynecologists now defines postpartum hemorrhage as "a cumulative blood loss of greater than or equal to 1000 mL, or blood loss accompanied by signs or symptoms of hypovolemia within 24 h after the birth process" [35].

Blood loss is most readily estimated either visually or by weighing pads and measuring accessible volumes in collection bags/containers, but is underestimated up to 50% of the time, regardless of the level of training and experience of providers deriving the estimates. Careful attention to vital signs, clinical signs, and urine output are essential in recognition and monitoring of hemorrhagic shock. Laboratory values may guide therapy, but may be misleading in the setting of early or active hemorrhage, before a patient equilibrates. Continual or unrecognized losses may contribute to or exacerbate coagulopathy.

Planning and preparation for postpartum hemorrhage ideally begins early in pregnancy. Early identification of preexisting conditions such as von Willebrand disease or immune thrombocytopenia allows ample time for consultation with a hematologist and/or transfusion medicine specialist and for delivery planning. Other conditions that increase risks for postpartum hemorrhage or the need for transfusion include iron deficiency anemia, multiple gestations, and abnormal placentation, such as with placenta previa or the placenta accreta spectrum [35]. While not all underlying conditions can be prevented, risk stratification can identify which patients may benefit from having typed and cross-matched blood ordered and available upon admission for delivery and whether additional resources should be in place for hemorrhage control.

Uterine Atony

Approximately 80% of primary postpartum hemorrhage is due to uterine atony or the failure of the uterus to become firm and contracted after delivery [36]. Risk factors for uterine atony include any condition that increases intrauterine volume, such as large fetal size, multifetal gestation, or polyhydramnios; chorioamnionitis; multiparity; history of atony; and prolonged labor, particularly after induction, and operative delivery [34]. Active management of the third stage of labor includes prophylactic use of uterotonics and delivery of the placenta by use of gentle, controlled traction on the umbilical cord while manually supporting the uterus from the abdomen. Active management of the third stage has been shown in two large trials to reduce the incidence postpartum hemorrhage by approximately 10% compared to expectant management [37, 38].

First-line management of uterine atony includes bimanual uterine massage (elevation of the uterus and cervix with a vaginal hand, combined with transabdominal pressure on the fundus and use of uterotonics (Table 12.2)). Oxytocin is the preferred agent in developed countries; however, it must be stored at 4 °C to maintain its efficacy and is given intravenously or intramuscularly. Misoprostol tablets are shelf stable for several years if kept dry, even in warm climates, and can be administered sublingually, buccally, or per rectum and therefore may be an alternative agent for use in low-resource settings [39–41]. Second-line agents such as methylergonovine (Methergine) or 15-methyl PGF2α may be needed. Should medical management fail to stop bleeding, the cervix and vagina should be inspected for lacerations needing repair.

Secondary therapy includes mechanical uterine tamponade with an inflatable balloon, such as the SOS Bakri™

Table 12.2 Commonly used uterotonic medications

Medication	Dose	Route	Precautions
Oxytocin	10 milliunits	IM	
	0.5–40 milliunits/min	IV	Avoid rapid IV infusion – may cause hypotension, hyponatremia
Methylergonovine (Methergine)	200 μg	IM, IV May repeat every 2–4 h	Avoid in patients with hypertension
	200 μg	Oral, 3–4 × daily up to 7 days	
Carboprost (Hemabate)	250 μg, may repeat at 1.5–3.5 h intervals, do not exceed 12 mg total dose or continuous administration >2 days	IM	Causes bowel motility Avoid in patients with asthma

(Cook, Spencer, IN, USA) or Ebb™ (Glenveigh, Chattanooga, TN, USA) balloons, which are specifically designed for intrauterine tamponade, or with a Sengstaken-Blakemore tube, Foley catheter, or condom secured to a straight catheter, placed within the intrauterine cavity, and filled with sterile saline. Packing with gauze can also effectively temporize bleeding long enough to correct coagulopathy and sometimes enough to avoid further intervention [42–44]. Reported success rates with balloon tamponade range between 65 and 100% [45, 46].

Should the above methods fail, the next step is surgical intervention. The definitive management of postpartum hemorrhage is hysterectomy; however, many affected women desire future fertility. Sequential vascular ligation of the uterine blood supply, including the bilateral uterine arteries and infundibulopelvic ligaments, reduces perfusion pressure to the uterus and placental bed. Compression sutures, such as B-Lynch [47] and Hayman [48] Cho (square) [49] sutures, physically brace a uterus that is manually compressed, by compressing the anterior and posterior uterine surfaces and by reducing the open spaces within the cavity. Success rates with use of compression sutures range between 76 and 100%, with a decreased rate of success when placement of the sutures was delayed by 2–6 h after delivery [50]. Ultimately, hysterectomy may be necessary as a definitive measure to stop bleeding.

Novel hemostatic agents have come to market serve as adjunctive measures to facilitate hemostatic control on the battlefield and trauma surgery and have increasingly been used for obstetrical hemostasis [51, 52]. These include items such as "trauma gauze" or laparotomy sponges infiltrated with chitosan (Celox Gauze™, MedTrade Products Ltd., Crewe, UK) or kaolin (QuikClot®, Z-Medica, Wallingford, CT, USA). These impregnated gauze products not only provide a source for hemostatic compression with the sponge, but the additional agents also activate the clotting cascade and activate clot formation without causing thermal reactions. Improvements in rotational thromboelastometry measures of clot formation and integrity have been demonstrated *in vitro* with the use of chitosan- or kaolin-impregnated gauze [53]. Cellulose mesh, collagen or gelatin foam, and microfibrillar collagen powders have long been available as hemostatic agents and provide a lattice upon which a clot may form (including, but not limited to, Surgicel®, Surgifoam®, and Surgiflo®, Ethicon US, LLC; AviteneTM, BD Bard, Warwick, RI, USA; Gelfoam®, Pfizer, NY, USA). A novel cellulose mesh product containing powdered thrombin and fibrinogen has been developed (Evarrest®, Fibrin Sealant Patch, Ethicon US, LLC) and used to control bleeding by forming an patch-like "clot" in areas difficult to suture. The fibrin sealant patch been shown to be cost-effective and easy to use for hemostatic control in areas not amenable to suture control; the design of the patch to be left internally gives it a potential advantage over trauma gauze, which must be removed prior to intracavitary closure [54–56].

The Placenta Accreta Spectrum (PAS): Placenta Accreta/Increta/Percreta

The placenta accreta spectrum (PAS) includes the various forms of placental invasion into or through the myometrium including placenta accreta, increta, and percreta. PAS affects between 1 in 533 [33] and 1 in 731 [57] pregnancies based on data from large, multi-center studies in the United States but may be lower, based on population-based national surveillance data. The United Kingdom Obstetric Surveillance System identified a rate of 1.7/10,000 maternities between 1 May 2010 and 30 April 2011 [58]. The Nordic Obstetrical Surveillance System identified 4.6/10,000 deliveries [59], and in Canada the most recent incidence is 14.4/10,000 deliveries [60].

The risk for a woman to have a placenta accreta spectrum disorder correlates with the number of prior cesarean deliveries (OR = 7 [95% CI 4.4–9.8] after 1 cesarean, OR = 55.9 [95% CI 25–110] after 3 or more cesareans), especially in the presence of placenta previa (OR = 292 [95% CI 196–40) [59]. Other risk factors include advanced maternal age, smoking, and other uterine surgery, such as myomectomy or septum revision, and in vitro fertilization, with a particularly high risk of invasion with cryopreserved embryos [58].

Cesarean hysterectomy is the definitive surgical treatment of PAS; however, increasingly conservative interventions have been employed, with an attempt to leave all or a majority of the uterus intact. Such measures include use of intrauterine balloon tamponade, partial myometrial resection along areas of invasion, intra-arterial balloon occlusion, and sequential devascularization [61]. Conservative management offers an alternative for women who are strongly motivated to preserve the uterus; however, in one of the most comprehensive reviews of case series in which patients with placenta accreta were managed conservatively, 58% of parturients required a delayed hysterectomy due to infection, hemorrhage, or DIC, in some cases as long as 9 months after delivery [62].

Massive hemorrhage at the time of delivery for PAS is common, with a mean estimated blood loss ranging between 4 and 7.5 liters, but may far exceed this in extreme cases [33, 63–65]. In 1 study of 66 patients with PAS, transfusion was required in 95% of patients, with mean RBC use of 10 +/− 9 units, with 11% of patients requiring 20 or more RBC units [66]. The invasive placenta often bulges out into the confined spaces of the pelvis, obstructing visualization and easy access to the uterine arteries. Additionally, placental invasion promotes abundant, irregular neovascularization – immature vessels that are a potential source of bleeding (Fig. 12.1).

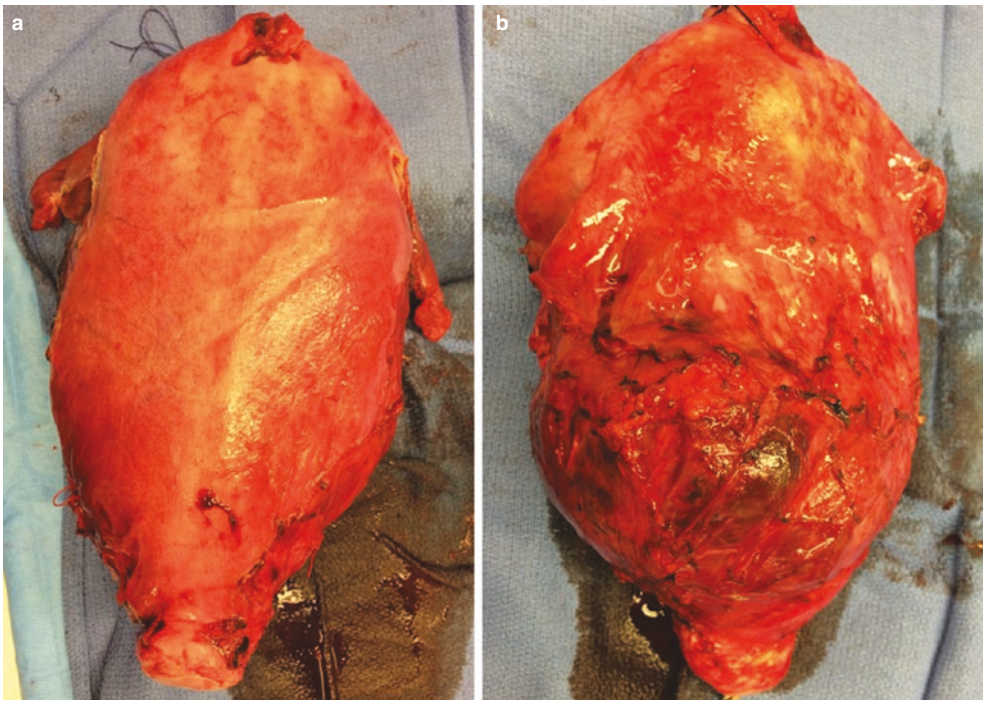

Fig. 12.1 Panel a: Normal, posterior uterine surface. Panel b: Anterior uterine with placenta accreta. Note the bulging placental tissue, covered by tortuous, irregular neovascularization

Any disruption of the placental surface can lead to torrential hemorrhage. Antenatal diagnosis and proper preparation; experienced, multidisciplinary team support; and avoidance of removal of the placenta have been shown to reduce mean estimated blood loss [65, 67]. Still, the rate of massive transfusion in PAS cases remains significant, and the early availability of blood and blood products in 1:1:1 or 2:1:1 ratio of RBC:FFP:PLT is essential to optimal outcomes [33].

Amniotic Fluid Embolism

Perhaps one of the most dreaded complications of pregnancy is amniotic fluid embolism (AFE), which occurs in approximately 1 in 40,000 deliveries [68]. AFE results from a maternal systemic, anaphylactoid reaction to exposure to multiple fetal antigens during delivery that trigger a cascade of responses, including initial pulmonary and systemic hypertension, followed by left ventricular depression, acute systemic hypotension, hypoxia, cardiac arrest, and fulminant, consumptive DIC. The maternal death rate is approximately 40–60% [68], and of survivors, only approximately 15% remain neurologically intact [69]. Amniotic fluid embolism occurs classically during delivery or within 30 min postpartum. The onset of symptoms is usually brisk and unpredictable. Emergent release and administration of group O Rh-negative or type-specific RBCs, plasma, and cryoprecipitate is essential to resuscitation efforts and should occur concomitantly with airway management, circulatory support, and hemorrhage control.

Massive Transfusion Protocols

Development and utilization of clear, easy-to-use massive transfusion protocols are a systems-level means to facilitate early blood product replacement when needed in obstetrical units, by providing a pathway for emergency release of blood and blood products, and sustained availability of blood until hemostasis is achieved. Use of 1:1:1 or 1.5:1:1 RBC:FFP:PLT ratios has been most widely studied in trauma settings and shown to reduce mortality due to hemorrhage [70–72]; however, obstetrical hemorrhage and trauma are similar in volume and likely in pathophysiologic mechanisms [73].

The American College of Obstetricians and Gynecologists has developed an Obstetrical Hemorrhage Safety Bundle that states “in order to provide safe obstetric care institutions must: have a functioning Massive Transfusion Protocol (MTP), have a functioning Emergency Release Protocol (a minimum of 4 units of O-negative/uncrossmatched RBCs), have the ability to obtain 6 units RBCs and 4 units FFP (compatible or type specific) for a bleeding patient, and have a mechanism in place to obtain platelets and additional products in a timely fashion” [74].

The availability of FFP is especially important, as low fibrinogen levels are a hallmark of acute obstetrical hemorrhage and the best early marker for severity of hemorrhage. In 1 prospective, population-based study of 106 maternity units in France, 738 women developed postpartum hemorrhage (PPH), defined as blood loss exceeding 500 mL in the first 24 h after delivery. Fibrinogen levels were checked at the time of diagnosis of PPH, with an initial mean value of

420 mg/dL in women without severe hemorrhage, but of 340 mg/dL for the 323 women who developed severe hemorrhage, defined as requiring embolization, uterine artery ligation, hysterectomy, transfusion, or transfer to intensive care. Women whose fibrinogen levels were between 200 and 300 mg/dL, which is considered normal outside of pregnancy, had a significantly increased risk for severe hemorrhage. This risk increased 12-fold when the fibrinogen levels dropped below 200 mg/dL [75]. Similarly, in a separate study, the positive predictive value for severe postpartum hemorrhage approached 100% when the fibrinogen level is less than 200 mg/dL [76].

Prospective Therapies/Management

Currently, the standard of care is to replace blood components early and aggressively for resuscitation. Some experts propose that goal-directed transfusion, using guidance by newer technologies such as thromboelastography (TEG™) and rotational thromboelastometry (ROTEM™), may allow rapid results [77, 78] and targeted resuscitation while minimizing use of blood products.

The use of adjunctive or alternative therapies such as recombinant activated factor VII (rFVIIa), factor concentrates, or fibrinogen concentrates for obstetrical hemorrhage is not standard, but has been reported. In one multi-center randomized controlled trial, rVIIa was shown to reduce the number of patients who needed secondary therapies including surgical intervention or transfusion, in about 1 in 3 patients, but with 1 in 20 patients developing non-fatal thrombotic events [79]. This product remains very expensive and only works in the presence of adequate fibrinogen, necessitating adequate transfusion of FFP or cryoprecipitate.

Use of fibrinogen concentrates in the setting of postpartum hemorrhage appears promising in the setting of hypofibrinogenemia [80]. Fibrinogen concentrate use has not proven to reduce the total estimated blood loss or total volume of transfusion if given in patients with normal or slightly altered fibrinogen levels(at or above 200–300 mg/dL) or with the FIBTEM A5 (amplitude of the alpha angle at 5 min) >12 mm (considering a normal A5 >15 mm) [81]. More data is needed before strong recommendations can be made for the routine use of fibrinogen concentrates in the setting of obstetrical hemorrhage.

Conclusion

Early recognition of obstetrical hemorrhage, starting with risk assessment of every patient, prior planning, and prompt attention to and treatment of the patient, including the utilization of massive transfusion protocols, are key to optimal patient outcomes in pregnancy-related hemorrhage. Ongoing efforts to curtail pregnancy-associated hemorrhage are crucial to reduce preventable obstetrical morbidity and mortality.

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Bleeding Associated with Thrombocytopenia

13

Sarah E. Sartain and Jenny Despotovic

Introduction

Platelets are a critical component of coagulation, most importantly in the formation of the hemostatic platelet plug, and are actively involved in secretion, aggregation, and adhesion [1–3]. Platelets also have an important role as immune cells, aiding in wound healing and vascular integrity [4, 5]. A normal platelet count is between 150,000 and 450,000/mm^3 regardless of age [6], and a decrease in circulating platelets can increase the tendency for bleeding. Low platelet count, or thrombocytopenia, can be caused by numerous abnormalities, broadly categorized by platelet production abnormalities in the bone marrow, loss of platelets after formation, or a combination of the two processes. There are also disorders of platelet function, characterized by platelet-type bleeding symptoms despite normal or slightly low platelet number, which will be discussed in this chapter in more detail. Peripheral loss of platelets can be caused by the immune system inappropriately targeting platelets and resulting in platelet destruction. There are several disorders that result from predominantly antibody-mediated platelet destruction and/or consumption. Three of these disorders, immune thrombocytopenia (ITP), heparin-induced thrombocytopenia (HIT)/thrombosis, and thrombotic thrombocytopenic purpura (TTP), will be discussed here. Immune-mediated platelet refractoriness will also be briefly reviewed.

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Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is a common cause of often-severe thrombocytopenia with variable bleeding symptoms occurring in both adults and children. ITP is an acquired autoimmune disorder with multifactorial etiology including generation of antiplatelet autoantibodies by an immune trigger (most commonly infection), direct T-cell cytotoxicity, and abnormal platelet production in the bone marrow [7–9]. There is no diagnostic test that is confirmatory; therefore, ITP is a diagnosis of exclusion. There are multiple disorders that should be ruled out with clinical history, blood count and smear review, and other laboratory testing as indicated [10]. See Table 13.1 for a list of diagnoses that should be considered in the differential diagnosis of ITP. The management of bleeding in ITP is different from other causes of thrombocytopenia, and therefore, accurate diagnosis is essential.

Primary and Secondary ITP

ITP can be primary (not triggered by another disorder), which is the case in up to 75% of children [14] but much less frequent in adults, or secondary to another disorder, including autoimmune diseases such as systemic lupus erythematosus (SLE), inflammatory bowel diseases (IBD), immunodeficiencies such as common variable immunodeficiency (CVID) or DiGeorge syndrome, thyroid disease, infection (human immunodeficiency virus (HIV), hepatitis C, hepatitis B, *Helicobacter pylori*), chronic lymphocytic leukemia (CLL), or pregnancy [14–16]. Secondary ITP is most successfully treated by optimal management of the underlying condition [17–19].

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Table 13.1 Differential diagnosis of immune thrombocytopenia

Category	Diseases
Macrothrombocytopenia	MYH9 group, familial thrombocytopenias, GATA-1 Group, Bernard-Soulier syndrome, gray platelet syndrome, Montreal platelet syndrome
Congenital thrombocytopenia	TAR, X-linked thrombocytopenias, Wiskott-Aldrich syndrome, Fanconi anemia, Bernard-Soulier syndrome, congenital amegakaryocytic thrombocytopenia, GATA-1-associated X-linked dyserythropoietic anemia, and thrombocytopenia; RUNX1-associated thrombocytopenia
Neonatal thrombocytopenia	Sepsis, congenital infections, perinatal insults, maternal ITP, neonatal alloimmune thrombocytopenia, trisomies [11–13], thrombosis, placental insufficiency
Acquired thrombocytopenia	Infections, drugs, toxins, splenomegaly
Thrombotic microangiopathies	Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, atypical hemolytic uremic syndrome
Marrow infiltration	Leukemia/oncologic process, marrow fibrosis, myelodysplastic syndrome
Other	Rheumatologic, autoimmune lymphoproliferative syndrome, paroxysmal nocturnal hemoglobinuria, common variable immunodeficiency syndrome, von Willebrand disease type 2B, Evans syndrome, pseudothrombocytopenia

TAR thrombocytopenia-absent radius, *ITP* immune thrombocytopenia

Categorization

The International Working Group (IWG) on ITP Consensus Report recommends the following categories to stratify ITP cases according to the duration of disease [15]:

- Newly diagnosed: 0–3 months from diagnosis
- Persistent: 3–12 months from diagnosis
- Chronic: >12 months from diagnosis

These categories guide therapeutic decisions and predict the likelihood of disease resolution.

Symptoms

Platelet-type bleeding, including petechiae, purpura, and bruising, is the most common manifestation. Moderate bleeding that may warrant treatment can include wet purpura, epistaxis, menorrhagia, and oral bleeding. Life-threatening bleeding occurs very rarely [11, 20–23]; examples include gastrointestinal bleeding, hematuria, and central nervous system (CNS) bleeding (including intracranial hemorrhage (ICH)). More significant bleeding is generally thought to occur at the lowest platelet counts (i.e., generally less than 20,000/mm^3), but platelet count correlates poorly with bleeding risk [21].

Natural History of ITP

Childhood ITP is generally self-limited, with about 80% of affected children experiencing spontaneous resolution without recurrence, regardless of interventions and treatments that may be necessary during the course of the disease [14]. Adult ITP is generally chronic, with about 80% of adults having a course that persists indefinitely [12, 24].

Diagnosis

Routine evaluation should include a complete history including documentation of historically normal platelet count (if available) and physical exam. Physical exam should be normal with the exception of any relevant bleeding manifestations. Significant lymphadenopathy or organomegaly is not expected in ITP, and the presence of these abnormalities should prompt consideration of an alternative diagnosis.

Laboratory Testing

The cornerstones of the laboratory evaluation of suspected ITP are the complete blood count (CBC) and peripheral blood smear. The CBC should be normal except for thrombocytopenia, and platelet size is generally variable to large. Significant white blood cell (WBC) or red blood cell (RBC) abnormalities warrant further evaluation. Reticulocytosis should not be present. The peripheral blood smear should show relatively normal erythrocyte and leukocyte populations, and platelets should appear normally granulated and variable in size with the presence of scattered large/giant platelets.

Direct antiglobulin test (DAT; formerly known as direct Coombs test) and serum immunoglobulins are recommended in all newly diagnosed ITP patients, as these markers may be associated with underlying tendency toward autoimmunity [13, 25]. Hepatitis C and HIV testing is recommended for all adults, and *Helicobacter pylori* testing is recommended for high-risk or symptomatic adult patients [13]. ANA (antinuclear antibody) testing can be obtained for patients with high suspicion of autoimmunity [25–28], but is rarely helpful in the absence of symptoms in adults with uncomplicated newly diagnosed ITP [19]. The role of bone marrow examination is controversial and generally recommended only in circumstances where the diagnosis is not clear due to the

presence of atypical features. Guidelines from the IWG recommend bone marrow examinations in patients >60 years old with newly diagnosed ITP [13]. However, the American Society for Hematology (ASH) guidelines do not advocate for routine bone marrow studies prior to initiating steroid treatment or in the case of a patient who fails intravenous immune globulin (IVIG) therapy, based on population studies [14, 29]. Antiplatelet antibody testing has not been shown to have adequate sensitivity and specificity for use in the diagnosis or management of ITP. There are many reports of the presence of positive antibodies in alternative diagnoses, and antibodies are not always present and identifiable in all cases of ITP because of the multifactorial etiology of the disease. Platelet-associated IgG or IgM (known as PA IgG or PA IgM) has a very low sensitivity (reported as low as 40–60%), which significantly limits the diagnostic utility in ITP [30–33]. Glycoprotein-specific antibody testing (direct antibody testing) has a high specificity (~75–95%), but the sensitivity is low [34, 35]. For these reasons, ASH and IWG guidelines recommend against routine platelet antibody testing for the diagnosis of childhood or adult ITP [13, 14].

Management of ITP in Children

Given the typically mild clinical symptoms and expectation of resolution in childhood ITP, most experts recommend observation without treatment regardless of the platelet count in children with no symptoms or with only mild cutaneous findings [14]. However, for children with "wet" bleeding symptoms, including wet purpura, epistaxis, or menorrhagia, treatment is recommended to elevate platelet count to a hemostatic range, facilitating cessation of bleeding and decreasing the risk of ICH and other forms of life-threatening bleeding [14].

Management of ITP in Adults

It is estimated that less than 30% of adults can be successfully managed with observation alone [14]. Current recommendations for management of ITP in adults advise treatment for those patients with a platelet count <30,000/mm^3 or those with bleeding symptoms or need for a procedure.

Management of ITP in Pregnancy

ITP in pregnancy is generally mild in women with no history of ITP prior to pregnancy. It can typically be followed with close observation if the platelet count is >30,000/mm^3 without bleeding symptoms [36]. Affected patients may require treatment for severe thrombocytopenia and bleeding or in anticipation of a procedure, including amniocentesis or delivery. Splenectomy is generally avoided as the ITP usually spontaneously resolves after pregnancy, but is considered a safe second-line intervention in the second trimester for severely affected patients [14, 36]. The optimal platelet count to achieve hemostasis during delivery has not been established. A count of 75,000–80,000/mm^3 is generally recommended [37], especially in the case of epidurals or spinal anesthesia [38], but for uncomplicated deliveries, a platelet count of 50,000/mm^3 is considered safe, even for cesarean section [39]. The ITP diagnosis itself is not an accepted indication for cesarean delivery, as the risk of ICH with vaginal delivery is low (<1%) [19]. The newborn should be monitored for at least 7 days post-delivery for thrombocytopenia secondary to passively acquired maternal antiplatelet antibody [37]. Maternal therapy and platelet count are poor predictors for the neonate's platelet count, with the only reliable predictor being the platelet count and course of thrombocytopenia of an older sibling [40]. In severely thrombocytopenic newborns, imaging to evaluate for ICH should be obtained regardless of symptoms, as it can be clinically silent. If treatment is required in the neonate, intravenous immune globulin (IVIG) can be considered. The affected neonate should have spontaneous resolution as the passively acquired antibodies clear the body, usually by 12 weeks of age [36].

Frontline Therapies

There are several treatment options for the temporary improvement in bleeding symptoms and thrombocytopenia in ITP. These therapies function by interfering with immune destruction of antibody-coated platelets and include corticosteroids, IVIG, or anti-D immune globulin. Steroid dosing and duration recommendations are varied, but the standard first-line treatment for many years has consisted of a course of 1–4 mg/kg/day of oral prednisone for 2–4 weeks (including a taper) [10, 13–15]. Other acceptable steroid regimens include high-dose IV methylprednisolone 30 mg/kg/day (maximum of 1 g/day) and oral prednisone 4–8 mg/kg/day for 3–7 days, followed by a prolonged taper to day 21 [36]. Recent work has investigated whether intensification of treatment using high-dose dexamethasone results in increased remission rates in adults with ITP. One randomized trial found that a complete response rate was higher in the high-dose dexamethasone arm (six 3-week cycles of 0.6 mg/kg/d of dexamethasone pulsed on days 1–4) compared to the standard prednisone arm (1–2 mg/kg/d × 2–4 weeks with taper) [41].

IVIG is typically administered at 1 g/kg IV × 1–2 doses and anti-D immune globulin at 50–75 μg/kg IV × 1 dose. These therapeutic modalities typically increase circulating

platelet count within 24–48 h, whereas corticosteroids usually take 3–5 days, but can take up to 2 weeks, for an effect to be seen [15]. Of note, Rh-negative patients have not shown benefit from anti-D immune globulin.

The choice of therapy depends on a variety of factors including the side effect profile of each agent and the indication for treatment, as well as patient-related factors. Platelet transfusion is generally avoided due to the expected rapid antibody-mediated clearance of transfused platelets and theoretical risk of increased antibody development. IVIG and corticosteroids are both considered acceptable frontline treatment options in pregnancy [14]. Medications that affect platelet number or function should be avoided (aspirin, NSAIDs), and activity restrictions may be required depending on the platelet count and bleeding symptoms. Antifibrinolytic agents (aminocaproic acid and tranexamic acid) can be helpful adjuncts to therapy for mucosal bleeding symptoms [13, 36].

Two small studies using thrombopoietin receptor agonists (TPO-RA) as up-front therapy in ITP have shown promising results [42, 43]. However, additional studies with greater patient numbers are needed in order to evaluate the long-term outcomes with these newer agents before official recommendations on their use as first-line agents can be made.

Second-Line Therapies

For patients who fail frontline therapy or have persistent/severe disease, a second-line therapy may be considered to achieve a more durable platelet response. The choice of agent/treatment is dependent on a variety of factors and should be made on a case-by-case basis. Examples of second-line treatments include splenectomy, rituximab, TPO-RA, and alternative immunosuppressive agents [10, 13, 14]. Encouraging data are becoming available on TPO-RA as second-line therapy for both adult and childhood ITP [44–49]. With the increasing use of TPO-RA, as well as risk for infection, thrombosis, and postoperative complications with splenectomy, fewer patients with ITP are undergoing splenectomy than before [50].

Management of Life-Threatening Bleeding

A patient experiencing life-threatening bleeding in the setting of ITP requires an aggressive treatment approach using a combination of therapies. IVIG and high-dose IV steroids should be given, with consideration of platelet transfusion/drip to facilitate hemostasis acutely [10, 13]. If the patient has signs and symptoms worrisome for ICH, expeditious imaging should be obtained with surgical and neurosurgical consultations as needed. Urgent/emergent splenectomy can be life-saving in the setting of uncontrolled bleeding or neurologic compromise [14].

Heparin-Induced Thrombocytopenia/Thrombosis

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening clinical syndrome caused by immune reaction and antibody formation to platelets upon exposure to heparin. HIT most commonly occurs after exposure to unfractionated heparin and, very rarely, to low molecular weight heparin products [51, 52]. Although the incidence of antibody development to heparin exposure is higher, actual development of HIT occurs in only about 1–3% of adults receiving treatment doses of unfractionated heparin [53–55]. The incidence is much lower in children, those receiving prophylactic dosing or with heparin used as line flush, and those receiving low molecular weight heparin products [53]. The highest risk appears to be in the cardiac surgery setting [56]. Thrombocytopenia, typically not severe, is the most common clinical manifestation of HIT [53]. Platelet counts rarely fall below 20×10^9/L [57], with median counts ranging from 40,000/mm^3 to 60,000/mm^3 [58]. HIT is not typically associated with bleeding symptoms and, in fact, is associated more commonly with thrombosis [53]. Venous thrombi are more common (occurring in ~30–60% of diagnosed patients) [53, 56, 59, 60] than arterial thrombi, which occur in ~3–10% of patients [53, 60, 61]. Patients with heparin-induced thrombocytopenia and thrombosis (HITT) have high morbidity and mortality rates [59, 60].

Pathophysiology

In susceptible individuals, heparin exposure results in the generation of IgG antibodies that react with heparin and platelet factor 4 (PF4) released from platelet alpha granules, resulting in the formation of heparin-PF4-IgG immune complexes. These complexes bind to Fc gamma receptors on the surface of platelets, subsequently resulting in mild-to-moderate thrombocytopenia, platelet activation, aggregation, and risk of thrombosis due in large part to thrombin generation [52, 53, 62–65]. The onset of thrombocytopenia is typically 5–10 days after first heparin exposure, but is much more rapid (usually within 24–72 h) if there has been previous heparin exposure within months [66, 67]. As in other immune disorders, the incidence of antibody development with heparin exposure is significantly higher than the incidence of clinical HIT [53, 56], and it is not clear why some patients are more susceptible to developing the clinical syndrome than others.

Diagnosis

HIT is a clinical-pathologic syndrome: diagnosis is based on the presence of one or more HIT-associated clinical symptoms and the detection of heparin-PF4-IgG immune complexes [53, 68, 69]. A precipitous drop in platelet count to <100,000/mm^3, or >50% reduction in platelet count in an individual exposed to heparin, should raise suspicion for this diagnosis [58]. Laboratory testing, often with long turnaround times, should only be pursued for patients with a high clinical suspicion. The 4T scoring system is a clinical prediction tool developed to assist clinicians in determining appropriate candidates for laboratory testing [53]. The 4Ts are *T*hrombocytopenia, *T*iming of platelet count fall, *T*hrombosis, and other causes for *T*hrombocytopenia. See Table 13.2 for calculation of the 4T score. Patients with a 4T score of 0–3 points have a low probability of HIT and likely do not require testing for PF4 antibodies. This tool does have limitations, as patients with a high 4T score may not have a diagnosis of HIT [70–72]. Laboratory diagnosis of HIT first involves the ELISA measurement of heparin-dependent IgG antibodies targeted to heparin-PF4 complexes; a negative ELISA test ensures that HIT can be excluded with high probability and heparin can be continued if clinically indicated [73]. However, when positive, confirmatory testing must be obtained because this test is associated with a high false positive rate [74, 75]. The platelet [^{14}C] serotonin release assay (SRA) is considered the gold-standard test for the confirmation of HIT and should be obtained when there is positive ELISA testing [76, 77]. Unfortunately, the SRA test is technically challenging and not widely available, limiting its usefulness when making treatment decisions [53, 74]. Other functional assays for confirmation of a HIT diagnosis have been developed, some of which allow for rapidly available results [73]. However, more data are needed before these tests can replace the current standard for diagnosis.

Table 13.2 The 4T scoring system for diagnosis of HIT

4Ts	Condition	Points
Thrombocytopenia	Platelet count fall >50% and nadir ≤20,000/mm^3	2
	Platelet count fall 30–50% or nadir 10–19,000/mm^3	1
	Platelet count fall <30% or nadir <10,000/mm^3	0
Timing of platelet count fall	Between days 5 and 10 or </= 1 day if prior heparin exposure within the last 30 days	2
	Consistent with fall between 5 and 10 days but unclear, onset after day 10, or fall ≤1 day with prior heparin exposure within 30–100 days	1
	Platelet count fall <4 days without recent heparin exposure	0
Thrombosis or other sequelae	Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus	2
	Progressive or recurrent thrombosis, non-necrotizing skin lesions, or suspected thrombosis, not proven	1
	None	0
Other causes of thrombocytopenia	None apparent	2
	Possible	1
	Definite	0

Interpretation
0–3 points, low probability
4–5 points, intermediate probability
6–8 points, high probability

Treatment

Upon suspicion of a HIT diagnosis, the most important intervention is immediate discontinuation of heparin from all sources, including line flushes, regardless of laboratory confirmation [54, 78]. Given the ongoing risk of thrombosis (as high as 25–50%) despite discontinuation of heparin, these patients require alternative anticoagulation [54, 79]. Generally, low molecular weight heparin should not be used due to the likely presence of cross-reacting antibodies [57, 80]. Warfarin is not a good substitution for heparin secondary to the risk of venous limb gangrene or skin necrosis on initiation [81–83]. Acceptable non-heparin anticoagulant alternatives include the direct thrombin inhibitors lepirudin, argatroban, and bivalirudin, as well as the factor Xa inhibitors danaparoid and fondaparinux [54]. In patients with renal insufficiency, argatroban should be considered, as it is not renally cleared [84]. Whereas there is an abundance of evidence supporting the use of lepirudin, argatroban, and danaparoid in the treatment of HIT, the evidence supporting the use of bivalirudin and fondaparinux is limited to case series and systemic reviews [53, 85], and therefore, these drugs are considered "off-label" in the treatment of HIT. The new direct oral anticoagulants (DOACs) are being used more frequently in patients with HIT and have shown safety and efficacy in case reports, case series, and retrospective reviews [86–88]; however, more data are needed before these agents become standard HIT therapy.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially life-threatening condition with an incidence of approximately 1–4 per million person years [89, 90]. The disorder is secondary to a deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [91], responsible for cleaving high molecular weight von Willebrand factor multimers [92, 93]. TTP can be congenital or, more commonly, acquired,

secondary to the development of inhibitory antibodies to ADAMTS13. Acquired TTP is more common in adults than in children, and within the adult population, women and African Americans have the highest incidence [90]. Acquired TTP is very rare in the pediatric population, with an incidence of 0.1 per million; within this group, adolescents are the most commonly affected [94]. TTP is a life-threatening condition with high morbidity and mortality. The mortality rate in untreated TTP approaches 90% [95], but with treatment is approximately 10–20% [96]. Therefore, timely recognition of symptoms is important in decreasing fatality from the disease.

Pathophysiology

The pathophysiologic abnormalities in TTP are secondary to the decreased concentration of the von Willebrand factor (VWF) cleaving protease, ADAMTS13, released by endothelial cells and megakaryocytes [92, 93, 97]. Physiologically, periods of shear stress result in a partial unfolding of ultra-large VWF multimers, allowing ADAMTS13 cleavage at the Tyr-Met bond in the second A-domain of VWF [92, 93, 98]. Without the metalloprotease, the high molecular weight VWF multimers are not cleaved from the surface of the endothelium, passing platelets adhere and aggregate to the long multimers, and platelet thrombi form within the microvasculature, leading to end-organ damage (especially of the kidneys, brain, and heart) and development of microangiopathic hemolytic anemia [99].

In acquired TTP, the ADAMTS13 protease is inhibited by IgG-type antibodies generated by a dysfunctional immune system [91, 100, 101]. Drugs, infection, underlying autoimmunity, pregnancy, and pancreatitis can all lead to the development of acquired TTP [102–109]. Medications implicated in drug-induced TTP include clopidogrel, tacrolimus, sirolimus, mitomycin, alpha interferon, gemcitabine, quinine, and cyclosporine [102, 109, 110]. The ultimate reason for ADAMTS13 inhibitor development is unknown, although the phenomenon likely arises in those patients otherwise predisposed to autoantibody development.

Presentation

The onset of acquired TTP is typically brisk due to overwhelming antibody formation. The clinical presentation varies and may include skin and mucosal bleeding; neurological symptoms that can range in severity from mild (headache) to severe (confusion, seizures, altered mental status); weakness; fever; nausea, vomiting, diarrhea, or abdominal pain; and renal insufficiency [109, 111–113]. Classically, the presentation of TTP has been described by a "pentad" of symptoms: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever [114]; however, the pentad is variably present with some features found more commonly than others [112]. Laboratory findings in TTP include anemia, thrombocytopenia (often <20,000/mm^3), and reticulocytosis on CBC, the presence of schistocytes and erythrocyte fragments on the peripheral blood smear, and elevated LDH from a combination of hemolysis and tissue damage/ischemia [99, 109, 115].

Diagnosis

The combination of thrombocytopenia, schistocytosis, and LDH is often sufficient to suggest a diagnosis of TTP [99, 112]. Measurement of low (<10%), or absent, ADAMTS13 activity is confirmatory of the disease; to further distinguish congenital vs. acquired types, plasma inhibitory and/or non-inhibitory anti-ADAMTS13 antibodies are measured [95, 113]. Both of these tests can be useful when followed over time to determine response to therapeutic interventions. The degree of ADAMTS13 reduction at presentation has been shown in some studies to be prognostic of risk of relapse [109, 116–118]. Additionally, the presence of detectable antibodies at initial diagnosis has been associated with higher mortality risk and worse clinical outcome [119–121]. ADAMTS13 antibody levels are performed at specialty hematology labs that can require up to a 7-day turnaround. Given the life-threatening and rapidly progressive nature of this disorder, the diagnosis should be made clinically and therapy instituted rapidly, rather than waiting for the results of this testing [120].

Differential Diagnosis

Microangiopathic hemolytic anemia and thrombocytopenia are present in other disorders, and therefore, the clinician must be alert to other possible diagnoses. The most common disease overlap is with atypical hemolytic uremic syndrome (aHUS) and diarrhea-associated hemolytic uremic syndrome (D + HUS). Historically, patients with neurologic symptoms were labeled as having TTP, and patients with more overt renal injury were labeled as having HUS; however, this distinction does not always hold true, leaving patients with an uncertain diagnosis and labeled with the spectrum disorder "TTP-HUS" [95]. Laboratory investigations now make it possible to make a distinction between the two disorders, which becomes crucial in treatment and overall prognosis. Other disorders on the differential include preeclampsia or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome in pregnancy; autoimmune disorders, including ITP, SLE, antiphospholipid antibody syndrome, and

scleroderma; sepsis; malignancy; disseminated intravascular coagulation (DIC), malignant hypertension, and others [109, 122, 123].

Screening for Other Disorders

A high percentage of patients with acquired TTP eventually develop other underlying autoimmune diseases, including SLE and antiphospholipid antibody syndrome [105, 122, 124]. Testing for autoimmunity, at least by a thorough screening for signs and symptoms specific to autoimmune disorders, should be performed, and development of symptoms should be monitored over time [122]. Additionally, these patients are at risk for thrombosis [107] and should avoid thrombotic risk factors, including estrogen-containing oral contraceptives and medications, long plane flights, smoking, and obesity.

Treatment

The treatment of acquired TTP is dependent on removal of the ADAMTS13 antibody, as well as the high molecular weight VWF multimers, by plasma exchange [99, 125]. Simultaneously, high-dose steroids should be initiated to inhibit antibody production for a more long-term, sustained response [99, 112, 126]. It is also important to remove/treat the offending cause (i.e., drugs, infection) as soon as possible, if known. TTP is a life-threatening disorder that can be rapidly progressive and fatal if plasma exchange is not instituted rapidly upon clinical suspicion. The mortality rate of TTP was over 90% prior to the institution of plasma exchange for treatment, but has now improved to 10–20% [96, 127]. If plasma exchange is not readily available, plasma transfusion can be initiated until exchange is available [128]. Plasma exchange requires a large-caliber catheter for removal of the patient's plasma in exchange for donor fresh frozen plasma (FFP) containing normal ADAMTS13 [99, 112]. Although the standard in exchange is FFP, an alternative is cryoprecipitate-poor plasma, which is deficient in VWF [129]. Plasma exchange should occur daily until the platelet count has normalized (>150,000/mm^3 for at least 1 day), LDH has decreased to normal or near normal, and hemoglobin has begun to rise [111, 118, 130]. More recent studies have demonstrated that ADAMTS13 levels should be >10% prior to discontinuing TPE [120]. LDH levels can also be followed as a marker for disease exacerbation [115].

Non-focal neurologic symptoms have been observed to resolve rapidly and radically upon the institution of plasma exchange, likely because of the removal of the high molecular weight VWF multimers [95, 130]. Platelet count begins to increase within the first few days and usually normalizes by day 7, whereas anemia may worsen initially, requiring continued red cell transfusion support [122, 130]. Renal damage usually requires a lengthier recovery—as long as several months—and full recovery is often uncertain [122]. Platelet count has proven an important predictor of response to plasma exchange; failure of response requires an increase in the number or volume of plasma exchange or addition of other treatment modalities [130]. Similarly, a decrease in platelet count after initial recovery should alert the clinician that control of the disease has not been achieved [130]. Measurement of ADAMTS13 at regular intervals during treatment and remission may provide information on the risk of relapse or persistence of disease [123, 131]. The duration of plasma exchange varies greatly, with most studies reporting a duration ranging from 7 to 20 days [96, 125, 132, 133].

Patients with a more severe course, those who have multiple exacerbations after cessation of plasma exchange, or those with relapses despite plasma exchange and glucocorticoid treatment may benefit from stronger immunosuppression [117]. Rituximab, an anti-CD20 monoclonal antibody, is an immunosuppressive agent now considered a standard second-line therapy for adults with antibody-mediated TTP [134, 135]. There have been recent studies evaluating the use of rituximab as a frontline agent in combination with plasma exchange in high-risk patients, as well as using rituximab as prophylaxis against relapse, with promising results [126, 134, 136, 137]. The drug is especially efficacious in patients with evidence of TTP and underlying systemic autoimmunity [138]. Rituximab depletes CD20-positive B-lymphocytes, preventing antibody formation that can last up to 6–9 months [136, 139]. The drug should be administered in four weekly doses at 375 mg/m^2 [116, 138, 140–142]. There have been concerns about the effectiveness of rituximab administration when given concurrently with plasma exchange because of drug clearance. Although there is evidence that 65% of rituximab is cleared by plasma exchange [139], studies have demonstrated improved outcomes and fewer relapses in patients receiving the combination therapy [135, 137]. Therefore, it is recommended to proceed with rituximab concurrent with plasma exchange, if medically indicated. It is, however, important that the drug be given immediately after plasma exchange to maximize the time in circulation prior to the next exchange. Additional doses of rituximab can be given if ADAMTS13 activity decreases or inhibitor levels increase or if there has not been total B-cell depletion after the standard course [142]. While rituximab is becoming standard of care for treatment of adult TTP, there is less evidence to date for the use of rituximab in pediatric TTP [113, 143].

A variety of other immunosuppressive agents have been trialed in the treatment of TTP, including vincristine, cyclophosphamide, azathioprine, cyclosporine A, IVIG, and others, and results of these case reports and retrospective reviews

are varied [95, 112, 122, 134]. Splenectomy has been performed in TTP patients in an effort to prevent additional relapse, with some success [128, 133, 144]; however, this treatment modality is not routinely recommended because of the complications and risks associated with it [128, 145].

Recurrence

Relapses occur in 20–65% of TTP patients [116, 118, 127, 146–148]. Relapse rates are high in patients presenting with severe ADAMTS13 deficiency (<10%) and can be common in patients with an underlying autoimmune disorder [116–118, 122]. Relapses are most common in the year following the TTP episode [116]. Resumption of plasma exchange is the first treatment choice for relapse, and often rituximab is initiated, if not previously administered. If remission cannot be achieved, other immunosuppressive agents may be trialed [128].

Congenital TTP

Congenital deficiency of ADAMTS13, also known as Upshaw-Schulman syndrome, is less common than acquired TTP and results in a relapsing/remitting TTP syndrome [149]. Approximately 75% of children have their first TTP episode in the neonatal period, and 25% present between 2 months and 4 years of age [113]. Patients with more mild mutations may present in adulthood, often during pregnancy [126, 150]. Neonates present with icterus, hyperbilirubinemia, severe hemolytic anemia that often leads to hemoglobinuria and acute renal insufficiency, and severe thrombocytopenia (<20,000/mm^3) [113]. Older children and adults often present after a triggering event, such as infection, stress, or hormonal changes, with thrombocytopenia and hemolytic anemia [113]. The disorder is inherited in an autosomal recessive pattern, leading to compound heterozygous or homozygous mutations of the ADAMTS13 gene [151, 152]. ADAMTS13 gene sequencing should be obtained (performed only by specialty laboratories) in patients without detectable ADAMTS13 antibodies to confirm the diagnosis of congenital TTP [113, 123, 153].

The approach to treatment of congenital ADAMTS13 deficiency is replacement of the ADAMTS13 protein, typically through transfusion of FFP [99]. This may be done periodically at the time of TTP exacerbation, but after several exacerbations, a scheduled regular transfusion of FFP is typically prescribed to prevent potentially life-threatening complications, usually at 2–3-week intervals [113, 154]. The schedule of transfusion should be based on the individual patient presentation, but increasing the interval between transfusions beyond 4 weeks can increase the risk of relapse [113]. Side effects of FFP, as well as donor exposure, cannot be taken lightly. Importantly, treatment of neonates with congenital TTP often requires plasma exchange, rather than FFP transfusion alone, secondary to the accompanying severe hyperbilirubinemia [113]. An emerging therapy for congenital TTP is a recombinant ADAMTS13 replacement product [145, 155]. Clinical trials with this agent are underway, showing initial safety and efficacy [156]. Therefore, recombinant ADAMTS13 may be a viable therapeutic option in the near future, eliminating the disadvantages of FFP transfusion [153].

Platelet Refractoriness

Platelet transfusions are required for a variety of causes of thrombocytopenia. In most cases, transfusion of platelets is a lifesaving intervention. Approximately 20% of hematology and oncology patients, however, do not achieve the expected response to platelet transfusions and are considered platelet refractory [157]. Platelet refractoriness is associated with an increased risk of morbidity and mortality and is related to significant bleeding events [158]. The definition of "optimal response" to platelet transfusion historically has been defined as an increase in platelet count of at least 5000–10,000/mm^3 1 h after transfusion [159]. More accurately, one can measure the 1-h corrected count increment (CCI), an objective measure of whether a patient is refractory to platelet transfusion [160, 161]. The formula requires the posttransfusion platelet increment, the body surface area of the patient, and the number of platelets transfused: CCI = (platelet increment/μL × BSA in m^2)/number of platelets transfused × 10^{11}. An acceptable CCI value is considered >5000 [162].

Pathophysiology

There are immune and non-immune causes for platelet refractoriness. Non-immune causes are far more common than immune causes and are secondary to acute events that lead to platelet consumption. Non-immune causes of platelet refractoriness include splenomegaly, veno-occlusive disease, DIC, febrile illnesses, sepsis, graft-vs.-host disease, bleeding, and medications, among others [157, 161, 163–166]. A percentage of frequently transfused patients become refractory due to immune destruction of transfused platelets. Immune platelet refractoriness is caused by alloimmunization to human leukocyte antigens (HLA) or, less commonly, human platelet antigens (HPA), after prior exposure (i.e., prior transfusions, maternal-fetal incompatibility during pregnancy, transplantation) [161, 167–169].

Diagnosis

A patient is confirmed to have platelet refractoriness if the 1-h posttransfusion CCI value is <5000 on at least two occasions [162]. To distinguish the type of refractoriness, it is helpful to additionally measure the platelet count at 18–24 h after transfusion to gain information about platelet survival. In non-immune cases of platelet refractoriness, patients typically have a normal 1-h CCI, but platelet survival is decreased (platelet count will return to pre-transfusion levels within 24 h), whereas in immune cases of platelet refractoriness, patients typically have a low 1-h CCI [160, 165, 170–172]. If further testing is desired in patients with suspected alloimmunization, testing for the presence of HLA antibodies should occur first, followed by HPA antibody testing if negative, as HLA antibody development is more common [167]. Some consider a less-than-expected 1-h CCI level diagnostic for alloimmunization and proceed to treatment without further testing.

Management and Prevention

For patients with non-immune platelet refractoriness, the most important intervention is treating the underlying illness or suspected cause [161]. Patients with alloimmunization require HLA-compatible platelet transfusions to raise platelet count increments [173]. This can be achieved by transfusing HLA-antigen-negative platelets (corresponding to specificity of anti-HLA antibodies), HLA-matched platelets, or crossmatch-compatible platelets [166]. Most commonly, patients are transfused with HLA-antigen-negative platelets, as this method does not require obtaining the HLA typing of the patient and provides a larger donor pool [174]. The donor pool for HLA-matched platelets is smaller because they are obtained from donors that are a match for the HLA-A or HLA-B loci [161]. Importantly, these platelet units should be irradiated prior to transfusion to decrease the risk of transfusion-associated graft-vs.-host disease [175]. Crossmatching involves identifying compatible platelet units by crossmatching with the patient's plasma. This method is quick (a few hours) and allows for a larger donor pool than HLA matching [161, 176]. After the introduction of leukoreduction procedures (removal of white blood cells from platelet products by filtration), a near 50% reduction in HLA alloimmunization was observed [177]. Therefore, platelets should be leukoreduced prior to transfusion in frequently transfused patients (i.e., hematology/oncology, parous patients) to prevent alloimmunization. However, it is important to note that leukoreduction does not reduce the incidence of platelet refractoriness if the patient develops HPA antibodies [167, 178, 179].

Platelet Function Disorders

Platelet function disorders are a group of hereditary or acquired disorders characterized by defective platelet function. The platelet count in patients with these disorders may be normal, reduced, or even elevated. Hereditary platelet function disorders are uncommon and often difficult to diagnosis [180]. There are many different types of hereditary platelet defects, which can be categorized broadly based on platelet size. Acquired platelet function disorders are more common than hereditary platelet function disorders, although still rare, and are caused by underlying diseases, infection, drugs, autoimmunity, or trauma [159, 181]. Here we will focus on hereditary platelet function defects.

Platelet Function Disorders with Giant Platelets

Giant platelet disorders include Bernard-Soulier syndrome (BSS), the MYH9 group of platelet disorders, gray platelet syndrome (GPS), and platelet-type von Willebrand disease (VWD). BSS is an autosomal recessive disorder characterized by thrombocytopenia, large platelets, and prolonged bleeding time [182]. The syndrome is secondary to a deficiency of the platelet glycoprotein complex GP1b/IX/V [183, 184], which normally functions to facilitate platelet adhesion to VWF on damaged endothelium [185]. The disorder can be diagnosed with an abnormal platelet function analyzer-100 (PFA-100) assay, by flow cytometry, or by platelet aggregation studies showing normal aggregation responses with ADP, arachidonic acid, collagen, and epinephrine, but absence of aggregation to ristocetin [186]. Presentation varies among patients and can include spontaneous epistaxis, mucocutaneous bleeding, ecchymosis, and gastrointestinal bleeding, all of which can be more severe than the degree of thrombocytopenia; severe bleeding can occur with trauma [180, 185].

The MYH9-related disorder is a syndrome caused by a mutation within the *MYH9* gene that is inherited in an autosomal dominant fashion [187, 188]. The syndrome includes the previously classified disorders May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome [180, 189]. It is characterized by macrothrombocytopenia and mucocutaneous bleeding in early life, with the development of hearing loss, glomerulonephritis, and cataracts with aging [190, 191]. Life-threatening bleeding is rare, but can occur with trauma [180]. Diagnosis should be strongly considered in a patient with macrothrombocytopenia in addition to glomerulonephritis, sensorineural hearing loss, and cataracts [180]. Platelet count is variable from patient to patient, but peripheral smear showing large or

giant platelets and/or neutrophils with Döhle-body inclusions is highly suggestive of MYH9 [190]. Definitive diagnosis is achieved with demonstration of a mutation in the *MYH9* gene.

GPS is a very rare hereditary platelet function disorder secondary to decreased alpha granule content within the platelet [192]. There are case reports of autosomal dominant and autosomal recessive inheritance, but it can also be sporadic [180, 190]. The syndrome is characterized by normal or low platelet count, large/giant platelets, and mucocutaneous bleeding of variable severity [190]. Platelets appear agranular and thus gray on peripheral smear, and platelet aggregation studies may be abnormal to one or more agonists [180].

Platelet-type VWD is an autosomal dominant macrothrombocytopenia secondary to gain-of-function mutations that increase the affinity of GP1b/IX/V for VWF, resulting in shortened platelet survival [190, 193]. Patients present with mucocutaneous bleeding that is usually mild-to-moderate in severity [190]. Diagnosis is confirmed with increased ristocetin-induced platelet aggregation, in addition to a mild reduction of plasma VWF levels and absence of large molecular weight VWF multimers [190]. Platelet-type VWD is similar to type 2B VWD, but is different in that the genetic defect affects the platelet rather than VWF [194].

Treatments of the giant platelet function disorders include antifibrinolytic agents for mild-to-moderate bleeding and platelet transfusions and/or recombinant activated factor VII (rFVIIa) for severe bleeding [180]. Desmopressin may also be used for mild-to-moderate bleeding in patients with BSS, GPS, and MYH9-related disorder. Although desmopressin has no direct effect on platelets, the ultra-large VWF released by desmopressin-stimulated endothelial cells may facilitate platelet adhesion and decrease the bleeding times in these patients [186]. Desmopressin should not be used in platelet-type VWD as it can worsen thrombocytopenia; in these patients, treatment of severe bleeding includes infusion of VWF-factor VIII concentrates and platelets [195].

Platelet Function Disorders with Small Platelets

Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT) are X-linked platelet function disorders characterized by thrombocytopenia and small platelets [190]. XLT presents with isolated thrombocytopenia, whereas WAS presents with a severe immunodeficiency leading to recurrent infections, allergies, eczema, autoimmunity, and lymphoid malignancy [190, 196]. The disorders are caused by mutations in the gene encoding the Wiskott-Aldrich syndrome protein (WASp) [197–199].

The incidence of WAS is 1/250,000 and usually occurs in patients of European decent [190]. Patients present at birth with bleeding and frequent illness related to the immune dysregulation, which worsens with age [199]. Bleeding may range from mild mucocutaneous bleeding to severe intracranial or gastrointestinal hemorrhage [190]. Immune dysfunction may present with frequent infections or other signs of dysregulation, including eczema, concurrent autoimmune disorders, IBD, vasculitis, arthritis, or lymphoproliferative disorders [190, 199]. Laboratory findings include thrombocytopenia and small platelet volume on CBC, prolonged bleeding time, a decrease in the number and function of T-lymphocytes, low IgM levels, and high IgA and IgE levels [190, 197]. Treatment for WAS includes prophylactic antibiotics against *Pneumocystis jirovecii* pneumonia in infants and children and platelet transfusions to treat severe bleeding [199]. IVIG is indicated for patients with antibody deficiency [199]. Splenectomy has been successful at correcting thrombocytopenia, but the risks of severe infection often outweigh the benefits [199]. The only curative treatment is hematopoietic stem cell transplantation [200, 201].

Platelet Function Disorders with Normal Platelet Size

Disorders of platelet function in which platelets are of normal size include Glanzmann thrombasthenia (GT), congenital amegakaryocytic thrombocytopenia (CAMT), and thrombocytopenia with absent radii (TAR).

GT is an autosomal recessive disorder resulting from homozygous or compound heterozygous mutations of either the *ITGA2B* or *ITGB3* genes [202], leading to a defective platelet integrin $\alpha_{IIb}\beta_3$ receptor (also known as the glycoprotein complex GPIIb/IIIa) [203–205]. This integrin is present in high concentrations on platelets and, when functionally intact, allows strong bonds to form between the platelet and fibrinogen and/or VWF [180, 186]. Absence results in inefficient platelet aggregation [180]. Patients with severe $\alpha_{IIb}\beta_3$ deficiency (<5% expression) are classified as having type I GT, patients with moderate deficiency (10–20% expression of $\alpha_{IIb}\beta_3$) are classified as having type II GT, and patients with a dysfunction $\alpha_{IIb}\beta_3$ receptor are classified as having the "variant" form of GT [186]. Although the degree of bleeding is variable among patients [202, 206], it has been observed that the greater the deficiency of the $\alpha_{IIb}\beta_3$ receptor, the more severe the bleeding symptomatology [204]. Patients typically present with mucocutaneous bleeding beginning in childhood, often before 5 years of age [186, 204]. The most common clinical features are purpura, epistaxis, gingival bleeding, and menorrhagia [204]. GT can be diagnosed with prolonged closure time of the PFA-100; with the absence of aggregation in response to collagen, ADP, epinephrine, or

arachidonic acid in platelet aggregation assays; and/or by absence/decreased levels of CD41 and CD61 and normal levels of CD42 by flow cytometry [180, 186, 193, 207]. Treatment of GT involves antifibrinolytics (tranexamic acid) for mild-to-moderate mucocutaneous bleeding and platelet transfusion and/or rFVIIa for severe bleeding [180, 208]. It is important to note that GT patients may develop antibodies to platelet membrane surface αIIbβ3 antigens on transfused platelets, resulting in inhibition of platelet function or rapid clearance of transfused platelets [208]. In these cases, platelet transfusion should be avoided and rVIIa treatment administered for severe bleeding. Menorrhagia can be treated with oral tranexamic acid and/or hormone therapy [180]. In cases of a severe bleeding phenotype, hematopoietic stem cell transplantation can be considered [208, 209].

CAMT, characterized by severe thrombocytopenia, is an autosomal recessive disorder affecting the *MPL* gene [210]. Mutations in this gene result in altered expression or function of the thrombopoietin receptor [210]. Patients typically present in the neonatal period with bleeding symptoms secondary to severe thrombocytopenia and often progress to pancytopenia and/or severe aplastic anemia within 5–10 years [180, 211]. Thrombocytopenia diagnosed in infancy, along with reduced or absent megakaryocytes in the bone marrow, is suggestive of the disease; definitive diagnosis is obtained with confirmation of mutations in the *MPL* gene [180]. Bleeding symptoms are treated with platelet transfusions, but progression of aplasia requires hematopoietic stem cell transplantation [180, 212–214].

TAR is an autosomal recessive disorder with an uncertain genetic basis that remains the subject of active investigation [195, 215]. Patients present in the neonatal period with severe thrombocytopenia and bilateral absent radii; other clinical features may be present, including cow's milk intolerance, skeletal defects, renal abnormalities, cardiac anomalies, and facial capillary hemangiomas [215, 216]. Unlike in CAMT, the severe thrombocytopenia generally improves throughout childhood [180, 190]. Diagnosis is suggested by congenital thrombocytopenia and the associated clinical abnormalities [180]. Bleeding in infancy may be severe and require platelet transfusions, but with aging, treatment is rarely needed [180].

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Bleeding in Acute and Chronic Liver Disease

14

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Introduction

The spectrum of liver disease is wide, ranging from slow, indolent disease to rapid progression. Acute and chronic liver disease causes significant morbidity and mortality in both adult and pediatric populations. The liver plays a central role in regulating hemostasis through protein production. Liver disease is associated with variable alterations of primary and secondary hemostasis due to qualitative and quantitative platelet defects, decreased synthetic ability, delayed clearance of activated factors, hyperfibrinolysis, and accelerated intravascular coagulation. Most of both procoagulants and anticoagulants are synthesized in the liver hepatocytes with only factor VIII (synthesized in endothelial cells in the liver) and (a) subunit of factor XIII (synthesized in the bone marrow). The production of factor V and factor XI is independent of vitamin K unlike the other procoagulant factors including factor VII which rely on vitamin K for production. The loss of both procoagulants and anticoagulants may create a more balanced hemostasis than traditional laboratory measures such as prothrombin time (PT)/international normalized ratio (INR) would predict [1] (Fig. 14.1). Though rare, bleeding events can be severe. These measures can be further confounded by concurrent, consumptive disease processes such as sepsis or disseminated intravascular coagulation (DIC). Different pathophysiological mechanisms form an underlying basis for bleeding in both acute and chronic liver disease. In acute liver failure (ALF), platelet counts may be normal, but more severe reductions in circulating procoagulant and anticoagulant factors can occur. In ALF, thrombocytopenia can occur with suppression from viral infection, destruction, or sequestration. Portal hypertension in chronic liver disease (CLD) can cause venous congestion leading to creation of varices. When present, varices greatly increase risk of brisk, upper gastrointestinal bleeds as they are often friable and highly vascular. In CLD, thrombocytopenia is more common, combined with coagulopathy due to decreased factor production. Decreased platelets in CLD can occur from sequestration in spleen with portal hypertension, and decreased production of thrombopoietin also likely contributes [2]. Approximately one-third of patients with CLD may also have ongoing hyperfibrinolysis that may be proportional to decrease in liver function though some have questioned the degree of fibrinolysis present in CLD [3]. Etiology of hyperfibrinolysis may be attributable to elevated tissue plasminogen activator (tPA) and decreased levels of α2 antiplasmin (α2AP), factor XIII, and thrombin-activatable fibrinolysis inhibitor (TAFI), which is synthesized by the liver.

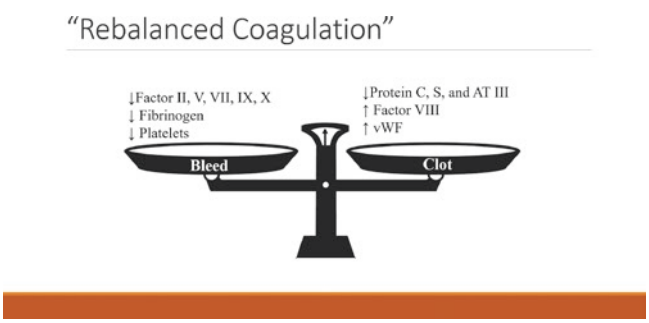

Fig. 14.1 Rebalanced coagulation of liver failure

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Acute Liver Failure (ALF)

ALF is defined by synthetic dysfunction causing coagulopathy, usually an INR greater than 1.5 with altered mental status in a patient without pre-existing liver disease or INR greater than 2 regardless of encephalopathy [4]. Incidence is still rare in developed world of about 10 cases per 1,000,000 with only approximately 2000 cases of fulminant hepatic failure in the United States per year [5]. Acute-on-chronic liver failure is decompensation with underlying liver disease with 50% of cases having unclear acute trigger [6]. In adults, drug-related hepatic failure is the most common etiology of ALF with the majority secondary to acetaminophen. Other common etiologies in the United States include hepatitis A, hepatitis B, ischemia, and autoimmune hepatitis (Fig. 14.2). In children, indeterminate, acetaminophen, autoimmune, viral, and metabolic are the most common etiologies [7]. Patients in ALF can present with severe derangement of laboratory coagulation measures, though the incidence of bleeding is relatively rare. According to the US Acute Liver Failure Study Group, despite an INR average of 2.7, bleeding was only noted in 11% of patients with 84% of those patients having upper gastrointestinal bleed as source [8]. In this group, most events were minor mucosal bleeds that did not require blood transfusion. Discordance between routine laboratory measures and prediction of bleeding risk has pointed toward a more complex balance of coagulation for those with liver disease.

Other than factor VIII which is made in the endothelial cells, and factor XIII which is made in bone marrow, the liver hepatocytes are responsible for production of the procoagulant factors as well as anticoagulants such as protein C and protein S. Decreased production as well as consumption can lead to significant reduction in the factors present. Factor VII and factor V show considerable decline due to short half-lives, which are about 5 hours and 15 hours, respectively [9]. Half-lives must be considered when assessing factor levels to gauge synthetic function especially if blood products have been recently given. At presentation, ALF can often be difficult to distinguish between other causes of an elevated INR, such as DIC or vitamin K deficiency. Low factor VIII may point to a consumptive process such as DIC instead of synthetic dysfunction as seen in liver disease. Factor V, specifically, is not vitamin K dependent, so low values of both factor VII and factor V would be more consistent with liver synthetic dysfunction as opposed to deficiency of vitamin K (Table 14.1). Low factor V levels have been shown to correlate with severity of outcome and eventual need for transplantation in acute liver failure [10]. Fibrinogen levels can vary as well with increases due to acute phase reactant as well as decreased liver production and hyperfibrinolysis that can occur with liver failure. Decrease in fibrinogen and declining factor VIII may be consistent with consumption though process such as DIC. Elevated fibrin split products and D-dimer may give some indication of DIC and/or hyperfibrinolysis though cannot be used in insolation to make a diagnosis as levels can be elevated during liver failure as well. Poor clearance of plasmin activators by liver along with decreased synthesis of fibrinolytic inhibitors such as plasminogen activator inhibitor type 1 (PAI-1) and α2AP may create a cycle on ongoing fibrinolysis [11].

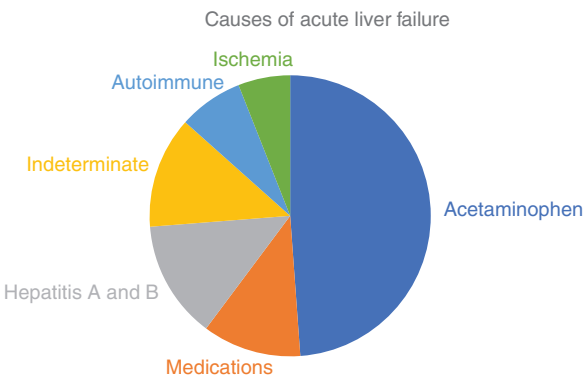

Fig. 14.2 Etiologies of acute liver failure

Table 14.1 Lab test results in liver failure, disseminated intravascular coagulation, and vitamin K deficiency

Lab tests	Liver failure	DIC	Vitamin K deficiency
INR/PT	Prolonged	Prolonged	Prolonged
aPTT	Variable	Prolonged	Variable
Platelets	Decreased (late effect)	Decreased	Normal
Fibrinogen	Decreased	Decreased	Decreased (late effect)
Factor levels	↓II, V, VII, IX, X, XI	↓ All factors including VIII	↓II, VII, IX, X
D-dimer	Variable	Increased	Normal

Mild thrombocytopenia may exist in ALF without a clear etiology; though thrombopoietin is synthesized in liver, levels seem to be normal during ALF [12]. There is evidence that a consumptive process may contribute as well as viral or immune dysregulation [9].Though platelets are present, there is a concern about whether function of these platelets may be altered, especially in setting of other metabolites and toxins that increase during ALF. (Tables 14.2 and 14.3)

Spontaneous unprovoked hemorrhage is mostly mucosal in nature presenting as hematemesis, hemoptysis, epistaxis, and hematuria, though any evidence of bleeding should prompt close monitoring or intervention. Rarely, spontaneous intracranial hemorrhages have been reported. Invasive procedures such as venous and arterial catheter placement or intracranial pressure (ICP) monitors may provoke severe bleeding

Table 14.2 *PCC* prothrombin complex concentrate, *rFVIIa* recombinant activated factor VII, *FIX* factor IX, *FXIII* factor XIII, *FFP* fresh frozen plasma

Factor	Name	Plasma half-life in hours	Plasma levels mg/L	Replacement product
I	Fibrinogen	90	3000	Cryoprecipitate, fibrinogen concentrate
II	Prothrombin	65	100	FFP, PCC
V	Proaccelerin	15	10	FFP
VII	Proconvertin	5	0.5	FFP, PCC, rFVIIa
VIII	Antihemophilic factor	10	0.1	FFP, cryoprecipitate, FVIII
IX	Christmas factor	25	5	FFP, FIX, PCC
X	Stuart-power factor	40	10	FFP, PCC
XI	Plasma thromboplastin antecedent	45	5	FFP
XIII	Fibrin-stabilizing factor	200	30	FFP, cryoprecipitate, FXIII

Table 14.3 Hemostatic changes in bleeding patients with acute liver failure

Abnormal hemostasis	Pathophysiology
Hypocoagulability	Decreased synthetic ability of liver and short half-life of certain factors
	1. Factors VII and V—highest decline
	2. Factors II and X—follows
	3. Factor XIII deficiency
	Vitamin K deficiency
	Factors X, IX, VII, and II
Hyperfibrinolysis	Plasminogen activation
	1. Decreased clearance of circulating tissue plasminogen activator
	2. Decreased production of fibrinolytic inhibitors such as PAI-1, α2AP, and TAFI
Thrombocytopenia	Decline in quantity
	1. Increased activation and consumption such as in DIC
	2. Thrombocytopathy

PAI-1 plasminogen activator inhibitor-1, *α2AP* α2 antiplasmin, *TAFI* thrombin-activatable fibrinolysis inhibitor, *DIC* disseminated intravascular coagulation

in 10% of patients undergoing such procedures [13]. A strong correlation between the location of the ICP monitor and increased risk of bleeding has been reported [14]. Certain other aggravating factors have to be kept in mind while managing bleeding in patients with ALF. Multiple antibiotics in patients with sepsis, dysbiosis, poor oral intake, and cholestasis could affect vitamin K absorption, and therefore severe vitamin K deficiency may be present [15]. Sepsis, DIC, and multiple prior transfusions of fresh frozen plasma (FFP) could contribute to the citrate toxicity and hypocalcemia [16]. Acidosis and hypothermia may result in disabling the activity of the transfused coagulation factors [17]. Prompt attention to underlying critical issues plays a pivotal role in enhancing the treatment measures taken to stop the hemorrhage.

Although published guidelines to effectively manage spontaneous bleeding in ALF do not exist, anecdotal evidence and some research studies form a basis for algorithms to help physicians systematically to assist in treatment decisions and personalized medical care. Based on the pathophysiology of ALF, several hemostatic factors are deficient. Inadequate fibrinogen substrate, insufficient amounts of thrombin generators including platelets and coagulation factors, and finally clot stabilizers are the main actors of bleeding diathesis in ALF. Fibrinogen levels of <150 mg/dL should be corrected by either cryoprecipitate or FFP. Cryoprecipitate is preferred over FFP due to its small volume and higher concentration of fibrinogen. Volume should be given carefully with risk of cerebral edema in patients with ALF though prevalence of intracranial hypertension has been decreasing with advances in care [18]. Alternatively, fibrinogen concentrates can be rapidly administered without the need for thawing and ABO typing. Similarly, prothrombin complex concentrates (PCCs) contain a higher concentration of factors and could replace FFP to provide vitamin K-dependent hemostatic factors that help in thrombin generation and seem to more quickly correct INR. PCCs have been shown to more quickly correct INR in cases of overdose of vitamin K antagonists such as warfarin, though further testing on relevance in liver disease. The decreased volume of PCC may also be an advantage especially if volume overload is a concern. Both of these agents provide necessary hemostasis without volume expansion but should be used with extreme caution due to potential thrombotic complications [19]. Simultaneous platelet transfusions, to maintain platelet count of 50,000–60,000/mm^3, are recommended to stop the bleeding episode and prevent another. However, if mucosal bleeding or oozing from the puncture site persists despite hemotherapy and administration of concentrates, antifibrinolytics such as aminocaproic acid can be used if there is laboratory evidence of hyperfibrinolysis [20]. The dosage and indications are found in Table 14.4.

Targets for correction still need to be further clarified in relation to clinical outcomes. Viscoelastic testing such as TEG™ and ROTEM™ may be useful to better model the whole blood clotting process instead of just testing presence of clotting factors [21]. Viscoelastic testing not only models the time to start a clot which parallels PT/INR, and activated partial thromboplastin time (aPTT), but also may model clot size and integrity [22].While viscoelastic may detect some hyperfibrinolysis, they may not be able to pick up more subtle cases [23]. One advantage of viscoelastic testing is being able to measure function of fibrinogen or platelets instead of

Table 14.4 Hemostatic agents of choice in ALF

Product	Commercial name	Dose	Indication
Phytonadione	Vitamin K1	10 mg single dose IM or SC	Vitamin K deficiency
Cryoprecipitate	None	Adults: 1 unit/10 kg	Fibrinogen level <150 mg/dL
		Children: 5 mL/kg	
FFP	None	10–15 mL/kg	Unprovoked bleeding and before invasive procedures
Platelets	None	1 unit/10 kg	<20,000/mm^3 in non-bleeders, <50,000/mm^3 in bleeders
Fibrinogen concentrate	RiaSTAP™	70 mg/kg[a]	Coagulopathy in volume overloaded patients, clinically significant bleeding
PCC	Kcentra™-4 factors	50 units/kg BW when INR >6	Coagulopathy in volume overloaded patients, acute massive bleeding
	Bebulin™, Profilnine™-3 factors	25–35 IU/kg	
FXIII	Fibrogammin P	40 IU/kg	Unstable clot
Aminocaproic acid	Amicar	4–5 g IV/PO during first hour, continuous IV infusion at 1 g/h or 30 mg/kg/h until bleeding stops	Hyperfibrinolysis and oozing from catheter insertion sites
rFVIIa	NovoSeven	20–40 μg/kg	Severe coagulopathy with significant intractable bleeding

[a]Indicates when fibrinogen levels are unknown
Four factors include factors X, IX, II, and VII and proteins C and S
Three factors include factors X, IX, and II and very small quantity of factor VII

just quantification of blood levels. These functional assays are becoming more frequently used both in resuscitation of patients in liver failure but also in guidance for product replacement during prior to invasive procedures. ALF can be a rapidly progressive disease that requires very careful surveillance. The rebalanced coagulation pathway of ALF is fragile, and bleeding can cause significant morbidity and mortality.

Chronic Liver Disease (CLD)

In 2016, cirrhosis and CLD were the 12th most common cause of death in the United States accounting for 29,432 deaths or 1.4% [24]. Incidence of chronic liver disease is estimated to be 360 cases per 100,000 per year with more common etiologies being chronic hepatitis B, hepatitis C, and alcoholic and non-alcoholic liver disease in adults. In the pediatric population, sources of CLD are broader and can stem from diseases such as biliary atresia, Alagille syndrome, metabolic disease, and vascular abnormalities. In most cases, liver-related mortality results from complications of CLD including advanced cirrhosis [25]. CLD can have a progressive worsening of changes to hemostatic system with more severe disease. As opposed to ALF, in CLD deficiency in clotting factors is likely due to synthetic defects, as opposed to consumptive events. Compared to healthy individuals, patients with CLD lack the reserve of procoagulants and anticoagulants, and when confronted with a consumptive event, such as in acute bleeding, they can have severe outcomes [3]. In addition to bleeding events, patients with CLD can have episodes of pathologic clot formation including portal vein thrombosis (PVT).

Platelets play a dual role in the primary hemostasis with formation of plug as well as providing the substrate for thrombin generation [3]. The prevalence of thrombocytopenia has been reported in up to 76% of patients with CLD [2]. In end-stage liver disease, reduced thrombopoietin is thought to contribute to thrombocytopenia, predisposing to bleeding tendency. Splenic sequestration also likely contributes especially in settings of portal hypertension. This chronic change is countered by increase in von Willebrand factor (VWF) and low ADAMTS13. Elevated VWF may allow normal platelet function in the setting of relative thrombocytopenia [26].

In CLD, the secondary hemostasis stage also exhibits a rebalanced state: low hepatic procoagulant factors I, II, V, VII, IX, X, and XI are balanced by reduced hepatic anticoagulant factors such as protein C, protein S, and antithrombin (AT). VWF and factor VIII are often increased as they are produced in the endothelial cells not in the hepatocytes. The serine proteases of the fibrinolytic system including plasminogen and α2AP are of hepatic origin and therefore are also reduced in cirrhosis. In severe liver disease, PAI-1 level and α2AP are decreased and thus causes bleeding due increased tPA.

Patients with cirrhosis also have an increased risk of bleeding due to other coexisting factors such as portal hypertension, hypersplenism-induced thrombocytopenia and thrombocytopathy, impaired endothelial function in hepatorenal syndrome, and presence of endogenous heparinoids. Although there is increased risk of bleeding, the prevalence of spontaneous bleeding due to coagulopathy is not high.

Prophylactic correction is not recommended during minor procedures such as paracentesis and central venous catheter insertion. However, liver biopsy and placement of ICP transducers are associated with bleeding in these patients with INR >1.7 and therefore necessitate pre-procedural administration of hemostatic agents to maintain fibrinogen levels to about 150 mg/dL and platelet count of 100,000/mm^3 [27]. In general, critically ill patients with CLD have concomitant sepsis with acidosis, uremia, hypocalcemia, and hypothermia and have an excess risk of bleeding. Therefore, it is important to address these issues in the context of reducing the risk and prevention of bleeding during elective procedures. Endoscopic intervention can be performed as surveillance as well as emergently to correct upper gastrointestinal bleeding, which most commonly occurs from variceal sources. Every attempt should be made at medical stabilization to give endoscopic treatment highest likelihood of success.

Thrombopoietin (TPO) agonists provide another tool that potentially decreases bleeding risk prior to invasive procedures in patients with CLD. Megakaryocyte growth and development factor (MGDF) or c-MpL ligand is a hormone which is synthesized in the liver and regulates the process of megakaryocytopoiesis [28]. Studies are ongoing to both show that these agonists increase platelet counts safely and reduce risk of bleeding in preparation for invasive procedures [29]. Initial studies have not shown that these medications raise the risk of pathologic clotting events such as venous thromboembolism (VTE) though further studies will be needed [30].

Unprovoked spontaneous variceal bleeding is often a severe complication secondary to portal hypertension. Bleeding management becomes very difficult when there is underlying coagulopathy along with thrombocytopenia and platelet function defects. Hence, it is very important to understand the pathophysiology of coagulation in chronic liver disease when one attempts to correct it. American College of Gastroenterology recommends acute variceal bleeding in cirrhotic patients should be primarily managed with endoscopic variceal band ligation and/or other surgical procedures combined with the use of pharmacotherapeutic agents such as vasopressin and somatostatin or its analogues [31]. In the pediatric population, banding may not be possible due to size, and sclerotherapy may be required to control acute bleeding and treat varices to prevent later bleeding. In addition, resuscitation measures should include blood products intending to restore hemodynamic stability and hemoglobin of 8 g/dL and a platelet count of >50,000/mm^3 [32, 33]. Volume should be given carefully because fluid overload can result in comparatively higher portal venous pressure and increase risk of rebleeding episodes. Correction of hemostatic abnormalities should be attempted in these patients, if they present with severe coagulopathy [34].

Several laboratory tests help physicians to assess hemostasis and are listed with their advantages and disadvantages in Table 14.5. INR is an inexpensive laboratory coagulation test that provides an overview of the severity of liver dysfunction and consequent hemostatic factor synthesis. Similarly, enumeration of platelets can help decide the platelet dose to be transfused for optimal hemostasis. Fibrinogen

Table 14.5 Lab tests to assess hemostasis

Laboratory test	What does it measure	Advantages	Disadvantages
PT, INR	Extrinsic pathway	Quick and cheap, available in all labs, indicator of severity of liver disease	Does not predict bleeding risk
aPTT	Intrinsic pathway	Quick and cheap, available in all labs	Does not correlate well with severity of liver disease
Platelet count	Platelets	Quick and cheap, available in all labs	Cannot assess function
Platelet function assays	Platelet function in primary hemostasis	Screening test, easy to perform	Utility in liver disease not known
VWF antigen and factor VIII assay	Primary hemostasis	Indicator of severity of liver disease	Complex test, not available in all labs
Fibrinogen	Fibrinolysis	Decreasing trend suggests hyperfibrinolysis or fibrin formation	Acts as an acute phase reactant and does not truly indicate severity of liver disease
D-dimer	Clot formation and lysis	Along with decreasing fibrinogen levels may suggest DIC	Utility in liver disease not known
Coagulation factor assays	Pro- and anticoagulant balance	Indicator of severity of liver disease	Does not predict bleeding or thrombotic risk
Viscoelastometry (TEG™, ROTEM™)	Global hemostasis	Can assess the interplay of platelet, fibrinogen, and coagulation factors in clot formation and lysis	Utility in liver disease being evaluated.
Euglobulin lysis time	Fibrinolysis	Can be used as a prognostic parameter to assess improvement during antifibrinolytic therapy	Not available in all labs

PT prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *VWF* von Willebrand factor

levels may suggest either consumption or an underlying hyperfibrinolysis during a variceal bleed. Close consideration of timing of administration of blood products also must be evaluated; elevated factor levels or decreased INR may only reflect given products not improving endogenous synthesis. Finally, viscoelastometric tests (TEG™ or ROTEM™) and thrombin generation assays are efficient tools for assessing global hemostasis and to guide hemotherapy. Viscoelastometric testing may also be helpful in liver disease as it can identify dysfunctional platelets as well as decreased number of platelets which is more easily identified. Studies have consistently shown that using TEG™ or ROTEM™ decreases total blood product use in patients with bleeding without increasing mortality especially during liver transplant though there remains a paucity of studies on use of these tests in acute liver failure [35]. As these functional clotting tests are further studied, they may both help predict bleeding and guide specific product transfusion more effectively than traditional clotting tests such as INR, especially in the setting of the rebalanced coagulation of liver disease.

Parenteral administration of vitamin K can alleviate deficiency generally seen in decompensated liver cirrhosis secondary to bile salt deficiency and broad-spectrum antibiotic usage. Intravenous (IV) vitamin K should be given in any new presentation of elevated INR to assess if reverses with vitamin K therapy. Of note, IV vitamin K does carry a greater risk of anaphylaxis than intramuscular. High-dose proton-pump inhibitor is generally used in an upper gastrointestinal bleed. Octreotide is often used for its vasoconstrictive properties in both variceal and non-variceal gastrointestinal bleeding. When octreotide is required, a bolus and maintenance continuous drip can be used. There is consensus among physicians and authors about correcting deficiencies to maintain fibrinogen levels at 100–150 mg/dL, platelet transfusion for a count of >50,000/mm^3, and aminocaproic acid or tranexamic acid to treat fibrinolysis [36]. Although more study is needed on the use of fibrinogen and PCC, it is still preferable over FFP due to smaller volumes. PCC has been shown to correct INR more quickly than FFP though whether that is clinically important is still unclear. Desmopressin has not shown any clinical benefit in controlling bleeding. rFVIIa has not been beneficial in variceal bleeding. It can be used with extreme caution and as a last measure to control intractable bleeding despite other treatment modalities due to its thrombogenicity.

Invasive endoscopic and vascular interventions may be required to control bleeding in patients with liver disease. Endoscopy can be used both in acute bleeding but ideally also to correct varices prior to bleeding event. Banding varices in ideal circumstances will prevent later bleeding episodes by surveilling with endoscopy in high risk patients. Treatment with injected sclerosing agent, electrocautery, or other topical therapies can be considered. The transjugular intrahepatic portosystemic shunt (TIPS) procedure, usually performed by interventional radiologists, decompresses the portal system to alleviate varices. Collateral veins that may be contributing to varices also can be sclerosed to reduce bleeding risk. The meso-rex bypass shunt can also be used to reduce portal hypertension though is more invasive than TIPS procedure.

In contrast to traditional thinking, patients with CLD may need prophylaxis to prevent pathologic clotting event such as VTE. While using a preventative medication in some studies showed a decreased in VTE risk in patients with CLD, others have noted that this may increase the bleeding risk of these patients [37, 38]. These studies are retrospective, and prospective studies are required to better stratify risk of bleeding and clot formation in patients with chronic liver disease.

Summary

The liver produces and regulates many steps during the formation and dissolution of a clot. Though sharing some synthetic dysfunction, ALF and CLD have distinct abnormalities that may affect hemostasis. DIC, sepsis, vitamin K deficiency, and other distinct processes can be concurrent with both ALF and CLD; factor levels and response to parenteral vitamin K may help elucidate the clinical picture. Even with severe derangements in laboratory measures such as INR and PT, the occurrence of significant bleeding in patients with liver failure is uncommon. Correction of INR with blood products or PCCs is not always recommended and can even predispose to thrombotic events. Products or concentrates may be required especially in setting of ongoing bleeding or plans for invasive procedures though guidance of proper parameters requires further study. Prophylactic administration of blood products to patients with high bleeding risk prior to invasive procedures such as implantation of ICP monitors can be considered. Viscoelastometric testing such as TEG™ and ROTEM™ may be useful to better model the whole blood clotting process; testing the function of fibrinogen, platelets, or factors may more accurately depict the ability to clot rather than just enumeration. The pathophysiology of each patient should be carefully considered with the large heterogeneity of liver disease; judicious use of product replacement and support is required to achieve hemostasis in acute and chronic liver disease.

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Bleeding and Hyperfibrinolysis

15

Wayne L. Chandler

Acquired Systemic Hyperfibrinolysis

Thrombolytic Therapy

Hyperfibrinolytic bleeding may occur for a variety of reasons (Table 15.1). A common acquired cause of hyperfibrinolytic bleeding is infusion of plasminogen activators to lyse a pathologic thrombosis of the coronary, cerebral or peripheral arteries, massive pulmonary embolism, and catheter-associated thrombosis. Absolute contraindications for thrombolytic therapy include prior intracranial hemorrhage (ICH), recent major surgery (head, chest, or abdomen), or a current bleeding site. The major side effect of thrombolytic therapy is bleeding, with ICH being the most serious form. ICH occurs in about 2% to 6% of patients receiving tPA for ischemic stroke, 0.6% to 2% receiving tPA for coronary thrombosis, and about 1% of patients undergoing thrombolysis for peripheral arterial thrombosis, with up to 50% of symptomatic ICH being fatal [1–3]. ICH is more common in patients older than 70 years, but they also have the greatest survival benefit from thrombolytic therapy. The risk of bleeding associated with thrombolytic therapy is directly related to the concentration of active plasminogen activator in the blood [2]. tPA levels can reach 5000 to 10,000 ng/mL during tPA infusion for myocardial thrombosis, 1000-fold higher than normal. Laboratory parameters including fibrinogen levels and D-dimer are not predictive of bleeding because the more fibrin-specific plasminogen activators like tPA show smaller decreases in fibrinogen during therapy compared to urokinase or streptokinase but are just as fast at lysing clots and thus have similar rates of bleeding [2, 4]. Patients on anticoagulants like heparin and aspirin and those with thrombocytopenia are at increased risk of bleeding during thrombolytic therapy. Standard treatment for thrombolytic bleeding should include stopping the plasminogen activator infusion and replacing fibrinogen and platelets if low. Of note, the half-life of tPA is only 2–4 minutes. This standard therapy may be inadequate in patients with worsening ICH associated with thrombolytic therapy which may require factor concentrates or antifibrinolytic therapy to stop or slow further bleeding [5].

Cardiopulmonary Bypass and Extracorporeal Life Support

Hyperfibrinolysis during cardiopulmonary bypass (CPB) is due primarily to an increase in the secretion of tPA combined with elevated levels of soluble and circuit-bound fibrin which accelerates the activation of plasminogen to plasmin by tPA (Fig. 15.1) [6]. Circulation of blood through the artificial surface of the pump/oxygenator leads to activation of the contact system and increased levels of circulating bradykinin (BK) and activated factor XII (FXIIa). Bradykinin in turn stimulates endothelial cells to secrete tPA. CPB stimulates about a fivefold increase in tPA secretion and an associated fivefold rise in active tPA levels [7]. tPA levels can rise to 50 to 250 ng/mL during CPB with the majority in the active form [8]. The amount of fibrin exposed to blood also increases due to elevated soluble fibrin from shed blood reinfusion and soluble and circuit-bound fibrin due to non-hemostatic thrombin generation in the bypass circuit. The combination of increased tPA activity and increased fibrin leads to a 10- to 30-fold rise in plasmin generation during CPB resulting in accelerated lysis of fibrin at or above the rate of new fibrin formation leading to a net loss of hemostatic fibrin and an increased risk of bleeding [9].

Fibrinolysis during CPB can be monitoring using viscoelastometry (see Chapter 5, "Hyperfibrinolysis," Fig. 5.3). Hyperfibrinolysis on viscoelastometry is almost always associated with bleeding and usually requires treatment with an antifibrinolytic medication. Since about two-thirds of patients show hyperfibrinolysis during CPB, [8] many patients routinely receive antifibrinolytics during open-heart

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Table 15.1 Mechanisms of systemic hyperfibrinolytic bleeding

	Production		Intravascular fibrin	Inhibition of		
	tPA	uPA		tPA	Plasmin	Clearance of tPA
Acquired disorders						
Thrombolytic Therapy[a]	↑↑	↑↑	**N**	**N**	**N**	**N**
Cardiopulmonary bypass	↑↑	**N**	↑↑	**N**	**N**	**N**
Liver cirrhosis	N	N	N	↓↓	↓↓	↓↓
Liver transplantation (anhepatic and reperfusion phase)	↑↑	**N**	↑↑	↓↓	↓↓	↓↓
Trauma	↑↑	**N**	↑↑	**N**	↓↓	**+/-**
DIC	↑↑	↑↑	↑↑	**N**	↓↓	**+/-**
Hereditary disorders						
PAI-1 deficiency	**N**	**N**	**N**	↓↓	**N**	**N**
Antiplasmin deficiency	**N**	**N**	**N**	**N**	↓↓	**N**
Quebec platelet disorder	**N**	↑↑	**N**	**N**	**N**	**N**
Increased tPA levels	↑↑	**N**	**N**	**N**	**N**	**N**

[a]Increased tPA or uPA during thrombolytic therapy comes from iatrogenic infusion, not in vivo production

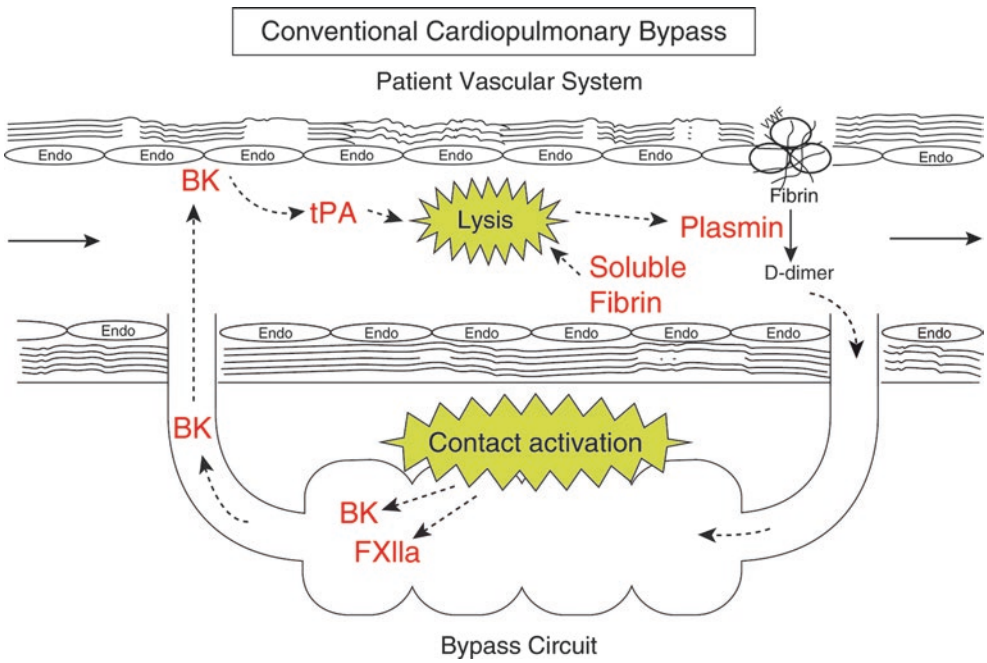

Fig. 15.1 Hyperfibrinolysis during cardiopulmonary bypass. Circulation of blood across the artificial surface of the pump/oxygenator circuit leads to activation of the contact system including formation of bradykinin (BK) and activated factor XII (FXIIa). Bradykinin formed in the bypass circuit flows back into the patient's vascular system stimulating release of tissue plasminogen activator (tPA) from endothelium (Endo). Increased tPA, in conjunction with soluble and circuit-bound fibrin, leads to increased plasmin formation and accelerated lysis of fibrin which correlates with increased blood loss during surgery

surgery to suppress fibrinolysis and reduce blood loss [10]. Two types of antifibrinolytics have been used, aprotinin and lysine-binding site antagonists like ε-amino-caproic acid (EACA) and tranexamic acid. Aprotinin is a peptide that inhibits plasmin directly. It was effective at reducing blood loss and transfusion requirements during CPB but was also shown to increase the risk of postoperative myocardial infarction and renal failure and was withdrawn from regular use during CPB. EACA and tranexamic acid are less effective at reducing blood loss and transfusion, but are not associated with postoperative myocardial infarction or renal failure [11]. Higher-dose tranexamic acid is associated with an increased risk of postoperative seizures after cardiac surgery [12].

Bleeding is also a common problem associated with extracorporeal membrane oxygenation (ECMO). Whereas CPB is used to divert all blood from the heart and lungs and stop the heart for a few hours, ECMO is used to oxygenate blood and/or provide cardiac support for days with the heart still beating. ECMO results in a more sustained inflammatory insult due to prolonged blood exposure to the artificial surface of the oxygenator circuit. In neonates ICH can occur in 5% of patients on ECMO and is a major cause of death, with significant hemorrhage after cardiac procedures in more than 30% of cases [13, 14]. In adults on ECMO, excessive bleeding occurs in more than 30% of patients [15], with evidence of ICH often found in those that died [14]. In infants older than 30 days, increased fibrinolytic activity as measured

by plasmin-antiplasmin complexes was associated with an increased risk of bleeding on ECMO [16]. EACA has been used to treat presumptive hyperfibrinolysis on ECMO and may reduce bleeding after surgical/cardiac procedures, but does not appear to improve survival, reduce ICH, or reduce transfusions and was associated with an increased incidence of oxygenator fibrin deposition and circuit change out [13].

Cirrhosis and Liver Transplantation

Four processes play a role in the hyperfibrinolysis that occurs in cirrhosis and liver transplantation: (1) decreased tPA clearance, (2) decreased fibrinolysis inhibition, (3) increased tPA secretion, and (4) enhanced tPA activity due to intravascular fibrin. Active tPA is removed from the blood through both liver clearance (half-life of 2–4 minutes) and inhibition by PAI-1. Liver cirrhosis increases fibrinolytic activity due both to decreased clearance of tPA and decreased production of PAI-1, antiplasmin and TAFI by the liver [17]. In severe cirrhosis bleeding associated with hyperfibrinolysis has been reported [18], but data is conflicting on which assay is best at detecting hyperfibrinolysis in cirrhosis, how often it occurs, and to what extent it is associated with bleeding versus other possible causes including coagulopathy and vascular abnormalities such as varices [19].

The worst form of liver-associated hyperfibrinolysis is during the anhepatic and early reperfusion phases of liver transplantation when there is essentially no clearance of tPA from the blood and reduced hepatic PAI-1 production. In patients with stable blood pressure and perfusion, the elevation in tPA that occurs may be associated with only a modest increase in blood loss. Liver transplant patients with shock and acidosis associated with difficult surgery or a poorly functioning graft have higher levels of plasma tPA activity likely due to increased secretion of tPA from injured or activated endothelium and higher levels of intravascular fibrin formation as indicated by decreased fibrinogen and increased fibrin degradation products [20]. In severe cases, tPA levels can rise of 400 ng/mL during the anhepatic and reperfusion phases. tPA requires fibrin as a catalyst; modest elevations of tPA in the absence of intravascular fibrin are not associated with increased clot lysis or D-dimer formation [21]. Liver transplant patients with both elevated tPA activity and increased intravascular fibrin may show hyperfibrinolysis with increased plasmin generation, fibrinogen degradation, generalized bleeding, and increased need for transfusion [20]. Approximately 30% of liver transplant patients show fibrinolysis severe enough to increase bleeding and transfusion requirements [20, 22]. If the new liver graft begins functioning normally, circulating tPA levels drop rapidly, and the hyperfibrinolysis resolves. In poorly functioning grafts, the duration of hyperfibrinolysis and bleeding may be extended.

Hyperfibrinolysis can be seen on viscoelastic testing during the anhepatic and reperfusion phases of liver transplant surgery [22, 23]. The coagulopathy of liver transplantation is complex and involves far more than hyperfibrinolysis. Hemostatic abnormalities include low fibrinogen and other coagulation factors, increased fibrinolysis, decreased platelets, and endothelial injury from shock and acidosis, requiring a coordinated treatment effort beyond the scope of this chapter.

Antifibrinolytics have been used in an attempt to reduce bleeding during liver transplantation in both a prophylactic manner and as specific treatment when hyperfibrinolysis is seen on viscoelastic testing [22]. While some studies have reported a reduction in blood loss with antifibrinolytic therapy, data from controlled trials is limited [24].

Trauma

Increased fibrinolysis in trauma patients has some of the same multifactorial mechanisms seen in cardiopulmonary bypass and liver transplantation: increased levels of tPA combined with increased wound and circulating fibrin resulting in clinically significant hyperfibrinolysis and bleeding [25, 26]. The cause of elevated tPA levels in severe trauma is likely due to increased secretion of tPA from endothelium injured by shock/tissue hypoxia/ischemia and stimulated by increased catecholamines associated with the neurohormonal stress response (Fig. 15.2) [27, 28]. tPA levels may reach 30 to 60 ng/mL with reduced antiplasmin in severe trauma [29–31]. Intravascular fibrin is elevated in severe trauma due to massive wounds and soluble fibrin related to the acute coagulopathy of trauma, leading to accelerated plasminogen activation on the fibrin surfaces. The presence of hyperfibrinolysis on viscoelastic testing in trauma patients is rare (2% to 11% of cases) but associated with a high mortality rate (54% to 76%) [32–34]. While viscoelastic testing can detect severe hyperfibrinolysis, more than half of trauma patients show evidence of increased fibrinolytic activity using more sensitive assays like plasmin-antiplasmin complex [29]. Trauma patients with moderate activation of fibrinolysis were at 12-fold higher risk of death, even though viscoelastic testing showed no evidence of fibrinolysis. Tranexamic acid safely reduces mortality in trauma patients that are bleeding, but it should be given as early as possible and within 3 hours of injury, as later treatment is unlikely to be effective and may be harmful [35].

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) and other consumptive coagulopathies are a complex set of disorders

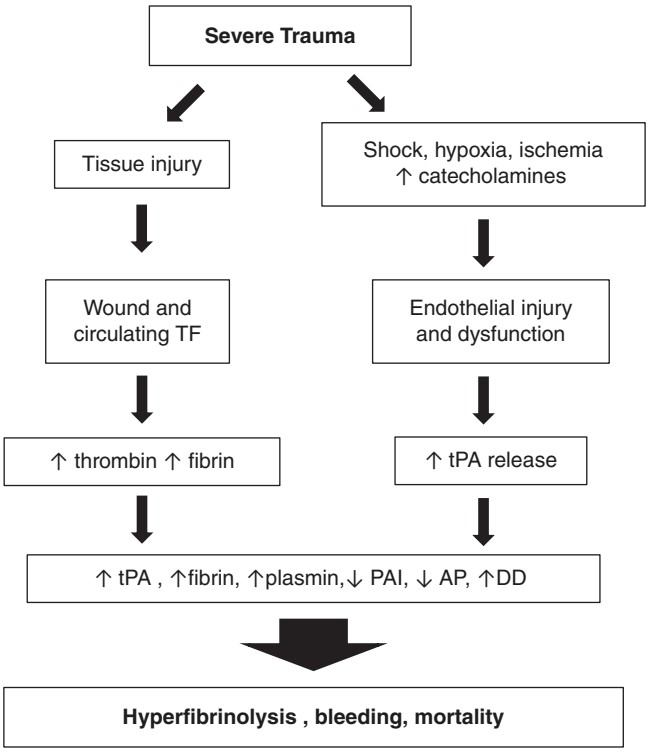

Fig. 15.2 Hyperfibrinolysis due to severe trauma. Severe trauma results in tissue injury exposing tissue factor at wound sites and increasing circulating tissue factor. This is associated with increased thrombin generation and fibrin formation, both at wounds and in the circulation. The combination of shock, hypoxia, and ischemia injuring endothelial cells and endothelial stimulation from increased catecholamines from the stress response results in increased tissue plasminogen activator (tPA) secretion. Elevated tPA and fibrin produces hyperfibrinolysis, reduced plasminogen activator inhibitor 1 (PAI-1), reduced antiplasmin (AP), and increased fibrin degradation products including D-dimer (DD). Hyperfibrinolysis in trauma patients is associated with increased bleeding and mortality

associated with many different diseases including sepsis, cancer, obstetrical complications, transfusion reactions, and almost any problem leading to severe systemic shock/hypoxia/ischemia. Severe DIC is characterized by widespread fibrin and platelet deposition, organ dysfunction, bleeding, and thrombosis. Activation of fibrinolysis occurs in some cases of DIC with increased tPA, increased plasmin-antiplasmin complexes, decreased antiplasmin, and increased fibrin degradation products [36–38]. Hyperfibrinolytic bleeding may occur in some cases of DIC, but studies have suggested that fibrinolytic activation in DIC may actually help prevent fibrin deposition and organ dysfunction [36]. Currently there are no clinically available assays that are useful in detecting hyperfibrinolysis during DIC. Antifibrinolytic medications should not be used in most cases of DIC as this may lead to widespread fibrin deposition and organ dysfunction but may be useful in patients where hyperfibrinolytic bleeding predominates such as trauma discussed above.

Acute promyelocytic leukemia (APL) is associated with a complex coagulopathy that accounts for most of the early deaths. Several mechanisms may enhance fibrinolysis in APL including tissue factor expression on promyelocytes leading to increased thrombin generation and circulating fibrin formation, enhanced plasminogen activation by tPA on the surface of the leukemia cells (annexin A2 binding), increased uPA, and decreased antiplasmin and TAFI (likely due to consumption) [17, 39, 40]. Antifibrinolytic therapy has not been shown to reduce bleeding in APL and may pose a higher risk of thrombosis [40]. Currently the best therapy for APL associated coagulopathy and hyperfibrinolysis is cell differentiation therapy with all-trans-retinoic acid or arsenic trioxide, which alters APL cells to a more mature, less coagulopathic phenotype.

Transient Hyperfibrinolysis

Massive but transient release of tPA leading to bleeding has been associated with electric shock, complicated labor, heat stroke, surgery, and other procedures [41]. It should be considered in patients with unexplained new onset bleeding with otherwise normal coagulation parameters and platelet count with no prior history of bleeding. Transient hyperfibrinolysis can be detected, if severe enough, using viscoelastic testing.

Amyloidosis

Hyperfibrinolytic bleeding in amyloidosis has primarily been associated with the monoclonal light-chain form of the disease [42]. Some studies have found increased levels of urokinase plasminogen activator. Hyperfibrinolytic bleeding in amyloidosis is usually associated with decreases in fibrinogen and antiplasmin activity and often responds well to antifibrinolytic therapy.

Acquired Localized Hyperfibrinolysis

Menorrhagia

One possible cause of idiopathic and nonfunctional heavy menstrual bleeding is increased fibrinolytic activity in the endometrium. Endometrium from women with menorrhagia produced higher levels of tPA and relatively lower levels of PAI-1 than control subjects without menorrhagia [43]. Menstrual fluid fibrinolytic activity was higher in women with menorrhagia and correlated with total blood loss [44]. Increased endometrial fibrinolytic activity in women with menorrhagia appears to be a form of localized hyperfibrinolysis; there is no evidence of increased systemic fibrinolysis

in women with menorrhagia [45]. The fibrinolytic inhibitor tranexamic acid has been shown to be a safe and effective treatment for women with menorrhagia, with 40% to 50% reduction in blood loss and improvement in quality of life [46, 47]. While not as effective as intrauterine administration of levonorgestrel in reducing blood loss (up to 97% reduction), tranexamic acid had less side effects [46, 48]. Part of the mechanism of reduced bleeding with intrauterine levonorgestrel may be increased endometrial production of fibrinolytic inhibitors to suppress the hyperfibrinolysis that was present [48].

Orthopedic Surgery

Tranexamic acid and EACA have been shown to reduce perioperative blood loss, transfusions and associated costs in total joint arthroplasty, pediatric scoliosis surgery, and adult reconstructive spine surgery, without clinically significant side effects [49]. Topical antifibrinolytic therapy applied at the time of joint or spine surgery has also been shown to reduce blood loss in some studies [50].

Hereditary Hyperfibrinolysis

Hyperfibrinolytic bleeding may be caused by hereditary abnormalities related to increased levels of plasminogen activators or decreased levels of the fibrinolytic inhibitors. In most patients with a hereditary fibrinolytic bleeding disorder, primary hemostasis is not affected, and they report delayed onset bleeding after surgery, trauma, dental procedures, or child birth. Hereditary hyperfibrinolysis should be considered in patients with unusual bleeding including intramedullary hematoma and umbilical stump bleeding and in unexplained cases of menorrhagia and associated miscarriage and preterm birth [17]. The euglobulin clot lysis time is sometimes reduced in hereditary hyperfibrinolysis but does not always detect symptomatic cases and is nonspecific, unable to determine the underlying cause. Specific measurement of fibrinolytic activators and inhibitors is required for diagnosis. Viscoelastic testing is too insensitive to detect many cases of hereditary fibrinolysis and should not be used as a screening test. The standard therapy is treatment with an antifibrinolytic agent, typically tranexamic acid.

Plasminogen Activator Inhibitor 1 (PAI-1) Deficiency

PAI-1 deficiency is an autosomal recessive disorder caused by homozygous or double heterozygous abnormalities leading to either no PAI-1 production or low levels of dysfunctional PAI-1 [51]. Individuals heterozygous for a PAI-1 defect are typically asymptomatic. Patients with PAI-1 deficiency rarely have spontaneous bleeding without provocation; they typically report mild to moderate bleeding including epistaxis, menorrhagia, and delayed bleeding associated with trauma or surgery. Recurrent wound hematomas are a common complaint after surgery. Other associations with PAI-1 deficiency include menorrhagia, miscarriage, preterm birth, and postpartum hemorrhage [17]. Diagnosis is based on undetectable PAI-1 activity, absent or reduced PAI-1 antigen, and decreased tPA antigen (cleared faster in the free form) measured in the morning when PAI-1 activity is at a maximum in normal patients. Potential causes of false-positive diagnosis of PAI-1 deficiency include an insensitive PAI-1 activity assay that cannot separate low normal PAI-1 from true PAI-1 deficiency, drawing samples in the afternoon when PAI-1 activity is lower and leaving the tourniquet on too long resulting in trapping tPA in the arm and neutralization of PAI-1 activity (high tPA in the sample). Viscoelastic testing is not useful as a screening test due to its lack of sensitivity to low to moderate hyperfibrinolysis.

Antiplasmin Deficiency

Antiplasmin deficiency is a rare autosomal recessive disorder with severe bleeding, often presenting in childhood with symptoms similar to severe hemophilia or factor XIII deficiency including umbilical bleeding and joint and intramedullary hemorrhage [52]. Menorrhagia and postpartum hemorrhage are also likely to be increased in antiplasmin deficiency [17]. Heterozygous deficiency is most often asymptomatic or mild, similar to that described for PAI-1 deficiency above. Diagnosis is based on the measurement of low (heterozygous) or absent (homozygous) antiplasmin activity.

Quebec Platelet Disorder

Quebec platelet disorder is a rare autosomal dominant disorder associated with reduced platelet counts and increased uPA expression and storage in alpha granules leading to plasmin-mediated degradation of alpha granule proteins, increased release of uPA, and hyperfibrinolysis [53]. Patients typically have a delayed bleeding disorder following surgery or trauma but may also report easy bruising, epistaxis, or menorrhagia similar to PAI-1 deficiency. The severity of the problem varies with some patients being asymptomatic and others suffering repeated bleeding, joint hemorrhage, and large bruises. Platelet and plasma transfusions are not effective; prevention and treatment of bleeding require antifibrinolytic agents. Viscoelastic testing was not useful in detecting

Quebec platelet disorder; if suspected it is recommended that genetic testing be performed for the Quebec platelet disorder mutation [53].

Increased tPA Levels

An unusual cause of hereditary hyperfibrinolytic bleeding is persistent elevation of tPA levels [54–56]. A small number of case studies have reported patients with lifelong elevation of tPA associated with delayed bleeding after surgery or trauma, shortened euglobulin clot lysis times, and normal or low normal fibrinolytic inhibitor levels. Some of these cases predate knowledge of PAI-1 and may have been due to inhibitor abnormalities resulting in high tPA activity. In other cases patients with cirrhosis have been reported with persistent tPA elevations potentially due to reduced tPA clearance.

Other Hereditary Abnormalities of Fibrinolysis

Inability to activate TAFI due to a polymorphism in the prothrombin gene has been associated with hyperfibrinolytic bleeding [57]. Decreased thrombin generation in hemophilias is associated with reduced activation of TAFI potentially leading to reduced inhibition of fibrinolysis [17, 39]. This is supported by the use of antifibrinolytics to control bleeding in hemophilia. One cause of bleeding in factor XIII deficiency is reported to be reduced cross-linking of antiplasmin to the fibrin, reducing plasmin inhibition at the clot surface [39].

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Bleeding of Unknown Etiology

16

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When a patient is actively and rapidly bleeding, it may need to be managed before making a diagnosis of bleeding etiology. The bleeding may be due to coagulopathy, overdose of anticoagulant, accidental/suicidal ingestion of rat poisoning, anatomical bleeding, or surgical bleeding, or the etiology may remain unknown. In an emergency, blood specimens may not have been drawn; however, treatment should be started without knowing the cause of bleeding. The work-up for bleeding usually starts with laboratory testing for prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and platelet count, included in complete blood count (CBC), as first-tier (Table 16.1) testing. In the setting of anemia, if both the MCV and MCH are decreased and red blood cell distribution width (RDW) is increased, it suggests chronic iron deficiency anemia. If PT, aPTT, fibrinogen, and platelet count are normal, second-tier testing may be performed, including coagulation factor assays, platelet aggregation studies, rotational thromboelastometry (ROTEM™) or thromboelastography (TEG™), PFA-100™, and factor XIII assay (Table 16.1).

Unclassified bleeding disorders may be defined as within normal limits in all tests listed in Table 16.1. Even in tertiary care hospitals, tests shown in Table 16.1 may not be performed in-house. If the tests listed in Table 16.1 are all normal, bleeding can only be defined as an unknown bleeding disorder.

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Hemophilia Carrier and Diagnostic Difficulty in Hemophilia A

Even if the PTT is within the normal range and factor VIII is normal, hemophilia carriers may experience excessive bleeding after surgery, hemarthrosis, or postpartum hemorrhage [1, 2]. Recently it had been shown that hemophilia carriers with normal baseline factor VIII levels but with abnormal bleeding scores had lower and less sustained factor VIII increase to DDAVP, suggesting an impaired ability to respond to hemostatic stress [3]. Diagnosis of hemophilia A is also dependent on the method of factor VIII assay. Even if one-stage clotting assay for factor VIII activity is normal, chromogenic factor VIII assay may give a low value or vice versa [4].

Factor XIII Deficiency

ROTEM™ or TEG™ may be used as a screening test for factor XIII deficiency. It may show normal clotting time and low maximal clot firmness in ROTEM™, or normal reaction time with low maximum amplitude in TEG™, with evidence of fibrinolysis [5, 6]. However, unless the factor XIII level is below 10–15%, TEG™ or ROTEM™ may be normal, while factor XIII less than 30% was already associated with a high variability of bleeding severity, and XIII >15% is a proposed target to start prophylaxis for prevention of major bleeding [7]. Factor XIII deficiency or acquired factor XIII inhibitor may cause delayed bleeding or intramuscular hematomas. A factor XIII assay is needed to make a diagnosis; however, before the result is available, factor XIII concentrate or recombinant factor XIII may be given based on the finding of ROTEM™ or TEG™ if the factor XIII assay is not performed in-house. The classic symptom of congenital homozygous factor XIII deficiency is bleeding from the umbilical cord on days 5–7 following birth. Still, patients with heterozygous factor XIII deficiency may not bleed until surgical procedure or dental extraction is performed [8]. If the patient has no bleeding history, but has developed

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Table 16.1 Laboratory tests related to hemostasis

First tier
PT
aPTT
Fibrinogen
Platelet count
Second tier
Thrombin time
Coagulation factor assay
Factor XIII assay
Viscoelastometry (ROTEM™ or TEG™)
PFA-100™
Von Willebrand panel (factor VIII, VWF activity, VWF antigen, activity/antigen ratio, VWF multimer assay). VWF collagen binding assay may also be included in the panel.
Third tier
Euglobulin lysis time
α2-Antiplasmin (α2AP)
Tissue plasminogen activator (tPA)
Plasminogen activator inhibitor-1 (PAI-1)
Plasmin–antiplasmin complex (PAP)
Tissue factor pathway inhibitor (TFPI)
Chromogenic factor VIII
Thrombin generation assay (TGA)
Bleeding time[a]

[a]In collagen disorder, bleeding time may be prolonged with a normal platelet aggregation study or PFA

new onset of bleeding such as intramuscular bleeding, a factor XIII inhibitor should be suspected [9]. If the patient has compartment syndrome due to intramuscular bleeding, fasciotomy should be performed after giving factor XIII concentrate or recombinant factor XIII and an increase in factor XIII level has been confirmed, or there is improvement of ROTEM™ or TEG™ parameters [10].

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AVWS) may not cause serious spontaneous bleeding; however, it may cause bleeding during invasive procedures or anticoagulation. Also, occasional spontaneous gastrointestinal bleeding due to AVWS and angiodysplasia (Heyde syndrome) occurred in dysfunctional prosthetic heart disease [11]. Since AVWS is under-recognized, knowledge of underlying conditions associated with AVWS is necessary (Table 16.2).

It should be noted that ROTEM™ or TEG™ cannot detect von Willebrand disease unless it is the severe type, i.e., Type 3. In the setting of Type 3 von Willebrand disease, clotting time in ROTEM™, or reaction time in TEG™, is prolonged due to a low factor VIII level. Since it is unlikely that factor VIII level is decreased enough to prolong clotting time (or reaction time) in acquired von Willebrand disease, ROTEM™ or TEG™ cannot accurately detect this condition. PFA-100™ may be useful to detect undiagnosed von Willebrand disease or acquired von Willebrand syndrome [12]. However, the PFA-100™ has several limitations. PFA-100™ may be prolonged by thrombocytopenia, anemia, high erythrocyte sedimentation rate, or medication. Therefore, this test is of limited utility in sick patients due to thrombocytopenia or the acute phase response. ROTEM™ and TEG™ are useful for moderate to severe platelet function defects in entities such as Glanzmann thrombasthenia or Bernard–Soulier syndrome [13]. Since they are not sensitive to mild to moderate platelet dysfunction, they cannot be used to monitor antiplatelet medication.

Table 16.2 Etiology of acquired von Willebrand syndrome

Autoantibody against VWF	Lymphoproliferative disorders
	Neoplastic disorders
	Immunologic disorders
Adsorption of VWF	Lymphoproliferative disorders
	Neoplastic disorders
	Myeloproliferative disorders
Increased shear stress	Congenital cardiac defects
	Aortic stenosis
	Mitral valve regurgitation
	Endocarditis
	Malformation of vessels (Kasabach–Merritt syndrome)
	Severe atherosclerosis
	β-Thalassemia
	VAD
	ECMO
Decreased synthesis	Hypothyroidism
Increased proteolytic degradation of VWF	Myeloproliferative disorders
	Uremia
	Ciprofloxacin
	Hyperfibrinolysis
Unknown mechanism	Wilms' tumor
	Valproic acid
	Cefotaxime
	Viral disease
	Liver transplantation
	Mixed cryoglobulinemia
	Amyloidosis
	Glycogen storage disease type 1
	Turner syndrome

VAD ventricular assist device, *ECMO* extracorporeal membrane oxygenation

Acute Bleeding but No Laboratory Test Results Are Available

When pediatric patients or newborns present with active bleeding, blood specimens may be difficult to draw from veins due to vasoconstriction. Whenever possible, blood specimens should be collected for first-tier testing, PT, aPTT,

Table 16.3 Available blood components

Red blood cells
Platelets
Fresh frozen plasma, thawed plasma, liquid plasma
Cryoprecipitate

fibrinogen, and platelet count. While the results are pending, or if specimens are unable to be collected, the patient needs to be managed empirically. When family history is available, such as known hemophilia or platelet disorders, targeted therapy may be initiated. Common causes of acquired coagulopathy include liver failure, disseminated intravascular coagulation (DIC), and vitamin K deficiency. Transfusion of plasma or platelets may be started. Red blood cells should also be transfused in order to prevent hemorrhagic shock or ischemic organ damage if bleeding is continuous. Table 16.3 shows possible blood component therapy and medications that may be employed. If the patient has liver failure, plasma transfusion and antifibrinolytics may be useful since hyperfibrinolysis is known to be associated with liver failure due to less inactivation of tissue plasminogen activator (see Chapter 11). TEG™ or ROTEM™ can show only moderate to severe hyperfibrinolysis, especially when associated with trauma or liver transplant surgery. Therefore, without evidence of hyperfibrinolysis in TEG™ or ROTEM™, clinically significant hyperfibrinolysis cannot be ruled out [14]. Individual laboratory tests for hyperfibrinolysis may not be readily available. Of note, antifibrinolytics may be beneficial without significantly increasing thrombotic risk (see Chapter 34).

Continuous Bleeding from the Catheter Insertion Site After Diagnostic Catheterization Without Pertinent Laboratory Data

If there is a suspicion of heparin overdose, such as after cardiac catheterization, it is prudent to give protamine for reversal. Although activated clotting time, also known as ACT, is not considered to be accurate or precise, if it is unreasonably prolonged, heparin or a heparin-like substance such as heparan sulfate or dermatan sulfate may be circulating. When aPTT is prolonged, but PT is normal, heparin overdose is likely. In this setting, protamine may be administered (Chap. 34 for dosing). PT is not usually affected by heparin up to 1–2 units/mL, depending on the reagent used [15], since PT reagent contains a heparin neutralizer such as polybrene.

Rare Bleeding Disorders

There are rare bleeding disorders which have been reported by very sophisticated evaluations. Work-up may be performed in a research laboratory. Table 16.4 shows examples of rare bleeding disorders. Finding the etiology of bleeding requires consultation with specialized laboratories, usually research laboratories. Tables 16.3 and 16.5 show available blood components and medications used to treat these disorders.

Table 16.4 Examples of rare bleeding disorder

Disease condition	Management
East Texas bleeding disorder [16]	
Factor V Amsterdam [17]	
Thrombomodulin (p.Cys537Stop) mutation [18]	Protein C concentrate
Antithrombin Pittsburgh [19]	
Ehlers–Danlos syndrome (connective tissue disorders) [20, 21]	DDAVP, antifibrinolytics
Quebec platelet disorder [22]	Antifibrinolytics
Scott syndrome [23]	Platelet transfusion

Table 16.5 Available medication for hemostasis

Desmopressin (DDAVP)
ε-Aminocaproic acid (Amicar™)
Tranexamic acid
Von Willebrand factor/factor VIII concentrate (Humate-P™)
Prothrombin complex concentrate (Kcentra™)
Recombinant activated factor VII (NovoSeven™)
Activated prothrombin complex concentrate (FEIBA™)
Vitamin K
Protamine

Usual dose and renal dose are stated in Chap. 34

Platelet transfusions are useful for not only thrombocytopenia or platelet function defects but also in other non-platelet-related disease conditions such as acquired factor V inhibitor or thrombomodulin mutation, which causes elevated levels of circulating activated protein C. It is explained that factor V stored in α-granules of platelets is sheltered from inhibition by activated protein C [24] or antibody against factor V [25, 26]. Likewise, platelet transfusions may be also effective for AVWS since von Willebrand factor is also stored in α-granules [27].

Among available medication, the administration of DDAVP and tranexamic acid may be considered since there are numerous platelet function defects which are not identified.

Suspected Overdose of Anticoagulant

If overdose of unknown anticoagulant is suspected, PT, aPTT, and thrombin time may be performed. Warfarin overdose may be managed by vitamin K administration, plasma transfusion, and/or prothrombin complex concentrate (Kcentra™), depending on the urgency of warfarin

reversal and INR. Hemodialysis may be performed for overdose of dabigatran, but is not effective for rivaroxaban and apixaban [28]. Idarucizumab for the reversal of the anticoagulant effect of dabigatran is already available; however, repeated dose of this drug is necessary for complete inactivation in patients with renal failure due to extravascular accumulation of dabigatran [29, 30]. There is not much data regarding the use of plasma exchange in order to remove direct oral anticoagulant [31]. Fibrinogen concentrate, antifibrinolytics, and oral charcoal can be considered as an additional therapy for direct anticoagulants-associated bleeding [32].

Anticoagulant Rodenticide (Superwarfarin) Poisoning

"Superwarfarin" includes derivatives of 4-hydroxycoumarin, such as difenacoum, bromadiolone, flocoumafen, and brodifacoum, and indanedione derivatives, such as chlorophacinone, pindone, and diphacinone. It is usually seen in suicide attempts [33]; however, recent outbreak of multiple (more than 150 cases) intoxications due to synthetic cannabinoids adulteration with different superwarfarins was reported [34]. If an accidental/intentional intoxication with superwarfarin is suspected, PT/INR should be measured. If only a very small amount of rat poisoning was ingested, PT/INR should be normal, and bleeding symptoms may not occur. If the patient has bleeding symptoms, INR >4 is a very common finding. Mild bleeding may be corrected with oral vitamin K1 at 25–100 mg daily; however, sometimes up to 400 mg is required [35]. Because of the very long half-life of superwarfarin in humans (brodifacoum 15–33 days, flocoumafen 6.7 days), the long-term treatment with vitamin K1 for several weeks to months is required to normalize PT/INR. Since these compounds are lipid soluble, plasma exchange is not effective. Severe bleeding should be managed with 3-factor or 4-factor prothrombin complex concentrate (PCC) or fresh frozen plasma (initial dose 15–30 mL/kg), plus intravenously 10–15 mg of vitamin K1 [36]. Rarely paradoxical thrombosis complicates superwarfarin bleeding, and the management in these cases is very challenging [37]. Thrombotic episodes were attributed to the administration of prothrombin complex concentrate, or if concomitant thrombosis and hemorrhage happened prior to any blood product infusion, thrombotic phenomenon was postulated to be provoked by rapid depletion of proteins C and S within the initial period of toxicity and, therefore, a transient thrombophilia that was later followed by a tendency for hemorrhage as other vitamin K-dependent factors became depleted.

Heparin-Like Effect

Described as early as 1951 [38], multiple case reports have surfaced regarding the production of an endogenous heparin-like anticoagulant associated with clinically significant bleeding. These compounds have been identified in numerous settings, but are most commonly reported in the setting of hematologic malignancy and liver disease [39]. The etiology of this disorder remains obscure; however, several pathogenic mechanisms have been proposed.

The heparin-like effect is mediated by heparin-like substances, i.e., glycosaminoglycans. These include heparan sulfate, dermatan sulfate, chondroitin sulfate, keratan sulfate, and hyaluronic acid. Anticoagulant activity has been observed associated with heparan sulfate, dermatan sulfate, and chondroitin sulfate. Heparan sulfate is a glycosaminoglycan found naturally on the surface of endothelial cells and produced by mast cells [40]. It is structurally similar to unfractionated heparin, though its anticoagulant effects are mediated mostly via complexing with antithrombin to inhibit factor Xa [41]. Dermatan sulfate is found primarily in the skin, blood vessels, and heart valves and plays roles in wound repair and fibrosis. The anticoagulant effects of dermatan sulfate are mediated via inactivation of thrombin by forming a complex with heparin cofactor II [41]. Both heparan sulfate and dermatan sulfate are less potent inhibitors of coagulation than pharmaceutical heparin, which is likely due to decreased sulfation of saccharide units [42, 43].

The heparin-like effect of endogenous glycosaminoglycans has been associated with multiple myeloma [39, 44], B-cell and T-cell lymphomas [39], systemic mastocytosis [45, 46], suramin therapy [47], metastatic transitional cell carcinoma [48, 49], metastatic breast cancer [50], systemic candidiasis [51], renal cell carcinoma [52], hepatocellular carcinoma [53], and mucormycosis [54]. This effect has been further described in patients with liver disease including in the setting of bacterial infection in cirrhotic patients [55], in portal hypertension [56], in acute variceal bleeding [57], and in the setting of liver transplantation [58–60]. The heparin-like effect is more commonly seen in patients with acute liver failure undergoing transplantation and is more pronounced at the time of reperfusion [59, 60]. More recently, this effect has been described in pediatric patients following liver transplantation [61, 62] and in patients receiving extracorporeal membrane oxygenation (ECMO) therapy [63, 64]. Heparan sulfate from mast cells may be produced in excess or released from the vascular endothelium in the setting of systemic inflammatory response syndrome (SIRS) and sepsis [65, 66]. Like heparin, heparan sulfate is metabolized by the liver and may build up in the setting of liver disease [47]. Increased production or systemic circulation of free glycosaminoglycans in

conjunction with decreased metabolism likely is responsible for coagulopathy associated with this disorder.

Patients may present with a variety of signs and symptoms listed in Table 16.6. Laboratory identification of heparin-like substance is difficult. Though we often identify heparin in association with a prolonged aPTT, this test may not always reliably demonstrate a heparin-like effect. The thrombin time has been reported to be the most reliable test when assessing for this disorder [67]. A reptilase time may be used in conjunction with the thrombin time to demonstrate the heparin-like effect. One would expect to find a prolonged thrombin time and normal reptilase time in this setting [67] (see Table 16.7). In addition, specific lyases can be used to help identify the glycosaminoglycan associated with the heparin-like effect. Hepzyme™ (heparinase, heparin lyase I), commonly used in the coagulation laboratory, may correct, or partially correct, the heparin-like effect associated with heparan sulfate. Other lyases such as heparin lyase III and chondroitinase B provide additional specificity for the glycosaminoglycans heparan sulfate and dermatan sulfate, respectively [47]. Prolongation of the clotting time on TEG™ or ROTEM™ can also demonstrate the heparin-like effect [52, 55, 58–60, 64] (Fig. 16.1).

Table 16.6 Signs and symptoms of heparin-like effect

Mucocutaneous bleeding
Petechiae
Ecchymosis
Bleeding from venipuncture sites/prolonged bleeding from surgical sites
Gastrointestinal bleeding
Deep-seated hematomas

Table 16.7 Tests for identification of heparin-like inhibitor

Prothrombin time	Normal or prolonged
Activated partial thromboplastin time	Normal or prolonged
Thrombin time	Prolonged
Reptilase time	Normal
aPTT with Hepzyme	Normal (may only see partial correction)
TEG/ROTEM	Prolonged clotting time
Anti-Xa	Normal or elevated

Appropriate treatment for heparin-like effect is not well defined. Some patients have been successfully treated with protamine sulfate [67]. A slow continuous infusion of protamine at 1 mg/min has resolved bleeding in some patients; however, protamine therapy does not always appear to work [51]. Plasma exchange in this setting has been described, but is of questionable benefit [67]. In our own recent case, protamine had a small, transient effect, while plasma exchange was successfully used to resolve bleeding [62]. The only reliable treatment appears to be eradication of the underlying disorder [67]. The prognosis for patients with bleeding associated with heparin-like effect is generally poor, as it typically presents in the terminal stages of disease when associated with malignancy or end-stage liver disease. However, the heparin-like effect identified in the setting of liver transplantation or ECMO appears to be transient [63, 64]. Ongoing research indicates that circulating glycosaminoglycans may be a marker for the development of critical illness [63, 64, 68]. A high index of suspicion is critical to identify this disorder.

Summary

Occasionally, patients present with bleeding without any apparent cause. Laboratory testing algorithms may be used to help guide treatment and determine the underlying etiol-

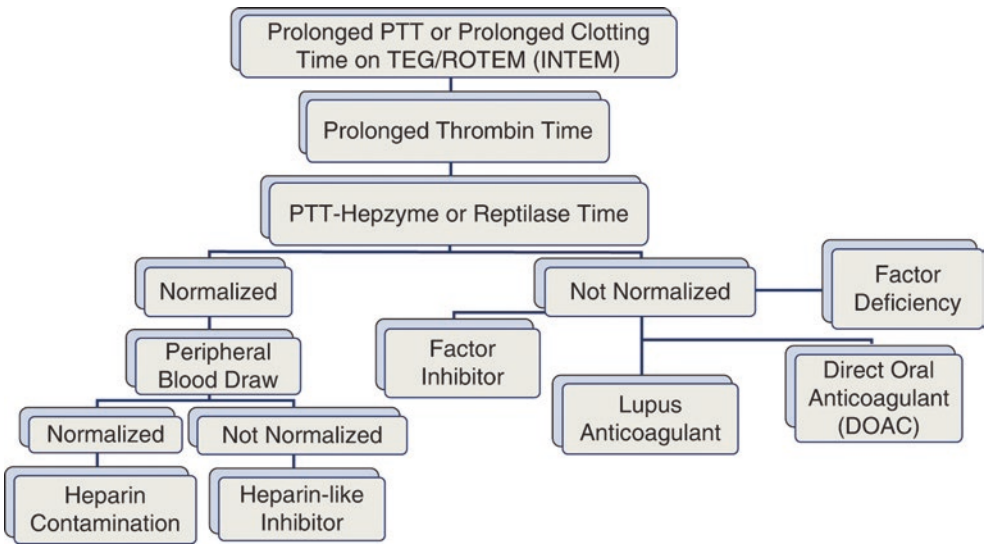

Fig. 16.1 Diagnostic algorithm. *PTT* activated partial thromboplastin time, *TEG* thromboelastography, *ROTEM* rotational thromboelastometry

ogy. When laboratory testing is incomplete or unavailable, patients must be treated empirically. There are a variety of blood components and medications available for treatment in an emergency. Of these, the use of DDAVP and/or tranexamic acid is the most important consideration when the cause of bleeding is unclear. Extended laboratory work-ups and expert consultation may be necessary to identify rare bleeding disorders.

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Bleeding Associated with Disseminated Intravascular Coagulation

17

Charles Eby

Abbreviations

aPTT	Activated partial thromboplastin time
DIC	Disseminated intravascular coagulation
PT	Prothrombin time
TF	Tissue factor

Overview of Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a complex pathologic immuno-hemostasis process with potential thrombotic and hemorrhagic consequences [1]. DIC defies a simple definition, unambiguous diagnosis, and straightforward management. There are several general concepts which apply to most clinical conditions involving DIC:

1. DIC is never a primary diagnosis. There must be an underlying disorder, acute or chronic, responsible for disrupting hemostasis balance.
2. The clinical and laboratory manifestations of DIC are primarily due to tissue factor pathway initiated excessive thrombin generation.
3. Regardless of the cause or location of excessive thrombin generation, the effects occur throughout the vascular system.
4. Variables affecting the clinical and laboratory consequences of DIC include preexisting morbidities and the type and severity of the underlying pathology driving DIC.
5. The primary treatment goal is to correct the underlying disorder.
6. Management strategies to restore hemostasis balance are mostly empiric.
7. Hyperfibrinolysis-dominant DIC is associated with a subset of underlying disorders.

This chapter will provide an overview of DIC with a focus on underlying precipitating conditions associated with hemorrhage and approaches to management of bleeding.

Clinical Consequences of DIC

The clinical consequences range from mild laboratory abnormalities to end-organ ischemia and failure (necrosis of adrenal glands and skin; renal, pulmonary, liver, central nervous system, and gastrointestinal dysfunction) and diffuse bleeding from mucous membranes, phlebotomy sites, and internal locations. A sustained, less intense rate of thrombin generation due to cancer or vascular defects can remain asymptomatic, promote venous thromboembolic events, or cause spontaneous hemorrhages. One controversial precipitant of DIC occurs in patients with chronic advanced liver disease who acutely decompensate, often due to bacterial infection or renal failure, and have bleeding complications. Since the liver synthesizes and metabolizes most hemostasis proteins, it is difficult to interpret whether worsening deficiencies of coagulation factors and regulatory proteins are due to increased consumption due to DIC or decreased synthesis; whether elevations of D-dimer are due to thrombin-driven enhanced fibrinolysis or decreased clearance of D-dimer fragments; and whether declines in fibrinogen are due to primary fibrinolysis or decreased protein synthesis [2] (this topic is discussed in more detail in Chapter 14, "Bleeding in Acute and Chronic Liver Disease").

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Table 17.1 Clinical disorders complicated by DIC

Acute process	Chronic process
Sepsis	Solid neoplasms
Major trauma, brain injury, major burns	Retained dead fetus
Heat stroke Cardiac arrest, drowning	
Obstetric emergencies Acute on chronic liver failure	Hemangiomas producing Kasabach-Merritt syndrome
	Aortic aneurysms, often with extensive dissection
Leukemias—acute promyelocytic most common	
Envenomation by vipers	
ABO-incompatible hemolytic transfusion reaction	

Pathophysiology of DIC

Hemostasis involves many complex cellular functions (endothelial cells, platelets, and leukocytes) and protein activation pathways (coagulation, fibrinolysis, complement, inflammation, and inate immunity). When external or internal disruptions perturb these processes, the consequence is often excess generation of thrombin. Exposure of blood to tissue factor (TF) is one of the most important initiators of DIC [3]. TF is ubiquitous in extravascular tissues, amniotic fluid, and cirrhosis-induced ascites, and contact with blood will activate clotting. TF is also expressed on endothelial cells and monocytes in response to infectious and inflammatory-associated cytokines as well as on many types of malignant cells. Table 17.1 lists the major clinical disorders complicated by DIC.

TF activates factor VII to VIIa which proceeds to activate factor X to Xa which converts prothrombin (factor II) to thrombin. Thrombin targets multiple substrates, most of which are prothrombotic: conversion of fibrinogen to fibrin; activation of factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI) to form durable fibrin clot; activation of platelets; and activation of factors XI, VIII, and V to amplify continued thrombin generation. Via interaction with the endothelial surface receptor thrombomodulin, thrombin activates protein C which inhibits thrombin generation by degrading factor VIIIa and factor Va. Thrombin also promotes fibrinolysis by stimulating release of tissue plasminogen activator from endothelial cells which activates plasminogen to plasmin which degrades fibrin into soluble fibrin degradation fragments including the neo antigen D-dimer. Acute, overwhelming thrombin generation generates fibrin and platelet microthrombi in multiple tissue beds; consumes and exhausts coagulation factors, fibrinogen, and coagulation regulatory protein (protein C, protein S, and antithrombin) reserves; and accelerates fibrinolysis of fibrin clot. Neutrophil extracellular traps (NET) consisting of histones and cell-free DNA [4], activated platelets and monocytes, and dysfunctional endothelial cells contribute to destabilizing hemostasis checks and balances. During an acute insult initiating unregulated thrombin activity and DIC, the hemostasis imbalance can fluctuate between hyperfibrinolysis and hypofibrinolysis with associated bleeding and microvascular thrombotic complications [5].

Subtypes of DIC and Underlying Causes

Acute and overt DIC is a companion to many sudden, life-threatening events (Fig. 17.1). The most common category is sepsis due to infectious diseases, predominantly gram-negative and gram-positive bacteria. Other infectious agents which can initiate DIC include fungi, malaria [6], and viruses including dengue hemorrhagic fever [7] and Ebola [8]. Recognition of the early onset of acute trauma-associated coagulopathy by military and civilian trauma and critical care specialists has changed initial management of massive trauma cases to include aggressive transfusion of components (red cells, plasma, and platelets) or whole blood guided by thromboelastography monitoring [9] (this topic is discussed in more detail in Chap. 21, "Bleeding Associated with Trauma," and Chap. 22, "Massive Transfusion Protocol"). Uncommon obstetric emergencies such as amniotic fluid embolism, placenta abruption, HELLP (hemolysis, elevated liver enzymes, and low platelets), and fatty liver of pregnancy can cause DIC and severe bleeding [10]. Cardiac arrest and prolonged hypoxia from drowning can precipitate DIC with brain injury and bleeding from hyperfibrinolysis [11, 12]. Envenomation from vipers is a major cause of

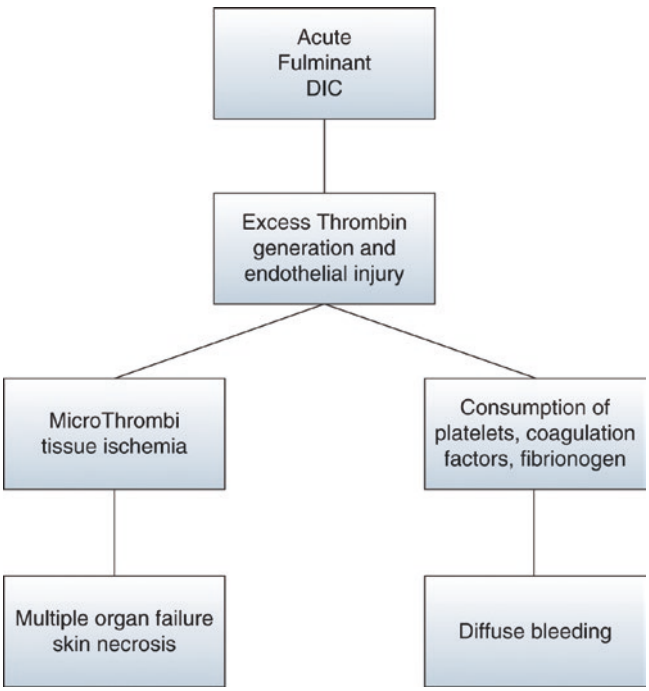

Fig. 17.1 Clinical consequences of acute and overt DIC

morbidity and mortality in tropical countries. Enzymes in hemotoxic snake venoms increase vascular permeability, activate coagulation factors, activate platelets but inhibit aggregation, and degrade fibrinogen [13]. Incompatible ABO blood transfusions initiate a humoral immune response starting with complement activation and subsequent release of tumor necrosis factor alpha and cytokines, endothelial damage, and procoagulant changes [14]. Heat stroke induces DIC via activation of leukocytes and endothelial cells via multiple pathways including direct cytotoxic effects of heat, release of inflammatory cytokines, and tissue factor expression [15]. Patients with acute promyelocytic leukemia (APL) typically have laboratory signs of DIC at presentation and are at high risk of major bleeding complications [16].

Conditions causing "smoldering" activation of the coagulation system, which is recognized as chronic DIC, are listed in Table 17.1. Laboratory evidence of chronic DIC is common in patients with solid tumors. Solid malignancies generate tissue factor as well as tumor procoagulant C which activates factor X [17]. Cancer-associated DIC may be asymptomatic; provoke predominantly venous thromboembolic events (VTE) when combined with other hypercoagulable risk factors including chemotherapy, surgery, and central venous catheters; and cause unprovoked isolated or migratory VTEs or nonbacterial thrombotic endocarditis with embolization. Spontaneous or treatment-related microangiopathic hemolytic anemia (MAHA) [18] and hyperfibrinogenolysis [19] are rare complications of cancer-associated chronic DIC (Fig. 17.2).

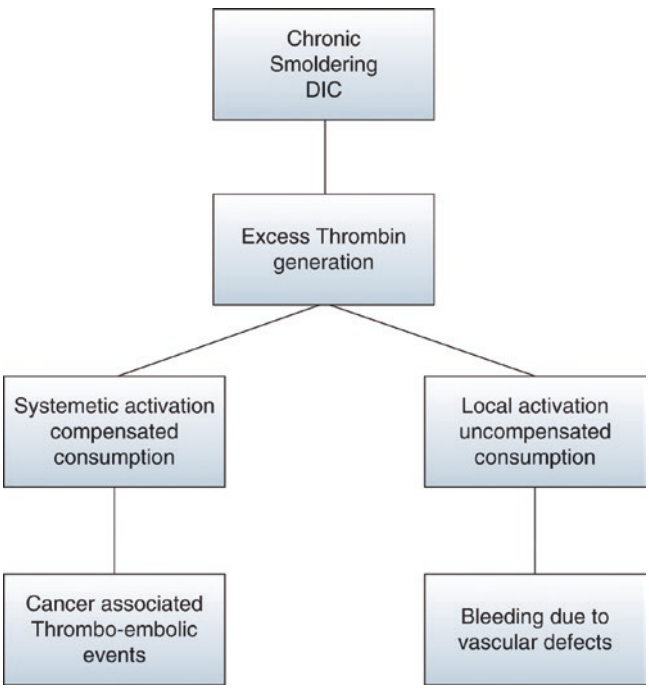

Fig. 17.2 Clinical consequences of chronic smoldering DIC

Two types of vascular abnormalities, congenital hemangiomas [20] and aortic aneurysms [21], can cause sufficient chronic local consumption of platelets, coagulation factors, and fibrinogen to produce spontaneous bleeding.

Laboratory Evaluation of DIC

One cannot diagnose DIC with any degree of accuracy by measuring a single analyte from blood due to the unpredictable effects a process capable of activating thrombin has on the nonspecific hemostasis tests which are routinely used to assess DIC [22]. Therefore clinicians must determine the likelihood that DIC is occurring and is an important complication by synthesizing information from a patient's presenting history and physical findings, underlying diagnosis, and concurrent laboratory, pathology, and imaging data. There are five practical laboratory tests to assess for DIC: platelet count, D-dimer which is specific for plasmin lysis of fibrin, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen. There is also value in reviewing a peripheral blood smear to confirm thrombocytopenia reported by an automated hematology instrument and to identify abnormal or malignant leukocytes. However, increased fragmented red cells (schistocytes) are both insensitive and nonspecific for DIC [23, 24]. The International Society on Thrombosis and Haemostasis (ISTH) scientific subcommittee on DIC developed a scoring system to evaluate patients at risk for DIC (Table 17.2). A score of ≥5 is highly supportive for DIC in acutely ill patients [25]. Validation studies have confirmed its clinical utility for diagnosing DIC and for predicting patient's survival [26]. Serially monitoring these tests may demonstrate trends consistent with resolving or persistent DIC and can be particularly use-

Table 17.2 Scoring system for overt DIC adapted from [25]

Patient has underlying disorder associated with DIC?	
No: stop	
Yes: continue	
Obtain following hemostasis tests; calculate points.	
Platelet count ($\times 10^3/\mu L$)	
(>100 = 0; ≤100, ≥50 = 1; <50 = 2)	____
D-Dimer[a]	
(WNL = 0; moderate increase = 2; strong increase = 3)	____
Prolonged PT (sec.)	
(<3 = 0; ≥3, ≤6 = 1; >6 = 2)	____
Fibrinogen (mg/dL)	
(>100 = 0; ≤100 = 1)	____
Add up score	____

[a]Moderate D-dimer if elevated but <10× upper limit of reference range; strong D-dimer if >10× upper limit. *WNL* within normal limit [19]
Score ≥5: consistent with overt DIC. Monitor with daily score
Score <5: suggestive for non-overt DIC. Repeat at intervals to observe for deteriorating or improving trends

ful when the underlying primary disorder is chronic and less potent. For example, a pregnant woman carrying a dead fetus may have a fibrinogen level within the laboratory's reference range yet may still have low-grade DIC due to fetal-derived tissue factor leaking into the maternal circulation. Serial fibrinogen measurements may demonstrate a downward trend consistent with excess consumption by thrombin leading to a decision to intervene.

Acute DIC Conditions Dominated by Bleeding

Viral hemorrhagic fever is a clinical syndrome caused by several different RNA viruses including Ebola [27]. Excessive pro-inflammatory cytokines and lack of an adaptive immune response are key contributors to vascular leak, hypovolemic shock, and DIC. Hemorrhage is a dominant complication in about half of infected patients [8]. Preliminary observations of COVID-19 induced critical illness indicates an increased risk for thromboembolic events without DIC like consumption.

While bleeding can be a sign of acute DIC, it is usually overshadowed by multiorgan damage induced by microvascular thrombi. However, there are some disorders where hemorrhage is a dominant sign of underlying hyperfibrinolysis usually accompanied by laboratory evidence of concurrent DIC.

The risk of early hemorrhagic death (first 30 days after diagnosis) is 2.7% in patients with APL enrolled in clinical trials and is fivefold higher if the WBC >20,000/ul [28]. Laboratory signs of DIC occur in most patients presenting with APL. Malignant promyelocytes express tissue factor and cancer procoagulant which generate thrombin; release prothrombotic microparticles; and induce endothelial cell dysfunction [16]. In addition, they cause hyperfibrinolysis by expressing annexin II and S100A10, receptors for plasminogen and tissue plasminogen activator and fibrinolysis [29]. To reduce bleeding-related morbidity and mortality, APL patients should receive transfusion support for thrombocytopenia and hypofibrinogenemia while rapidly initiating all-trans-retinoic acid to induce maturation of malignant APL cells. Pharmacologic interventions to reduce thrombin generation and inhibit fibrinolysis have not been definitively shown to be beneficial [16].

Severe bleeding is a common complication of prolonged tissue hypoxia due to asphyxia from drowning. Laboratory findings provide evidence for both thrombin generation and excess, primary fibrinolysis due to release of tissue plasminogen activator from endothelial cells due to prolonged hypoxia [11]. Patients suffering out of hospital cardiac arrest and subsequent return of circulation are also at risk for hypoxia-induced hyperfibrinolysis, demonstrated by thromboelastography, as well as microvascular thrombi due to excess thrombin generation; however overt hemorrhage is uncommon [12, 30].

Several obstetric complications with laboratory findings frequently consistent with DIC are accompanied by uterine hemorrhage and coagulopathy. Post-partum hemorrhage due to retained placenta, uterine atony, or injury may initially be a dilutional coagulopathy. However, protracted and severe blood loss may cause tissue hypoxia and injury, induced excess thrombin generation, and DIC [10]. Administration of the anti-fibrinolytic, tranexamic acid reduces mortality from post-partum hemorrhage [31].

Placental abruption, either overt or concealed, is associated with entrance of placental trophoblast tissue factor into the maternal circulation, DIC, and exacerbated uterine bleeding [10]. Amniotic fluid embolism is a rare, peri-labor complication characterized by abrupt cardiovascular collapse without other explanation and subsequent uncontrollable uterine hemorrhage and DIC, precipitated by prothrombotic material in amniotic fluid entering the maternal circulation [32]. Finally, acute fatty liver of pregnancy (AFLP) and HELLP/preeclampsia can cause coagulopathies, thrombocytopenia, and excess peri-partum bleeding [33, 34]. AFLP causes a hyposynthetic coagulopathy and positive ISTH DIC scores in most cases. The pathophysiology of HELLP is more complex, combining endothelial dysfunction and microvascular hemolysis and thrombocytopenia and coagulopathy due to hepatic dysfunction, and is less often complicated by severe bleeding and DIC [33].

Major trauma-induced coagulopathy is an extremely complex and incompletely understood derangement of multiple cellular, enzymatic, inflammatory, and signaling pathways [35, 36]. Excess fibrinolytic activity is a consistent initial finding, identified by increased clot lysis on thromboelastography. Early treatment with tranexamic acid improved survival in the CRASH-2 randomized study of major trauma patients which lead to routine use of antifibrinolytics, in addition to aggressive transfusion support to correct a combined dilutional and consumptive coagulopathy [36]. Investigators debate whether acute coagulopathy of trauma shock and DIC have the same or different underlying pathophysiology [37] and whether there is a transition from initial, hemorrhagic hyperfibrinolytic state to a later fibrinolysis shutdown state with complications from microvascular thrombi [38].

Chronic DIC Conditions Dominated by Bleeding

Severe bleeding due to excessive fibrinolysis, coagulopathy, and thrombocytopenia is a rare complication of cancer-related chronic DIC, almost always due to refractory meta-

static prostate cancer [19, 39]. The underlying mechanism for hyperfibrinolysis is unclear, but a tumor source of plasminogen activator is plausible. Management includes supportive transfusions of platelets and a source of fibrinogen while starting some type of cancer salvage treatment. In a few cases, a fibrinolysis inhibitor (tranexamic acid or epsilon aminocaproic acid) with or without low-dose heparin or low-molecular-weight heparin has successfully controlled bleeding and improved hemostasis parameters [19, 40].

Very rarely, a sustained, local activation and consumption of platelets and coagulation factors and concurrent (reactive) fibrinolysis produce a generalized bleeding diathesis in pediatric patients with hemangiomas, called Kasabach-Merritt syndrome (KMS) [20]. Management of bleeding due to KMS is complex and patient specific requiring coordination of surgical, radiation, or medical approaches to remove or shrink the abnormal capillary bed while correcting thrombocytopenia and hypofibrinogenemia by transfusion.

A similar clinical and laboratory presentation can occur in patients with extensive, and frequently inoperable, aortic aneurysms [21]. A severely atheromatous or dissecting aortic aneurysm exposes sufficient tissue factor to create a systemic depletion of platelets, fibrinogen, and coagulation factors, elevate D-dimer, and cause major bleeding complications. When surgical repair is not an option, therapeutic anticoagulation with or without a fibrinolytic inhibitor can reverse the laboratory abnormalities and stop the bleeding and bruising for months to years [21]. Case reports are beginning to appear supporting control of hemorrhage from congenital hemangiomas and dissecting aneurysms with direct oral anticoagulants [41, 42].

Management of DIC

"Treat the underlying disease" is a standard and valid recommendation when DIC is added to an acutely ill patient's problem list [43]. Monitoring a DIC test panel provides guidance for replacing consumed platelets, coagulation factors, and fibrinogen. A long-standing concern is: will replacement of consumed hemostasis components "feed the fire" of ongoing microvascular thrombi if the precipitating cause of DIC is still generating excess thrombin? Therefore, replacement is only indicated to stop serious bleeding or to prophylaxis against bleeding complications prior to necessary invasive procedures [1].

Multiple clinical trials have evaluated pharmacologic interventions to reduce sepsis and DIC-related mortality by blocking thrombin generation with negative or inconsistent results including anticoagulation with heparin using different dosing strategies [44]; restoring natural anticoagulants by infusing antithrombin [45] or recombinant activated protein C (APC) in moderately septic patients [46]; and blocking TF with infusion of recombinant tissue factor pathway inhibitor (TFPI) [47]. Antithrombin, APC and TFPI were later proven to be ineffective to treat sepsis-induced DIC. While it is discouraging to observe a lack of clinical utility for promising strategies to improve survival for septic patients in DIC, research with novel therapeutics is continuing. In Japan recombinant thrombomodulin (TM) is used to treat patients with sepsis and DIC. Endothelial expression of TM is downregulated in sepsis, reducing TM-bound thrombin activation of protein C. By providing soluble TM, increase activated protein C would degrade factors VIIIa and Va and reduce thrombin generation. However, there is not convincing evidence of decreased mortality in septic patients administered [48], and it has not been adopted by clinicians in other countries.

Summary

DIC represents a spectrum of disruptions and injuries to the vascular system initiated by various acquired systemic or localized disorders culminating in accelerated activation and deregulation of thrombin and fibrinolysis. The consequences range from nonspecific alterations in routine coagulation tests to life-threatening ischemic and hemorrhagic complications. Aggressive treatment of the underlying disorder and judicial replacement of consumed hemostasis components are the mainstay of management. In select situations overt bleeding is the dominant sign of DIC requiring additional therapeutic interventions as outlined in this chapter.

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Bleeding and Vitamin K Deficiency

18

Charles Eby

Abbreviations

aPTT	Activated partial thromboplastin time
DIC	Disseminated intravascular coagulation
INR	International Normalized Ratio
PIVKA-II	Protein induced by vitamin K absence-prothrombin
PT	Prothrombin time
VKDB	Vitamin K deficiency bleeding

Vitamin K is a cofactor for human glutamic acid carboxylase enzymes in multiple tissues and organs [1] (Table 18.1). The dominant vitamin K activity is gamma-carboxylation of selective glutamic acid residues on coagulation factors X, IX, VII, and II (prothrombin) plus coagulation regulatory proteins C, S, and Z (Fig. 18.1) which enhances secretion of these proteins from hepatocytes and provides binding sites for Ca^{2+} ions to efficiently localize coagulation factors on negatively charged phospholipid cell membranes at sites of vascular injury [2]. The most clinically important consequence of vitamin K deficiency is acquired coagulopathy due to diminished clotting activity of hypo-gamma-carboxylated factors X, IX, VII, and II.

Vitamin K is a generic term which includes two naturally occurring forms and one synthetic form of a fat-soluble quinolone molecule and attached alkyl side chain [3] (Fig. 18.2). Since humans cannot synthesize vitamin K, we are dependent upon consumption of green vegetables for phyloquinolones (K_1) and bacterial cultured (cheeses) and fermented (soy beans) foods or animal liver for menaquinones (K_2) or synthetic provitamin K_3 (menadione) which is converted in hepatocytes to a menaquinone with 4 prenyl subunits. Vitamin K_1 is the dominant type of vitamin K in the diets of most cultures, and serum levels range from 0.2 to 1.0 ng/mL in adults [4]. Recommended adult minimal daily vitamin K_1 requirements are 90 μg/day for women and 120 μg/day for men. Both K_1 and K_2 are lipophilic and require bile salts to form emulsions which are absorbed in the small intestines and transported as chylomicrons first through the lymphatics and then in the blood. Bacteria in the human colon produce vitamin K_2, but its absorption by the host is marginal at best and is unable to prevent vitamin K deficiency in the absence of oral vitamin K [5].

Clinical and Laboratory Consequences of Vitamin K Deficiency

Excess bleeding and bruising are the clinical hallmarks of vitamin K deficiency due to insufficient hepatic synthesis of fully functional coagulation factors X, IX, VII, and X. However, these are nonspecific symptoms which could be caused by accidental or abusive traumas, congenital or acquired coagulation factor deficiencies and primary hemostasis disorders, or complications of anticoagulation therapies. A symptomatic patient presenting with a normal activated partial thromboplastin time (aPTT) and minimal or moderate prolonged prothrombin time (PT) and International Normalized Ratio (INR) which correct after performing a PT/INR mixing study (patient plasma/normal

Table 18.1 Examples of human tissues expressing gamma glutamate carboxylase activity

Tissue	Substrate	Biological activity
Hepatocyte	Coagulation factors X, IX, VII, and II. Coagulation inhibitors proteins C, S, and Z	Formation and regulation of fibrin clot
Bone	Osteocalcin	Bone remodeling
Bone, soft tissue, blood vessel walls	Matrix Gla protein	Inhibit soft tissue calcium deposition

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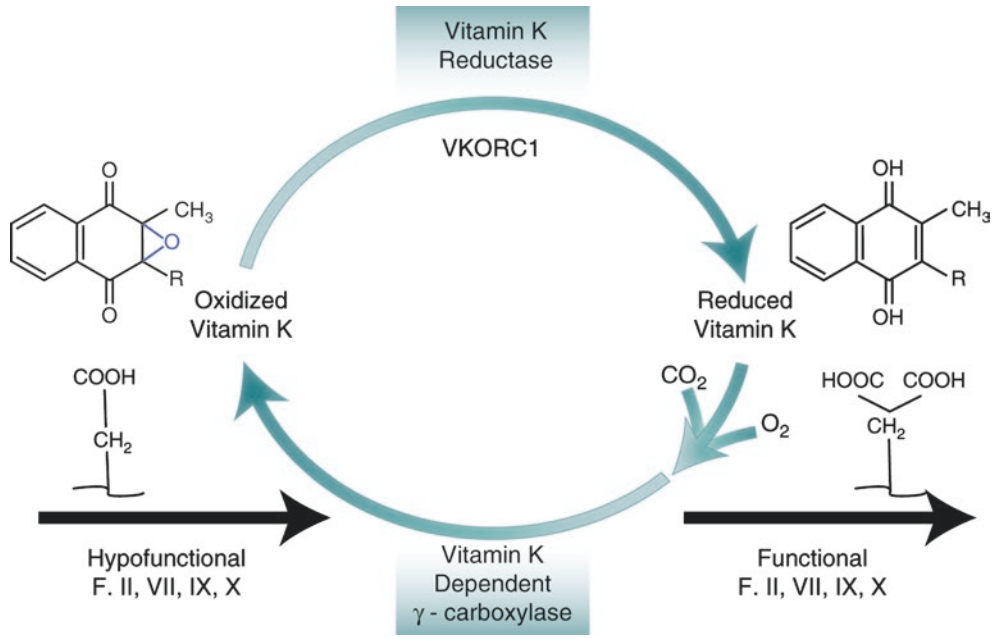

Fig. 18.1 Hepatic vitamin K cycle. Posttranslational gamma-carboxylation of selected glutamic acid residues converts hypofunctional proteins to functional coagulation factors (X, IX, VII, II) and regulators (proteins C, S, and Z), while the cofactor, reduced vitamin K, is converted to an oxidized epoxide. Vitamin K epoxide is recycled to reduced vitamin K by vitamin K reductase (VKOR)

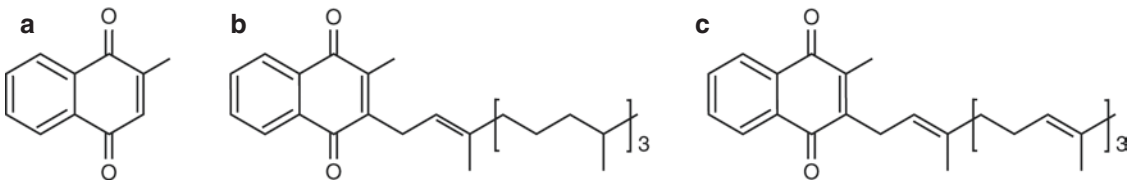

Fig. 18.2 Members of the vitamin K family have a common naphthoquinone ring and side chains of varying length and saturation. (**a**) Synthetic menadione, (**b**) plant-derived phylloquinone, and (**c**) an example of bacteria-derived menaquinone (MK4 with 4 isoprenyl units)

pooled plasma ratio 1:1) is also nonspecific and may be due to vitamin K deficiency or antagonism, acute or chronic causes of liver disease, disseminated intravascular coagulation (DIC), dilutional coagulopathy, or, rarely, a congenital deficiency of factor VII. More often, the first sign of acquired vitamin K deficiency is an unexpected prolonged PT/INR in an asymptomatic patient. The aPTT can be prolonged, and the PT/INR markedly prolonged, when the vitamin K-induced coagulopathy is severe. The PT/INR is actually an insensitive biomarker of vitamin K deficiency since it requires substantial reductions of factors X, VII, and II to produce a prolonged clotting time. A more sensitive biomarker is the concentration of circulating undercarboxylated prothrombin proteins induced by vitamin K absence (PIVKA-II) [6]. Commercial immunoassays are available for PIVKA-II, but none is designed for rapid performance on a coagulation instrument and reference ranges are method dependent. One group reported PIVKA-II levels of <2.4 ng/mL in healthy controls increasing to 750–13,400 ng/mL in patients on stable vitamin K antagonist anticoagulant therapy [6]. However, elevated PIVKA-II concentrations are not entirely specific for vitamin K deficiency and may be elevated due to hepatocellular carcinoma and other liver diseases [7]. Vitamin K deficiency also produces elevations of undercarboxylated osteocalcin and matrix Gla protein (MGP) [8]. Gamma-carboxylated osteocalcin maintains bone health by binding to hydroxyapatite mineral crystals [9]. Gamma-carboxylated MGP inhibits calcification in soft tissues and vessel walls. Calciphylaxis, also known as calcific uremic arteriolopathy, presents with painful skin lesions which progress to tissue necrosis due to calcification of small arterioles. This poorly understood, rare disorder occurs primarily in patients with end-stage renal disease. Likely risk factors include vitamin K antagonists like warfarin and nutritional deficiency of vitamin K causing undercarboxylation of MGP [10]. However, there is a lack of convincing evidence to date to support vitamin K supplementation to prevent osteoporosis, calciphylaxis, or generalized vascular damage [9, 10]. The measurement of vitamin K levels by high-performance liquid chromatography or mass spectrometry is available through some reference laboratories but is not clinically necessary for prevention, diagnosis, or management of vitamin K deficiency-induced coagulopathy.

Table 18.2 Patterns of vitamin K deficiency in newborns

Onset	Timing	Bleeding sites	Risk factors
Early	Day of birth	Scalp, intracranial, internal	Maternal drugs inhibiting vitamin K
Classic	2–7 days	GI, skin, circumcision, umbilicus	Idiopathic or second low breast milk intake, no vitamin K prophylaxis
Late	2–12 weeks	Intracranial, skin, GI	Idiopathic or second to poor nursing, temporary or disease-related malabsorption, no vitamin K prophylaxis

GI gastrointestinal tract

Table 18.3 Causes of vitamin K deficiency

Decreased oral intake	Malabsorption	Hospital acquired
Newborns	Biliary disease:	Interrupted oral intake
	Primary biliary cirrhosis	
	Primary sclerosing cholangitis	
	Biliary atresia	
	Alpha 1 antitrypsin deficiency	
Eating disorders	Pancreatic disease:	Increased vitamin K turnover
	Cystic fibrosis	
Parenteral nutrition without vitamin K supplement	Small intestinal disease:	Temporary malabsorption
	Celiac disease	
	Inflammatory bowel disease	
	Short bowel syndrome	
Anorexia due to chronic illness		Possible antibiotic interactions:
		Beta-lactam inhibition of VKOR
		Reduction of colonic bacteria vitamin K_2 synthesis

Newborn Vitamin K Deficiency

Hemorrhagic complications, or asymptomatic PT/INR prolongation, due to acquired vitamin K deficiency may occur at any age, including at birth. Newborn vitamin K deficiency bleeding (VKDB) (Table 18.2) is a rare hemorrhagic complication with potentially devastating consequences and can be prevented by oral or intramuscular (IM) vitamin K prophylaxis at birth [11]. Placental transfer of vitamin K from mother to fetus is inefficient causing all newborn infants to be relatively vitamin K deficient [12]. This is further complicated by immature hepatic synthesis of coagulation and regulatory factors at birth, a process which does not stabilize until 6–12 months old. Nevertheless, healthy term newborns have a balanced, if precarious, hemostasis system, provided they obtain sufficient postnatal vitamin K nutrition. Breast milk is an inefficient delivery system for vitamin K, and if either the mother's production or an infant's consumption of breast milk is insufficient, symptomatic bleeding and bruising may occur with concurrent prolongation of PT/INR and elevation of PIVKA-II. Due to the tenuous supply of vitamin K in breast milk, an infant who malabsorbs fat-soluble vitamin K due to subtle and temporary, or more severe and permanent, causes of biliary, small intestinal, or pancreatic insufficiencies is at risk for delayed newborn vitamin K deficiency. Table 18.3 outlines the three recognized presentations of newborn VKDB and associated causes [11]. While there are different newborn VKDB case definitions, the essential requirements include confirming a prolonged PT/INR compared to reference ranges for age-matched vitamin K-replete controls, ruling out other causes for bleeding including inherited coagulopathies, DIC, and thrombocytopenia, and demonstrating correction of the coagulopathy after administration of vitamin K. In developed countries, the incidence of classic or delayed newborn VKDB is approximately one per 5.0×10^5 births rising tenfold in some underdeveloped countries [11].

Prevention of newborn VKDB requires prophylactic vitamin K administration to all infants since there are no reliable risk stratification guidelines. Either a single IM injection of 0.5–1.0 mg vitamin K or oral doses of 2.0 mg of vitamin K at birth, repeated twice between weeks 2 and 8, are effective [13]. However, one IM injection is preferred over multiple oral doses of vitamin K due to higher rates of late VKDB with the latter route of administration [13]. Formulas provide ten times more vitamin K than breast milk and should be used to supplement or replace breast-feeding for infants who are struggling to obtain sufficient intake, especially if they did not receive prophylactic vitamin K. Unfortunately, some newborns do not receive vitamin K prophylaxis, either due to healthcare policy or resource disparities or due to parental refusal because of concerns about adverse consequences including cancer. However, a 1992 report of an association between IM vitamin K and subsequent increased risk for malignancies was not substantiated by subsequent investigators [14]. Parents who refuse IM vitamin K for a newborn must be compliant with multiple oral vitamin K doses.

Acquired Vitamin K Deficiencies

During childhood, adolescence, and adulthood, acquired abnormal bruising or bleeding due to vitamin K deficiency-induced coagulopathy is rare. However, humans maintain low reserves of vitamin K stores which can be readily

depleted without regular dietary intake. In populations at high risk for vitamin K deficiency, asymptomatic elevated PIVKA-II and PT/INR prolongation are common [15]. Causes of vitamin K deficiency may be divided into inadequate oral or parenteral intake, inadequate solubility from ingested foods, malabsorption, or acute medical and surgical conditions requiring hospitalization, and they are not mutually exclusive (Table 18.3).

Clinical experiments and patient data support the dominant role of dietary vitamin K_1 in gamma-carboxylation. Complete or partial deprivation of healthy controls of dietary sources of vitamin K_1 can produce clinically meaningful prolongation of the PT or elevation of PIVKA-II, respectively [16, 17]. Patients suffering from prolonged malnutrition due to eating disorders [18], cancer-related anorexia [19], and perioperative limited intake can become vitamin K deficient and have major bleeding complications in the absence of antibiotic therapy.

There are reports of acquired coagulopathies in part attributed to antibiotic-induced depletion of intestinal bacteria leading to acquired vitamin K deficiency [20, 21]. However, the extent of bacterial vitamin K_2 bioavailability to the human host remains controversial [3]. Anecdotal [22], and case control reports [23] linking vitamin K deficiency-induced coagulopathy to the beta-lactam class of antibiotics with N-methyl-thio-tetrazole (NMTT) (cefoxitin, cefamandole, cefotetan) or a methyl-thiadizaole (MTDT) side chain (cefazolin). Inhibition of hepatic gamma-carboxylase activity and reduction of oxidized vitamin K by side chains released from the parent beta-lactam are possible mechanisms [24, 25]. However, patients who experience antibiotic-related signs or symptoms of vitamin K deficiency usually have additional risk factors including poor nutrition.

Vitamin K Replacement

There are several options for correction of a vitamin K-deficient coagulopathy depending upon the clinical situation. If a patient is not experiencing major bleeding, then vitamin K_1 supplementation, either oral, if there is no barrier to absorption, or intravenous, will produce a dramatic rapid correction of the coagulopathy within ≤24 hours. The pharmacokinetics of replenishment of fully gamma-carboxylated factors X, IX, VII, and II are not consistent with de novo protein synthesis which would take several days. Most likely hepatocytes harbor hypo-gamma-carboxylated molecules which are rapidly carboxylated and secreted when reduced vitamin K cofactor becomes available. If a patient is actively bleeding or requires an urgent invasive procedure, infusion with a plasma-derived coagulation factor concentrate containing the four vitamin K-dependent factors, for example, Kcentra™, plus IV vitamin K_1 (5–10 mg), would be appropriate. However, when warfarin-induced coagulopathy is reversed with 5–10 mg of vitamin K_1, patients will be transiently "resistant" to resumption of warfarin until vitamin K stores return to baseline. In the United States, Kcentra™ is only approved to reverse warfarin-induced coagulopathy. Fresh frozen plasma would be a less efficient replacement therapy due to the large transfusion volume (10–20 mL/kg) required to partially and only temporarily replenish deficient vitamin K-dependent factor levels.

Patients with advanced hepatitis and cirrhosis and hepatocellular cancer frequently have moderately prolonged PT/INRs. The primary cause of the acquired coagulopathy is decreased hepatocyte protein synthesis due to the underlying disease, although PIVKA-II is elevated in some cases. It is common practice to administer vitamin K_1 to these patients prior to invasive procedures or during management of active bleeding in case vitamin K deficiency is a reversible contributor to the coagulopathy. However, vitamin K_1 supplements rarely shorten a prolonged PT/INR in patients with advanced liver disease [26, 27], and there are no randomized controlled trial data to assess the risk or benefit of this routine practice [28]. While there are no documented dose-dependent acute or chronic adverse consequences from oral vitamin K supplements, the risk of an anaphylaxis or hypersensitivity reaction during IV vitamin K administration is approximately 3 per 10,000 doses [29, 30].

Reversal of Vitamin K Antagonist: Warfarin and Rodenticides

Warfarin produces a hypocoagulable state by competing with oxidized vitamin K for the hepatic enzyme vitamin K reductase (VKOR), thus reducing the pool of reduced vitamin K to be a cofactor for gamma-carboxylation of factors X, IX, VII, and II and protein C, protein S, and protein Z [31]. The anticoagulant effect of warfarin will diminish over several days by holding future doses allowing gradual metabolism of warfarin. When it is necessary to more rapidly correct warfarin-induced coagulopathy, oral or IV vitamin K is more effective than the IM route. To treat or prevent acute bleeding complications, Kcentra™ is preferred over fresh frozen plasma due to lower risk of fluid overload [32].

Accidental or surreptitious ingestion of vitamin K antagonist rodenticides can result in a life-threatening coagulopathy [33], highlighted by an outbreak of major bleeding in patients using a synthetic cannabinoid adulterated with brodifacoum [34]. To combat warfarin resistance mutations in rat and mouse VKOR genes, biochemists synthesized "super-warfarin" molecules with greater potency for VKOR inhibition to prevent recycling of oxidized vitamin K. Table 18.4 provides brand names of some rodenticides and VKOR

Table 18.4 Examples of superwarfarin rodenticides and brand names

Examples of superwarfarin rodenticides	
Chemical name	Brand names
Brodifacoum	d-Con, Havoc, Final
Bromadiolone	Contrac
Difenacoum	Multi-kill
Flocoumafen	Storm
Bromethalin	Tom Cat, Just One Bite
Difethialone	First Strike
Diphacinone	Ramik

inhibitor molecules. The superwarfarins are highly lipophilic requiring weeks to months to completely eliminate them. Patients typically present with active bleeding and severe coagulopathies. Laboratory findings include dramatic prolongations of aPTT and PT which correct after mixing 1:1 with normal pooled plasma, normal fibrinogen and thrombin time (to rule out DIC and heparin), and normal factor V activity (a non-vitamin K-dependent clotting factor to rule out liver failure) activity and profound (typically <10% activity) deficiencies of factors X, IX, VII, and II. Reference toxicology laboratories can detect and characterize superwarfarins. However, this is not necessary in cases of accidental ingestion since treatment is not rodenticide specific. In the absence of evidence supporting accidental ingestion, the possibility of criminal or psychiatric causes should be entertained. Options to manage acute major hemorrhage due to rodenticides are the same as those used for warfarin. Unlike the need for cautious reversal of a prolonged PT/INR with vitamin K_1 in a patient taking warfarin to prevent thromboembolic events, aggressive dosing of vitamin K is indicated to correct a superwarfarin coagulopathy. Chronic treatment consists of daily ingestion of milligram doses of vitamin K_1, guided by PT/INR monitoring, to support hepatic gamma-carboxylation of coagulation factors without recycling of oxidized vitamin K [33] until the rodenticide is metabolized.

Summary

1. Vitamin K is an essential cofactor for posttranslational gamma-carboxylation modification of multiple proteins. The most important clinical consequence of vitamin K deficiency is acquired coagulopathy due to defective synthesis of factors X, IX, VII, and II by hepatocytes.
2. Dietary sources of vitamin K include green vegetables (K_1), foods containing K_2 produced by bacteria, and liver. Intestinal bacteria produce vitamin K_2, but its bioavailability to the human host appears to be limited.
3. Neonates are the most vulnerable population to vitamin K deficiency bleeding complications. Parenteral vitamin K supplementation at birth dramatically reduces this risk.
4. During childhood and adulthood, regional or systemic disorders affecting intake or absorption of fat-soluble vitamin K may lead to asymptomatic coagulopathies and rarely to overt serious hemorrhage.
5. Acutely ill patients can quickly become vitamin K deficient due to exhaustion of limited reserves, inadequate oral intake, and malabsorption. Antibiotic-induced alterations in the intestinal microbiome and select beta-lactam side chain interference with hepatic synthesis are unlikely to be major causes of clinically important vitamin K deficiency in the absence of other risk factors.
6. Superwarfarin rodenticide ingestion causes prolonged vitamin K antagonism which is managed with daily oral vitamin K supplementation until the poison is eliminated.

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Bleeding in Uremia

19

Jens Lutz and Julia Weinmann-Menke

Introduction

Bleeding episodes substantially contribute to morbidity and mortality in patients with end-stage renal disease. Here, uremia with the accumulation of uremic toxins plays an important pathogenic role [1]. In particular, an impaired function of platelets, the disturbed interaction between the vessel wall with its endothelium and its extracellular matrix with the platelets, and anemia are all involved in the complex problem of the increased bleeding tendency in uremic patients [1, 2]. Bleeding episodes occur in 24–50% of patients on hemodialysis (HD) [3–5]. A hospital-based analysis reported an approximately twofold increased risk of bleeding in patients with renal failure [6]. Furthermore, bleeding events and access site bleeding requiring transfusion were significantly associated with degrees of renal insufficiency in patients undergoing percutaneous coronary intervention [4]. Clinically, an increased bleeding tendency in patients with renal failure may present as gastrointestinal bleeding, bleeding from cannulation sites, retinal hemorrhage, subdural hematoma, epistaxis, hematuria, ecchymosis, purpura, bleeding from the gums, gingival bleeding, genital bleeding, hemoptysis, telangiectasia, or hemarthrosis [4, 5].

Anticoagulants, particularly direct oral anticoagulants (DOACs) with their potential to accumulate in patients with renal failure, may further interfere with this system, thus promoting bleeding episodes in such patients [7]. While DOACs were associated with a non-statistically significant decreased risk for major bleeding compared to vitamin K antagonist in patients with eCrCL (estimated creatinine clearance) <50 mL/min, they differ from each in their relative risk, with only apixaban and edoxaban being associated with a decreased risk while rivaroxaban and dabigatran are not [8].

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Pathophysiology of Bleeding in Patients with Uremia

Clot Formation and Platelets

Patients with advanced chronic kidney disease seem to have an increased clot strength [9–11]. Furthermore, the clot formation is delayed and lysis is decreased in these patients, which is associated with increased fibrinogen levels. A delayed clot formation may predispose to bleeding complications in patients with advanced chronic kidney disease, while the increased clot strength and decreased breakdown may be related to thrombosis [6, 12]. This increased clot strength seems to be associated with increased levels of fibrinogen in patients with advanced chronic kidney disease [13]. This could be a compensatory mechanism to regulate the deranged hemostasis in these patients [10, 14]. Thus, increased levels of fibrinogen and increased clot strength could be also responsible for the thrombotic events in chronic kidney disease patients. Patients on hemodialysis on the other hand have a decreased clot strength and increased lysis as compared to chronic kidney disease patients not on dialysis. This could be related to the decreased levels of fibrinogen and von Willebrand factor (VWF) or increased tissue plasminogen activator levels after dialysis [15, 16].

However, platelet function itself is also heavily disturbed in uremia [1, 8]. This is emphasized by the observation that platelet function returns to normal after successful kidney transplantation [17]. The pathogenesis of bleeding complication is believed to be multifactorial, including an acquired platelet function disorder characterized by reduced integrin activation and aggregation in response to agonist stimulation [18]. On the other hand, a study in patients with chronic kidney disease undergoing percutaneous coronary

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intervention showed that the prevalence of high residual platelet reactivity for ADP was higher among patients with more severe chronic kidney disease (CKD G 3–5) [19]. High residual platelet reactivity was not associated with major cardiocirculatory events in a 2-year follow-up of these patients. Interestingly bleeding risks were significantly lower in patients with high residual platelet reactivity for ADP.

Uremic toxins such as phenol, phenolic acid (impairment of primary aggregation to ADP), and guanidinosuccinic acid (inhibition of the second wave of ADP-induced platelet aggregation) influence platelet function [20–22] although a correlation between the bleeding time and the concentration of the dialyzable uremic metabolites was not detected so far [23]. However, dialysis improves platelet function and reduces the bleeding risk [24–28]. Urea itself does not seem to interfere with platelet function [29]. Platelet components such as α-granules [25, 30] have an increased ATP/ADP ratio and a reduced content of serotonin in uremia. Furthermore, the thrombin-triggered release of ATP together with an increased calcium content and a disturbed intracellular calcium flux could contribute to the impaired platelet function in uremia [25]. The disturbed arachidonic acid and prostaglandin metabolism with an impaired synthesis and/or release of thromboxane A2 leads to a reduced adhesion and aggregation of platelets contributing to bleeding episodes [25, 31], which can be reversed by dialysis [32]. In addition, ultrafiltrates collected from uremic patients inhibited platelet-activating factor synthesis that could account for the decreased platelet activity [33]. Furthermore, circulating fibrinogen fragments have been demonstrated that can also interfere with hemostasis as they competitively bind to the glycoprotein (GP) IIb/IIIa receptor on platelets resulting in a decreased adhesion and aggregation potential of platelets [34]. Oxidative stress and inflammation also have a profound effect on platelet function [35].

Platelet–Vessel Wall Interactions

A decreased amount of GPIb on platelets [4] together with the insufficient binding of VWF and fibrinogen to activated platelets from uremic patients can reduce the function of the GPIIb/IIIa complex that is important for the binding of platelets to the vessel wall in order to stop bleeding. In addition, a functional defect in VWF–platelet interaction can be related to an increased bleeding tendency in uremic patients [36, 37].

Moreover, vasoactive substances such as nitric oxide (NO), inhibiting platelet aggregation through the formation of cGMP, or prostacyclins, which modulate vascular tone, can also play a role in defective hemostasis in uremia. Plasma levels of prostacyclin, NO generation of platelets, and the concentration of NO metabolites, which is also related to the lower hemoglobin levels (see below), are increased in the plasma of uremic patients, thus contributing to dysfunctional hemostasis with an increased bleeding risk [38, 39].

Anemia

Anemia can promote bleeding episodes in uremic patients as it directly influences the bleeding time [40–42]. In anemia platelets flow in the middle of the bloodstream due to the lower number of erythrocytes. This impairs the interaction between platelets and the vessel wall resulting in a prolonged bleeding time. And erythrocytes significantly improve platelet adhesion and aggregation in in vitro flow chamber systems, and negative correlations have been found between hematocrit and bleeding time. Furthermore, the low number of erythrocytes with a reduced hemoglobin amount leads to a reduced scavenging of NO [43], thus decreasing ADP and thromboxane A2 release via an enhanced activation of guanylyl cyclase [44] with increased cGMP levels. This inhibits platelet aggregation and inactivation of prostacyclin [45]. Consistently, erythropoietin treatment has a beneficial effect on the bleeding time, but not platelet activation, in renal failure patients [18].

Drugs

Drug–platelet interactions have fundamental effects on platelet function and thus on bleeding disorders, which is also the case in patients with uremia. Antibiotics such as third-generation cephalosporins and β-lactam antibiotics play a role under these circumstances [46, 47]. β-Lactam antibiotics interact with platelets through an interference with ADP receptors. These effects are related to dose and duration of the therapy. Acetylsalicylic acid has been shown to significantly prolong the bleeding time in patients with renal failure [48]. Furthermore, other nonsteroidal anti-inflammatory drugs also alter platelet function through the inhibition of cyclooxygenase, although this is reversible after discontinuation of the drug.

As many anticoagulants are eliminated by the kidney, they can accumulate if their dose is not adapted to the patient's renal function [7]. Anticoagulants that can accumulate in patients with renal impairment include low-molecular-weight heparins (LMWHs), direct factor Xa inhibitors like danaparoid and fondaparinux, and the DOACs such as rivaroxaban, edoxaban, or apixaban as well as the direct thrombin inhibitors refludan and dabigatran. Interestingly, the effect of vitamin K antagonists such as phenprocoumon or warfarin could be aggravated in patients with end-stage renal disease as these patients can develop a vitamin K deficiency [49].

Discussions on the use of the different anticoagulants at different stages of chronic kidney disease are presented in a comprehensive recent review [50].

Management of Bleeding in Patients with Uremia

Management of bleeding in patients with uremia encompasses substances, blood compounds, and procedures that can be used alone or partly in combination (see Table 19.1). However, it must be emphasized that while treating bleeding episodes in uremic patients with potential comorbidities, clot formation is promoted that could lead to other clinical problems in terms of thrombus formation or embolism at other sites (i.e., myocardial ischemia, fistula occlusion).

Table 19.1 Management of bleeding in uremic patients

	Dose	Comment
Dialysis	Individually adequate	PD with better platelet aggregation than HD
Erythropoietin	40–150 U/kg	Target Hb 10.5–11.5 g/dL (see text)
Vasopressin analogues	0.3–0.4 µg/kg as a single dose s.c.	Tachyphylaxis; repeat doses are not effective
	0.3–0.4 µg/kg over 30 min. i.v.	
Conjugated estrogens	0.6 mg/kg/day i.v. for 5 days	Effect lasts 4–5 days
	50 mg/kg/day p.o.	
	50–100 µg/day (patch)	
Fresh frozen plasma	2–3 units	Contains all coagulation factors; use in patients with vitamin K antagonist overdose
Cryoprecipitate	Bags (n) = 0.2 × weight (kg) → provide about 100 mg/dL fibrinogen	Use in hypofibrinogenemia (fibrinogen <1 g/L)
	Standard dose: 10 units; repeat if needed	
Factor VIIa	90 µg/kg i.v. bolus every 2 h until hemostasis	Successful use documented in case reports
	Continue every 3–6 h after hemostasis achieved according to clinical judgment	
Platelet transfusion	1 apheresis unit or equivalent	Emergencies; alloimmunization in transplant candidates possible
Tranexamic acid	20 mg/kg every 48 h i.v.	Not over longer time periods; accumulation in renal failure
	10 mg/kg every 48 h p.o.	

PD peritoneal dialysis, *HD* hemodialysis

Dialysis

Uremic toxins contribute to the bleeding tendency in patients with end-stage renal disease. The removal of uremic toxins by dialysis improves platelet function with a reduced risk of bleeding [24–28]. On the other hand, hemodialysis itself can enhance the bleeding tendency, due to the intradialytically administered anticoagulants (i.e., heparin) but also due to continuous platelet activation at the dialyzer membrane resulting in a decreased platelet activity [28, 51, 52]. Furthermore, an activation defect of the platelet GPIIb/IIIa complex could be involved in the bleeding tendency of some patients related to hemodialysis [24] as the expression of the GPIIb/IIIa receptor on thrombocytes is higher in peritoneal dialysis [53], which has been shown to maintain in vitro platelet aggregation better as compared to hemodialysis [54]. Moreover, peritoneal dialysis was associated with better platelet aggregation as compared to hemodialysis [55]. The reasons include apart from anticoagulant administration during hemodialysis also the removal of pro-coagulation factors, platelet loss related to the dialyzer, disruption of platelet cytoskeleton, a decrease of RNA-rich platelets, and a reduction of reticulated platelets [56]. Furthermore, a better elimination of middle molecules could be responsible for the advantages of peritoneal dialysis with respect to hemodialysis [54]. However, it is not known how actual dialysis procedures such as hemodiafiltration (HDF) compare to peritoneal dialysis as also HDF effectively eliminates middle molecules. Of note, hemodialysis and peritoneal dialysis could also promote coagulation [57, 58].

Future studies should analyze the effect of modern dialysis techniques (i.e., HDF) or an increase in dialysis time on the bleeding tendency of uremic patients.

Erythropoietin

Chronic kidney disease, particularly in advanced stages, is associated with anemia due to the lack of erythropoietin (EPO). As anemia is associated with an increased bleeding tendency in uremia, the administration of erythrocytes [59] or EPO [60, 61] reduces the bleeding time as well as bleeding episodes. Administration of recombinant erythropoietin leads to an increased number of erythrocytes, thus shifting platelets more to the vessel wall where they can interact with injured sites and stop bleeding [61–63]. Furthermore, the number of reticulated platelets with an increased metabolic activity is higher after the administration of EPO [64, 65], the platelet aggregation and the platelet interaction with the

sub-endothelium is higher [61–63], and erythropoietin improves platelet signaling through tyrosine phosphorylation [66]. Additionally, the scavenging capacity of NO is improved with higher hemoglobin levels after EPO therapy resulting in a lower stimulation of guanylyl cyclase with reduced production of cGMP leading to an improved platelet aggregation (see above) [43].

EPO at a dose of 40–150 U/kg intravenously three times a week has been studied in uremic bleeding [61, 63, 64]. A hematocrit greater than 30% is associated with a normalization of the bleeding time [61–63]. The effect occurs rather slowly after 7 days. However, EPO can be beneficial also in an acute setting as it can improve platelet function by increasing the number of GPIIb/IIIa receptors on platelets as well as increasing thrombin-induced phosphorylation of platelet proteins [62, 63, 66]. Thus, it can be used in acute bleeding episodes but also as a prophylaxis.

However, problems exist with the target parameter: the 2012 KDIGO (Kidney Disease Improving Global Outcomes) guidelines for the management of anemia in patients with renal failure refer to the hemoglobin level as the target parameter for the guidance of the EPO therapy which should be ≤11.5 g/dL as higher hemoglobin levels were associated with an increased incidence of myocardial infarction and a higher mortality [67]. The hematocrit is more variable and should be used with caution as a target parameter. Furthermore, a potential deficit of iron should also be treated before the administration of EPO can be effective. Thus, EPO should be used with caution in patients with bleeding episodes only if anemia is present with a hemoglobin below 10.5 g/dL and normal iron stores.

Vasopressin Analogues

Bleeding disorders can be treated with desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) in patients with end-stage renal disease [37]. Most studies analyzed the bleeding time that cannot properly predict the bleeding tendency in uremic patients [56]. However, also with the in vitro closure time test, the beneficial effects of desmopressin on primary hemostasis could be demonstrated [68]. A prospective non-controlled study in uremic patients on antiplatelet drugs demonstrated that a single dose of desmopressin before invasive procedures could improve platelet function measured by collagen/epinephrine closure time of PFA-100™ and was also well tolerated [69]. Furthermore, it can be also used as a prevention of bleeding episodes in such patients (i.e., renal biopsies, endoscopy, and surgery). It is administered at a dose of 0.3–0.4 μg/kg as a single dose subcutaneously or over 30 min intravenously. Both administration routes can effectively restore primary hemostasis in uremic patients [70]. So far no data exist on orally administered desmopressin although it should also be theoretically effective. Due to its rapid onset, it is recommended as the first-line treatment in uremic patients with active bleeding [56]. However, its effect reaches its maximum after 4–6 h and has nearly vanished after 8–24 h [37]. Even after one dose, tachyphylaxis might occur; thus its duration of activity is rather short [56] and treatment should not be repeated after one dose [56]. In patients with antiplatelet drugs [69] as well as heparin, desmopressin can also reduce the prolonged bleeding time [71]. Its mechanism of action is an increase of VWF, factor VIII, and tissue plasminogen activator (tPA) from storage sites mediated via the activation of vasopressin V2R receptors on endothelial cells. Plasminogen activator inhibitor 1 (PAI-1) level is diminished due to tPA release and tPA and PAI-1 complex formation. Furthermore, functional protein C level is also decreased in patients with uremia after administration of desmopressin [5, 72, 73]. Furthermore, it increases the expression of GPIb on platelets [72]. This minimizes the effects of dysfunctional VWF and leads to larger VWF multimers that reduce bleeding time [74, 75].

Conjugated Estrogens

Bleeding episodes can be also treated with conjugated estrogens in patients with uremia [76–80]. A double-blind randomized crossover study revealed that the administration of estrogens (0.6 mg/kg/day i.v. for 5 days) leads to a reduced bleeding time as well as an increased platelet activity in patients on hemodialysis [81]. The therapeutic effect was achieved for 7–14 days after treatment where the effect starts already 6 h after administration of the substance. An oral dose of 50 mg/kg/day leads to a measurable reduction of the bleeding time 2 days after administration and lasts for approximately 4–5 days [72, 82]. Furthermore, a transdermal estradiol patch with a dose of 50–100 μg/day can be applied twice a week [83]. This approach is also suitable for longer treatment periods as it was used for 2 months during this study. Even transdermal doses ≤50 μg daily might be effective [84]. Successful treatment of nasal bleeding has also been achieved with topical intranasal estrogens in patients with von Willebrand disease and hemophilia [85].

An increase of platelet reactivity could be mediated through the increase of β-thromboglobulin and thromboxane B_2 as well as an increased synthesis of VWF and factor VIII together with a reduction of protein S levels [5]. Furthermore, uremia is associated with an increased generation of endothelium-derived NO [86], which can be prevented by estrogens [87]. Estrogens need more time until the therapeutic effect begins, while its duration is substantially longer in comparison to desmopressin [76].

Fresh Frozen Plasma, Cryoprecipitate, and Factor VIIa

Cryoprecipitate contains substantial amounts of VWF, factor VIII, fibrinogen, factor XIII, and fibronectin and thus can immediately correct defects in primary hemostasis. However, this effect will last for only 4–12 h [5, 36, 45]. It should be used only in emergency situations where a rapid correction of hemostatic defects is needed, particularly if hypofibrinogenemia with fibrinogen levels <1 g/L is present [72]. However, the effect in patients with end-stage renal disease is difficult to predict [36, 37, 88]. Infections, anaphylactic reactions, and volume overload could be adverse reactions in patients with renal failure [5, 72]. In contrast to cryoprecipitate, fresh frozen plasma contains all coagulation factors and should be used in patients with severe bleeding due to warfarin or phenprocoumon therapy where cryoprecipitate is not effective due to its low content in vitamin K-dependent coagulation factors [89].

Moreover, some case reports describe the use of recombinant activated factor VII (rFVIIa) for treatment of bleeding in uremic patients [90–93]. This approach seems attractive, as it should act only locally at the site of bleeding [94]. Thus, it has been successfully used also in a patient with bleeding after a kidney biopsy [94]. However, due to the lack of studies, only little experience exists with the use of rFVIIa in uremic patients.

Platelet Transfusion

Platelet transfusions are immediately effective in reducing the bleeding risk for approximately 4–5 h [5]. This approach should be used in emergency situations if immediate correction is warranted or if the pharmacologic approach is not effective. In transplant candidates a risk of alloimmunization, although low, exists [5].

Tranexamic Acid

Tranexamic acid inhibits fibrinolysis by forming a reversible complex with plasminogen and preventing its conversion to plasmin [5]. It can be administered orally or intravenously [72, 95]. Tranexamic acid effectively stops cerebral, gastrointestinal, or angiodysplasia-associated bleedings of the colon in patients on hemodialysis [96–98]. However, as it is eliminated via the kidneys, the dose should be limited to 20 mg/kg every 48 h i.v. or 10 mg/kg every 48 h p.o. [72]. Thus, tranexamic acid should not be administered over longer time periods. Single doses of tranexamic acid can be combined with other compounds in uremic patients in order to control bleeding.

Summary

Uremia develops in patients with end-stage renal disease without an adequate renal replacement therapy. Bleeding episodes are a significant clinical problem in such patients. They could be of mild character but could also result in fatal outcomes. The increased bleeding tendency in uremia results from an impaired function of platelets and a disturbed platelet–vessel wall interaction. Furthermore, anemia and anticoagulants/antiplatelet drugs contribute to the increased risk of bleeding in these patients. Management of bleeding episodes in uremic patients includes an adequate dialysis for the removal of uremic toxins that could interfere with the function of platelets and the correction of anemia with EPO in order to increase the number of red blood cells that shift platelets more to the vessel wall where they can interact with sites of injury as well as a better capacity to scavenge NO through increased amounts of hemoglobin. Furthermore, estrogens can be administered that alter VWF, factor VIII, compounds of the arachidonic acid metabolism, and the production of NO. Desmopressin improves platelet function through the release of VWF and factor VIII. In severe cases, also fresh frozen plasma or rFVIIa can be administered. Moreover, tranexamic acid that inhibits the conversion of plasminogen to plasmin can be given. In severe bleeding episodes, also combinations of the above therapeutic approaches can be considered (Table 19.1).

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Bleeding Associated with Connective Tissue Disorders

20

Dominder Kaur and Bryce A. Kerlin

Introduction

Connective tissue, being the most abundant form of tissue in the body, plays essential roles in many systemic functions [1]. For hemostasis, connective tissue is important as a major component of the vessel wall and its surrounding tissue. Virchow's triad notes the importance of vessel wall integrity in blood clotting and deems it equivalent to that of the coagulation system as well as of the blood flow dynamics [2]. Connective tissue disorders are implicated in bleeding disorders due to alteration of this interaction between vessel wall, platelets, and coagulation proteins and due to the inherently increased vessel wall and subcutaneous tissue fragility.

Connective tissues are primarily comprised of collagen, elastic fibers, glycoproteins, and proteoglycans [3]. The collagen family of proteins together make up many extracellular matrix and structural vascular materials. Collagen types I and III (and type V in a supportive role) are important components of the vessel wall. Type IV collagen is the primary structural and networking protein of the subendothelial basement membrane. Inheritable defects in these proteins lead to modified local cellular interactions and may result in bleeding manifestations.

Role of Connective Tissue in Hemostasis

Exposure of subendothelial collagen at sites of vessel injury is the initial stimulus for platelet adhesion, activation, and aggregation. Platelets bind directly to collagens I through IV via their glycoprotein (GP) VI receptor [4]. Indirectly, von Willebrand factor (VWF) binding to exposed collagen induces a conformational change of the VWF A1 loop that supports platelet-VWF binding via the platelet glycoprotein Ib-IX-V receptor complex. This binding leads to platelet activation and supports the subsequent processes leading to hemostatic plug formation at sites of vessel injury.

The common connective tissue disorders known to be associated with bleeding are Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, and few other non-specific benign hypermobility syndromes.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a conglomerate of heritable collagen disorders that manifest with skin and connective tissue hyperextensibility, laxity, and friability [5]. EDS affects about 1 in 5000 people [6]. There are 13 heterogeneous EDS clinical subtypes that result from collagen or collagen-related defects [7, 8]. Collagen forms an essential part of vascular basement membranes and vessel walls and may thus result in vascular fragility. Thus, it is unsurprising that some degree of easy bruising is noted in almost all EDS subtypes [9]. Other features include joint laxity, generalized hypermobility and hyperextensibility, thin skin with increased injury propensity, and vascular friability.

Here, we will focus on the EDS subtypes that have bleeding as a common manifestation. These are classical EDS, hypermobile EDS, and vascular EDS. All three of these are primarily transmitted in an autosomal dominant fashion.

Classical EDS

Classical EDS (cEDS) is diagnosed based on clinical findings, but more than 90% of cEDS patients have at least one of two major criteria (skin hyperextensibility/atrophic scarring and generalized joint hypermobility) or one major crite-

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rion and at least three minor criteria (Table 20.1) for the cEDS diagnosis [8]. Molecular genetic testing (through targeted sequencing/gene panel) for COL5A1 and COL5A2 genes can help confirm diagnosis. The bleeding manifestations in these patients are typically mild (e.g., bruising, gum bleeding, bleeding after tooth extraction).

Hypermobile Ehlers-Danlos Syndrome

Hypermobile EDS (hEDS) is the most prevalent of all types of EDS, but its genetic pathophysiology is not yet well defined. The diagnosis, thus, relies on clinical findings. In order to guide correct identification and reduce clinical heterogeneity in hEDS, the 2017 EDS classification proposes meeting strict criteria for this diagnosis. The primary criterion is generalized hypermobility, and other criteria are focused on systemic manifestations (soft velvety skin, skin hyperextensibility, recurrent or multiple hernias, atrophic scarring, narrow palate, mitral valve prolapse, and aortic root dilatation) and musculoskeletal complications (joint pain and/or joint dislocation). Bleeding in hEDS is similar to cEDS. Women with EDS and other connective tissue disorders are prone to heavy menstrual bleeding.

Vascular Ehlers-Danlos Syndrome

Vascular EDS (vEDS) is associated with severe and potentially fatal complications (e.g., arterial aneurysm, spontaneous dissection, and rupture) leading to a poor prognosis [10]. Fortunately, it is much less common with an estimated prevalence of only 1 in 90,000 [7]. The hallmarks of vascular EDS (vEDS) are abnormal and friable medium- to large-sized vessels. The most common mutation in vEDS is in the COL3A1 gene [11]. Bleeding issues may manifest earlier in vEDS than in other EDS subtypes and may present in toddlers and school-aged children. Initial symptoms may include epistaxis, easy bruising, gum bleeding, and other oral bleeding. The more concerning manifestations are those with spontaneous vessel wall rupture, which can occur in any anatomic location (e.g., aorta, abdominal, or pulmonary vessels) [12]. Bleeding from arterial rupture can prove life-threatening.

Table 20.1 2017 Classification for Ehlers-Danlos syndrome [8]

Type	Diagnosis requirement	Major criteria	Other criteria detail
Classical EDS (cEDS)	Major criterion (1) skin hyperextensibility and atrophic scarring *plus* Either formating major criterion (2) GJH OR at least 3 minor criteria Confirmatory molecular genetic testing is *also obligatory* (in COL5A1, COL5A2, COL1A1, and COL1A2 genes)	(1) Skin hyperextensibility and atrophic scarring (2) Generalized joint hypermobility (GJH) [≥5 out 9 on Beighton score]	*Minor criteria for cEDS* 1. Easy bruising 2. Soft, doughy skin 3. Skin fragility (or traumatic splitting) 4. Molluscoid pseudotumors 5. Subcutaneous spheroids 6. Hernia (or history thereof) 7. Epicanthal folds 8. Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot) 9. Family history of a first-degree relative who meets clinical criteria
Vascular EDS (vEDS)	A family history of vEDS, arterial rupture or dissection in individuals ≤40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vEDS followed by specific diagnostic studies. Testing for vEDS should also be considered in the presence of a combination of the other "minor" criteria Identification of a causative variant in one allele of COL3A1 is *also obligatory*	(1) Family history of vEDS with documented causative variant in COL3A1 (2) Arterial rupture at young age (3) Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology (4) Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears (5) Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma	*Minor criteria for vEDS* 1. Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back 2. Thin, translucent skin with increased venous visibility 3. Characteristic facial appearance 4. Spontaneous pneumothorax 5. Acrogeria 6. Talipes equinovarus 7. Congenital hip dislocation 8. Hypermobility of small joints 9. Tendon and muscle rupture 10. Keratoconus 11. Gingival recession and gingival fragility 12. Early-onset varicose veins (under age 30 and nulliparous if female)

Table 20.1 (continued)

Type	Diagnosis requirement	Major criteria	Other criteria detail
Hypermobile EDS (hEDS)	Simultaneous presence of criteria (1) AND (2) AND (3) Criterion (1): Generalized joint hypermobility (GJH) Criterion (2): Two or more among the features (A–C) MUST be present (e.g., A and B; A and C; B and C; A and B and C) Criterion (3): All the prerequisites MUST be met Molecular genetic basis for hEDS remains unknown	*Feature A*: systemic manifestations of a more generalized CTD (a total of 5 must be present): 1. Unusually soft or velvety skin 2. Mild skin hyperextensibility 3. Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts, and/or abdomen in adolescents, men, or prepubertal women without history of significant gain/loss of body fat or weight 4. Bilateral piezogenic papules of heel 5. Recurrent or multiple abdominal hernia(s) (e.g., umbilical, inguinal, crural) 6. Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in cEDS 7. Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women without a history of morbid obesity or other known predisposing medical condition 8. Dental crowding and high/narrow palate 9. Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Steinberg sign) on both sides; (ii) positive thumb sign (Walker sign) on both sides 10. Arm span-to-height ≥1.05 11. Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria 12. Aortic root dilatation with Z-score >+2 *Feature B:* positive family history with one or more first-degree relatives *Feature C:* musculoskeletal complications (must have at least one): (1) Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months, (2) chronic, widespread pain for ≥3 months, (3) recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b): **a.** ≥3 atraumatic dislocations in the same joint or ≥ 2 atraumatic dislocations in two different joints occurring at different times **b.** Medical confirmation of joint instability at 2 or more sites not related to trauma *Prerequisites:* (1) Absence of unusual skin fragility, which should prompt consideration of other types of EDS. (2) Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. (3) Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g., myopathic EDS, Bethlem myopathy), other HCTD (e.g., other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g., OI)	

Generalized/Peripheral Hypermobility Spectrum Disorder (HSD)

There are other connective tissue disorders that lie on the EDS/hypermobility spectrum that have evidence of joint hypermobility (JH), but do not meet all the criteria to be diagnosed as an EDS subtype using the 2017 diagnostic system [8]. Patients with HSD may have evidence of hypermobility in some joints (e.g., peripheral JH in hands/feet), may be asymptomatic, or may have only localized symptoms (single joint or body part affected). The 2017 nosology recognizes that conditions with evidence of JH may fall somewhere on the hypermobility spectrum but in order to better understand various manifestations of EDS, diagnosis of its subtypes now requires specific clinical findings. Therefore, even though the hypermobility disorders may be related, difference in HSD from the various subtypes of EDS, especially hEDS, is primarily based upon the inability to meet all diagnostic criteria for other EDS subtypes per the 2017 classification (Table 20.1). Bleeding manifestations in persons with HSD are typically mild because the collagen defects are likely not as disruptive. Easy bruising and slightly prolonged skin and mucus membrane bleeding may be seen in these patients, with hemostatic management being similar to that of hEDS.

Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) is a more recently described connective tissue disorder that can be associated with increased bruising and bleeding tendency [13]. LDS is an autosomal dominant disorder, emanating from mutations in the transforming growth factor β receptor I (TGFBR1) and transforming growth factor β receptor II (TGFBR2) genes. Both of these receptors are important mediators in collagen regulation. Organ systems affected include skin, musculoskeletal, and cardiovascular. There is substantial phenotypic overlap with both vascular EDS and Marfan syndrome due to the propensity toward large vessel aneurysms and major hemorrhage. Hemorrhage from vessel wall dissection may be seen early in life in patients with LDS (as young as 3 months old). Typical features include hypertelorism, cleft palate, craniosynostosis, cardiac anomalies, as well as tortuous and aneurysmal arteries. Complications like aortic dissection, cerebral hemorrhage, and uterine rupture in women may prove fatal [14]. Thin and velvety skin with easy bruising is commonly present in LDS with mild cutaneous bleeding symptoms.

Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue affecting nearly 1 in 5000 people [15]. MFS is an autosomal dominant condition with multisystem manifestations occurring at all stages of life. It affects the skeletal, integumentary, ocular, respiratory, and cardiovascular systems and has frequently been identified to have major as well as minor hemorrhagic complications.

The defect in MFS is most commonly due to mutations in the FBN1 gene which encodes fibrillin-1 protein [16]. Fibrillin-1 is a microfibrillar protein that provides structural support in connective tissues via polymerization and interaction with other microfibrillar proteins (e.g., elastin). Due to the defective microfibril production in MFS, a wide range of phenotypic manifestations may be seen in all major organ systems. Common features found in patients with MFS include ectopia lentis, cardiovascular issues like mitral valve prolapse and aortic root dilatation, arachnodactyly, increased arm span, joint laxity, pectus excavatum, kyphoscoliosis, and skin striae [17]. The diagnosis can be established clinically using the revised Ghent nosology (Table 20.2), which assigns a score for physical features. For young patients, subtle evidence with few physical features and some cardinal features (e.g., aortic root dilatation or lens dislocation) should prompt testing for mutations in FBN1 [18]. Easy bruising is a common issue, but more severe hemorrhage can be seen in patients with MFS due to vessel friability.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) or "brittle bone disease" is an inheritable disorder of bone fragility resulting from defects in type I collagen (encoded by the COL1A1 and COL1A2 genes). It is a form of skeletal dysplasia and can have physical manifestations and evident features present as early as infancy. It is inherited in an autosomal dominant fashion

Table 20.2 Marfan syndrome diagnostic criteria per revised Ghent Nosology [55]

Based on presence/absence of family history:	Scoring of systemic features of MFS
In the absence of family history: 1. Aortic root diameter (Z-score ≥2) AND ectopia lentis = MFS* 2. Aortic root diameter (Z-score ≥2) AND causal FBN1 mutation = MFS 3. Aortic root diameter (Z-score ≥2) AND systemic score ≥7 points = MFS* 4. Ectopia lentis AND causal FBN1mutation with known aortic root dilatation = MFS	1. Wrist & thumb sign – *3 points* (wrist or thumb sign – *1 point*) 2. Pectus carinatum deformity – *2 points* (pectus excavatum or chest asymmetry – *1 point*) 3. Hindfoot deformity – *2 points* (plain pes planus – *1 point*) 4. Protrusio acetabuli – *2 points* 5. Reduced upper segment/lower body segment ratio and increased arm/height and no severe scoliosis – *1 point* 6. Scoliosis or thoracolumbar kyphosis – *1 point* 7. Reduced elbow extension – 1 point 8. Facial features (3/5) – 1 point (dolichocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, retrognathia) 9. Pneumothorax – 2 points 10. Skin striae – 1 point 11. Myopia >3 diopters – 1 point 12. Mitral valve prolapse (all types) – 1 point 13. Dural ectasia – 2 points Maximum total score points of 20 points can be obtained Systemic features 1–8 are considered as "skeletal score," while systemic features 9–12 are considered "non-skeletal score"
In the presence of family history: 5. Ectopia lentis and family history of MFS (as defined above) = MFS 6. Systemic score ≥7 points and family history of MFS = MFS* 7. Aortic root diameter (Z-score ≥2 above 20 years old, ≥3 below 20 years) and family history of MFS (as defined above) = MFS* *Caveat: without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular form of Ehlers-Danlos syndrome AND after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated	

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MFS Marfan syndrome

with an incidence of about 1 in 20,000 live births. Based on varying clinical, radiographic, and genetic findings, OI is classified into several subtypes (types I–VII). Bleeding is a common feature in OI, seen in an estimated 75% of patients per one study, and can occur with minor trauma [19]. Those with severe types of OI may have intracranial hemorrhage at birth and spontaneous fractures in infancy. Patients with other types of OI experience a spectrum of bleeding manifestations between easy bruising to spontaneous retinal hemorrhages and subdural hemorrhage. This pathology is difficult to differentiate from child abuse because of the presenting features often including generalized bruising and multiple fractures (including rib and skull fractures) [20]. Review of family history and physical findings like blue sclerae, poor dentition, bony abnormalities (osteopenia, pathologic fractures, Wormian bones, short stature), and abnormal bone scan findings may aid appropriate diagnosis.

Differential Diagnosis

Bleeding in connective tissue disorders (BCTD) resembles that seen in disorders of primary hemostasis with easy bruising and other mucocutaneous bleeding symptoms being most common. These symptoms are similar to the bleeding symptoms that are commonly seen in patients with von Willebrand disease (VWD) or platelet disorders. There is a body of literature reporting concomitant platelet dysfunction in patients with connective tissue disorders, especially EDS. There are also reports of concomitant clotting factor deficiency (i.e., factors XI, XIII) and von Willebrand disease among patients with BCTD [21–25]. Non-connective tissue coagulopathies should therefore be excluded, even in patients with a confirmed diagnosis of connective tissue disease. Published data on these concomitant diagnoses show laboratory findings consistent with both pathologies, suggesting that the comorbidities are not misdiagnoses, but the underlying pathophysiologic link between these systems is unknown. For example, with regard to platelet dysfunction, whether the CTD association is a coincidence or if the collagen abnormality somehow causes platelet dysfunction is unclear and has not been well studied. It would be reasonable to hypothesize that some of the collagen-modifying enzymes (mutations of which cause some forms of EDS – e.g., lysyl hydroxylase 1 in kyphoscoliotic EDS or fibronectin-deficient EDS) may have important roles in platelet biology, but such a link has not yet been established [26]. Other possibilities such as hyperfibrinolysis have been proposed as a cause of BCTD, but not scientifically proven. Thus, further investigation is needed to fully understand the mechanisms involved in BCTD [19].

Diagnostic Evaluations

As easy bruising, hematoma, and fractures are common features seen in patients with BCTDs, these disorders can often lead to concerns for abuse and non-accidental trauma in pediatric practice. A thorough history, including a careful three generation family history, are useful to narrow the differential diagnosis. Overall, connective tissue disorder-related bleeding is less common and is often a diagnosis of exclusion. Therefore, a complete evaluation to rule out other disorders of primary hemostasis is indicated while maintaining a high index of suspicion for connective tissue disorders.

Personal History, Family History, and Bleeding Assessment Questionnaires

The bleeding history review in BCTD evaluation should be extensive to ensure all types of bleeding complaints are elucidated. Young children often have a limited history, and as such unusual complaints like vaccination site bleeding or prolonged bleeding from superficial injuries may prove informative. Bleeding assessment tools (BAT) like the International Society on Thrombosis and Haemostasis (ISTH) BAT and the pediatric bleeding questionnaire (PBQ) may prove helpful in guiding historical interrogation [19, 21]. The PBQ includes important child-specific questions like circumcision-related bleeding and umbilical cord site bleeding. It has been validated for VWD and platelet function disorders but can be used in connective tissue disorders as well [27, 28]. A score of 2 or more is suspicious for an underlying bleeding tendency in children, whereas for adults, ISTH-BAT scores $\geq$4 for males and $\geq$6 in females are considered abnormal [29]. Coagulation laboratory studies are often normal in persons with BCTDs; thus, BAT scores may prove supportive in the pursuit of specialized connective tissue disorder diagnostic testing [28].

Clinical and Laboratory Testing

Clinical laboratory hemostasis testing algorithms reveal normal findings in most BCTDs. There are no validated, reliable assays to effectively assess the hemostatic capacity of subendothelial collagen. Even in vitro laboratory diagnostic assays that incorporate collagen as a reagent do not assess the hemostatic capacity of the patient's collagen, rather only the ability of the patient's hemostatic system to respond to reagent-grade collagen (usually derived from equine sources). Nonetheless, to rule out other hemostatic abnormalities, the diagnostic evaluation should be thorough, including a complete blood count looking for platelet counts and size, prothrombin time and activated partial thrombo-

plastin time to ensure normal coagulation proteins of secondary hemostasis, and a primary hemostasis assay (such as the PFA-100™) [30]. The in vivo bleeding time may be a useful test in BCTDs because this in vivo assay includes the patient's collagen and, when prolonged, may even be diagnostic [31]. However, it is increasingly unavailable in most clinical laboratories due to its well-known standardization problems. Platelet aggregation studies and electron microscopy, when available, may further elucidate concomitant platelet dysfunction (esp. platelet storage pool deficiency). The most commonly diagnosed bleeding disorder that presents with mucocutaneous bleeding symptoms is VWD; thus, it is important to consider this diagnostic possibility during the BCTD evaluation [32]. Von Willebrand antigen and activity levels, with or without VWF multimer analysis, are essential to rule out this defect of primary hemostasis. Fibrinolytic disorders often present with mucosal bleeding and thus should be kept on the differential, especially in the absence of BCDT family history.

The Beighton score is a physical exam-based scoring system that quantifies joint laxity in an objective fashion to help identify hypermobility syndromes [33]. A score of 5 or more out of 9 is considered positive for hypermobility [8]. The Beighton score should only be utilized for patients aged 9 years and above due to the possibility of non-specific and developmental hypermobility in younger children [28].

The Hess test or the Rumpel-Leede test, also known as the tourniquet test, is a clinical test that can identify increased capillary fragility [3]. A tourniquet or blood pressure cuff is used to maintain pressure on the forearm for 10 minutes, and then petechiae are subsequently counted in a 5 cm^2 area. The presence of >15 petechiae/5 cm^2 indicates increased capillary fragility [34]. This test may prove useful in some cases of EDS, OI, and MFS.

An abnormal bleeding score with a positive Beighton score (with or without evidence of capillary fragility) is suggestive of BCTD. If this evaluation is negative with a strong history of bruising and mild bleeding or a borderline abnormal bleeding score with points emanating from integumentary complaints, one should still consider connective tissue disorders in the differential. Confirmation requires physical exam findings that meet the diagnostic criteria and, whenever possible, supportive evidence from tissue or genetic testing.

There are genetic testing panels available for EDS that can be utilized to confirm diagnosis if the physical exam findings meet the criteria as defined in the classification. Specific mutation testing is also available for the other disorders discussed above (FBN1 for MFS, TGFRB1 or TGFRB2 for LDS, COL1A1 or COL1A2 for OI) [3, 16]. Additionally, skin biopsy and fibroblast culture may be helpful in some cases to identify abnormal collagen or microfibrillar proteins. Biochemical analysis of collagen proteins may also be informative, but may have lower specificity than comprehensive genetic testing.

Management

Management of BCTD is determined entirely by the clinical presentation and underlying defect. For these pathologies, prevention of bleeding goes a long way and comprises a large part of the management. An important part of caring for patients with BCTD is educating them about how to minimize bleeding concerns and when hemostatic therapy may be helpful.

Prevention of Bleeding

Patients and families should be educated on the importance of minimizing trauma and use of protective gear. Avoidance of contact and collision sports can keep large bruises and hematomas at bay, especially for patients who seem to have more bruising propensity. Exercises and activities like swimming, tai-chi, non-acrobatic dancing, golf, and rowing are low risk for bleeding and should be encouraged to maintain muscle health and physical activity. Patients should be advised a healthy diet with balanced intake of all major food groups, including fruits and vegetables to avoid concomitant scurvy, rickets, or vitamin K deficiency.

Avoiding drugs and agents that can worsen the bleeding tendency is another important piece of education for these patients. Platelet inhibitory agents like aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are best avoided. In conditions where patients may need antipyretic or anti-inflammatory medications, acetaminophen is advisable. Selective cyclooxygenase-2 inhibitors like celecoxib are reported to not inhibit platelet function and may be acceptable anti-inflammatory agents in persons with BCTDs [35]. Vitamin C and D supplementation may hypothetically support connective tissue health, although there is insufficient data to back this claim, which is largely based on reported associations between scurvy and vitamin D deficiency in patients with CTDs [23, 36, 37].

Maintenance of gum health through regular dental cleaning and flossing is advised to minimize oral bleeding. We advise visiting the dentist at least once a year, preferably twice. Invasive dental procedures should be planned with input from a hematologist such that adequate interventions for periprocedural hemostasis can be planned. Use of topical sealants and fibrillar collagen products may be recommended along with systemic hemostatic therapies (below) [38, 39].

Treatment

Underlying defects in connective tissue disorders are non-modifiable, and some therapies, thus, are based on augmentation of the coagulation supportive processes. Physical pressure at the site of bleeding is of utmost importance. Some of the skin-related bleeding and small hematomas can be addressed via first aid measures alone. All patients should be advised on the importance of RICE (rest, ice, compression, and elevation) in the setting of bleeding and hematomas. The pharmacological interventions that may be helpful in BCTDs include antifibrinolytic agents and desmopressin, but none of these have been subjected to randomized controlled trials in persons with CTD.

Desmopressin/DDAVP

Desmopressin or DDAVP (1-desamino-8-D-arginine vasopressin) is a synthetic analogue of vasopressin that enhances circulating levels of VWF and factor VIII. It promotes endothelial Weibel-Palade body secretion, thereby increasing plasma VWF and factor VIII. It has been shown to improve bleeding times in patients with hEDS-associated bleeding [31, 40–43]. This hemostatic effect is postulated to come from augmentation of the VWF to platelet and collagen interaction which is otherwise weakened in BCTDs [31, 44].

The response to DDAVP can be assessed through a challenge test, but past data show good responsiveness with shortened bleeding times in >90% of patients studied [31, 40]. At centers where bleeding time assessment is not available, DDAVP may thus be prescribed empirically and continued if clinical improvement is seen. An increase in post-DDAVP circulating VWF or factor VIII levels may, hypothetically, be a surrogate measure of BCTD DDAVP responsiveness [45, 46]. Intravenous DDAVP (0.3 μg/kg) sufficiently increases circulating VWF in most patients. An intranasal formulation (Stimate™) is also available and can be utilized for outpatient and home use [47]. Dosage of the intranasal form is 300 μg for patients >50 kg or 150 μg for those weighing <50 kg [48]. Tachyphylaxis is seen with DDAVP because once the stored VWF/factor VIII is released, any further beneficial effect is dependent on the rate of additional endothelial protein synthesis. Maximal efficacy can be seen with every 24 hours usage, for 3–4 doses, and this often suffices to establish hemostasis. Common side effects with DDAVP include flushing, uneasiness, headache, tachycardia, decreased urination, and water retention [32]. The patient and family should be educated about the water retention as consumption of excessive free water in the following time period can lead to dilutional hyponatremia. It is prudent to calculate the patient's maintenance fluid requirement and advise them to restrict all fluid intake to that amount in the 24 hours following a DDAVP dose. DDAVP can have worse side effects in patients with history of migraines/severe headaches, seizures, or autonomic dysfunction. Appropriate counseling and risk-benefit evaluation should be carried out with these patients.

Antifibrinolytic Agents

Two synthetic lysine analogues that are frequently used in disorders of primary hemostasis are (1) ε-aminocaproic acid (EACA) and (2) tranexamic acid (TXA). The mechanism of action for these agents is via inhibition of plasmin activity. In mucosal bleeding and in sites of high fibrinolysis (e.g., nasopharynx, oral cavity, gastrointestinal and genitourinary tracts), antifibrinolytics prove tremendously helpful. They are also useful adjunctive therapies when DDAVP use is limited by its tachyphylaxis or there are concerns for hyponatremic complications.

EACA is available in intravenous and both liquid and tablet oral formulations. The typical dose is 50 mg/kg every 6 hours, and some authors recommend that the initial dose be increased to 100 mg/kg as a loading dose (6000 mg maximum dose). Typical duration of EACA therapy is 5–10 days from the onset of bleeding symptoms.

TXA is available as a tablet or injectable. The adult dose is 1300 mg and pediatric dose is typically 10 mg/kg, three times a day for 5–7 days at a time. Tablets remain effective even if crushed and consumed, while some support is also available for the liquid injectable form being active for hemostasis when used topically for superficial bleeding [49].

Perioperative Management

There is a paucity of quality data to guide perioperative management of patients with connective tissue disorders. There are a few case reports and series that are helpful, however, and indicate adequate hemostasis with the use of antifibrinolytics, DDAVP, or recombinant activated factor VII (rFVIIa) [50]. Some patients with mild bruising manifestations alone, especially with EDS, may do well without periprocedural hemostatic interventions with minor procedures but should be monitored closely [31]. Generally, elective invasive procedures with elevated bleeding risk are best avoided in patients with BCTD. In the absence of alternative management options, careful perioperative hemostasis planning should be undertaken. Precautions including handling of the vascular structures with extreme care, consistent use of tamponade, liberal suturing, and minimizing tissue injury wherever possible are advisable and should be discussed with the surgical team during the preoperative planning phase.

DDAVP, given about an hour prior to an invasive procedure, can lead to swifter hemostasis intra- and postoperatively [40]. Doses can be repeated at 24 hours and again at 72 hours from time of procedure if the concern for bleeding persists. Adjuvant therapy with antifibrinolytics can further

help perioperative hemostasis. For surgeries in regions of high fibrinolysis (naso- and oropharyngeal procedures or dental extractions), EACA is quite useful. The liquid formulation can be used in a swish and swallow manner, or tablets can also be used when the patient is able to swallow. There is evidence reporting use of TXA for invasive orthopedic surgeries, both intraoperatively and postoperatively [51, 52]. The doses are similar to those noted above although the frequency of TXA in the perioperative phase can be increased to four times a day. Also, duration of therapy can be increased based on invasiveness of the procedure, with some providers considering about 10–14 days of antifibrinolytic treatment.

Intravenous rFVIIa at a dose of 20 μg/kg/dose 15 minutes before surgery and postoperatively is reported to be useful in major surgeries [50, 53]. This dose is not associated with any reports of pathologic thrombosis in patients with bleeding disorders in the perioperative period. The dose frequency can be based on bleeding concern, but can be every 6 hours on day 1 and every 12 hours for 2–3 additional days, if needed.

Outcomes and Follow-Up

The frequency of hematologic follow-up varies by disease type and clinical severity. BCTD is best addressed by specialized centers that allow a multidisciplinary approach. Patients with Marfan syndrome, Loeys-Dietz syndrome, osteogenesis imperfecta, and vEDS often need regular input from orthopedics, cardiology, genetics, and vascular surgery. Patients with mild bleeding manifestations do quite well, and morbidity is generally from joint pain and other manifestations of the connective tissue disorders. Those with MFS and vEDS are at higher risk of major hemorrhagic complications. Close follow-up, education about how to minimize acquired risk factors for vascular disease (e.g., smoking, obesity), and ultrasonographic screening for vascular complications may prevent some complications [54]. Hematological follow-up can be semi-annually to biennial based on the degree of symptoms. It can be tailored to be more frequent in patients who have had more bleeding issues. It is important to ensure periprocedural involvement by hematologists familiar with the perioperative management of BCTDs whenever invasive procedures are being planned. Regular collaboration with the patients' primary care physician and other subspecialists ensures the best preventative approach for bleeding and other complications.

Clinical Pearls

- Bleeding tendency is prevalent in patients with connective tissue disorders.
- Easy bruising and cutaneous bleeding in the presence of hypermobility are the common findings.
- Bleeding assessment tools can guide personal history in a systematic and comprehensive fashion and prove helpful in excluding more serious disorders of hemostasis.
- Perioperative management in BCTDs should include hematology consultation to minimize bleeding complications.

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Patient Resources

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Bleeding Associated with Trauma

21

Christoph J. Schlimp and Martin Ponschab

Introduction and Pathophysiology

Exsanguination is responsible for about one-third of trauma-related deaths, and most fatalities occur in the prehospital setting [1, 2]. Of those trauma patients admitted to the hospital, one-third will die of exsanguination mostly within a few hours, compared to those dying of traumatic brain injury within 24 h and those with multiorgan failure dying within a few days [3]. It has been shown that the occurrence of coagulopathy in about one-quarter to one-third of patients is responsible for a worse outcome and an increase of mortality compared to those patients with a normal coagulation pattern [4–6]. Massive transfusion in trauma is pathognomonic for bleeding and coagulopathy, as well as for morbidity such as multiorgan failure and mortality.

The acute coagulopathy after trauma has several "exogenous" causes: firstly, loss and consumption of coagulation factors due to bleeding; secondly, dilution of coagulation factors due to fluid therapy; and thirdly, dysfunction of coagulation factors due to hypothermia and acidosis (Fig. 21.1). The trauma-induced coagulopathy of "endogenous" origin is considered to be triggered by the release of tissue factor from traumatized tissue, causing localized activation of coagulation factors with accompanying consumption of platelets and fibrinogen. Additionally, impaired tissue perfusion triggers an increased expression of thrombomodulin and thus activation of protein C, resulting in systemic anticoagulation and increased fibrinolysis [7–9]. It has been recognized that the coagulation factor fibrinogen, the main substrate in the coagulation process, is central to trauma-induced coagulopathy [10, 11]. Fibrinogen levels are often low on hospital admission and are related to the grade of injury, shock, blood loss, and mortality [12, 13].

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Coagulation Monitoring in Trauma

Initially, coagulopathy in trauma was defined by Brohi et al. [4] and described as a 1.5-fold prolongation of the standard coagulation tests, namely, prothrombin time, activated partial thromboplastin time, and thrombin time. However, standard coagulation tests were designed to monitor anticoagulative measures, but not coagulopathy after trauma and acquired bleeding [14]. Interestingly, pathologic standard coagulation test values in this setting might also be the result of plasma fibrinogen levels below 1 g/L [15]. On the other hand, prolonged prothrombin and activated partial thromboplastin times have been observed in the trauma setting after administration of prothrombin complex concentrate, suggesting erroneously a hypocoagulative status, although thrombin generation was above normal over several days [16]. Furthermore, it has to be kept in mind that results of routine clinical standard coagulation tests performed at a central laboratory are not available in a timely manner [17, 18]. Recently, it has been recognized that there is actually no sound evidence from

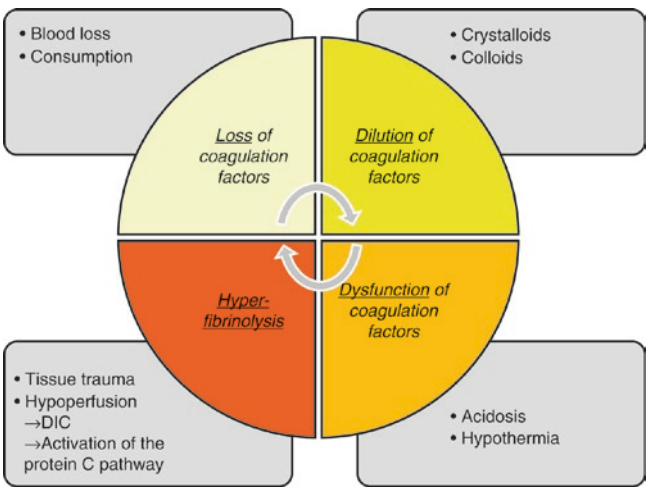

Fig. 21.1 Typical contributors to acquired coagulopathy in bleeding trauma patients. *DIC*, disseminated intravascular coagulation

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well-designed studies to confirm the usefulness of standard coagulation tests for diagnosis of coagulopathy or to guide hemostatic therapy [14].

Estimation of fibrinogen levels appears to be essential for the diagnosis and guidance of treatment for traumatic and acquired bleeding [19]. However, measurement of plasma fibrinogen levels has the same limitations regarding short-term availability of results in routine clinical practice.

Over the last decade, viscoelastic tests have been increasingly used to assess general properties of blood clotting, as well as to focus on fibrin polymerization in whole blood. Viscoelastic tests, most commonly thrombelastography (TEG) or rotational thromboelastometry (ROTEM), provide a rapid and dynamic bedside assessment of the initiation and kinetics of clot formation, maximum clot firmness, and clot breakdown [20]. Viscoelastic tests can characterize the range of acute coagulopathies present in patients with traumatic injury and can identify the presence and type of coagulopathy at an early stage, effectively replacing other coagulation tests [21, 22].

Systemic Hemostatic Therapy in Trauma

Besides the replacement of red blood cells to provide oxygen-carrying capacity and intravascular fluid therapy to maintain perfusion, hemostatic therapy is mandatory in the bleeding trauma patient.

Allogeneic Blood Component Therapy

A typical approach in clinical routine of many trauma centers is to mimic whole blood replacement as close as possible by transfusion of red blood cells, plasma, and platelets in a fixed ratio. The 1:1:1 mixture of red blood cells, plasma, and platelets for transfusion has been proposed as this ratio suggests the best survival rates as compared to other ratios [23]. However, it has to be kept in mind that even this 1:1:1 mixture may contain reduced amounts of coagulation factor activity, especially fibrinogen [24]. Moreover, a markedly reduced functionality of platelets in such allogeneic blood component mixtures has been observed [25]. In order to supplement concentrated fibrinogen with blood products, the use of cryoprecipitate has been shown to be feasible in trauma patients [26]. Fresh whole blood transfusions have been carried out for this purpose in patients with combat-related traumatic injuries in the military setting [27]. However, this approach does not appear to be suitable in the civilian setting.

Pharmacological Therapy

Another approach for hemostatic therapy in trauma is purified coagulation factor concentrates (Table 21.1) [28]. Coagulation factor concentrates are immediately available without the need for blood group matching, contain a well-defined concentration of coagulation proteins, and carry a low risk for transfusion-related lung injury and virus transmission [29]. Together with the use of viscoelastic tests for goal-directed coagulation management, the use of fibrino-

Table 21.1 Recommendations for systemic hemostatic therapy in addition to or instead of the 1:1:1 massive transfusion packages, as per currently published guidelines [28]

Agent	Recommendation
Antifibrinolytic agents	*Within 3 h after injury; consideration to administer en route to the hospital*
Tranexamic acid	1 g loading dose over 10 min followed by an infusion of 1 g over 8 h
ε-Aminocaproic acid	Loading dose of 150 mg/kg followed by a continuous infusion of 15 mg/kg/h
Calcium	Ionized calcium levels should be monitored and maintained within the normal range during massive transfusion
Fibrinogen supplementation	*In case of significant bleeding and viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5–2.0 g/L*
	Repeat doses may be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels
Fibrinogen concentrate	Initially 3–4 g
Cryoprecipitate	Initially equivalent to 15–20 single donor units
Platelets	Platelet count above 50×10^9/L
	Platelet count above 100×10^9/L in patients with ongoing bleeding and/or traumatic brain injury
	Initial dose of four to eight single platelet units or one apheresis pack
Desmopressin	0.3 μg/kg in patients treated with platelet-inhibiting drugs or with von Willebrand disease
Prothrombin complex concentrate	Early use for the emergency reversal of vitamin K-dependent oral anticoagulants
	Use in the bleeding patient with thromboelastometric evidence of delayed coagulation initiation
	Administration to mitigate life-threatening post-traumatic bleeding in patients treated with novel oral anticoagulants
Idarucizumab	5 g intravenously in patients treated with dabigatran and life-threatening bleeding
Recombinant activated coagulation factor VII	Use be considered if major bleeding and traumatic coagulopathy persist despite standard attempts to control bleeding and best-practice use of conventional hemostatic measures

gen concentrate and prothrombin complex concentrate has been shown to be effective in treating major trauma patients [30, 31].

The use of recombinant activated coagulation factor VII may be considered if major bleeding and traumatic coagulopathy persist, despite standard attempts to control bleeding and best-practice use of conventional hemostatic measures (Table 21.1) [28].

Tranexamic acid is currently considered the best treatment option for hyperfibrinolysis and has been shown to reduce mortality in a large cohort of bleeding trauma patients [32]. Tranexamic acid has also been used successfully in the military trauma setting, resulting in reduced mortality, which is further reduced when combined with cryoprecipitate [33, 34]. Tranexamic acid must be given early (less than 3 h) in the course of trauma (Table 21.1) [35].

ε-Aminocaproic acid has a potency tenfold weaker than that of tranexamic acid and may be used as an alternative if tranexamic acid is not available [28].

Calcium should be supplemented to maintain ionized calcium levels within the normal range during massive transfusion [28].

Desmopressin may be administered in patients treated with platelet-inhibiting drugs or with von Willebrand disease but should not be administered routinely in the bleeding trauma patient (Table 21.1) [28].

Specific antidotes for bleeding patients on direct oral anticoagulants have recently been approved in some countries. In 2018 andexanet alfa for factor Xa inhibitors (such as rivaroxaban, apixaban, or edoxaban) and already in 2015 idarucizumab for the thrombin inhibitor dabigatran. The current trauma guidelines have recommendations for idarucizumab only (Table 21.1) [28]. Idarucizumab has been successfully used in traumatic bleeding situations thereafter [36].

In summary, the acute coagulopathy after trauma has several causes including loss, consumption, dilution, and dysfunction of coagulation factors, as well as hyperfibrinolysis. Standard coagulation tests are not useful in guiding hemostatic therapy in the acute bleeding trauma patient. In contrast, viscoelastic tests appear to be appropriate in this setting. Recommended therapeutic options include antifibrinolytic agents and a concept of a fixed mixture of red blood cells, plasma, and platelets for transfusion for all bleeding patients or the goal-directed coagulation management using an algorithm to supplement individually only those coagulation components that are needed.

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Massive Transfusion Protocol

22

Megan E. Cunningham and Adam M. Vogel

Introduction

Massive transfusion (MT) is an evolving field in the treatment of the bleeding patient. There are several definitions used to describe MT including replacement of the entire blood volume in 24 hours, replacement of 50% blood volume in 3 hours, transfusion of more than 10 or 20 units of red blood cells (RBC) in 24 hours, and transfusion of more than 3 or 4 units of RBC in 1 hour [1–3]. Definitions used in pediatric transfusion vary even further with weight playing a larger role [4–6]. In children, 40 mL/kg of total blood products administered over 24 hours has evolved as a well-accepted definition [5]. While defining MT using a 24-hour time period is useful for research, it is not practical in the clinic setting when treating an actively exsanguinating patient. Currently there is no consensus on a universal definition.

A number of associations recommend that institutions develop a massive transfusion protocol (MTP) when caring for patients with high risk of hemorrhage [7–9]. The American College of Surgeons Trauma Quality Improvement Program has generated comprehensive, evidence-based guidelines describing MTP best practice [9]. MTPs are a component of damage control resuscitation, a systematic approach to reducing hypothermia, acidosis, and coagulopathy in order to prevent death by exsanguination [10]. Although introduction of MTPs have been shown to reduce morbidity and mortality in several trauma studies, further study is needed to validate this evidence [11, 12]. A recently published systematic review on the use of MTPs on non-trauma patients showed reduction of mortality in five studies, although there was no significant difference upon meta-analysis [13]. Elements of an MTP include guidelines for crystalloid administration, timing and ratio of blood transfusion, use of adjuvant hemostatic agents, and resuscitative monitoring.

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Development of a Massive Transfusion Protocol

When developing a MTP at an institution, it is important that a multidisciplinary team be involved to assess the literature and to provide input on local resources. The protocol should be a written document that can be easily understood and implemented by all providers across the institution. It is important that location, timing, and dosing of product administration and laboratory testing be established. Communication is essential in emergent situations where MT is necessary. The MTP should clearly delineate roles and lines of communications. Clear criteria should be agreed upon for activation and completion of an MTP to prevent waste of resources and to provide appropriate patient care [7–9].

Indications for Massive Transfusion

Hemorrhage can result from many processes including, but not limited to, trauma, obstetric complications, gastrointestinal pathology, surgery, and ruptured aneurisms. The body undergoes distinct physiological changes as blood loss increases, including tachycardia, tachypnea, hypotension, decreased urine output, and changes in mentation. Based on these parameters, there are four classes of hemorrhagic shock. It is important to note that age, physiology, medication, and other drug use may alter the signs of blood loss. Decrease in core body temperature, coagulopathy (including thrombocytopenia), and acidosis (demonstrated as a decreased pH or increased base deficit) result in increased morbidity and mortality. Occurrence of all three findings is referred to as the "lethal triad" [10].

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Deciding when and for whom to initiate an MTP is important in improving patient outcomes, preventing adverse events in those not requiring MT, and reducing waste of precious resuscitative resources. More than 21 models have been created to predict MT, all of which are of low-quality data [14]. Currently, the scoring systems recommended by major societies such as the American College of Surgeons (ACS), the American Society of Anesthesiologists (ASA), and the European Society for Advanced Bleeding Care in Trauma are the ABC and TASH scores [15, 16]. The assessment of blood consumption (ABC) score contains four variables (pulse >120 bpm, systolic blood pressure (SBP) <90 mmHg, positive focused assessment with sonography for trauma (FAST), and penetrating torso injury), each assigned one point where a score of two or more activates the MTP activation. Although, in general, the tool overestimates the need for transfusion, it is excellent at identifying who will not need MT [17].

Resuscitative Products

Crystalloid

During the early years of MT, use of crystalloid to sustain normal blood pressure was encouraged. Practice began to change as evidence revealed that large volume crystalloid resuscitation increases the risk of edema, compartment syndrome, and acute lung injury [17]. Additionally, hemodilution exacerbates anemia, thrombocytopenia, and coagulopathy resulting in further bleeding [18]. It is suggested that permissive hypotension be allowed while hemorrhage control is ongoing with a goal SBP of 80–100 mmHg. One exception is in the case of patients with traumatic brain injury, as low blood pressure along with hypoxia can further the damage of injured neuronal tissue [7]. Currently, the maximum time to safely allow permissive hypotension is not known.

Component Blood Therapy

There have been several trials looking at outcomes of component therapy, all of which have involved trauma patients [19]. When comparing blood product transfusion ratios, evidence suggests no difference in morbidity or mortality when comparing a 1:1:1 (plasma/platelets/PRBC) replacement to a 1:1:2 replacement, although the evidence is of moderate and low quality [19]. As a result, several societies with recommendations on massive transfusion suggest a minimum transfusion ratio of 1:1:2 [8, 9, 20]. In children, the impact of component ratios on outcome is unclear with some retrospective studies showing no benefit and others demonstrating a survival benefit [21–23].

There are a limited number of studies look at cryoprecipitate administration during MT. A single feasibility trial showed no difference in 28-day mortality or morbidity when cryoprecipitate was administered early in an MTP for trauma [24]. On the other hand, a number of trials concerning administration of fibrinogen concentrate during MT have shown mixed results concerning feasibility and outcomes. The trial patient populations vary and include postpartum hemorrhage, trauma, and bleeding during cardiac surgery. So far the literature has shown no difference in survival when compared to those who did not receive fibrinogen concentrate [25–29]. There is limited evidence to suggest benefit of administering cryoprecipitate over fibrinogen concentrate or vice versa [30].

Whole Blood Therapy

Use of whole blood (WB) as a part of MT has been ongoing in the military since World War I. Development of the "walking blood bank" allowed for transfusion of fresh WB from one individual to another in an austere military environment [17]. Over the years, the safety and efficacy of WB use has continued to develop, and the US Tactical Combat Casualty Care Committee recommends that WB be the first-line resuscitative product for patients with traumatic hemorrhagic shock [31].

Within the civilian population, studies have only begun to look at use of WB for MT. The type of WB being studied is cold-stored, O-positive, low-titer of anti-A and anti-B. This blood product is stored at 1–6 °C up to 21 days in ACD or CPD and 35 days in CPDA-1 with most institutions limiting to 21 days. It is composed of O-positive blood that has anti-A and anti-B antibody titers of <1:256 but may be as low as <1:50 [32]. Ongoing studies have shown safety with transfusion of up to 4 units in non-group-O trauma patients [33]. While administration of this type of WB had been standard for the military in decades past, modern outcomes data is limited and ongoing [17, 34].

Adjuvant Hemostatic Agents

Recombinant activated factor VII (rFVIIa) is a coagulation factor that has been approved by the US Food and Drug Administration for use in patients with hemophilia A or B with inhibitors, Glanzmann's thrombasthenia, and congenital factor VII deficiency. Many studies document its off-label use in other hemorrhaging patients, but there is limited evidence showing improvement in long-term outcomes, including mortality [35, 36]. Even more concerning is the risk for

thrombotic events, although current literature is inconsistent on that matter [37]. At this time, it is not recommended for use in critically bleeding patients other than hemophiliacs [7, 8, 36, 37].

Recently made available within the United States, but used in Europe and other regions for many years, is prothrombin complex concentrates (PCC). This product is composed of three (factors II, IX, and X) or four (factors II, VII, IX, and X) clotting factors. It has been approved for use in bleeding patients with warfarin-induced coagulopathy. There is little evidence to suggest use in the general MT population [8, 38, 39].

Another adjuvant hemostatic agent is tranexamic acid (TXA), a synthetic antifibrinolytic medication. It works by impeding plasminogen-lysine binding sites, increasing clot stability [40]. Cornerstone studies for the use of TXA in hemorrhagic trauma patients include the CRASH-2 trial for adult patients and the PED-TRAX trial for pediatric patients [41]. Both trials showed decrease in mortality when TXA was administered early in resuscitation [42, 43]. Use of TXA in nontrauma MT has shown similarly encouraging results [42]. One particular trial is the WOMAN trial which showed decreased mortality without increased adverse events when TXA was used in the setting of post-partum hemorrhage [44]. Unfortunately, not all studies have been devoid of adverse events, as two large retrospective trauma reviews have suggested an increase in thrombotic events in those that receive TXA [42]. An ongoing trial designed to bring more clarity on the benefits and adverse events of TXA administration is the PATCH-Trauma trial [45].

Monitoring Strategies

In an actively hemorrhaging patient, it is important to monitor physiological processes at the time of resuscitation in order to guide care. This may be done using both invasive and noninvasive tools such as a pulse oximeter, capnometer, blood pressure cuff, arterial line, and urine catheter, to name a few. Independent predictors of mortality include hypothermia, thrombocytopenia, increased international normalization ration (INR), prolonged prothrombin time (PT), low fibrinogen, low pH, and low bicarbonate levels [46]. Several of these predictors are determined through laboratory testing which should be obtained at the initiation of an MTP and repeated frequently during the resuscitative process. It is important to note lag time associated with laboratory testing and that treatment should not be delayed while awaiting results [1].

In the hemorrhaging patient, development of coagulopathy is a well-documented phenomenon [47–49]. There is an array of laboratory tests that may be performed to identify alterations in the coagulation cascade including traditional assays such as activated partial thromboplastin time, PT, and INR and, the more modern, viscoelastic hemostatic assay (VHA) which includes thromboelastography (TEG™) and thromboelastometry (ROTEM™). VHAs have been utilized in bleeding surgical patients for over two decades but only recently became of interest in trauma resuscitation. Use of a VHA in goal-directed resuscitation, as part of an MTP, has been shown to reduce blood product administration volumes and improve mortality, suggesting overall benefit [50, 51].

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23 Lupus Anticoagulant-Hypoprothrombinemia Syndrome (LAHPS)

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Introduction

Patients with various inflammatory disorders, autoimmune diseases, and malignancies have been well documented to have acquired factor deficiencies [1]. Less commonly, these transient factor-deficient states have also been described in people without identifiable disorders. Most of these individuals, fortunately, do not present with significant clinical symptoms [1]. However, rare cases of hemorrhagic and thrombotic manifestations of varying severity do occur in healthy individuals in association with specific coagulation inhibitors, including those directed against factors II, V, VIII, IX, X, XI, and XIII, with and without associated levels of lupus anticoagulant (LA) [2].

Since 1972, the term *lupus anticoagulant* has caused considerable confusion [3]. Most patients who test positive for LA do not have systemic lupus erythematosus (SLE). Furthermore, in the absence of concurrent thrombocytopenia, factor deficiencies, or factor inhibitors, having LA alone is not a risk factor for bleeding. The term *anticoagulant* arises from the prolongation of phospholipid-dependent clotting assays, which results from the LA's specificity to phospholipids. This prolongation is purely an *in vitro* phenomenon manifested as a prolongation of the activated partial thromboplastin time (PTT). At one time, the Subcommittee for the Standardization of Lupus Anticoagulant of the International Society on Thrombosis and Haemostasis (ISTH) tried to change the name by sending a nomenclature survey. Unfortunately, due to a lack of consensus, the nomenclature of *lupus anticoagulant* and its abbreviation (LA) remain to this day [4].

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Detection Assays

Guidelines for LA detection, developed in 1991 (subsequently revised by the ISTH in 2005), require fulfillment of at least one of the following criteria: (1) prolongation of >1 phospholipid-dependent clotting test, (2) failure to correct prolonged screening coagulation test upon mixing with pooled normal plasma, (3) evidence that inhibitory activity is dependent on phospholipids, and (4) ruling out other coagulopathies (such as factor VIII inhibitors, heparin). Unfortunately, cutoff levels vary from laboratory to laboratory, based on internal standardization. Some centers equate regular PTT screening for the presence or absence of LA (weakest evidence). PTT-LA (screening test for the hexagonal phase phospholipid neutralization test (StaClot™)) contains less phospholipid, which is more sensitive to LA.

In the dilute Russell's viper venom test (DRVVT), Russell's viper venom (RVV) activates factor X directly. Sensitivity is improved by diluting both RVV and phospholipids. DRVVT confirmatory testing contains more phospholipids (phosphatidylserine and phosphatidylcholine) which may neutralize LA. Positivity is based on the ratio of screening/confirmatory (S/C) testing. While deficiencies of factors I, II, V, and X and warfarin therapy may prolong the DRVVT confirmatory screening, it will not affect the S/C ratio.

In the StaClot™ test, the subject's plasma is incubated with and without hexagonal phase phosphatidylethanolamine (HPE). A PTT is performed on both tubes using a lupus anticoagulant-sensitive reagent. If LA is present in the test plasma, it would be neutralized by HPE, and this would result in the shortening of the clotting time. Heparin levels greater than 1 IU/mL and thrombin inhibitors may lead to falsely positive results.

Despite several commercially available assay kits for testing of LA, studies have suggested suboptimal performance of these assays [5, 6]. The absence of a single gold standard assay has created clinical challenges in interpreting the results of these assays because of test nomenclature and the inherent heterogeneity of LA.

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Risk Factor for Thrombosis

There are important clinical implications to the presence of LA. LA is a risk factor for venous or arterial thrombosis and recurrent pregnancy loss. One meta-analysis revealed that the odds ratio for venous thrombosis is 11.1 (95% confidence interval [CI], 3.81–32.3) with LA compared with 3.21 (95% CI, 1.11–9.28) with anticardiolipin antibodies (ACA) [7]. Additionally, a multivariate analysis found that the odds ratio for venous and arterial thromboembolism is 4.4 (95% CI, 1.5–13.3) with LA and 1.2 (94% CI, 0.5–2.7) with ACA [8]. Compared with other risk factors, positivity for LA and long-term elevation of factor VIII have the highest odds ratio for a first episode of venous thromboembolism in individuals with a thrombophilic defect compared with individuals without a defect [9]. Making a correct laboratory diagnosis of LA as part of a thrombophilia evaluation may be critically important in determining the dose or duration of anticoagulant therapy in a patient with thrombosis. However, there is no consensus regarding assay methods for LA, leaving many questions unanswered [6].

Etiology

Antiphospholipid antibodies (APA) comprise a heterogeneous group of autoantibodies directed against phospholipid-bound plasma proteins with an affinity for anionic surfaces, mainly prothrombin (factor II), β2-glycoprotein I, low molecular weight kininogens, annexin V, (activated) protein C, and protein S. They consist of the LA, detected by their *in vitro* prolongation of phospholipid-dependent coagulation tests, and ACA, determined by their reactivity to cardiolipin in solid-phase immunoassays [10, 11]. APA occur in autoimmune disorders, most commonly SLE, in association with malignancies, drugs, and infections, and in otherwise healthy individuals [12–14]. In theory, since most of the antigens are involved in blood coagulation, some APA may inhibit physiologic hemostasis. APA are not uncommonly associated with a variety of clinical manifestations such as arterial and venous thrombosis, recurrent fetal loss and/or other obstetric complications, or thrombocytopenia. Less commonly, they can be associated with hemolytic anemia, neuropsychiatric complications, or livedo reticularis [15]. If there are no signs of underlying disease, the presence of these clinical manifestations has been termed primary APAS [16]. Thromboembolic events occur in about 30–40% of adults with APA depending on the underlying conditions. Bleeding complications are rare in adults with LA positivity, despite their *in vitro* effects on coagulation assays [12].

In children, little is known about the occurrence of APA and associated clinical manifestations. In a series of pediatric patients with SLE, prevalences of 19–62% for LA and 19–79% for ACA were reported [17–22], and thrombosis occurred in 37–44% of patients with LA or ACA [18, 21, 22]. Several cases of APA-related thrombosis in children without SLE have also been reported [23–26]. Higher frequencies of APA were found in children with ischemic cerebral stroke [27, 28] and other neurologic symptoms [29]. Bleeding symptoms have also been reported in children with presence of LA but in most cases were related to additional specific coagulation factor inhibitors [2, 30–33] or thrombocytopenia [34].

Recent evidence suggests that the presence of LA alone in children, in most cases, does not lead to clinical symptoms and tends to be transient [30, 32, 34, 35]. LA was found in 0.7–2.4% of children who were free of symptoms during preoperative coagulation screening [1, 36] and who eventually had surgery without bleeding complications and had negative test results for LA after weeks to months. The lack of correlative evidence regarding LA often leads to extensive and repeated laboratory workups, making it challenging for clinicians to establish which children are at risk for bleeding or thrombosis.

Male et al. [37] provided additional evidence that the presence of LA does not lead to clinically relevant complications and is transient in most children. They also postulated that there are two major types of LA in children. The first is a frequent, benign, and transient (possibly "post-infectious") LA of young age, which does not lead to symptoms in the majority of children. In a subset of children, this type is associated with bleeding, caused by transient hypoprothrombinemia. The second is the "autoimmune" LA of the adult type, which mainly occurs in adolescence, persists, and is more likely to be associated with thromboembolic complications [37].

A relationship between bacterial or viral infections and LA in these children has also previously been suggested [1, 30, 32, 35]. Currimbhoy et al. [1] found a significantly higher prevalence of LA positivity in asymptomatic children younger than 12 years of age as compared with older children (3.1% vs. 0.5%). This could be explained by the higher incidence of infections in early childhood. However, there are no solid data to prove a relationship between infections and presence of LA.

Diagnosis

Moderate bleeding occurred in approximately 10% of children with presence of LA and, in most cases, was secondary to additional hypoprothrombinemia [37]. This acquired factor II deficiency is due to prothrombin-binding antibodies, which are non-neutralizing but form antigen-antibody com-

plexes leading to increased clearance of prothrombin from the circulation [38]. A significant association was found between transient high-affinity prothrombin antibodies and a preceding adenovirus infection [39].

The antibody against factor II (antiprothrombin antibody) differs from other autoantibodies. Unlike the other coagulation factor inhibitors, it does not interfere with the enzymatic function, as it does not bind to the active site. Instead, it binds to inactive epitopes on the molecule to form prothrombin antigen-antibody complexes, which are cleared by the reticuloendothelial system [38]. Since the antibody is non-neutralizing, prothrombin time corrects with mixing studies, while other inhibitor-related coagulopathies do not. Furthermore, as the antibody is non-neutralizing, the Bethesda assay is not useful and may, in fact, yield a false positivity due to the concurrent presence of LA. It is important for clinicians to follow the prothrombin time, factor II levels, and antiprothrombin antibodies (IgM and IgG) to determine response to medical management.

In the literature, "lupus anticoagulant-hypoprothrombinemia syndrome" (LAHPS) has been described in children without and with SLE, both with and without bleeding complications. Children without SLE were between 1.5 and 7 years of age, and all had transient hypoprothrombinemia and LA [2, 33]. Reported children with SLE and LA-associated hypoprothrombinemia were all older than 10 years of age and only showed improvement with treatment [2, 31].

LA associated with thrombosis has rarely been reported in children younger than 10 years of age [26, 32], and female predominance can be noted in some series [18, 26]. In the literature, primary APAS is frequently found among children with LA-related thrombosis [23–26], but an underlying systemic disease may not have manifested and may develop with time [40]. High-titer ACA IgG, as observed in this and other series of pediatric patients with thrombosis [19, 21, 22], is an established risk factor for thrombosis in adults [41]. Anti-dsDNA that show a high association with APA in pediatric patients with SLE [18, 21] may similarly occur in primary APAS [42]. These data suggest that LA associated with thrombosis usually represents a chronic autoimmune process. The increasing incidence during adolescence and the gender distribution are similar to those of SLE or related autoimmune syndromes [43]. However, a few cases of thrombosis in young children related to post-infectious presence of LA without signs of autoimmune disease have been reported [25]. The presence of LA was transient, and there was no recurrent thrombosis. Recent evidence shows that concurrent specific protein S autoantibodies, leading to transient severe protein S deficiency, appear to be responsible for hypercoagulability in some of these cases [44].

Historical Evidence

Children with lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) are unique in that they are at risk for both bleeding and thrombotic sequelae [45]. LAHPS in children and adolescents may be more common than previously considered [46]. Although LAHPS cases have been associated with SLE, others have been noted subsequent to viral prodromes, mycoplasma infections, and/or drug ingestion (i.e., quinidine, phenytoin) [47, 48].

In 1959, Loeliger [49] described a case where the LA activity was more pronounced in a mixture of the patient's plasma with normal plasma than in the patient's own plasma. The patient's plasma prothrombin level was also decreased. A series of adsorption experiments of the patient's plasma with $BaSO_4$ led the investigator to suggest prothrombin was the necessary cofactor for the expression of this LA activity. A year later, Rapaport et al. [50] reported a case of SLE whose LA was associated with severe acquired hypoprothrombinemia. The patient's severe bleeding complications were described and discussed in relation with reported cases. The authors concluded that the SLE-associated coagulopathies resulted from a combination of an inhibitor impeding the activity of the prothrombin activator complex and an acquired hypoprothrombinemia.

Over the course of several decades, patients with SLE continued to be reported demonstrating a bleeding diathesis associated with a LA and acquired hypoprothrombinemia [51–55]. However, none of these patients demonstrated a neutralization of the circulating inhibitor with the addition of prothrombin to their plasma. Feinstein and Rapaport [3] subsequently concluded that although the LA impaired clotting *in vitro*, abnormal bleeding was only seen in cases of severe hypoprothrombinemia and/or thrombocytopenia. Lechner [55] and Natelson et al. [56] provided additional evidence that the hypoprothrombinemia associated with LA involved a reduction of both prothrombin activity and prothrombin antigen.

It was not until the 1980s when Bajaj et al. [38] provided the first evidence that the plasma of patients with LA and severe hypoprothrombinemia contained non-neutralizing antibodies, which bound prothrombin without inhibiting its conversion to thrombin in the reaction mixtures used to measure plasma prothrombin activity. The investigators postulated that hypoprothrombinemia results from the rapid clearance of prothrombin-antiprothrombin antibody complexes from the circulation. Edson et al. [57] finally demonstrated the presence of antiprothrombin antibodies in the plasma of patients with lupus anticoagulant but without severe hypoprothrombinemia in prothrombin-crossed immunoelectrophoresis experiments. Fleck et al. [58] confirmed

and extended these experiments, finding antiprothrombin antibodies in 31 of 42 LA-positive patients (74%), 15 of whom had prolonged prothrombin time. Adsorption of patients' plasma with insoluble prothrombin reduced both the immune complexes and the anticoagulant activity. Eluates of the insoluble prothrombin contained IgG that displayed lupus anticoagulant activity. This group concluded that these LA were polyspecific, because they reacted with anionic phospholipids and prothrombin.

LAHPS is an uncommon disease with a heterogeneous spectrum. Infection-associated LAHPS appears to be transient, and hemorrhagic manifestations rarely occur. Conversely, LAHPS associated with autoimmune diseases, such as SLE or APAS, or with lymphoma is more persistent, and hemorrhagic complications are a common feature. A recent case report described hematomas of the bilateral gluteus maximus muscles and subclavian area in a patient with Bence-Jones protein κ-type multiple myeloma [59].

Treatment

Currently, there is no consensus in the international community regarding the best therapy for LAHPS [45, 60]. Primary indications for treatment have included peri-operative prophylaxis of bleeding to therapy for life-threatening hemorrhages (e.g., intracranial, pulmonary, gastrointestinal, and uterine) to initiation of long-term immunosuppression to eliminate the inhibitor. Several patients were noted to have incomplete responses to fresh frozen plasma and/or blood transfusions. Incomplete responses to vitamin K may, in fact, be secondary to an unrecognized vitamin K deficiency. Some have been successfully treated with corticosteroids but with recurrence of hypoprothrombinemia after tapering [61].

Mulliez et al. [60] reviewed 77 cases available in the peer-reviewed literature. Twenty-one cases involved infection-associated LAHPS and described therapeutic strategies, with 16 (76%) of these hypoprothrombinemia associated with transient LA cases appearing to resolve spontaneously. Only 3 out of the 21 cases (14%) needed supportive treatment (e.g., fresh frozen plasma, red blood cells, and/or vitamin K), with the remaining 2 cases (10%) receiving corticosteroids or intravenous immunoglobulin (IVIg). None of these patients subsequently relapsed. Two cases [47, 48] reported patients with drug-induced (quinidine and phenytoin, respectively) LAHPS. Discontinuing the offending drug sufficiently reduced prothrombin time (PT) with no further interventions indicated [60].

When autoantibodies persisted, immunosuppression was recommended to eliminate the factor inhibitor. Corticosteroids were consistently used as first-line therapy (53% of 77 cases), with the intent of decreasing clearance of the prothrombin-antiprothrombin complexes. The most common corticosteroid used was prednisone (1 mg/kg/day or 60 mg/day), resulting in normalization of both PT and prothrombin levels and concurrent improvement of bleeding manifestations [60].

However, in 6 of the 41 cases, tapering of the steroid treatment resulted in decreases in the prothrombin levels and relapse. Cyclophosphamide was prescribed in nine cases, with four cases receiving cyclophosphamide after developing lupus nephritis. Cyclophosphamide was initiated after treatment failure resulting from tapering of steroid treatment in two cases. In six out of nine cases, cyclophosphamide was combined with corticosteroid treatment, while in three cases, cyclophosphamide treatment followed corticosteroid treatment in a single maintenance therapy. Eleven cases received azathioprine (all in combination with corticosteroids) with variable efficacy. All but one recipient were SLE patients (single exception had idiopathic lymphoma) [60].

Eight patients received IVIg, with 50% receiving it as a first-line therapy. The remaining four patients were given IVIg prior to elective surgery or after failure of corticosteroid treatment. Efficacy of IVIg therapy was difficult to assess due to concurrent therapy with corticosteroids. Rituximab, an anti-CD20 monoclonal antibody, was administered to 3 of the 77 patients, with variable effectiveness (potential second-line therapy): (a) increase of the prothrombin levels from 20% to 30% after 4 weekly doses of 375 mg/m^2, (b) no improvement after 2 courses of rituximab 1 g/dose, and (c) relapse after corticosteroids and IVIg, improved after 4 weekly doses of 375 mg/m^2 with prothrombin levels up to 74% [60].

Finally, other treatments, such as plasma exchange, hydroxychloroquine, and danazol, recombinant activated factor VII, and prothrombin complex concentrate have been used. Although therapeutic plasma exchange was initiated in two cases resulting in improvement of clinical and laboratory values, it is poorly understood whether the improvement was due to the plasma exchange or the concurrent multi-agent regimens. Hydroxychloroquine is a drug routinely used for the management of SLE, and given that LAHPS frequently occurs in the setting of SLE, hydroxychloroquine was initiated in seven cases, but always in combination with corticosteroids, with good responses noted in all patients. A single case reported a patient with LAHPS, who was treated with danazol after corticosteroid therapy failure, with subsequent improvements in prothrombin levels [60]. Use of recombinant activated factor VII or prothrombin complex concentrate has been reported; however, the dose and the risk of thrombosis versus the benefit of controlling ongoing bleeding have not been established [61, 62].

In the absence of a standardized plan of care, most clinicians recommend that therapy be reserved for severe cases of bleeding. In minor bleeding, corticosteroids are considered first-line therapy, with supportive care managed with fresh

frozen plasma and blood transfusions. Close follow-up is recommended, with immunosuppressive therapies reserved for patients presenting with life-threatening or severe hemorrhage or recurrent episodes of bleeding [45].

Based on the available data, corticosteroids prescribed at an initial dose of 1 mg/kg/day should be considered the first-line treatment for more severe cases. Alternative therapeutic strategies are still unclear, as other immunosuppressive treatments such as azathioprine, cyclophosphamide, rituximab, or IVIg were prescribed only in a few patients, usually in combination with corticosteroids. It is also important to remember that the risk of thrombosis increases during treatment, as the improvement of PT and prothrombin levels shifts the balance from a pro-hemorrhagic hypoprothrombinemia to a pro-thrombotic LA state, resulting in catastrophic thromboses and even death [45, 63, 64]. Further progress in the knowledge and management of this uncommon coagulation disorder is necessary.

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Part III

Bleeding from Specific Organs

Intracerebral Hemorrhage: An Overview of Etiology, Pathophysiology, Clinical Presentation, and Advanced Treatment Strategies

24

Burhan Z. Chaudhry and Edward M. Manno

Introduction

Spontaneous intracerebral hemorrhage (ICH) represents direct intraparenchymal bleeding, usually from rupture or leakage of the arterioles or small arteries of the brain. Extension or bleeding into the ventricles or subarachnoid space is common. The annual incidence for the United States ranges from 10 to 30 per 100,000. ICH accounts for 10–30% of stroke-related hospital admissions, with an overall 50% 30-day mortality. Hispanic, African Americans, and Native Americans have a higher incidence in North America. Similarly, Asiatic populations have a much higher incidence, most likely secondary to poor control of hypertension [1–9].

Etiologically, ICH can be grouped into primary spontaneous ICH, which is mainly associated with hypertension (70%) and amyloid angiopathy (30%). Secondary causes include hemorrhages due to oral anticoagulant therapy, neoplasms, vascular malformations, or aneurysms [6, 7].

Several risk factors have been identified over the last several decades for spontaneous ICH, consisting mainly of genetic aspects, pre-existing medical conditions, and lifestyle factors. Two different apolipoprotein E alleles (e2/4) have been related to an increased risk and a greater recurrence of ICH. Further genetic associations relate to ethnic differences. The most relevant prior medical history is the diagnosis of arterial hypertension which—if treated—may lead to a risk reduction of ICH in patients with cerebrovascular disease. Moreover, ICH-associated lifestyle factors include a history of smoking, drug abuse, or heavy alcohol intake. Predictive factors of poor outcome may be divided into non-modifiable or modifiable (potentially treatable) features. The initial hematoma volume, age, neurological status on admission, and ICH location are non-modifiable, whereas potentially treatable factors are avoiding hematoma growth, treating acute hydrocephalus, reducing brain edema, and managing medical comorbidities and complications [1–6, 9].

Pathophysiology

Regional Cerebral Blood Flow and Metabolism in ICH

In ICH, a localized hematoma can enlarge over time. Growth of the hematoma occurs within the first 6 h but may continue up to 24 h. Blood may dissect along white matter pathways, until regional pressure increases limit the spread of the hematoma or until the hemorrhage relieves this pressure gradient by emptying into the ventricles or the cerebrospinal fluid (CSF) space on the pial surface of the brain. Damage from the enlarging hematoma may develop directly through physical compression of the hematoma or indirectly from perihematomal ischemia (Fig. 24.1) [4–6].

Regional cerebral blood flow is also affected during ICH and occurs in specific phases (Fig. 24.1).

- The first phase, referred to as the hibernation phase, occurs within the first 48 h. During this phase, there is decreased cerebral blood flow and metabolism in both ipsilateral (predominantly in the perihematoma region) and contralateral hemispheres.
- The second phase, referred to as the reperfusion phase, occurs anywhere from 48 h to 14 days and is described by a combination of areas of hypo- and hyperperfusion in the perihematoma regions.
- The third phase, referred to as the normalization phase, occurs more than 14 days later and is characterized by normal cerebral blood flow in the localized surrounding tissue [4–6].

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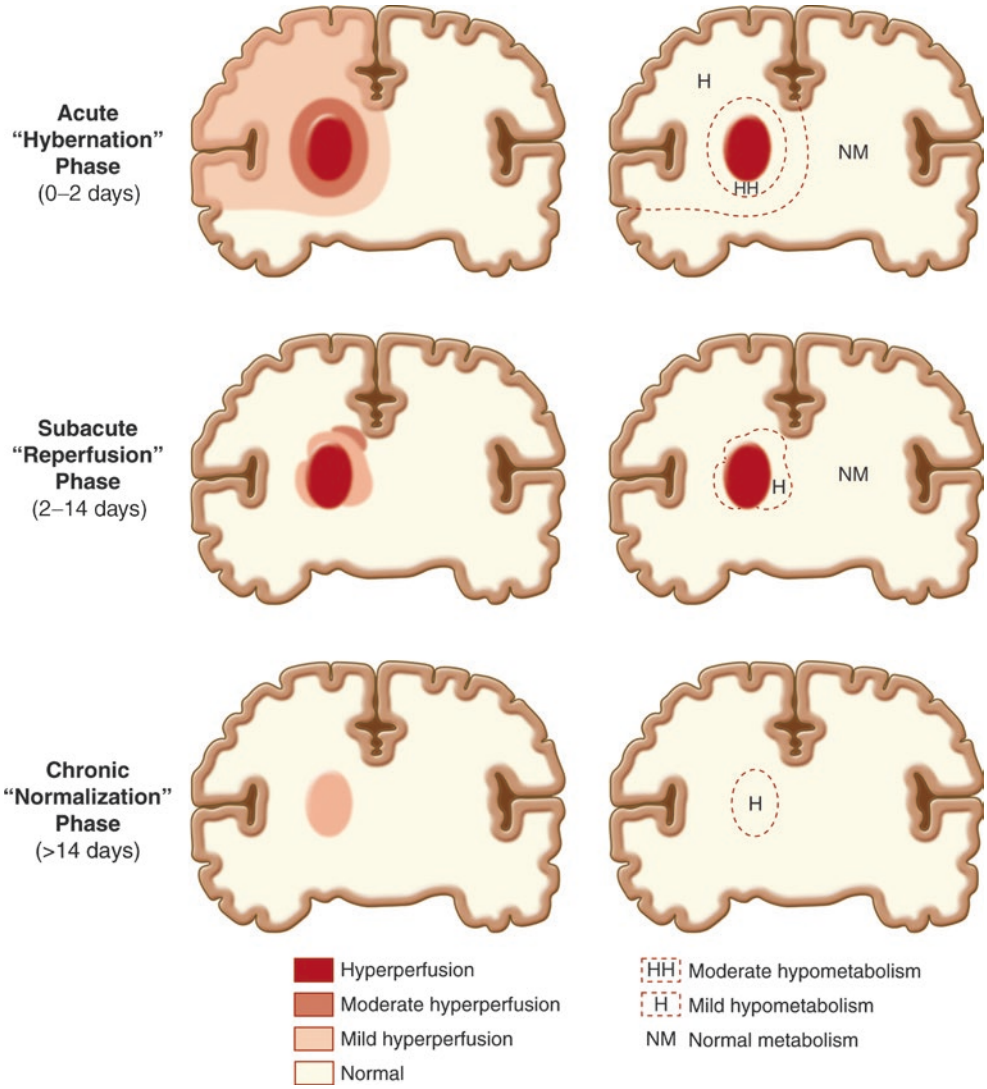

Fig. 24.1 Diagrammatic representation of the three phases of cerebral blood flow and metabolism changes in the acute, subacute, and chronic phases after intracerebral hemorrhage. (From Alqadri and Qureshi [6])

Pathophysiology

Primary ICH secondary to long-standing hypertension commonly affects the deep white matter, the basal ganglia, the thalamus, the brain stem (predominantly the pons), and the cerebellum as a result of ruptured vessels affected by hypertension-related degenerative changes. Most bleeding in hypertension-related ICH is at or near the bifurcation of small penetrating arteries that originate from basilar arteries or the anterior, middle, or posterior cerebral arteries. Small artery branches of 50–700 μm in diameter often have multiple sites of rupture; some are associated with layers of platelet and fibrin aggregates. These lesions are characterized by the breakage of elastic lamina, atrophy, and fragmentation of smooth muscle, dissections, and granular or vesicular cellular degeneration. Severe atherosclerosis including lipid deposition can affect elderly patients. Fibrinoid necrosis of the subendothelium with subsequent focal dilatations (microaneurysms) may lead to rupture in a small proportion of patients [4–6].

ICH secondary to cerebral amyloid angiopathy most commonly leads to cortical hemorrhages. Cerebral amyloid angiopathy is characterized by the deposition of amyloid-β peptide and degenerative changes (microaneurysm formation, concentric splitting, chronic inflammatory infiltrates, and fibrinoid necrosis) in the capillaries, arterioles, and small- and medium-sized arteries of the cerebral cortex, leptomeninges, and cerebellum. Cerebral amyloid angiopathy leads to sporadic ICH in elderly people, commonly associated with variations in the gene encoding apolipoprotein E. A similar syndrome exists in young patients with mutations in the gene encoding amyloid precursor protein. White matter abnormalities (e.g., leukoaraiosis) seem to increase the risk of both sporadic and familial ICH, suggesting a possible shared vascular pathogenesis.

Anticoagulant-induced ICH typically affects patients with vasculopathies related to either chronic hypertension or cerebral amyloid angiopathy [4–6].

The region surrounding hematomas are characterized by inflammation, edema, apoptosis, and necrosis. Hematomas induce injury (Fig. 24.2) by the mechanical disruption of neurons and glia. Mechanical deformation of local tissue causes secondary oligemia with subsequent neurotransmitter release and membrane depolarization, which culminates in mitochondrial dysfunction. Depending on the severity of mitochondrial dysfunction, the results of injury range from temporary metabolic suppression (hibernation phase) to cellular swelling and necrosis.

A secondary cascade of injury is initiated through the by-products of coagulation and hemoglobin breakdown. Thrombin generation activates microglia within a few hours of injury. Activated microglia release products that induce breakdown of the blood–brain barrier. This leads to the development of vasogenic edema, and direct and indirect cell death in neurons and glia.

Perihematomal edema increases in volume by about 75% in the first 24 h after ICH, peaks around 5–6 days, and lasts up to 14 days. Large edema volume relative to hematoma volume portends worse neurological outcome.

The initial size of the hemorrhage and the rate of hematoma expansion are important prognostic variables in predicting neurologic deterioration. Hematoma size >30 mL is associated with increased mortality. Following the expansion, cerebral edema forms around the hematoma, secondary to inflammation and disruption of the blood–brain barrier. This perihematoma edema is the primary etiology for neurological deterioration and develops over a period of days following the initial insult. In up to 40% of ICH cases, the hemorrhage extends into the cerebral ventricles, causing intraventricular hemorrhage (IVH). This is associated with acute obstructive hydrocephalus and also worsens prognosis. ICH and accompanying edema may also disrupt or compress adjacent brain tissue, leading to neurological dysfunction.

Displacement of brain parenchyma may cause elevation of intracranial pressure (ICP), with the potential for the development of herniation syndromes. Figure 24.3 illustrates the progression of hematoma and edema on computed tomography (CT) [4–6].

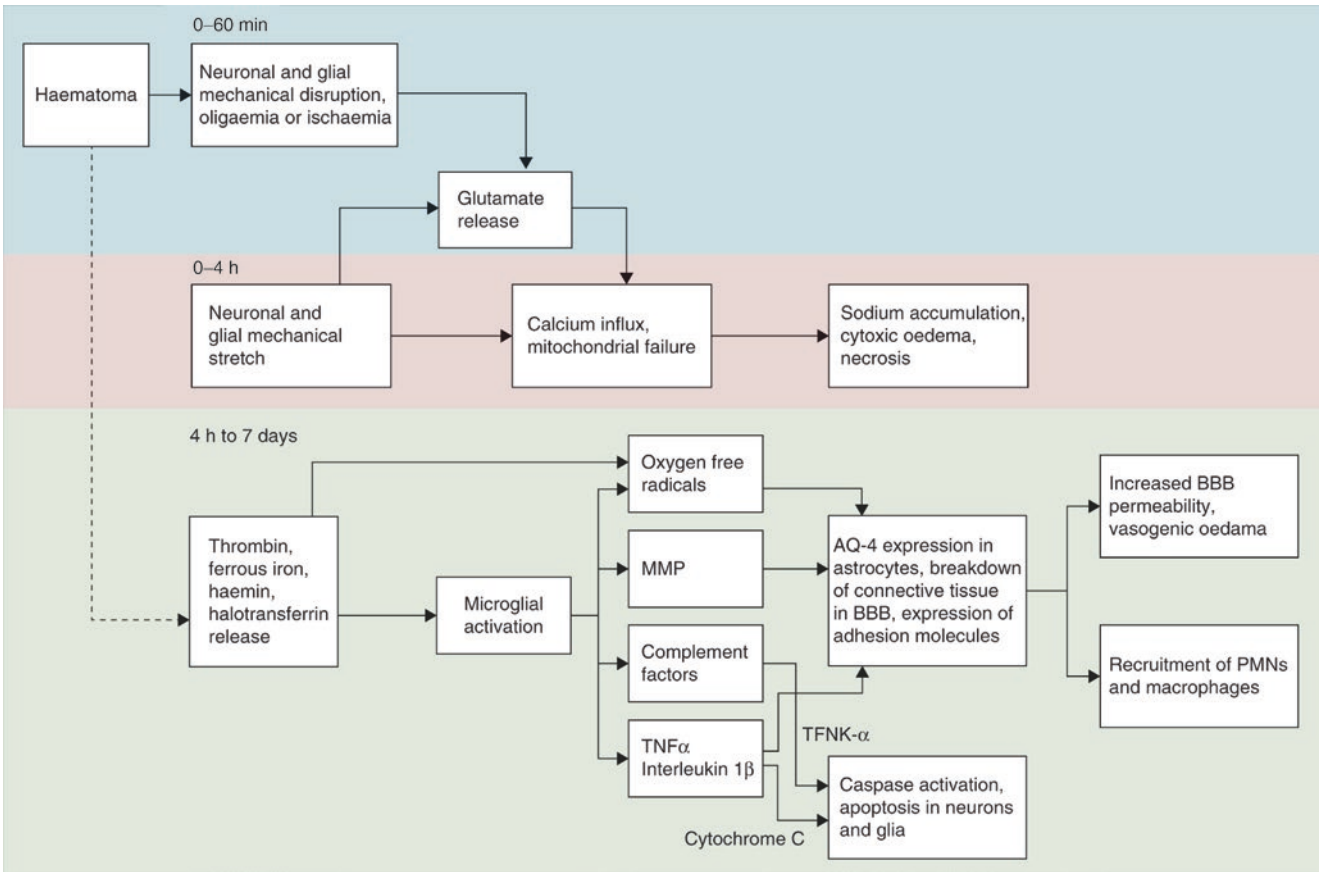

Fig. 24.2 Cascade of neural injury initiated by intracerebral hemorrhage. The initial process in the first 4 h is related to the direct effect of the hematoma, while later steps are accounted for through the release of products from the hematoma. *BBB* blood–brain barrier, *MMP* matrix metallopeptidase, *TNF* tumor necrosis factor, *PMN* polymorphonuclear cells. (From Qureshi et al. [26]. With permission from Elsevier)

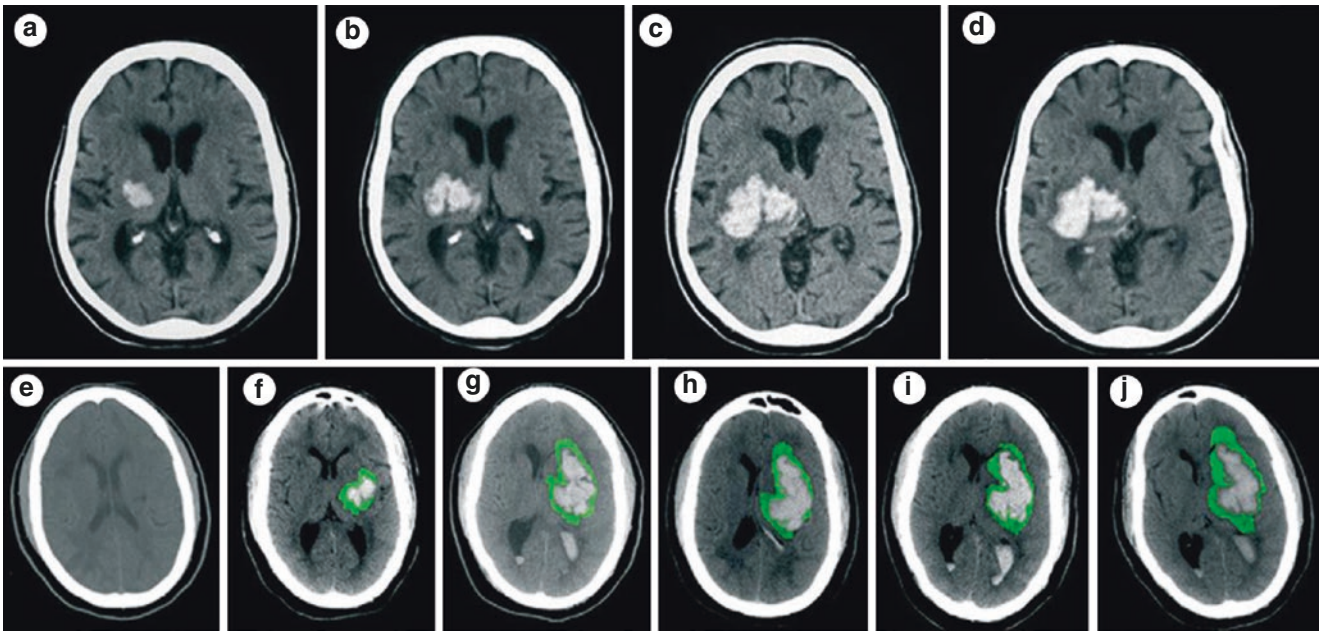

Fig. 24.3 Progression of hematoma and edema on computed tomography (CT): hyperacute expansion of hematoma in a patient with intracerebral hemorrhage on serial CT scans. Small hematoma detected in the basal ganglia and thalamus (**a**). Expansion of the hematoma after 151 min (**b**). Continued progression of the hematoma after another 82 min (**c**). Stabilization of the hematoma after another 76 min (**d**). Bottom: progression of hematoma and perihematomal edema in a patient with intracerebral hemorrhage on serial CT scans. The first scan (**e**) was acquired before the intracerebral hemorrhage. Perihematoma edema is highlighted in green to facilitate recognition of the progression of edema. At 4 h after symptom onset, there is a small hematoma in the basal ganglia (**f**). Expansion of hematoma with extension into the lateral ventricle and new mass effect and midline shift at 14 h (**g**). Worsening hydrocephalus and early perihematomal edema at 28 h (**h**). Continued mass effect with prominent perihematomal edema at 73 h (**i**). Resolving hematoma with more prominent perihematomal edema at 7 days (**j**)

Clinical Manifestation

Rapid recognition of ICH is crucial. Rapid clinical progression during the first several hours can quickly lead to neurological deterioration and cardiopulmonary instability. The classic presentation in ICH is the progressive onset of focal neurological deficits in minutes to hours, with accompanying headache, nausea, vomiting, decreased level of consciousness, and elevated blood pressure. Compared to ischemic stroke and subarachnoid hemorrhage, there is typically a more abrupt progression of focal deficits. Symptoms of headache and vomiting are also observed less often in ischemic stroke compared with ICH. Large hemorrhages may increase ICP, as evidenced through the presence of Cushing's triad—hypertension, bradycardia, and irregular respiration. Dysautonomia is also frequently present in ICH, accounting for hyperventilation, tachypnea, bradycardia, fever, hypertension, and hyperglycemia. Classic neurological deterioration is common before and during hospital admission and is related to early hematoma enlargement or late worsening of edema. Several descriptors of disease severity are predictive of early death, including age, initial score on the Glasgow Coma Scale (GCS), hematoma volume, ventricular blood volume, and hematoma enlargement [6].

The GCS is a neurological scale that aims to give a reliable, objective way of recording the conscious state of a person for initial as well as subsequent assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 15 (Table 24.1).

Table 24.1 Glasgow coma scale

	1	2	3	4	5	6
Eye	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion/withdrawal to painful stimuli	Localizes painful stimuli	Obeys

Stroke can often be confused with other neurological conditions that mimic stroke in their clinical presentation. The most common stroke mimics are seizure, syncope, and sepsis. Sensory symptoms such as vertigo, dizziness, and headaches are non-discriminatory between stroke and non-stroke. Furthermore, ICH is particularly difficult to diagnose because symptoms of syncope, coma, neck stiffness, seizure, diastolic blood pressure (BP) of >110 mmHg, nausea, vomiting, and headache are typically present. As a result, early neuroimaging becomes vital in the diagnosis of ICH. The most common symptoms of hemorrhagic and ischemic stroke are acute onset, limb weakness, speech disturbances, and facial weakness.

Mortality in patients with ICH is high. Various studies have reported mortalities of 31% at 7 days, 59% at 1 year, 82% at 10 years, and more than 90% at 16 years. Subsequent risk of other cardiovascular events is 2%. Lobar hemorrhages have a high rate of recurrence (4% per patient-year). Recurrent bleeding can be changed by antihypertensive treatment; whether progressive functional impairments are equally treatable is unknown. Asymptomatic disease progression is particularly common when microbleeds and white matter abnormalities are taken into account [6].

Diagnosis and Assessment

ICH is a medical emergency. Rapid diagnosis and attentive management of patients with ICH is crucial because early deterioration is common in the first few hours after ICH onset. More than 20% of patients will experience a decrease in the GCS score of 2 points between the pre-hospital emergency medical services assessment and the initial evaluation in the emergency department. For those patients with pre-hospital neurological decline of greater than 6 points, the mortality rate is 75%. The risk for early neurological deterioration and the high rate of poor long-term outcomes underscore the need for aggressive early management. The crucial resources necessary to manage patients with ICH include neurology, neuroradiology, neurosurgery, and critical care facilities [6].

Neuroimaging

The abrupt onset of focal neurological symptoms is presumed to be vascular in origin until proven otherwise. However, it is impossible to know whether symptoms are due to ischemia or hemorrhage based on clinical characteristics alone. Vomiting, systolic BP 220 mmHg, severe headache, coma or decreased level of consciousness, and progression over minutes or hours all suggest ICH, although none of these findings are specific; neuroimaging is, thus, mandatory. CT and magnetic resonance imaging (MRI) are both reasonable for initial evaluation. CT is very sensitive for identifying acute hemorrhage and is considered the gold standard; gradient echo and T2 susceptibility weighted MRI are as sensitive as CT for the detection of acute blood and are more sensitive for the identification of prior hemorrhage. Time, cost, proximity to the emergency department, patient tolerance, clinical status, and MRI availability may, however, preclude emergent MRI in a sizeable proportion of cases [6–8].

The high rate of early neurological deterioration after ICH is, in part, related to active bleeding. The closer symptom onset is to the first neurological image, the more likely subsequent images will demonstrate hematoma expansion. Among patients undergoing head CT within 3 h of ICH onset, 28–38% have hematoma expansion of greater than one-third on follow-up CT. Hematoma expansion is predictive of clinical deterioration and increased morbidity and

mortality. As such, identifying patients at risk for hematoma expansion is an active area of research. CT angiography and contrast-enhanced CT may identify patients at high risk of ICH expansion based on the presence of contrast extravasation within the hematoma.

MRI/angiogram/venogram and CT angiogram/venogram are reasonably sensitive at identifying secondary causes of hemorrhage, including arteriovenous malformations, tumors, moyamoya, and cerebral vein thrombosis. A catheter angiogram may be considered if clinical suspicion is high or non-invasive studies are suggestive of an underlying vascular cause. Clinical suspicion of a secondary cause of ICH may include a prodrome of headache, neurological, or constitutional symptoms. Radiological suspicions of secondary causes of ICH should be invoked by the presence of subarachnoid hemorrhage, unusual (non-circular) hematoma shape, the presence of edema out of proportion to the size of the hematoma, an unusual location for hemorrhage, and the presence of other abnormal structures in the brain, like a mass. An MRI or CT venogram should be performed if hemorrhage location, relative edema volume, or signal abnormalities in the cerebral sinuses suggest cerebral vein thrombosis [6–8].

Medical Management of ICH

Acute Hemostatic Treatment

For patients being treated with oral anticoagulants (OACs) who have life-threatening bleeding, such as intracranial hemorrhage, the general recommendation is to correct the international normalized ratio (INR) as rapidly as possible. Infusions of vitamin K and fresh frozen plasma (FFP) have historically been recommended but, in general, take too long to administer and be effective in anticoagulation reversal for ICH and can have significant side effects [10–14].

More recently, prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) have emerged as potential therapies. PCCs are plasma-derived factor concentrates primarily used to treat factor IX deficiency. Because PCCs also contain factors II, VII, and X in addition to factor IX, they are increasingly recommended for warfarin reversal. PCCs have the advantages of rapid reconstitution and administration, having high concentrations of coagulation factors in small volumes, and processing to inactivate infectious agents. Though different PCC preparations differ in relative amounts of factors, with factor VII the most likely to be low, several studies have shown that PCCs can rapidly normalize the INR (within minutes) in patients taking OACs. Reviews and study have shown more rapid correction of the INR with vitamin K and PCC than vitamin K and FFP, with differences in the clinical outcome as well. In fact, the US Food and Drug Administration (FDA) approved, in 2013, the use of a certain PPC (Kcentra™) which contains higher concentrations of factor VII compared to other PCCs for the urgent reversal of warfarin therapy in adult patients with acute ICH. Although PCCs may theoretically increase the risk of thrombotic complications, this risk appears to be relatively low. Despite the lack of large, well-controlled, randomized trials, PCCs are being increasingly recommended as an option in guidelines promulgated for warfarin reversal in the setting of OAC-associated life-threatening or intracranial hemorrhages. Table 24.2 provides a list of several products for factor replacement in warfarin reversal that are commercially available in the United States at the present time [10–14].

rFVIIa is also used in spontaneous ICH, as studies have shown that it reduced growth of the hematoma and improved survival and functional outcomes. However, it is not commonly used in acute warfarin reversal.

The use of antifibrinolytics was also studied for the treatment of acute ICH with a pilot study carried out to investigate their effects in halting ICH enlargement. Aminocaproic acid (Amicar™) is a derivative and analog of the amino acid lysine, which makes it an effective inhibitor for enzymes. Such enzymes include proteolytic enzymes like plasmin, the enzyme responsible for fibrinolysis. For this reason, it is effective in the treatment of certain bleeding disorders. The study concluded it was unlikely that the rate of ICH enlargement in patients given Amicar within 12 h of ICH is less than the natural history rate, although the treatment appeared to be safe.

A direct antibody has been developed to reverse the effects of dabigatran. Further studies with these types of agents are warranted [10–14].

Current Guidelines on the Management of Acute Hypertensive Response

The current guidelines for hypertension in ICH are based on incomplete evidence, since there are still ongoing trials of BP intervention. However, certain factors are generally taken into account, such as chronic hypertension, age, time of onset and presentation, maintaining mean arterial pressure (MAP) between the therapeutic range of 90 and 130 mmHg, and targeting cerebral perfusion pressure maintenance at >70 mmHg if there is evidence of increased ICP [14–20]. Suggested guidelines for treating elevated BP in spontaneous ICH, as recommended by the American Stroke Association (ASA) and the American Heart Association (AHA), include the following:

– If a patient presents with a systolic blood pressure (SBP) of >200 mmHg or MAP of >150 mmHg, then aggressive

Table 24.2 Products for factor replacement in warfarin reversal

Product	Factor(s)	Dose (consultation with a hematologist is recommended for specific dosing)	Uses
Fresh-frozen plasma	I (fibrinogen), II, V, VII, IX, X, XI, XIII, antithrombin	10–15 mL/kg with ideal recovery would raise factor levels by 15–20%	OAC reversal
			Consumptive coagulopathy Hepatic dysfunction
Cryoprecipitate	I, VIII, XIII, VWF	1–2 U/10 kg	Hypo/a-fibrinogenemia
			Lack of factor-specific products for factor VIII deficiency or VWD factor XIII deficiency
Prothrombin complex concentrates			
	II, IX, X (small amounts of VII)	Assayed in factor IX activity	Factor IX deficiency (hemophilia B)
Bebulin VH (Baxter), Profilnine SD (Grifols), Kcentra (CSL Behring)		Both Bebulin and Profilnine are three-factor PCCs that have approximately 1/10th the factor VII activity relative to factor IX activity. Kcentra is a four-factor PCC	OAC reversal (not FDA-approved)
		Dosing for factor IX deficiency—1 U/kg raises activity by 1%	
		Dosing for OAC reversal has not been well established	
NovoSeven RT (Novo Nordisk)	Recombinant activated VII	Higher risk of thromboembolic complications with higher doses	Factor VIII or IX deficiency with inhibitors to factor VIII or IX
		For hemophilia A or B patients with inhibitors, 90 μg/kg every 2 h	Congenital factor VII deficiency
		For factor VII-deficient patients, 15–30 μg/kg every 4–6 h	Not recommended for spontaneous ICH or OAC reversal
Factor VIII concentrates			
Plasma-derived	VIII	Each factor VIII unit/kg raises the plasma factor VIII level by 2% (typically, a 50-U/kg dose is used to raise the factor VIII level to 100%)	Factor VIII deficiency (hemophilia A)
Alphanate (Grifols)[a,b]			
Humate-P (CSL-Behring)[a,b]			
Koate-DVI (Bayer)[a]			
Wilate (Octapharma)[a,b]			
Immunoaffinity purified			
Hemofil-M (Baxter)			Wilate is not indicated for hemophilia A
Monarc-M (Baxter)			
Monoclate-P (CSL-Behring)			
Recombinant			
Advate (Baxter)			
Helixate FS (CSL-Behring)			
Kogenate FS (Bayer)			
Recombinate (Baxter)			
Xyntha (Wyeth)			
Factor IX concentrates			
Plasma-derived	IX	Each factor IX unit/kg raises the plasma level by 1% (typically, a 100-U/kg dose is used to raise the level to 100%)	Factor IX deficiency (hemophilia B)
AlphaNine SD (Grifols)			
Mononine (Baxter)			
Recombinant			One unit of BeneFix raises the plasma level by 0.83%, so 120 U/kg raises the activity to 100%
BeneFix (Wyeth)			

From Morgenstern et al. [37]

VWD von Willebrand disease, *FDA* US Food and Drug Administration, *PCCs* prothrombin complex concentrates

[a]Also contains von Willebrand factor

[b]Indicates for von Willebrand disease (dose by ristocetin cofactor units; ratio of factor VIII to ristocetin cofactor unit varies by product)

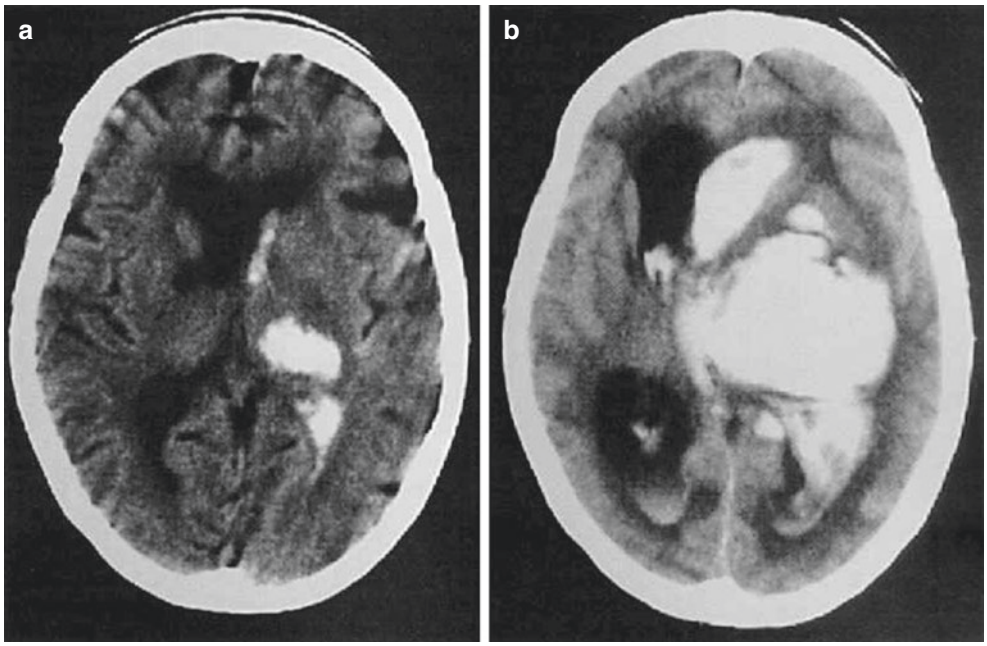

Fig. 24.4 Illustrates lack of BP control. (**a**) Initial head CT, (**b**) head CT in the same patient whose SBP was consistently more than 140 mmHg

lowering of BP is recommended with continuous intravenous (IV) infusion of antihypertensive medications (i.e., labetalol, nicardipine, esmolol, hydralazine, nitroprusside, or nitroglycerine). If the patient presents with an SBP of >180 mmHg or MAP of >130 mmHg with suspected increased ICP, monitor ICP and use intermittent or continuous IV antihypertensives mentioned above to maintain cerebral perfusion pressure at a safe range of >50–70 mmHg. If a patient presents with an SBP of >180 mmHg or MAP of >130 mmHg with no increase in ICP and then moderately reduce BP using intermittent or continuous IV antihypertensives.

– In patients presenting with a systolic BP of 150–220 mmHg, acute lowering of systolic BP to 140 mmHg is probably safe and desirable (new recommendation).

Acute hypertensive response is defined as "SBP≥140 mmHg or diastolic BP of ≥90 mmHg demonstrated on two recordings taken 5 min apart within 24 h of symptom onset." A large prevalence study showed that 75% of ICH patients presented with SBP more than 140 mmHg. Recent data have highlighted the importance of acute hypertensive response as a therapeutic target. The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial and Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) have shown that reducing the SBP to 140 mmHg is well tolerated and associated with reduction of hematoma expansion. The effect of lowering BP on death and severe disability was evaluated by both the phase III ATACH II and INTERACT 2 trials and showed both outcomes to be similar in both the control and experimental groups [15–21].

Figure 24.4 illustrates the importance of aggressive SBP control. Table 24.3 provides the major trials looking at BP management in ICH.

Seizure in ICH

Eight percent of patients with ICH have clinical seizures within 1 month of symptom onset, associated with lobar location or hematoma enlargement. However, continuous electroencephalographic monitoring in an observational study showed that 28% of patients with ICH had (predominantly subclinical) seizures within the first 72 h of admission. Seizures were associated with neurological worsening, an increase in midline shift, and poorer outcomes. Therefore, a low threshold for obtaining electroencephalographic studies and the use of anticonvulsants in patients with ICH might be advisable. Patients who have a seizure more than 2 weeks after ICH onset are at greater risk of recurrent seizures than those who do not and might need long-term prophylactic treatment with anticonvulsants [22–25].

Management of Intraventricular Hemorrhage and Hydrocephalus

Clinical trials have confirmed that IVH and hydrocephalus are independent predictors of poor outcome in spontaneous ICH. Impaired flow of CSF and direct mass effects of ventricular blood lead to obstructive hydrocephalus. External drainage of CSF through ventricular catheters reduces intracranial

Table 24.3 Major trials assessing BP management in ICH [6]

Time period	ATACH I 2004–2008	INTERACT 1 2005–2007	ATACH II 2010–2015	INTERACT 2 2008–2012
Study design	Prospective, multicenter, randomized, safety, efficacy study, open-label	Randomized, active-control, parallel-assignment, safety, efficacy study, open-label	Randomized, multicenter, parallel-assignment, treatment efficacy study, open-label, phase III	Randomized, multicenter, parallel-assignment, safety, efficacy study, open-label
No. of cases	60	404	1280	2800
Inclusion criteria	ICH on CT	ICH on CT	ICH on CT	ICH on CT
	<6 h of symptom onset	<6 h of symptom onset	<3 h of symptom onset	<6 h of symptom onset
	SBP ≥170 mmHg	SBP 150–220 mmHg on ≥2 readings	SBP ≥180 NIHSS score ≥4	SBP 150–220 mmHg on ≥2 readings
	GCS ≥8		GCS score ≥5	
	Hematoma volume <60 cc		Hematoma volume <60 cc	
Intervention	Patients randomized to three tiers of SBP reduction with IV Nicardipine:	Patients randomized to two target groups with IV antihypertensives:	Patients randomized to two target BP groups with IV Nicardipine +/− IV Labetalol for 24 h:	Patients randomized to two target groups with IV antihypertensives:
	170–200 mmHg 140–170 mmHg 110–140 mmHg	Control: BP ≤180 mmHg	Control: 140–180 mmHg	Control: BP ≤180 mmHg
		Intensive therapy: BP ≤140 mmHg	Intensive therapy: 110–140 mmHg	Intensive therapy: BP ≤140 mmHg
Outcomes	Target treatment goals maintained and achieved for 18–24 h post-ictus. Safety and tolerability achieved	Target treatment goals maintained for 24 h. Safety and tolerability achieved	Ongoing trial	Ongoing trial

ICH intracerebral hemorrhage, *CT* computed tomography, *SBP* systolic blood pressure, *GCS* Glasgow Coma Scale, *NIHSS* National Institutes of Health Stroke Scale, *IV* intravenous, *BP* blood pressure

pressure but has an inherent risk for developing infections and clotting off. Shortening the length of external ventricular drainage with early ventriculoperitoneal shunt placement or lumbar drainage for communicating hydrocephalus might lower the rate of infections. Substitution of lumbar drainage for external ventricular drainage in patients with communicating hydrocephalus might also lessen the need to change temporary ventricular catheters [18, 26–28].

IVH is a dynamic process that follows ICH. The presence of IVH at any time and growth of this hemorrhage increase the likelihood of death or severe disability by 90 days. To facilitate early and effective clearance of blood in the ventricles, recent efforts have focused on the intraventricular use of thrombolytic drugs in patients who have IVH in association with spontaneous ICH. Clinical trials have not clearly shown improved neurological outcome in survivors of IVH. The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR-IVH) trial is investigating this issue [18, 26–28].

Deferoxamine

Hemoglobin degradation products, in particular iron, have been implicated in secondary neuronal injury following ICH. The iron chelator deferoxamine (DFO) mesylate exerts diverse neuroprotective effects, reduces perihematoma edema and neuronal damage, and improves functional recovery after experimental ICH in animal models. It is hypothesized that treatment with DFO could minimize neuronal injury and improve outcome in ICH patients. As a prelude to test this hypothesis, a phase I, open-label study to determine the tolerability, safety, and maximum tolerated dose (MTD) of DFO in patients with ICH was done. Intravenous infusions of DFO in doses up to 62 mg/kg/day (up to a maximum of 6000 mg/day) were well tolerated and did not seem to increase serious adverse events or mortality. As a result, a multicenter, double-blind, randomized, placebo-controlled, phase II clinical trial [Intracerebral Hemorrhage Deferoxamine (iDEF) trial] was initiated to determine if it is futile to move DFO forward to phase III efficacy evaluation. It is currently in phase II [29].

Surgical Evacuation

Surgical evacuation may prevent expansion, decrease mass effects, block the release of neuropathic products from hematomas, and, thus, prevent the initiation of secondary injury. The Surgical Trial for Intracerebral Hemorrhage (STICH) compared early surgery (median time of 20 h from presentation to surgery) with medical treatment. Overall, the results did not show any improvement with open surgery; however, hematomas extending to within 1 cm of the cortical surface had a trend toward more favorable outcome with surgery within 96 h. STICH II was designed to evaluate this subgroup,

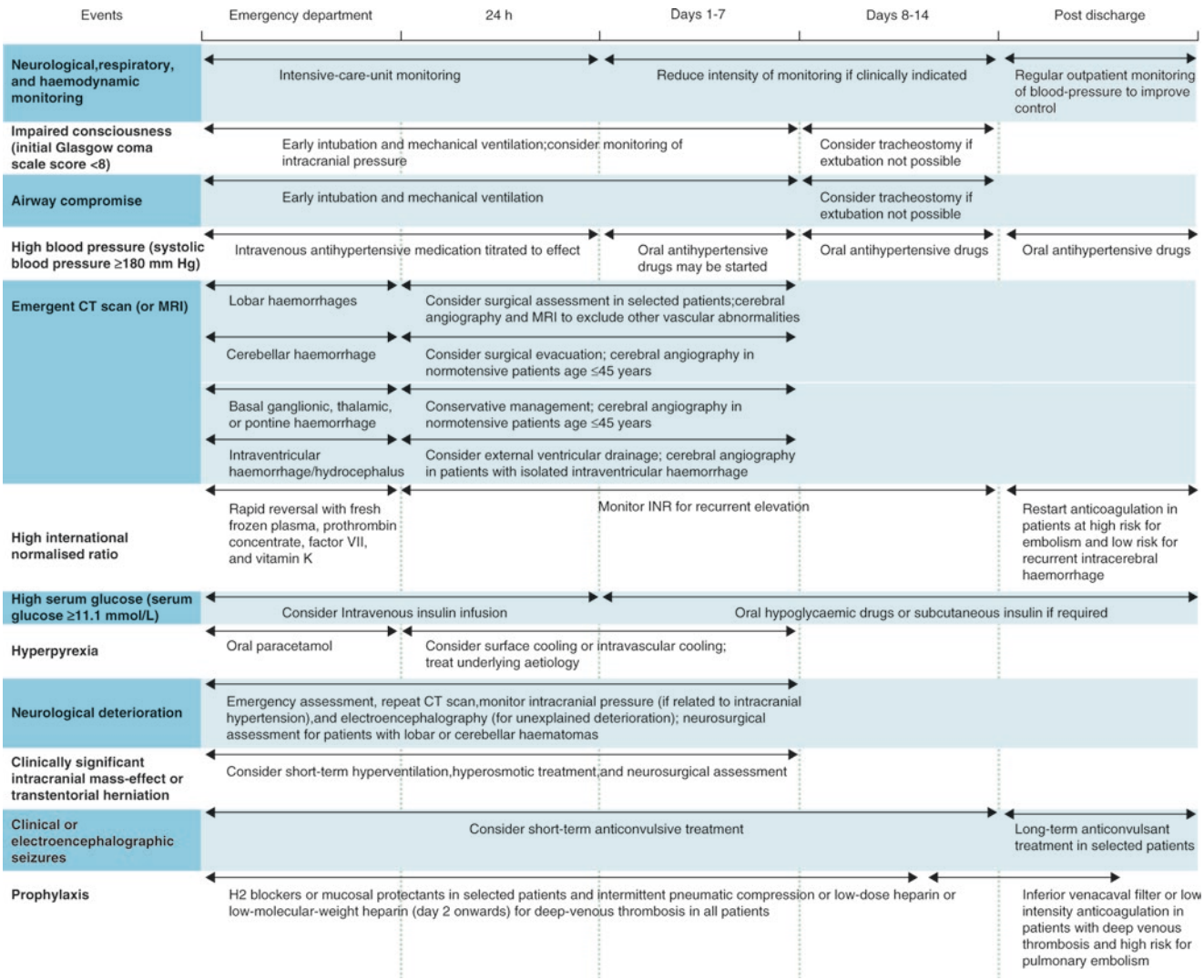

Fig. 24.5 Management algorithm for patients with intracerebral hemorrhage

which revealed only a marginal benefit in this subgroup. The failure of open surgery to provide significant benefit has led to the study of minimally invasive techniques to remove deep hematomas. Preliminary work has been encouraging and phase III trials are currently being developed [30–36].

Cerebellar hemorrhages, however, are treated differently to supratentorial hemorrhages. According to the AHA/ASA guidelines, patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible. Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended (new recommendation). To limit neural damage and the risk of recurrent bleeding associated with open craniotomy, studies are now focusing on less invasive stereotactic and endoscopic evacuation with the use of thrombolytic drugs [30–36] (Fig.24.5).

Conclusion and Future Studies

Clinical evidence suggests the importance of three management tasks in ICH: limiting hematoma expansion, removing the clot or preventing secondary injury from developing, and controlling cerebral perfusion pressure. The precision needed to achieve these goals and the degree of benefit attributable to each clinical goal will be clarified as the results of trials in progress become available. An NIH workshop identified the importance of animal models of ICH and of human pathology studies. The use of real-time, high-field MRI with three-dimensional imaging and high-resolution tissue probes

is another priority. Trials of acute BP treatment and coagulopathy reversal are also medical priorities. Trials of minimally invasive surgical techniques including mechanical and pharmacological adjuncts are surgical priorities. A better understanding of methodological challenges, including the establishment of research networks and multispecialty approaches, is also needed. New information created in each of these areas should add substantially to our knowledge about the efficacy of treatment for ICH [37].

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Epistaxis

25

Elton Lambert and Ellen M. Friedman

Epistaxis is a common presenting symptom. From 2009 to 2010, there were over 1.2 million healthcare visits for epistaxis, with 400,000 of them being emergency room visits [1]. Older children are more likely to present for epistaxis. The average age of presentation for pediatric epistaxis is 12 years old with a male predominance [2]. Of patients presenting for an ambulatory visit with a chief complaint of epistaxis, 69% present to a pediatric clinic, 18% to otolaryngology, and 13% to a family medicine/general clinic [3]. In children, most cases of nosebleeds are not life threatening, are simple, and are not associated with an underlying disorder. However, even non-complicated epistaxis can be associated with increased parental anxiety [4]. A thorough history and physical examination is needed to elucidate the etiology of the nosebleed. Close vigilance is needed as epistaxis can be the initial presenting symptom for a wide array of systemic diseases. The differential diagnosis for epistaxis is shown in Table 25.1.

Table 25.1 Differential diagnosis of epistaxis

Anatomic	*Inflammatory*
Septal deviation	Allergic rhinitis
Inferior turbinate hypertrophy	Bacterial rhinitis or bacterial colonization
Dilated septal vessels	Atrophic rhinitis
Traumatic	*Hereditary/blood dyscrasias*
Digital trauma	Thrombocytopenia
Nasal trauma	von Willebrand disease
Head and skull base trauma	Hemophilia A and B
Iatrogenic due to insertion of nasal tubes, e.g., nasogastric or endotracheal tubes	Coagulation factor deficiency
Nasal surgery	Hereditary hemorrhage telangiectasia
Endoscopic sinus surgery	Disseminated intravascular coagulation (DIC)
Skull base surgery	
Vascular	*Medications/drugs*
Hypertension	Aspirin
Petroclival carotid aneurysm	Clopidogrel
Carotid-cavernous fistula	Nonsteroidal anti-inflammatory drugs
	Nasal steroid sprays
	Warfarin
	Heparin
	Argatroban
	Fondaparinux
	Cocaine
Neoplastic	*Systemic diseases*
Juvenile nasopharyngeal angiofibroma	Chronic liver disease Chronic kidney disease
Melanoma	
Soft tissue sarcomas, e.g., rhabdomyosarcoma	
Nasopharyngeal carcinoma	
Squamous cell carcinoma	
Benign intranasal tumors, e.g., inverting papilloma	

Relevant Anatomy

The blood supply to the anterior nasal septum is a confluence of the superior labial artery (branch of the facial artery), the anterior ethmoid artery (branch of the ophthalmic artery), the posterior septal artery (branch of the sphenopalatine artery), and the greater palatine artery (branch of the descending palatine and sphenopalatine artery) through the incisive canal. This confluence of arteries on the anterior septum forms the Kiesselbach's or Little's area. This is the most common site for anterior epistaxis. The posterior septum is

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supplied by the posterior ethmoid artery (branch of the ophthalmic artery) and branches of the sphenopalatine artery (terminal branch of the internal maxillary artery). The lateral nasal wall is supplied by the anterior and posterior ethmoidal arteries and branches of the sphenopalatine artery. The sphenopalatine artery anastomoses with the posterior pharyngeal artery on the lateral nasal wall. This is termed the Woodruff's plexus and is the most common site for posterior epistaxis.

History

Many historical factors should be sought after in the workup of the patient with epistaxis. The side of the nosebleed should be clarified. This may clue the practitioner into any anatomic abnormalities that may be contributing to the nosebleed. Patients and caregivers may note bilateral nosebleeds, but clarification as to whether there is a dominant side will often help. Nosebleeds can be classified by their location. Anterior nosebleeds occur when the bleeding comes from the front of the nose and is often due to some anatomic aberration including prominent septal vessels, septal deviation, or nasal trauma. Posterior nosebleeds are those where the bleeding goes posteriorly to the back of the throat. Some patients may swallow blood (causing nausea and vomiting), and there may be aspiration of blood in susceptible patients. Posterior nosebleeds are more commonly associated with systemic conditions, such as bleeding disorders and hypertension. These differences can be somewhat arbitrary, since both the amount of bleeding and the head position of the patient can contribute to where the blood presents. Occasionally, patients with hemoptysis or hematemesis may actually have epistaxis as the source of bleeding.

The amount, frequency, and timing of nosebleeds are also helpful. A nosebleed that begins soon after nasal or head trauma has a clear etiology. The amount of bleeding can range from a few spots of blood to massive hemorrhage. A history of visits to the emergency room as well as a history of hospitalizations/blood transfusions can give the practitioner a sense of the severity. It is difficult to correlate the frequency of symptoms to the etiology, but this can be helpful to get a sense of how the nosebleeds are affecting the patient's quality of life. Seasonality of epistaxis has been a controversial topic, although there is evidence that higher ambient temperature leads to an increase in epistaxis rates, while changes in humidity do not seem to have an affect [5].

A history of nasal or head trauma should be investigated. A post-injury septal deviation may contribute to the presentation of a simple, uncomplicated nosebleed, while massive nasal hemorrhage following skull base trauma could point to etiologies such as a vascular laceration, carotid aneurysm, or carotid-cavernous fistula. Patients who have a history of nasal, endonasal (including sinus or pituitary surgery), skull base, and orthognathic surgery can also be susceptible to nosebleeds. Epistaxis resulting from these entities can present in the immediate postoperative period or years later. Local or digital trauma to the nose is an important consideration, especially in the pediatric population. Iatrogenic causes of nosebleeds include instrumentation of the nasal cavity with nasogastric tubes, nasal trumpets, endotracheal tubes, or any other intranasal device.

A complete medication review is also important, when a patient presents with a nosebleed. Intranasal medications such as nasal steroid sprays may cause minor intranasal trauma that can lead to nosebleeds. It may also be pertinent to review the manner in which the patient uses these medications, as a slight error in its introduction into the nose may predispose the patient to nosebleeds. Noncompliance with hypertensive medication may uncover a history of uncontrolled hypertension. Hypertensive urgencies with associated nosebleeds may be an adult's first presentation of high blood pressure. Additionally, antiplatelet medications including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and clopidogrel and anticoagulants such as warfarin, heparin, direct oral thrombin inhibitors (DOAC), and intravenous (IV) direct thrombin inhibitors such as bivalirudin and argatroban can contribute to the development of nosebleeds. Intranasal illicit drug use, e.g., cocaine, can be associated with nosebleeds.

Many symptoms can accompany the presence of nosebleeds. Nasal symptoms such as nasal congestion and rhinorrhea may suggest allergies or sinus disease. Nasal obstruction may suggest anatomic factors including septal deviation or even nasal tumors, both benign and malignant.

There must be a high degree of suspicion in the adolescent male who presents with unilateral nasal obstruction and epistaxis for juvenile nasopharyngeal angiofibroma (JNA). It is the most common presenting tumor in the nose and nasopharynx seen almost exclusively in young men ages 9–19. It is a cellular, vascular, and locally aggressive tumor accounting for 0.05% of all head and neck tumors with an incidence of 1 in 150,000 [6]. Hormonal influences are thought to be central to the pathogenesis of the tumor with variable expressions of androgen, progesterone, and estrogen receptors. Epistaxis associated with a JNA is more often painless, unilateral, and profuse. Associated nasal obstruction is common [7].

Associated cranial nerves or vision problems are more worrisome for the presence of a lesion. Headaches can be also associated with skull base lesions and JNA's with skull base extension, but many patients with hypertension can also present with headaches. Conductive hearing loss and serous otitis media can also be associated with obstructing lesions that affect Eustachian tube dysfunction.

A patient with a history of easy bruising or bleeding may have an associated coagulation disorder, which may need

further workup. A history of liver or renal dysfunction may have a related coagulation disorder. Chronic liver disease is associated with a decreased synthesis of factors II, V, VII, IX, X, and XI as well as a qualitative platelet deficiency [8]. Patients with chronic kidney disease especially those with uremia have decreased platelet function. Those on dialysis are exposed to heparin on a regular basis [9].

A family history of nosebleeds is an important part of the history that may point to an underlying condition. It is true that nosebleeds are so prevalent that family members can often present with them without having an underlying entity, but the importance of gathering this vital piece of history cannot be overstated. Nosebleeds can be the initial presenting symptom in patients who have congenital disorders of primary hemostasis including thrombocytopenia, platelet function abnormalities, and von Willebrand disease or disorders of secondary hemostasis including hemophilia A and B, type 3 von Willebrand disease, and rare coagulation factor deficiency [10].

Hereditary hemorrhage telangiectasia (HHT) or Osler–Weber–Rendu is an important cause of familial epistaxis that is associated with visceral, pulmonary, and cerebral arteriovenous malformations. As with other systemic disorders, epistaxis may be the only presenting symptom of HHT, but there can be associated pulmonary and gastrointestinal bleeding. HHT affects 1 in 5000 to 10,000 persons. 95% of patients with HHT have recurrent nosebleeds, some requiring multiple transfusions and the development of iron-deficiency anemia. The underlying mechanism involves the arteriovenous shunting between arterioles and venules, which presents as telangiectasias and AVMs in the skin, small and large intestines, brain, lung parenchyma, and liver. There is structural weakness of vessel walls that lead to dilation and ultimate rupture with minimal trauma [11]. HHT is autosomal dominant with two subtypes. HHT1 maps to the gene Endoglin on the long arm of chromosome 9, whereas activin receptor-like kinase (ALK1) maps to the long arm of chromosome 12 [12]. Both genes modulate signaling the transforming growth factor-beta (TGF-β) pathway. Its diagnosis can be suggested or confirmed by the Curacao criteria (Table 25.2). The recognition of familial causes of epistaxis is important, since both the workup and management of epistaxis can vary in these cases.

Table 25.2 Curacao criteria for the diagnosis of hereditary hemorrhagic telangiectasia [13]

Criteria	Description
Epistaxis	Spontaneous, recurrent nosebleeds
Telangiectasias	Multiple, at characteristic sites (lips, oral cavity, fingers, nose)
Visceral lesions	Gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformation (AVM), hepatic AVM, cerebral AVM, spinal AVM
Family history	A first-degree relative with HHT according to these criteria

Definite: three or more criteria are present
Possible or suspected: two criteria are present
Unlikely: less than two criteria are present

Physical Exam

A complete nasal examination is necessary in the patient who presents with epistaxis. When a patient is not actively bleeding, it allows for a thorough examination. The external nose should be inspected and palpated for any signs of irregularity that may point to a recent or remote history of trauma. With anterior rhinoscopy, one should note the presence of a septal deviation or inferior turbinate hypertrophy and as to whether these structures touch each other. With dry ambient air, the interaction between a deviated septum with a contact point to the inferior turbinate can cause desiccation of the mucosa and recurrent nosebleeds. Inferior turbinate hypertrophy can be present in allergic rhinitis. Prominent anterior septal vessels may be noted during the examination. If these are present on the side in which the patient complains of the nosebleeds, it is highly likely that this is the cause. Patients who have septal perforations may also present with nosebleeds. Excoriations on the anterior septum may present with a history of digital trauma or with intranasal steroid use. Bacterial colonization with associated bacterial biofilms may also be seen on anterior rhinoscopy. Bacterial colonization may contribute to the development of friable nasal mucosa that is susceptible to epistaxis [14].

Nasal endoscopy, performed by an otolaryngologist, allows for a closer examination of the intranasal structures. The middle meatus may be swollen or have purulence in acute or chronic rhinosinusitis. Nasal and nasopharyngeal masses can be seen on nasal endoscopy. JNA's appear as smooth, lobulated often pedunculated masses with focal hemorrhagic surfaces [6]. Extensive intranasal trauma and lacerations of the nasal mucosa can be seen in patients with iatrogenic causes or form previous attempts of epistaxis control. At times, blood emanating posterior to the inferior turbinate on the lateral nasal wall may be the source of a posterior nosebleed. The presence of diffuse telangiectasias should raise a suspicion for HHT. The nasal exam should be done in the native state, as well as the decongested state, after application of oxymetazoline or Neo-Synephrine nasal spray.

It is important to have the appropriate personal protective equipment (PPE) with a patient who is having an active nosebleed. At minimum a facemask, face shield, and gown should be utilized by the healthcare professional to protect themselves from blood exposure. A light source whether from a headlight or nasal endoscope should be available. With the aid of a suction, the bleeding source can usually be visualized.

The general physical examination is also important. Blood pressure should be taken as uncontrolled hypertension can contribute to nosebleeds. Telangiectasias may be present in the oral cavity, as well as on the skin, particularly on the fingers and toes. Skin bruising or hemarthrosis may be present in patients with coagulation and platelet disorders due to an underlying condition or medication use.

Workup and Management

In simple epistaxis with a clear bleeding source, no additional workup is usually required. However, in the patient with recurrent epistaxis, massive hemorrhage, or a significant family history, additional testing may be required. Complete blood count (CBC), prothrombin time (PT), and activated partial thromboplastin time (PTT) may be ordered to screen for anemia, thrombocytopenia, and other coagulation disorders. Fibrinogen levels are also helpful, especially in the case of disseminated intravascular coagulation (DIC) especially in critically ill patients. Some centers have used viscoelastography such as thromboelastography or thromboelastometry as an adjunct to evaluate the coagulation cascade, but its utility is still being questioned [15]. von Willebrand factor may be assayed if there is a suspicion for von Willebrand disease. A hematology consult may be necessary to guide further workup, unless the aberrations in these tests can be easily explained by medications or states such as chronic liver disease. Patients with severe bleeding should have a type and screen in case a transfusion is needed.

If possible, contributing underlying conditions should be reversed. Hypertension should be controlled. Anticoagulation medications should be stopped if clinically safe. Minor nosebleeds may not require the discontinuation of these medications, but a consideration should be made in the case of life-threatening nosebleeds. Medications such as aspirin and clopidogrel do not have viable reversal options. Warfarin can be reversed with oral or injectable vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrates. Unfractionated heparin can be reversed with protamine. Direct thrombin inhibitor agents such as bivalirudin and argatroban have no direct reversal. Some centers will dialyze patients on these medications, in cases of life-threatening bleeding. Reversal of anticoagulation for epistaxis control must be balanced with the management of the disease process for which the patient is being anticoagulated.

Anemic patients may require transfusions with a lower threshold used for those with signs of hemodynamic instability or with a history of cardiovascular disease. Platelet transfusions may be necessary in patients with thrombocytopenia, while FFP transfusion or specific factor infusion may be utilized for other hypocoagulable states including chronic liver disease or specific factor deficiencies.

Conservative measures include nasal humidification and moisture. This can be achieved with nasal saline sprays throughout the day and the placement of ointment and petroleum jelly intranasally. There are also many commercially available intranasal gels and moisturizers. Patients with evidence of bacterial colonization may benefit from treatment with topical antibiotics such a mupirocin and 0.5% neomycin +0.1% chlorhexidine (Naseptin™). Topical antibiotics alone can effectively treat recurrent epistaxis in some patients with improved efficacy over nasal saline or Vaseline application alone [16]. Oxymetazoline and Neo-Synephrine nasal spray may be used as a temporizing measure during active nosebleeds. Their alpha-adrenergic activity allows for vasoconstriction and may slow down or stop active bleeding. Intranasal estrogen may have some benefit in patients with coagulation disorders [17]. During episodes patients can also be instructed to pinch the cartilaginous portions of the nasal alar and septum together to stop bleeding, to place ice on the nose to help with nasal vasoconstriction, and to bend the head forward to prevent blood from dripping posteriorly.

There are a variety of ways that the source of bleeding can be managed. Prominent anterior septal vessels can be cauterized with silver nitrate or electrocautery. This can be done under local anesthesia. Nasal cautery plus topical antibiotics may be more effective that nasal cautery alone [16]. One must be cautious not to cauterize both sides of the septum or a septal perforation may form. Refractory cases may require an intranasal exam under anesthesia with cautery with or without an endoscope.

Nasal packing is a good means by which one can control bleeding. It is most effective when the bleeding source can be identified and packing material placed directly over the area. Gelfoam (Pfizer, New York, NY) and Surgifoam (Ethicon, Somerville, NJ) are dissolvable packing materials that can serve as a hemostatic agent. Surgicel (Ethicon, Somerville, NJ) and other similar materials made from oxidized cellulose polymer can also be used as a hemostatic dressing. Floseal (Baxter International, Deerfield, IL) and other hemostatic matrices can be used in the management of nosebleeds, especially when there is diffuse bleeding in the nasal cavity. Once again, these materials work best when the bleeding source is clearly identified and a small amount of material is placed over the area. However, more packing may be needed if source is not easily identified. These materials can be used solely or in combination with each other.

Classic nasal packing includes the use of up to 6 ft of strip gauze for anterior epistaxis control but is not needed often today. Posterior packing involves the use of Foley catheters and their associated balloons to tamponade bleeding from the posterior nasal cavity. Sponges could also be placed in the nasopharynx to establish control of posterior nosebleeds. Most posterior packs require additional anterior packs, as well as admission to a monitored unit for pain control, as

well as the monitoring of vital signs secondary to the hemodynamic instability, which they can cause.

There are a variety of commercially available nasal tampons, e.g., Merocel (Merocel Surgical, Mystic, CT), which may be utilized. In some products a balloon is present in the anterior or posterior portion or both to further help epistaxis control, e.g., Rhino Rocket (Medline, Katy, TX). One issue is that the very placement of these devices can cause trauma to the nasal cavity. This should be considered in the hypocoagulable patient where more bleeding may arise. Packing can be left in anywhere from 2 to 5 days. Anti-staphylococcal antibiotics should be given to decrease the risk of toxic shock syndrome, although there is mounting evidence that prophylactic antibiotics may not be necessary in many patients [18].

There are surgical options available in cases where nosebleeds continue despite conservative management, packing, and cauterization. Endoscopic guided cauterization can be performed with the assistance of bipolar electrocautery or a laser. Carbon dioxide, holmium:yttrium–aluminum–garnet (Ho:YAG), and potassium titanyl phosphate (KTP) lasers have been utilized for epistaxis control [19].

Transnasal endoscopic sphenopalatine artery ligation (TESPAL) is an endoscopic procedure where the sphenopalatine artery and its branches are identified in the lateral nasal wall and ligated with surgical clips or bipolar cautery. It is very effective and may be the most cost-effective means of managing posterior epistaxis when compared to nasal packing or embolization [20]. There is a subset of patients where surgical management of the anterior circulation is necessary. Ligation of the ethmoid artery can be achieved by an open approach or endoscopic approach. This procedure does carry an increased risk of orbital complications due to the potential of retraction of the anterior ethmoid artery into the orbit.

Classically, an open transmaxillary approach to ligation of maxillary artery or transcervical approach to ligation of the external carotid artery was performed in retractable life-threatening epistaxis. These are required less and less due to the development of newer endoscopic and angiographic techniques.

Embolization techniques are usually reserved for those with refractory epistaxis including those who have undergone surgical procedures. It may be also helpful in massive epistaxis caused by vascular injury after trauma. The technique allows for identification of the bleeding vessel via angiography followed by the introduction of embolic agents. Occasionally, no bleeding vessels are identified, and a bilateral internal maxillary artery embolization is performed. Embolization of the anterior circulation is generally not performed due to the risk of stroke. Cost is a major disadvantage of the procedure.

Despite these various modalities, the vast majority of pediatric epistaxis can be managed as an outpatient. Life-threatening epistaxis is rare, but hospitalization is sometime needed. Many of the aforementioned techniques can be used to control epistaxis in the inpatient setting. The most common co-morbidities associated with pediatric epistaxis are thrombocytopenia (sometimes accompanying hematologic malignancies), von Willebrand disease, and chronic sinusitis [21].

Patients with intranasal masses should have appropriate cross-sectional imaging, either computed tomography (CT) or magnetic resonance imaging (MRI), to determine the extent of the disease. Nasal biopsy is necessary in some cases to confirm the diagnosis except in the case of JNA where the history and physical, demographics of the patient, and appearance on endoscopy and imaging are confirmatory as shown in Fig. 25.1. On CT JNA's are characterized as a soft tissue mass originating in the posterior nasal cavity and nasopharynx in the area of the sphenopalatine foramen with extension often into the pterygopalatine fossa. There is often bony remodeling and/or destruction with bowing of the posterior maxillary wall, referred to the Holman-Miller sign, being common. The medial pterygoid plate can often be eroded as well. On MRI pre-contrast T1 and T2 weighted images have heterogeneous low to high intensities signals. Flow voids and intense enhancement after contrast administration display the vascular nature of these tumors [7] (Fig. 25.1).

Many of the conservative measures described above can be utilized to manage the nosebleeds until the causative nasal or nasopharyngeal mass is treated appropriately. JNA's once recognized are treated with surgery, except in cases of unresectable disease in close proximity to neurocritical structures or recurrent/residual disease. Radiation therapy is considered in these cases. Transnasal endoscopic resection is modality of choice due to lower recurrence rates (4.7%) and lower intraoperative blood loss, when compared to an open approach [22]. Preoperative angiographic evaluation of a JNA can be used to evaluate the feeding vessels of the tumor (Fig. 25.2). Branches of the internal maxillary artery are the most common feeding vessels [23]. Preoperative embolization can decrease blood loss during surgical treatment of JNA's [24].

A special word on the management of HHT: Firstly, investigations must be made for the visceral manifestations of the disease. This should include cross-sectional imaging to identify cerebral, pulmonary, and hepatic AVMs. Upper and lower endoscopy may be necessary to identify and manage gastrointestinal telangiectasias. Referrals to the appropriate services can be made if there are concerns for these conditions.

HHT patients often require many procedures to manage their epistaxis. Local therapies used with variable success include intranasal estrogen, tranexamic acid gel (antifibrinolytic effects), tamoxifen (an estrogen receptor modulator),

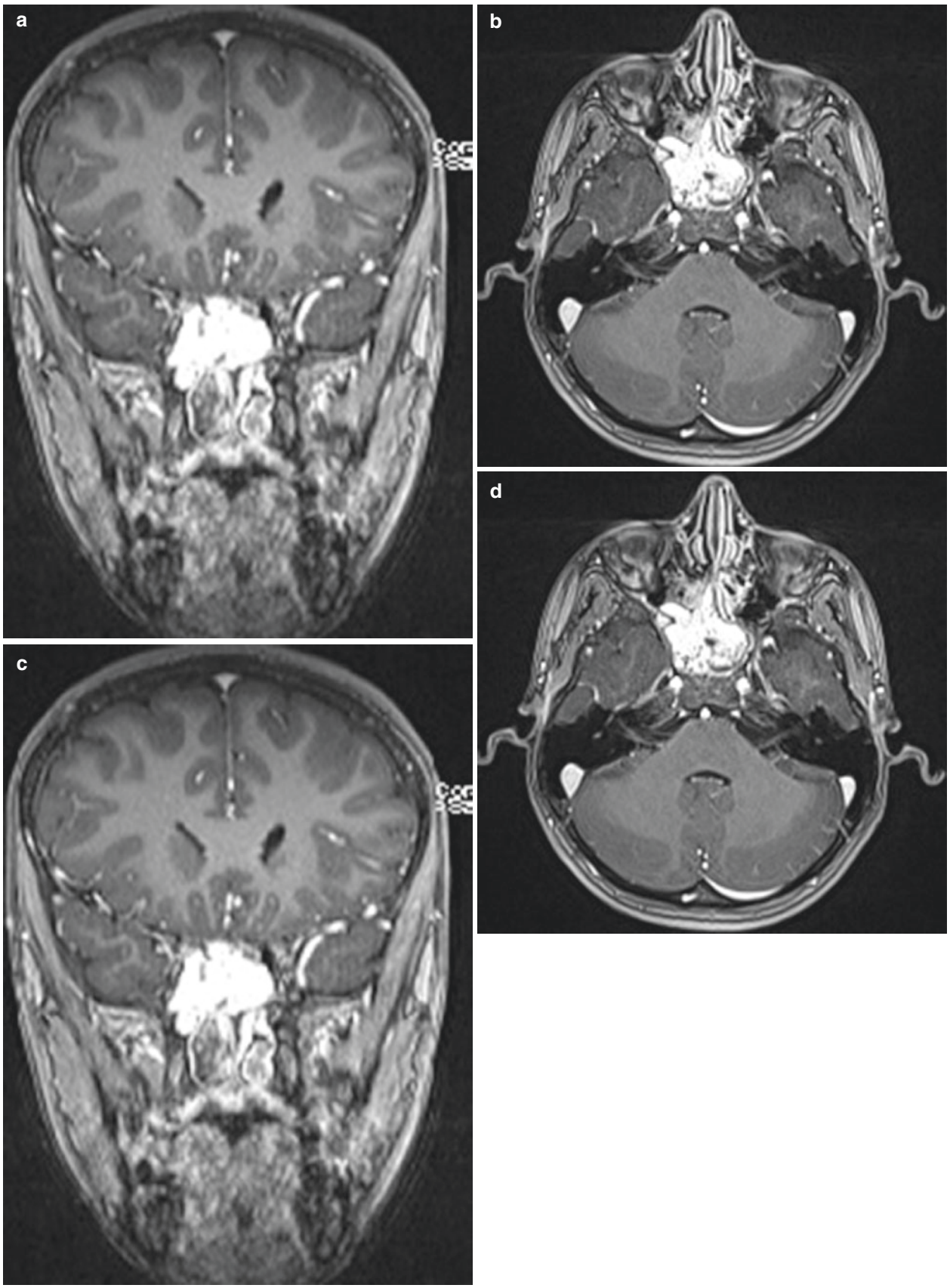

Fig. 25.1 14-year-old male with a history Juvenile Nasopharyngeal Angiofibroma. (**a**) Computer tomography (CT) showing mass in the nasal cavity and nasopharynx with widening of the sphenopalatine foramen (blue arrow). (**b**) Axial T1-non-contrasted magnetic resonance imaging (MRI) showing mass filling the posterior nasal cavity and sphenoid sinus. (**c**) Post-contrast T1 weight coronal MRI showing enhancement of mass. (**d**) Post-contrast T1 weight axial MRI

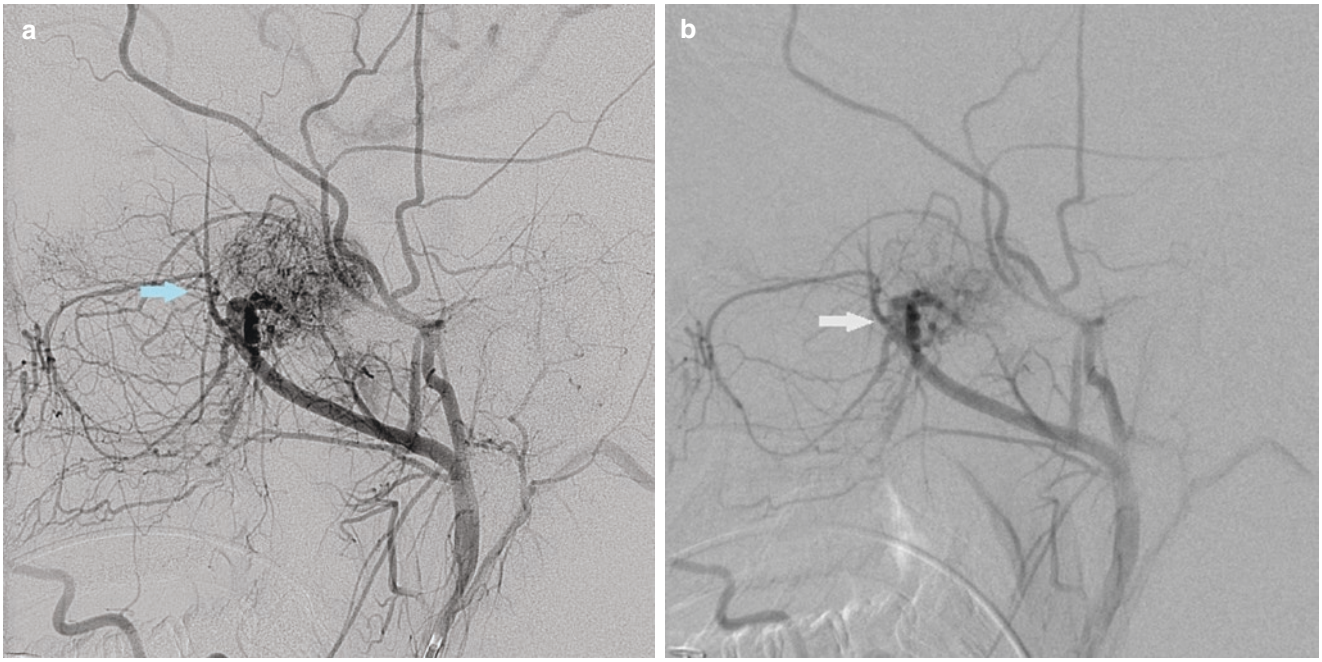

Fig. 25.2 Angiographic images of juvenile nasopharyngeal angiofibroma. (**a**) Pre-embolization image showing hypervascular tumor within posterior nasal cavity (arrow). (**b**) Post-embolization image showing decreased flow through tumor

and intranasal bevacizumab (anti-vascular endothelial growth factor agent). Antiestrogen agents and bevacizumab can be used systemically in HHT patients as well [25]. A recent meta-analysis of medical treatment for HHT revealed that tranexamic acid, and estrogen regardless of route of administration had no effect on frequency of epistaxis. Tamoxifen may have an effect on both frequency and severity of epistaxis. Systemic and nasal bevacizumab did not appear to have an effect on severity and frequency of symptoms, but intranasal submucosal injections of bevacizumab lower epistaxis duration [26]. Nasal cautery with silver nitrate is usually not as effective for nosebleeds due to HHT. Surgical therapy may include the use of endoscopic bipolar cautery, KTP and neodymium-doped yttrium–aluminum–garnet (Nd:YAG) laser, or coblation. Septodermoplasty, where the nasal lining is replaced by a skin graft, is used in severe cases, while the rarely used Young's procedure in which the nasal anterior nasal cavity is surgically closed is used in life-threatening cases.

Conclusion

Epistaxis is a common presenting symptom that can be simple and uncomplicated or associated with an underlying complex issue. Knowledge of the blood supply to the nose is important to help differentiate between anterior and posterior epistaxis. The differential diagnosis of epistaxis is wide, and a thorough history and physical examination is necessary to identify the etiology. Additional testing may be necessary in refractory cases or in those with a personal or family history suggested by an underlying coagulation disorder. Treatment for nosebleeds can range from conservative measures and nasal packing to surgical intervention and embolization depending on severity and etiology. Juvenile nasopharyngeal angiofibroma is the most common intranasal tumor in children, is an important consideration in any adolescent male presenting with epistaxis, and is typically treated with endoscopic surgery with or without embolization. Hereditary hemorrhagic telangiectasia is the most common inheritable etiology of epistaxis, and there are various medical and surgical modalities to treat recurrent nosebleeds.

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Bleeding Disorders Related to Lung Disease

26

David R. Spielberg, Timothy J. Vece, and George B. Mallory Jr.

Introduction

Extravasation of blood elements within the lung may manifest dramatically as hemoptysis or more subtly with dyspnea and anemia without expectoration or cough. Across all age groups, the pulmonary endothelium may be the most vulnerable of all endothelial systems in the human body. It is large in surface area and thinnest in anatomic dimensions, is exposed to high mechanical stress with respiration at rest and exercise, and is in contact with the highest oxygen tensions of all vascular beds [1, 2]. Because of the scope of this book, our goal will be to cover the full range of lung and heart diseases that can be associated with hemorrhage within the lungs at all ages followed by a brief discussion of diagnosis and management.

The capillary surface area of the lungs is larger than that of any other organ in the body. With each heartbeat, the lungs receive the entire cardiac output, normally into a highly compliant, low-pressure network with huge anatomic and physiologic capacitance. The conducting airways of the lungs receive a much smaller volume of blood flow at systemic pressures from the bronchial arterial system, branching from the aorta. Bleeding can occur from either circulation.

Clinical presentation may provide some clue as to the likely circulation involved. The majority of cases of massive hemoptysis, where blood is overtly expectorated, originate from the bronchial arterial system. Up to a third of bleeds within the low-pressure alveolar capillaries may have no associated hemoptysis. Clearly, though, the presence or absence of hemoptysis cannot definitively localize the source of bleeding.

There are many classifications by which bleeding disorders in the lungs can be categorized. Table 26.1 shows a simplified list of categories and prominent examples that span the lifespan from infancy through adulthood. There are many

Table 26.1 Causes of hemoptysis by category

Cardiopulmonary disorders
Congenital heart disease
Pulmonary hypertension
Left heart disease (including valvular disease)
Hematologic disorders
Complication of anticoagulant therapy
Thrombocytopenia
Von Willebrand disease
Pulmonary embolism
Neoplastic disorders
Carcinoid tumors
Neoplastic disorders, especially metastatic and endobronchial carcinomas
Other pulmonary vascular disorders
Pulmonary immune-mediated vasculitis
Pulmonary arteriovenous malformations
Lung disease
Necrotizing pneumonia
Angioinvasive fungal infection
Tuberculosis
Chronic bronchiectasis
Diffuse alveolar damage as in adult respiratory distress syndrome
Pulmonary hemosiderosis
Complication of bone marrow transplantation
Trauma
Transbronchial biopsy or bronchoscopic needle aspiration
Blunt or penetrating trauma with injury to pulmonary vascular bed
Airway foreign body
Miscellaneous exposures (typically leading to diffuse alveolar damage)
Cocaine
Nitrogen dioxide toxicity
Complications of biologic therapies

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disorders that are either rare themselves or are rarely associated with pulmonary hemorrhage. In this chapter, we will discuss each of the major categories with pertinent clinical and laboratory insights.

Cardiopulmonary Vascular Disorders Without Lung Disease

Congenital heart disease represents a broad array of anatomic defects, only a few of which put the pulmonary vascular system at risk for hemorrhage. Nevertheless, acute presentation as frank hemoptysis by such patients is not rare in childhood [3]. In general, lesions associated with an elevation in postcapillary pressures can be associated with either occult or overt pulmonary bleeding. Such lesions include pulmonary vein stenosis and mitral valvular disorders. Pulmonary edema is the classic manifestation of high left heart pressures as in mitral valvular disorders and left ventricular failure. Edema results from increased vascular pressures in the pulmonary capillaries. From the same mechanical forces at higher levels, frank bleeding can also occur, albeit not commonly and often subclinically [4]. From the published literature, complex congenital heart disease, particularly in association with Eisenmenger syndrome, is a more common clinical scenario in which hemoptysis may occur and be life-threatening [5, 6].

In pulmonary arterial hypertension (PAH), hemoptysis is rare, but multifocal ground glass densities on chest computed tomography (CT) are common with 41% of patients recently reported with this finding [7]. The mechanisms by which precapillary arteriolar disease results in alveolar hemorrhage remain obscure. When hemoptysis occurs in patients with PAH, it often portends a poor prognosis either in childhood or adulthood [8, 9]. In some situations, the bleeding may derive from silent bronchial artery collaterals. On the other hand, pulmonary hemorrhage in pulmonary veno-occlusive disease, a rare form of pulmonary hypertension, is well documented although usually subtle [10] and is more easily explained by the anatomic abnormality in this severe and rare form of pulmonary hypertension.

Hematologic Disorders, Including Thromboembolism When Patients Report the Production of Blood

It is uncommon for patients with congenital or acquired hemorrhagic disorders to have pulmonary hemorrhage unless there is associated cardiopulmonary disease. In a large published series of patients from France with hemoptysis, 3.5% were attributed to anticoagulant therapy [11]. Pulmonary hemorrhage is rare in hemophilia and in thrombocytopenic disorders. The prevalence of pulmonary hemorrhage in von Willebrand disease, in the absence of cardiopulmonary disease, appears to be low as well.

One clinical scenario in which pulmonary bleeding may be of particular clinical importance is after hematopoietic cell transplantation. The complex and intense inflammatory processes that result can lead to alveolar hemorrhage. A multiplicity of factors including infection and deficiency in number and function of platelets and other coagulation factors makes the treatment and outcomes of these patients particularly challenging [12]. Mortality is high.

Pulmonary embolism (PE) is most commonly associated with deep vein thrombosis and often occurs in the clinical context of trauma, inactivity, and acquired peripheral vascular disease. The prevalence of PE is much higher in adults than in early life. Although hemoptysis may occur in a significant percentage of patients in some published series, up to 40%, the volume of blood expectorated tends to be low [13]. The likely anatomic source of pulmonary hemorrhage in the context of PE is pulmonary infarction distal to the site of the embolism. Massive hemoptysis is rare [14]. For this reason, anticoagulation is a mainstay of therapy, even soon after the diagnosis of PE.

Neoplasms

Hemoptysis is an unusual but important heralding sign of pulmonary neoplasms. Endobronchial tumors, such as carcinoid tumors, are more commonly associated with hemoptysis [15, 16]. Massive hemoptysis is an unusual presenting sign or complication of most pulmonary neoplasms. However, hemoptysis is the single most specific presenting symptom of lung cancer in adults. In a large series of adults presenting with hemoptysis, the second most common cause at 17.4% was lung cancer [11]. Both primary pulmonary malignancies and metastatic disease may present this way. Benign lesions may also rarely present with hemoptysis; numerous individual case reports describe hemoptysis arising from airway hemangiomas, though the incidence is unknown.

Dieulafoy's disease is a rare noncancerous vascular abnormality of the bronchus that can be associated with massive hemoptysis [17]. It is curable by surgical resection.

Immune-Mediated Lung Disease

Among the most clinically important groups of diseases that lead to pulmonary hemorrhage are the immune-mediated disorders. While the specific pathogenetic mechanism can vary, the overarching etiology is immune dysregulation, leading to inappropriate inflammation of the pulmonary endothelium and pulmonary hemorrhage. In most cases, the bleeding does

not cause massive hemoptysis and an indolent presentation is common [18]. Immune-mediated pulmonary hemorrhage affects the pulmonary vasculature, a low-pressure system, leading to relatively low levels of bleeding. Since massive hemoptysis is uncommon in immune-mediated hemorrhage, patients usually present with chronic respiratory symptoms, which may include small amounts of hemoptysis, worsening exercise intolerance, and hypoxemia [18, 19]. Massive, life-threatening pulmonary hemorrhage is rare but does occur in a minority of patients. Even if not an acute process, immune-mediated pulmonary hemorrhage can present with patients in significant respiratory distress from long-standing hemorrhage and can be fatal at presentation.

The most common immune-mediated pulmonary hemorrhage syndrome in adults and children is granulomatosis with polyangiitis (GPA), formerly called Wegener's granulomatosis [18, 20]. GPA is one of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, which also includes microscopic polyangiitis (MPA). ANCA antibodies were previously classified by their staining pattern as cytoplasmic staining or c-ANCA or perinuclear or p-ACNA; however, the molecular targets of the autoantibodies have been identified as anti-proteinase 3 (c-ANCA) and anti-myeloperoxidase (p-ANCA) antibodies, which are the now preferred defining terms [21, 22]. The autoantibodies lead to neutrophil activation and inappropriate inflammation of the pulmonary and renal vasculature, leading to pulmonary hemorrhage, proteinuria, and hematuria. Anti-proteinase 3 antibodies are associated with GPA, while anti-myeloperoxidase antibodies are associated with MPA; however, either antibody can be seen in either disease.

GPA can affect any level of the respiratory system from the nose to pulmonary capillaries and is characterized by granulomatous inflammation of small- and medium-sized blood vessels [23]. MPA, in contrast, involves small vessels and capillaries, is more often limited to the lungs and kidneys, and does not involve granulomatous inflammation [21]. Diagnostic testing for immune-mediated hemorrhage includes routine laboratory evaluation including complete blood count (CBC); basic chemistry profile; ANCA antibodies; specific antibody testing with anti-PR3 antibodies, anti-MPO antibodies, and anti-glomerular antibodies; and a urinalysis [24]. Imaging studies are important to help identify pulmonary involvement with CT scan being the most useful. CT imaging often shows diffuse ground glass opacities, septal thickening, and, in GPA, nodular disease. In most cases, a compatible clinical presentation, positive autoantibodies, and imaging consistent with pulmonary hemorrhage are sufficient for diagnosis [21]. A histopathologic diagnosis is required if there are inconsistencies in the above testing or if there are no autoantibodies present such as in idiopathic pulmonary capillaritis [25]. Lung histopathology shows interstitial widening with neutrophilic inflammation of pulmonary capillaries and fibrinoid necrosis. In GPA, granulomas are also present [23]. Renal biopsy is also an option if there is kidney involvement. For clinical management, serial lung function testing is an essential tool.

Treatment of ANCA-associated vasculitis and idiopathic pulmonary capillaritis has significantly improved since GPA was first described in 1938. GPA was initially a fatal disease with close to 100% mortality within 2 years of diagnosis. The prognosis for GPA improved with the advent of cyclophosphamide therapy in the late 1970s [23, 26]. Cyclophosphamide, along with systemic corticosteroids, for prolonged periods was the mainstay of therapy and leads to significant treatment-related mortality and morbidity. In the 1990s, a new model of therapy was adopted, modeled after cancer therapy, and included induction and maintenance phases of therapy [27]. High-dose systemic corticosteroids and cyclophosphamide were used for induction, followed by maintenance with methotrexate and reduced corticosteroid dosages. This regimen had less toxicity and similar relapse rates to cyclophosphamide-only regimens. Progress in subsequent years has expanded therapy options. Rituximab is now commonly used for induction as it has similar success rates as cyclophosphamide and may have fewer side effects [20]. Azathioprine is as effective as methotrexate for maintenance therapy and is often used [28]. In severe cases of vasculitis, adjuvant therapies have been shown to be effective and include plasmapheresis and intravenous immune globulin at immunomodulatory dosage [29, 30]. Relapse is 30–50% in GPA even with aggressive immune suppression regimens, so ongoing monitoring of the disease is needed. Mortality rates have significantly improved and are currently 10–20% [31]. Finally, newer evidence has shown the induction with cyclophosphamide followed by maintenance with repeated dosage of rituximab may be preferable with 2-year relapse rates falling from 30% to 5% in a recent study [19].

A number of other immune-mediated lung diseases can cause pulmonary hemorrhage. These disorders include Goodpasture syndrome, systemic lupus erythematosus, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), and Henoch-Schonlein purpura. Diagnostic presentation varies based on disorder, with the presence of uncontrolled asthma being important for the diagnosis of eosinophilic granulomatosis with polyangiitis. Treatment is similar to the other immune-mediated pulmonary hemorrhage syndromes with immune suppression playing a central role in therapy.

Pulmonary Arteriovenous Malformations

Another cause of pulmonary bleeding is pulmonary arteriovenous malformations (PAVMs). PAVMs occur when there is an anomalous connection between a pulmonary artery and

vein that bypasses the pulmonary capillary bed. These lesions, based on their size and the volume of shunted blood, cause an intrapulmonary shunt and hypoxemia. The connection can be fragile and prone to rupture and bleeding which causes pulmonary hemorrhage [32]. There are multiple potential causes of PAVM. One common disorder is hereditary hemorrhagic telangiectasia (HHT). HHT has been associated with mutations in *ACVRL1*, *ENG*, and *SMAD4* [33]. All of the genes are inherited autosomal dominantly, and all family members should be evaluated for mutations in patients with HHT caused by a mutation in one of these genes. HHT leads to multiple AVMs in the pulmonary vasculature as well as other systems including the central nervous system, likely due to inappropriate angiogenesis signaling [33]. Due to the possibility of extrapulmonary malformations, people with HHT can present with cerebral vascular accidents or recurrent, severe nosebleeds, which are the most common symptoms in HHT. The risk of PAVM increases with age in HHT, so surveillance for lung disease is necessary. While HHT causes the majority of PAVM, another well-documented risk for PAVM is hypoxemic congenital heart disease, even after surgical repair. Therefore, such patients should be monitored for hypoxemia.

Diagnosis of PAVM involves identifying the intrapulmonary shunt and, when possible, imaging the areas of abnormal connections. The first sign of PAVM is often hypoxemia with or without associated digital clubbing. Hypoxemia is often unresponsive to supplemental oxygen therapy as they represent true shunt lesions. Contrast echocardiography is the preferred method for identifying PAVM and involves rapid injection of agitated saline via a peripheral vein [34]. The agitated saline contains bubbles, which are easily identified by echo. The presence of bubbles in the left atrium prior to the 4th heart cycle indicates an intrapulmonary shunt, and an attempt to visualize any malformations should be made. PAVMs are generally visualized in one of the two ways—CT angiography or pulmonary angiography via heart catheterization [35, 36]. Via both CT angiography and pulmonary angiography, large PAVMs can be directly visualized; however, small PAVMs may not be seen. Depending on the circumstances, angiography may allow better visualization of vasculature with directed installation of contrast. It also is advantageous in that procedures can be both diagnostic and therapeutic, as discussed below. Finally, an evaluation for liver disease is required for any patient presenting with hypoxemia and PAVM as hepatopulmonary syndrome, a disorder that causes intrapulmonary shunt through distention of pulmonary capillaries without an abnormal connection in patients with severe liver dysfunction, can mimic PAVM [37].

Therapy for PAVM involves occlusion of the abnormal connections. This is usually accomplished during a heart catheterization with identification of the vessel with angiography followed by the placement of various occlusive materials or a metal coil that causes obstruction of the abnormal vessels [35]. In the case of micro PAVM, or with PAVM too extensive to coil, supportive care is currently the only treatment option other than lung transplantation in severe cases. In hepatopulmonary syndrome, liver transplantation is usually curative. In rare cases with a PAVM limited to one lobe, lobectomy has been described.

Parenchymal Lung Disease

While previous sections have concentrated on diseases of the pulmonary vasculature and metastatic diseases, the most common causes of pulmonary hemorrhage are diseases that affect the pulmonary parenchyma directly. All of the vasculature in the lungs can be involved including the pulmonary and bronchial circulations. Hemoptysis caused by parenchymal disease is usually massive and can be life-threatening. Prompt identification and therapy are necessary. We will next review specific disease processes in which hemoptysis can occur.

Infections are a common cause of hemoptysis in both adults and children. Throughout much of the world, *Mycobacterium tuberculosis* (TB) remains an important cause of hemoptysis. In countries with lower TB rates, the most common infectious disease process is necrotizing pneumonia, with *Staphylococcus aureus* being the most common bacterial pneumonia to cause hemoptysis [38]. Influenza infection, often with a *Staphylococcus aureus* superinfection, is a common viral cause, especially during a 2009 outbreak of H1N1 influenza A [39]. Angioinvasive fungal disease, commonly seen in invasive aspergillosis, but in other fungal diseases as well, can cause significant hemoptysis [40]. Treatment for all infectious causes of pulmonary hemorrhage involves specific diagnosis and appropriate antimicrobial treatment and supportive care. For necrotizing pneumonia with or without empyema, surgical intervention with either video-assisted thoracoscopy debridement or chest tube drainage with fibrinolytics decreases antibiotic need and recovery time [41]. Lobectomy is occasionally required for angioinvasive fungal disease.

Chronic bronchial infection with bronchiectasis is also an important cause of hemoptysis. Patients with cystic fibrosis in particular are at risk of hemorrhage from bronchiectasis, with the incidence of significant hemoptysis increasing with age in this population [42]. Other forms of bronchiectasis, including those associated with primary ciliary dyskinesia and immunodeficiency, also have an increased risk of hemorrhage, but there is less known about the natural history of these diseases in relation to hemoptysis risk. Patients with bronchiectasis develop mucostasis and chronic infection. While the exact pathogenic mechanism is unknown, it is

thought that this lung microenvironment induces local neovascularization from the bronchial circulation. The vessels are often tortuous and prone to rupture. As they are high-pressure systemic blood vessels, they can result in massive hemoptysis, uncommonly causing fatal pulmonary hemorrhage [42, 43]. Therapy for pulmonary hemorrhage due to bronchiectasis is bronchial artery embolization, performed via access by a vascular catheter. Due to the risks of bronchial artery embolization, the procedure is usually reserved for cases of massive hemoptysis or repeated moderate hemoptysis with significant morbidity [44].

Noninfectious pulmonary parenchymal causes of pulmonary hemorrhage are less common and include diffuse alveolar damage and idiopathic pulmonary hemosiderosis. Diffuse alveolar damage is a histologic diagnosis that is the result of many disease processes including infections, systemic inflammatory response syndrome, and adult respiratory distress syndrome. There are three phases of diffuse alveolar damage: acute/exudative, proliferative, and fibrotic [45]. Hemorrhage more commonly occurs during the acute or proliferative phase. Treatment is supportive. Pulmonary hemorrhage associated with diffuse alveolar damage is a poor prognostic sign.

Idiopathic pulmonary hemosiderosis is an uncommon disorder seen most commonly in childhood and is clinically indistinguishable from the immune-mediated hemorrhage syndrome known as idiopathic pulmonary capillaritis. Patients present with a classic triad of anemia, hypoxemia, and pulmonary infiltrates on imaging [46]. Histopathology from lung biopsy is needed to distinguish it from idiopathic pulmonary capillaritis with the former showing diffuse bland hemorrhage without septal thickening or signs of capillaritis [25]. Treatment differs from immune-mediated hemorrhage with systemic steroids often being sufficient to induce remission. If needed, hydroxychloroquine can be added in recalcitrant bleeding.

A rare cause of life-threatening pulmonary hemorrhage has been described in infants—idiopathic pulmonary hemorrhage of infancy—and usually responds to supportive care. It can relapse. Etiology remains controversial [47, 48]. A recent single-center retrospective series noted that a majority of cases appeared to have underlying comorbidities, most notably congenital heart disease (36.6%) and prematurity (34.6%) [49].

Trauma

Trauma to the lungs and tracheobronchial tree can be accidental or iatrogenic. If a large pulmonary artery or pulmonary vein or the systemically supplied bronchial arteries are involved, bleeding can be substantial. Hemoptysis in the clinical setting of blunt trauma is usually not massive and is of less critical clinical importance than air leak [50, 51]. An airway foreign body can cause significant internal trauma, both acute at time of aspiration depending on the material and chronically as inflammatory reactions occur or erosion develops.

Iatrogenic injuries can derive from a variety of diagnostic and therapeutic procedures and can be fatal. Pulmonary artery catheterization for monitoring in the ICU setting can lead to hemorrhage [52]. Nonsurgical techniques to ablate endobronchial tumors can inadvertently lead to pulmonary hemorrhage [53]. Transbronchial biopsies via the flexible bronchoscope carry a low but important risk of pulmonary hemorrhage [54, 55]. Although the newly introduced technique of transbronchial cryobiopsies has been introduced with some enthusiasm, pulmonary hemorrhage is not entirely obviated [56].

Miscellaneous

A variety of drug therapies excluding anticoagulation have been associated with pulmonary hemorrhage including new biologic agents like alemtuzumab [57] and abciximab [58]. Environmental exposures like nitrogen dioxide can rarely manifest with hemoptysis [59]. Recreational drug use, most commonly cocaine, can lead to pulmonary hemorrhage [60].

Diagnostic Considerations

When patients report the production of blood from the mouth of any amount, the anatomic location may be obscure. Oral, nasal, and gastrointestinal locations for bleeding are important diagnostic considerations regardless of the age of the patient; it is essential to differentiate hemoptysis from hematemesis or epistaxis. Initial evaluation begins with a thorough history and physical examination. Estimating the volume of blood loss is crucial, if it can be measured, though this may be more informative when bronchial artery bleeding is the source. The physical description of the specimen, its admixture with other materials (mucus or stomach contents), its frequency, and its associated symptoms, especially cough or emesis, are all critical aspects of the history that should be carefully sought. If the source of the blood is unclear and the association of cough is uncertain, a careful examination of the nasopharynx and oropharynx is important. A general physical examination with particular attention to the auscultation of the lung and heart and the palpation of the abdomen for organomegaly is mandatory. The skin should be evaluated for bleeding sites, petechiae, telangiectasias, or excessive ecchymosis; dermatologic findings may also accompany a variety of rheumatologic diseases, providing important clues in diagnosis.

A CBC and an initial superficial coagulation profile with prothrombin time, activated partial thromboplastin time, and fibrinogen begin the laboratory investigations. An index of systemic inflammation such as C-reactive protein and/or erythrocyte sedimentation rate is indicated. If anemia is present, an iron panel and reticulocyte count should be ordered. If a pulmonary source appears to be very likely based on history and physical examination, chest radiography and complete lung function testing with diffusing capacity should be performed. Routine liver and kidney function labs may help to screen for additional processes and suggest other organ involvement in systemic disease. If autoimmune disorders are in the differential diagnosis, an ANA panel and screen for ANCA-related antibodies should be performed.

Unless massive hemoptysis with acute respiratory failure is present, chest CT with contrast may be helpful. Chest CT angiography is preferred if pulmonary embolism is a consideration. Although not as frequently diagnostic, flexible bronchoscopy is occasionally helpful in evaluating the location and appearance of the bleeding source [61, 62]. Bronchoscopy can directly identify endobronchial lesions or foreign bodies or may demonstrate a specific anatomic site (lobe, segment, or subsegment) of bleeding (even if the lesion itself is not visualized). Bronchoalveolar lavage with cytologic evaluation for hemosiderin-laden macrophages should be performed as indicated, especially if chronic bleeding is considered. Sputum evaluation for hemosiderin-laden macrophages can also be illuminating [10]. The duration of detectable hemosiderin in alveolar macrophages is uncertain but likely is a matter of months [63]. Bronchoalveolar lavage (or expectorated sputum, if the patient can provide it) can provide specimens for microbiologic testing as well.

If etiology is unclear, in some patients a lung biopsy by the open or thoracoscopic technique may be critical to making the specific diagnosis. Pulmonary capillaritis can only be definitively identified by this approach and may require an experienced pulmonary pathologist [25].

In the face of acute massive hemoptysis, rapid diagnosis and therapy may be life-saving. Endotracheal intubation and institution of positive pressure ventilation is often performed prior to diagnostic studies. Relatively high ventilatory pressures, particularly positive end expiratory pressure, may staunch the flow of blood. The anatomic site of bleeding is of therapeutic importance. If the hemorrhage is from a bronchial artery, isolation of the bleeding site via a bronchial blocking device [64] followed by bronchial artery embolization may be the therapeutic approach of choice [65]. In adults and well-grown children, single lung ventilation can be accomplished either with a double-lumen endotracheal tube or selective intubation of one lung. If a focal bleeding site is identified as in the process of bronchoscopy with transbronchial biopsy, acute vasoconstriction with topical iced saline [66] or topical epinephrine [67] may slow or transiently stop the bleeding. Other endobronchial therapies include topical thrombin [68]. In some situations, laser or electrocautery via bronchoscopy can be used. If bleeding is repetitive, tranexamic acid, inhaled, bronchoscopically administered, or given systemically, may be useful in some patients [69, 70], as may topical recombinant activated factor VII [71, 72]. If patients can be stabilized and a focal inflammatory or neoplastic process is suspected, surgical resection may be life-saving.

Clearly, the use of blood products is critical to maintaining oxygen delivery. Patients with coagulopathies should receive platelet transfusions, fresh frozen plasma, and other specific products as indicated. Red blood cell transfusions and fluid resuscitation will be critical to maintain intravascular volume and to deliver oxygen to vital organs.

In patients with autoimmune disorders, specific therapies aimed at controlling the underlying process are often successful in the treatment of pulmonary vasculitis with or without pulmonary hemorrhage. Details of these therapies have been referenced above. It is often a challenge to arrive at a specific diagnosis in rapid fashion when patients are critically ill with massive hemoptysis. Systemic corticosteroids are a standard component of almost all therapeutic regimens, but use prior to definitive histopathologic diagnosis may obscure the presence of pulmonary capillaritis.

The key to successful treatment of pulmonary hemorrhage will remain timely diagnosis and specific treatment.

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Heavy Menstrual Bleeding

27

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Introduction

Heavy menstrual bleeding (HMB) is a common complaint in adolescents [1, 2] and women of reproductive age [3]. HMB is a public health challenge reported in at least 5–10% of women of reproductive age group, affecting an estimated 18 million women worldwide [3–5]. It is even more prevalent in the adolescent population with 37% [6] to 56% [7] of school-aged girls reporting HMB.

The differential diagnosis for females with HMB is vast and ranges from physiologic anovulation to pathologic causes [8, 9]. A commonly overlooked etiology of HMB is an underlying bleeding disorder or bleeding risk factor found in up to 44% of adolescents with HMB [2]. Both the American Academy of Pediatrics and American College of Obstetricians and Gynecologists recommend evaluation for bleeding disorder in all adolescents with HMB and high-risk adults [10]. Although anovulatory bleeding is frequently seen in adolescents after menarche [11], bleeding disorder can exacerbate HMB in females with anovulation. Often, adolescents may present to the primary care provider with iron deficiency anemia (IDA), which should prompt a detailed discussion about menstrual cycles among post-menarchal females, as HMB is commonly associated with IDA [12].

Definition of Menstrual Cycle and HMB

In 2006, the ACOG Committee on Adolescent Health Care and the American Academy of Pediatrics Committee on Adolescence stated the importance of using the menstrual cycle as a vital sign, with a normal cycle length of 21–45 days, length of bleeding <7 days, and use of no more than 3–6 pads or tampons a day [10]. Historically the terms menorrhagia (regular and cyclic HMB), metrorrhagia (irregular menstrual bleeding), and menometrorrhagia (heavy and irregular menstrual bleeding) have been used while referring to heavy menstrual flow in females [10]. The recent recommendations of the International Federation of Gynecology and Obstetrics Menstrual Disorders Working Group have replaced confusing terminologies with clear and simple terms related to the PALM-COEIN classification system [13]. The PALM refers to structural causes such as polyp, adenomyosis, leiomyoma, and malignancy/hyperplasia. The COEIN refers to nonstructural causes such as coagulopathy, ovulatory dysfunction, endometrial causes, iatrogenic, and a not-yet-classified category. The terms menorrhagia, metrorrhagia, and menometrorrhagia have been discarded. The term HMB is recommended to define an excessive menstrual blood loss of ≥80 mL per menstrual cycle. Prolonged menstrual bleeding (PMB) is defined as a period lasting ≥8 days with heavy, prolonged menstrual bleeding (HPMB) as both heavy and prolonged. For the purpose of simplicity, the term HMB will be used in this chapter as inclusive of both PMB and HPMB [13].

Prevalence of HMB and Bleeding Disorders

Among women with bleeding disorders, HMB is the most common symptom, reported in 32–100% of women with von Willebrand disease (VWD), 51–95% with severe plate-

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Table 27.1 Prevalence of bleeding disorders in adult [3] and adolescent females [2, 15] with heavy menstrual bleeding

Bleeding disorder	Prevalence in adult women (%)	Prevalence in adolescents (%)
VWF deficiency	5–20	4–48
Platelet function defect	1–47	2–44
Thrombocytopenia	–	1–20
Coagulation factor deficiency	<1–4	3–21
Fibrinolytic pathway defect	–	1

let dysfunction, 10–57% of hemophilia carriers, and 35–70% with coagulation factor deficiencies [3]. Surveillance of 319 female patients with inherited bleeding disorders through the Female Universal Data Collection project in the US hemophilia treatment centers reported 76% of menstruating adolescent and adult females as having HMB and 57.6% of these patients requiring health-care provider intervention [14]. Bleeding phenotypes of adolescents and adults with HMB and bleeding disorder have been reported to be different with more frequent bleeding complications, anemia, and delay in diagnosing bleeding disorder in adults, calling for prompt evaluation of adolescents with bleeding disorder to prevent complications during adulthood [15]. Also among adolescents and adult women experiencing HMB, there is an increased prevalence of bleeding disorders. In adult women with HMB, several studies have reported an increased prevalence of VWD, platelet dysfunction, and coagulation factor deficiencies including hemophilia carrier state [3] (Table 27.1). During the past 2 decades, several studies have evaluated adolescent females with HMB and reported prevalence rates of various bleeding disorders as illustrated in Table 27.1 [2, 15]. The prevalence rate for the disorders varied among these studies depending on the medical setting, how the bleeding disorders were defined, and the extent of hemostatic evaluation. A multicenter retrospective cohort study demonstrated 1183 admissions for HMB and anemia in the USA between 2012 and 2015. Hemostatic evaluation was found to be inconsistent in many cases [16]. Nevertheless, these studies demonstrate the increased prevalence of bleeding disorder among females with HMB, emphasizing the need for prompt and thorough evaluation and management.

Other Causes

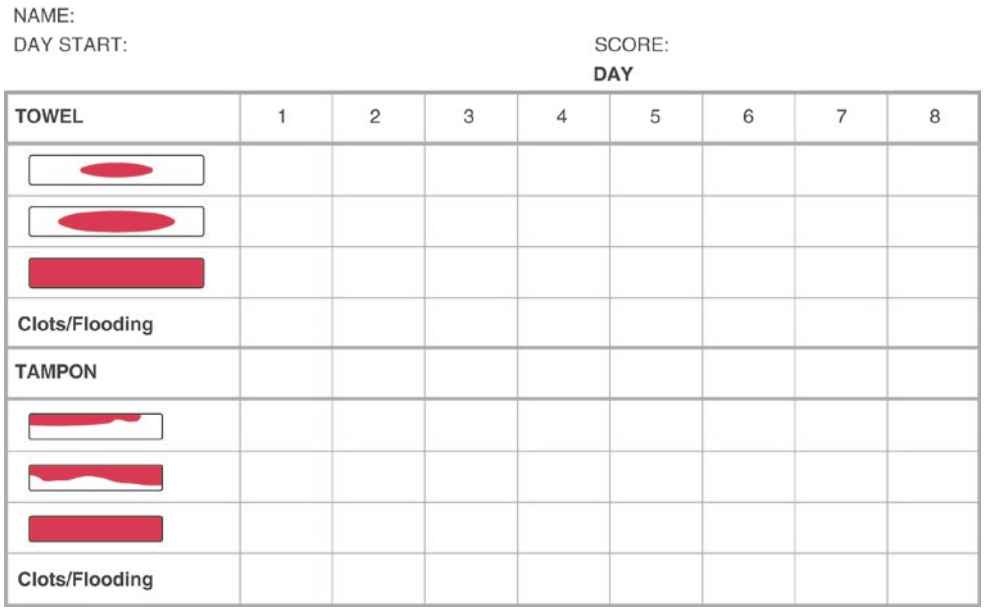
In general, the differential diagnosis for HMB is complex, and underlying causes vary with age. In adult women, the most common causes of HMB are uterine polyps, adenomyosis, leiomyoma, endometrial hyperplasia/cancer, and ovulatory dysfunction commonly due to polycystic ovarian syndrome [13]. In adolescents, ovulatory dysfunction with resulting menstrual irregularities due to immature hypothalamic–pituitary–ovarian axis is frequently seen during the initial 2–3 years after menarche [11], and structural causes of HMB are less common. For this reason an ultrasound should be done routinely in adult women with HMB, whereas it may be considered in adolescents, but is not necessary [17]. Underlying thyroid dysfunction can result in HMB in women of all ages [9, 10]. As some studies have shown an association between hypothyroidism and low von Willebrand factor (VWF) levels [18], it is important to check VWF levels in the setting of thyroid abnormality. Pelvic infection and pregnancy/miscarriage are other causes that can cause or exacerbate HMB. Antithrombotic medication-associated HMB and other gynecologic bleeding complications are common, yet underreported complications in adult and adolescent females, which can result in anemia, hospitalization, transfusions, or surgery [19, 20].

Evaluation of HMB

Bleeding Disorder Evaluation

Careful evaluation of females with HMB includes focused history, physical examination, and thorough laboratory evaluation for underlying bleeding disorder [9, 10, 21]. History of pad or tampon change hourly, passage of clots >1 inch in diameter, and soiling through clothes are considered red flags for bleeding disorder. HMB since menarche also warrants a prompt bleeding disorder workup. Other history suggestive of bleeding disorder includes history of easy bruising, recurrent epistaxis, gum bleeding, prolonged bleeding with trauma or surgery, postpartum hemorrhage, and anemia requiring transfusion and family history of bleeding or bleeding disorder [22].

Several bleeding scores [23] and HMB-specific short screening tools [24] have been developed to help distinguish between healthy subjects and patients with bleeding disorder, which need further validation in HMB prior to clinical application. The pictorial blood assessment chart (PBAC) score is a quick tool that allows providers to assess the heaviness of a patient's cycle [25]. This tool is meant for patients to track bleeding during each cycle by recording the number of soaked pads or tampons used and presence of clots/flooding (Fig. 27.1). A score of >100 was found to be sensitive for a diagnosis of HMB, equivalent to blood loss of >80 mL [26]. Initial studies on the PBAC score evaluated adult women; a more recent study on adolescents determined that their normal PBAC score was >100, suggesting a more stringent cutoff for adolescents before assigning the diagnosis of HMB [27]. The combination of modified Phillip tool, PBAC score of >185, and


NAME:
DAY START:
SCORE:
DAY

TOWEL	1	2	3	4	5	6	7	8
Clots/Flooding								
TAMPON								
Clots/Flooding								

Fig. 27.1 PBAC chart. (Higham J, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. BJOG. 2005 Aug 22;97(8):6)

ferritin level </=20 ng/mL has been evaluated in a cohort of 248 adolescents with HMB from 4 children's hospitals. This combination increased the specificity, but decreased the sensitivity toward diagnosis of a bleeding disorder [28]. Population screening tools have been assessed in a study involving 673 girls age 10–17 years; claims data from 2007 to 2011 were utilized, which showed that 10% of patients with HMB underwent a VW screening test within 12 months from their diagnosis and when subdivided into females with non-severe HMB and severe HMB, screening occurred in 7.9% and 23.8% of the patients, respectively [29]. Another study evaluated the likelihood for girls with HMB to undergo VW screening and showed that those living ≥1 hour from a hemophilia treatment center had lower screening rates and younger age at presentation, living within a metropolitan radius, and having commercial insurance were associated with higher screening rates [30]. A mobile screening tool was assessed in a population of 45 adolescents with known HMB and bleeding disorders, 23 of whom completed the study. The aim of the study was to use an electronic approach to enhance compliance with treatment. Lastly, the iPod Touch served as a useful tool to follow adolescents with HMB and bleeding disorders (BD) to allow for self-monitoring, provider monitoring, and increased educational access through technology use [31].

Physical examination should include vital signs, awareness of dermatologic signs such as pallor and petechiae, and abdominal exam. Speculum exam is typically well tolerated in adults; however in the adolescent, it is usually not necessary especially in nonsexually active girls with HMB [9, 10].

Laboratory Evaluation for Bleeding Disorders

In patients with HMB requiring a bleeding disorder workup, the clinician should consider a stepwise evaluation for bleeding disorders including complete blood count, VWD, platelet disorders, factor deficiencies, and lastly fibrinolytic pathway defects; the workup should also include evaluation for anemia with iron profile.

Despite the cost-effectiveness of screening adolescents with HMB for VWD [32], a recent study demonstrated that <15% of adolescents with HMB were screened for VWD [29]. Initial VW testing includes VWF antigen, VWF activity, and factor VIII (FVIII) assays [33] (Table 27.2). Further tests including VWF multimer, assays for evaluating increased clearance of VWF, VWD type 2 directed testing, and genetic testing may be needed to clarify and confirm the type of VWD (type 1 with increased clearance of VWF, type 2A, type 2B, type 2M, and type 2N). PFA-100 has a limited utility as a screening test to detect VWF deficiency [34]. According to the US National Heart, Lung, and Blood Institute guidelines, the most common type 1 VWD is diagnosed when VWF level is <30 IU/dL with normal multimer [35]. Patients with low VWF levels between 30 and 50 IU/dL and clinically significant bleeding may be treated similar to those with type 1 VWD. Recent data have shown that adolescent and adult females with low VWF frequently have HMB and significant bleeding phenotype, suggesting that this should be considered a bleeding disorder and managed accordingly [36, 37].

Knowledge about VW exon 28 polymorphisms and their impact on VWF levels is important while interpreting test results [38]. These limitations can be overcome by utilizing

ristocetin-independent assays such as the VW glycoprotein 1b assay [39]. Specific precautions to be undertaken include repeating borderline values to detect false-positive/false-negative results, on-site testing to avoid sample processing and storage issues, and testing during the first 3 days of menses when VWF levels will be lowest. Some guidelines recommend avoiding VW testing while the patient is on estrogen therapy; a study on healthy women did not show statistically significant change in VWF levels between contraceptive and control groups [40]. Though blood group O can cause subnormal VWF levels in ~15% of patients, as the treatment decision depends on bleeding symptoms and VWF levels, routine testing of ABO blood group is not required for VWD diagnosis [33].

In females with platelet disorders comprising of thrombocytopenia and platelet function defects, HMB is the most common bleeding symptom [42, 43, 47]. Thrombocytopenia is predominantly due to immune etiology but can also be due to malignancy, chemotherapy, aplastic anemia, hypersplenism, and congenital/hereditary causes. Inherited platelet disorders encompass Bernard–Soulier syndrome (BSS), Glanzmann thrombasthenia (GT), myosin heavy chain 9 (MYH9)-related disorders, Scott syndrome, primary secretion, signal transduction, and receptor agonist defects [42, 44]. The initial step in evaluating for platelet disorders includes platelet count and size with review of blood smear. Previous platelet counts can help distinguish congenital versus acquired thrombocytopenia. PFA-100 does not have sensitivity or specificity for screening for platelet function defect and hence is not utilized in routine clinical practice [44]. The reference standard for diagnosing mild platelet function defect is the light transmission aggregometry [48]. Avoiding platelet function impairing medications 10–14 days prior to testing and using freshly drawn, non-thrombocytopenic specimens that are not activated by tubing the sample and on-site testing are essential requisites for platelet function testing. Supplemental testing includes evaluation of storage pool and secretion defects by means of ATP secretion release, platelet electron microscopy for alpha and dense granule defects, flow cytometry for detecting platelet glycoprotein Ib-IX-V (BSS) and IIb–IIIa (GT) defects, and genetic testing where required for congenital platelet disorders.

Carriers of hemophilia with low factor VIII and IX levels can present with HMB as a predominant complaint [49, 50]. Other rare coagulation factor deficiencies (factors II, V, VII, X, XI, and XIII) in isolation or in combination can cause significant HMB [41]. The workup for these disorders includes prothrombin time, activated partial thromboplastin time, fibrinogen activity, fibrinogen antigen, thrombin/reptilase time, specific factor assay when required, and genetic testing as needed. Fibrinolytic pathway defects such as plasminogen activator inhibitor-1 (PAI-1) deficiency [45] and alpha-2 antiplasmin deficiency [51] can be difficult to detect due to the rarity, lack of availability of optimal tests, and variation in assay results. PAI-1 activity assay and alpha-2 antiplasmin assay when available and surrogate tests such as euglobulin clot lysis time, thromboelastography, and ROTEM may be utilized to aid in the diagnosis of fibrinolytic pathway defects. ROTEM can give insight into overall clot formation and is currently used mainly for emergent situations in HMB, but may play a role in the diagnosis of bleeding disorders [46].

Vascular malformations affecting the uterus can lead to severe bleeding often difficult to control. In addition to detailed hemostatic evaluation to rule out other contributing causes, imaging of the uterus with computerized tomographic scan or magnetic resonance angiography can help to delineate the lesions [41]. Acquired bleeding disorders include acquired coagulation factor deficiencies, VWD, platelet deficiency or dysfunction due to liver disease, vitamin K deficiency, cardiac disease, uremia, autoimmune disorders, medications, malignancy, and other systemic disorders. For these reasons, it is important to detect and manage the underlying cause for bleeding in addition to prompt evaluation of the bleeding defect.

A tiered, stepwise evaluation for bleeding disorders in females with HMB, done in conjunction with a hematologist (Table 27.2), is necessary for accurate diagnosis [52]. Concurrent assessment by the gynecologist for other causes of HMB including infection, endocrine abnormalities, uterine pathology, and pregnancy will help to complete a comprehensive evaluation of the patient.

Management

Management of HMB depends on the female's choice of therapeutic options, which need to be tailored to the individual patient's medical and psychosocial needs [53]. Females with HMB and underlying bleeding disorder are typically managed in conjunction with a hematologist and gynecologist while addressing HMB with medical and/or procedural therapy but also simultaneously managing acute and long-standing hematologic and gynecologic complications.

Hemostatic Therapy

For VWF deficiency, increase in VWF level can be accomplished in two ways [33]. Intranasal or intravenous (IV) administration of desamino-D-arginine vasopressin (DDAVP) (subcutaneous (SC) preparation available only in Europe) will lead to the release of stored VWF into the circulation. Prior to use, DDAVP challenge test is recommended to confirm positive response. DDAVP can be used for mild to mod-

Table 27.2 Evaluation of heavy menstrual bleeding and bleeding disorders [1–3, 33–46]

	Bleeding disorder	Tests	Supplementary tests
Tier 1 [1–3, 33, 41]	Thrombocytopenia Clotting factor deficiency von Willebrand disease	Complete blood count Prothrombin time Partial thromboplastin time Fibrinogen activity von Willebrand panel	Clotting factor assays Fibrinogen antigen Thrombin time Reptilase time Other tests for VWD (VW clearance assay, 2B, 2N panels), genetic tests for VWD
Tier 2 [42–44]	Platelet function defect	Platelet aggregometry Platelet secretion analysis	Platelet electron microscopy Flow cytometry for platelet glycoprotein analysis Genetic tests for congenital platelet disorders
Tier 3 [45, 46]	Fibrinolytic pathway defects Factor XIII deficiency	Fibrinolytic pathway analysis Coagulation factor XIII assay	Thromboelastography/ROTEM Euglobulin clot lysis time Plasminogen activator inhibitor-1 assay Alpha-2 antiplasmin assay Specific factor assay (if available)

erate bleeding for short duration of therapy due to tachyphylaxis beyond 3 days of therapy. Few patients with severe type 1 and most patients with type 2 and type 3 VWD will not respond to DDAVP, and type 1 patients with increased clearance will not have a sustained response. In these patients, replacing VWF will be the preferred mode of therapy. For severe VWD or prolonged use, IV replacement of VWF is required. Virally inactivated VWF products that also contain FVIII are available in the USA (Humate-P, Alphanate-SD, and Wilate). The dosing for acute and severe bleeding typically is 40–60 ristocetin cofactor units/kg and for maintenance therapy and moderate bleeding including HMB is 20–40 ristocetin cofactor units/kg. A highly purified VWF concentrate (Wilfactin) is available in Europe. Recombinant VWF (Vonvendi) has been approved for clinical use in adults and is currently undergoing trials in children <18 years of age in the USA [54].

Thrombocytopenia other than due to immune etiology can be managed with platelet transfusion for severe bleeding [42]. Due to the risk of platelet refractoriness in patients with severe platelet function defects, recombinant factor VIIa (rVIIa) has been used, especially in patients with BSS and GT. IV immunoglobulins and corticosteroids among other options form the mainstay of therapy for immune thrombocytopenia purpura. In minor platelet function disorders, intranasal DDAVP has been shown to be effective in controlling HMB.

Coagulation factor and fibrinogen deficiencies can be managed with specific factor concentrates when available (rVIIa; factor VIII, IX, X, and XIII products; and fibrinogen concentrates) or with fresh frozen plasma (FFP)/prothrombin complex concentrates [41]. When using the latter, concerns regarding volume overload, risk for viral infection, and thrombotic complications need to be carefully addressed. Antifibrinolytic agents form the mainstay of therapy for fibrinolytic pathway defects [45].

Antifibrinolytic therapy can also be used for the management of HMB with or without underlying bleeding disorders, used as primary or adjunct therapy to other hemostatic agents or hormonal therapy. These include epsilon-aminocaproic acid (EACA/Amicar; recommended dose, 50–100 mg/kg/dose orally every 6 h; maximum daily dose, 30 gm) and tranexamic acid (TXA/Cyklokapron, Lysteda; recommended dose of Lysteda, 1300 mg tid orally for 5 days) [55]. TXA has been used effectively as a stand-alone agent in HMB in European countries and Canada [56, 57], and the FDA approval of the oral formulation in 2009 has increased its use in the USA. Vascular anomalies may be managed with general hemostatic therapy and hormonal therapy as needed but may need major interventions such as endometrial ablation and hysterectomy [45].

Hormonal Therapy

A number of hormonal agents are available for the acute and long-term management of HMB. Acute HMB is defined as excessive menstrual or intermenstrual bleeding in a woman of childbearing age, excluding pregnancy, postpartum bleeding, trauma, and malignancy, requiring emergency treatment [58]. Multiple hormonal options exist; however, acute HMB is often treated with IV estrogen. A randomized controlled trial demonstrated efficacy in 72% of patients with two doses compared to 38% of controls [59]. IV estrogen is typically dosed as 25 mg every 4–6 h until bleeding stops [59–63] usually within 24–48 hours. Side effects of estrogen include nausea, headache, elevated blood pressure, potential for blood clot formation, rare risk for causing hepatic adenomas, and breast discharge. Adolescents requiring IV estrogen should be transitioned to maintenance therapy (usually a combined oral contraceptive) via a tapering regimen following control of acute bleeding [58]. Failure to taper slowly

will cause rapidly decreasing estrogen level which can cause a return of HMB. For patients with a contraindication to estrogen or intolerance to side effects, progesterone-only options are desired. High-dose medroxyprogesterone acetate pills (10 mg every 4 h) or norethindrone acetate (5–10 mg every 4 h) may be used in this setting [58]. A tapering regimen is also preferred for progestin-only options. Progesterone side effects mainly include breast tenderness, mood change, and breakthrough bleeding. In patients who fail all other treatments for severe HMB, gonadotropin-releasing hormone (GnRH) analogs such as depo-leuprolide acetate (LA) may be considered. LA induces a hypoestrogenic environment in approximately 4 weeks with resulting amenorrhea [64]. There are long-term consequences of inducing medical menopause in an adolescent, and hence, this should be used with caution.

Long-term management of HMB includes all hormonal therapy options which can range from daily hormonal pills to long-acting reversible devices such as the intrauterine device (IUD). Involving the adolescent in the decision-making process is a priority, as this will aid in finding an agent the adolescent is comfortable with, thereby improving compliance. Studies show that all hormonal agents, whether estrogen plus progesterone versus progesterone alone, will aid in reducing menstrual cycle blood loss and recovery of hemoglobin [65]. In addition, some variability exists among various providers prescribing hormonal therapies to control HMB in adolescents [66]. As maintenance therapy, combined oral contraceptives (COCs) are very effective. Adolescents with HMB may benefit from extended-cycle regimens instead of more traditional monthly withdrawal bleeds [61]. Other combined hormonal contraceptives such as the contraceptive ring and patch have not been as well studied for treating HMB in adolescents specifically but are commonly used in teenaged and adult women [67]. Combined contraceptive patches have also shown benefit for bleeding control as well. In one study undertaken in Austria, 2 combined patches were compared in 432 adult women. Both patches using ethinyl estradiol and either gestodene or norelgestromin contributed to fewer bleeding days and decreased the episodes of breakthrough bleeding [68]. Another study compared combined oral contraceptives (COCs) to patches in 593 adult women and found similar bleeding patterns and cycle control with both methods, with most women achieving improvement within 3 months [69].

Progesterone-only options such as progesterone-only pills (POPs) and depot medroxyprogesterone acetate (DMPA) injections can be used in the treatment of HMB. The POPs are not traditionally considered first-line therapy for adolescents as compliance is very important for POPs to be effective [70]. Norethindrone is another useful option for controlling HMB in patient whether a bleeding disorder has been diagnosed or not. In one study, 76 girls (10–18 years of age) who presented to the menorrhagia clinic with HMB were identified. Among subjects with bleeding disorders, norethindrone was found to be effective 83% of the time compared to 42% of the time with COCs [63]. DMPA injections given intramuscularly (IM)/SC every 3 months are good options in adolescents who may be unable to take daily pills and/or need an estrogen-free option. The SC form is especially useful in patients with underlying bleeding disorder who cannot tolerate IM injections [71]. Cyclic MPA (given for less than 21 days each month) and the etonogestrel implant are additional progesterone-only options that can be used for long-term treatment of HMB but in general are less effective [65, 71]. Although amenorrhea rates are as high as 20% in the first year, the etonogestrel implant may result in more episodes of unscheduled bleeding [58, 71].

The ACOG Committee on Adolescent Health Care reported that levonorgestrel IUD (LNG-IUD) use in adolescents is considered safe and effective; this is now considered one of the most effective medical treatments for HMB in adolescent girls and women [65, 72]. In a large study, 17% of adolescents had a LNG-IUD placed for menorrhagia alone with 85% continuation rate after 1 year due to improved bleeding symptoms [73]. The LNG-IUD has also been effective in treating HMB among adolescents with bleeding disorder that are refractory to other treatments [74]. Among patients with HMB diagnosed with a bleeding disorder, the therapeutic benefit of the LNG-IUD for bleeding control was assessed in a cohort of 13 adolescents <21 years of age. All patients required pre-IUD placement hemostatic agents, and no bleeding complications were recorded. One patient did expel the IUD, but had a successful replacement. All patients experienced improvement in HMB following placement with a mean time to improvement of 94 days. Hemoglobin levels and ferritin levels were also shown to increase during this time frame [75, 76].

Combination Therapy

In general, hormonal therapy and specific/general hemostatic treatment options are discussed in detail with the patient while presenting the therapeutic advantages and side effect profile of each modality, and therapy tailored to the patient's needs is chosen, with one administered as either primary or supplemental therapy for HMB. A single-center crossover trial of COC and oral TXA in a cohort of 17 adolescents with HMB showed equal efficacy of both agents in the management of HMB, with improvement in PBAC scores and cycle length and quality of life scores [77].

Optimal management of HMB in females on antithrombotic therapy can be challenging. Progesterone-only therapy, TXA, or combined hormonal contraceptives with low-dose estrogen may be used as effective therapy for controlling

HMB. Interrupting anticoagulants in the setting of active thromboembolism is not recommended as this will increase the risk of thrombosis worsening or embolization. Selection of type of hormonal therapy is based on patient preference, other indications for and contraindications to therapy, adverse effect profile, and ongoing thrombotic risk factors. Surgical therapy may be appropriate for women who do not respond to medical treatment or who do not wish to retain fertility [19, 78].

Supportive and Other Therapies

Anemia and iron deficiency secondary to HMB are frequent complications [79, 80]. These can be managed with oral and/or intravenous iron supplementation or with red blood cell transfusion when severe. Platelet transfusion and FFP transfusion may be needed in patients with platelet disorders and coagulation factor deficiencies with severe HMB. Such patients are typically hospitalized to monitor cardiovascular stability. Other identified causes of HMB such as infection, endocrine disorders, uterine pathology, and pregnancy-related issues will need directed therapy.

Surgical Treatment

When medical therapy fails in the treatment of acute HMB, or if the patient has contraindications to medical management, surgical options may need to be considered. The choice of the surgical procedure considered is based on both the underlying etiology and the desire for fertility maintenance. Endometrial balloon tamponade can be an effective means of controlling acute HMB and allow for stabilization of the patient in anticipation of further medical (hemostatic, hormonal) therapy [81–84]. Ultrasound can be helpful during placement to diagnose intrauterine pathology and to confirm the adequacy of balloon placement [81–84]. Uterine artery embolization (UAE) has been successful in the control of acute HMB in adult women but would not be a first-line choice for the adolescent females [85, 86]. While successful pregnancies have been reported after this procedure [86], rates of pregnancy complications are increased after UAE, and future fertility is still generally considered a contraindication to this procedure. Loss of ovarian function (transient or permanent) due to embolization of utero-ovarian collaterals can occur after UAE, leading to premature menopause in some cases. The risk of this complication is age related and reported to be 1–2% in women younger than 45 years. Hence, this option should only be used as a lifesaving measure in young women as pregnancy is contraindicated in women who have undergone UAE [86, 87]. An endometrial ablation and hysterectomy are more definitive surgical treatments for menorrhagia but are not first-line options for the management in the adolescent due to the resulting infertility and can often be avoided by employing one or more of the above measures [88–90]. Nonetheless, in a patient with acute, life-threatening hemorrhage, hysterectomy should not be delayed in favor of potentially less effective measures [88–90]. To prevent excessive bleeding during surgery and procedures including IUD placement, tailored therapy with general and/or specific hemostatic agents is needed perioperatively. Rarely, in the situation an arteriovenous malformation may be diagnosed, there will be an ability to reach the malformation from an intrauterine location. One case report illustrates this situation and how it was successfully managed using a hysteroscopic approach to ablate the vascular malformation using cautery [91].

Innovative Tools

Adolescents need to be engaged in their health and gain an understanding of underlying conditions in an age-appropriate fashion, and this is no different for HMB and bleeding disorder. Numerous studies have shown that using tools to engage the adolescent can be helpful toward enhancing compliance rates for needed medical therapies and follow-up appointments [92–95]. Our institution conducted a study on adolescents diagnosed with bleeding disorder and HMB utilizing the iPod Touch device, using the iPeriod app (previously downloaded onto the device) to engage the adolescent in recording the menstrual cycle characteristics and the use of medications to control HMB and to access websites to learn about their condition. Twenty-four adolescents who completed the study within the 12-month time frame frequently charted in their iPod Touch on menstrual flow (83.3%), cramps (100%), breakthrough bleeding (95.8%), mood (95.8%), and medication use (91.7%). More than half used hormones to control HMB; of these, none stopped or missed medications. None required admission for HMB after starting therapy and enrolling in the compliance program. Finally, all subjects reported accessing websites using their iPod Touch device to learn about their BD [31]. Other tools shown to have had impact on this patient population include an online "Let's Talk Period" program in Canada initiated to increase awareness and knowledge about bleeding disorders. Most sessions (60%) occurred in Canada with other sessions occurring in the USA, Ireland, UK, Australia, and the Philippines. Of the women aged 12–76 years who completed the validated self-assessment, 45% had abnormal bleeding assessment scores. Those individuals with abnormal scores commonly reported experiencing bleeding symptoms such as menorrhagia (98%), postpartum hemorrhage (82%), oral bleeding (76%), bruising (72%), and gingival bleeding with tooth extraction (55%) [96]. In addition, another tool was

studied at a single children's hospital to evaluate the benefit of using a mobile application versus a paper PBAC chart to record menstrual blood loss. Fifty-eight girls aged 13–21 years participated comparing paper record keeping to mobile app record keeping. The majority (80%) preferred the mobile app over the paper diary [97].

Complications of HMB

More Than Menorrhagia

Among women and girls with HMB and an established bleeding disorder, other gynecologic conditions such as endometriosis and hemorrhagic ovarian cysts (HOC) are more commonly reported [98]. Nonetheless, a number of hormonal medical treatments can aid in the control of these secondary concerns to keep endometriosis under control and/or to prevent HOC formation. Ultimately, it is best to treat early, as late diagnosis for endometriosis or repetitive surgeries for expanding HOC may impact fertility in the future.

Iron Deficiency and Anemia

Excess menstrual blood loss can lead to iron deficiency anemia [79, 80] and hypotension, necessitating hospitalization and red blood cell transfusion. A recent study identified 1183 admissions for HMB and anemia over a 3-year period in children's hospitals through the Pediatric Health Information System data, with two-thirds of the patients requiring transfusions for severe anemia [99]. As iron deficiency can cause fatigue and impaired learning, accurate diagnosis and oral and/or IV iron supplementation can correct anemia and also positively impact concentration, verbal learning, and memory [79, 80].

Quality of Life Issues

The heavy bleeding and the associated pain and discomfort in females with HMB can interfere with completing day-to-day activities and negatively impact their family life, travel, sports participation, school attendance, work life, social functioning, and overall physical, emotional, and psychological well-being, leading to decreased health-related quality of life (HRQOL) scores [7, 99–101]. Adolescents with established bleeding disorders should be counseled that medications which prevent platelet function such as nonsteroidal anti-inflammatory drugs should be used only after consultation with a hematologist.

Collaborative Approach

While managing females with HMB, it is essential to have a collaborative management by hematology and gynecology providers; in addition, a comprehensive approach by nursing staff, patient educators, genetic counselors, and social workers will provide the patients with a wholesome care. Patient-centered efforts such as small group meetings and patient camps can further improve patient education, provide emotional support, and increase health awareness through social networking.

Conclusion

HMB is a common condition among post-menarchal females. Systematic evaluation for underlying bleeding disorder and other causes will aid in establishing a correct diagnosis. Utilizing hormonal and/or hemostatic therapy for management of HMB and underlying bleeding disorders is critical for optimizing patient care, to prevent hematologic and gynecologic complications, keeping in mind fertility preservation for women of reproductive age. Essentially, a collaborative approach among gynecology and hematology providers will ensure a holistic approach to restore the overall well-being of the female patient with HMB.

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Gross Hematuria

28

Monica Velasquez and Adam S. Feldman

Introduction

Gross hematuria defined as the presence of visible blood in the urine has a wide spectrum of symptoms at presentation, varying between a slight discoloration (as little as 1 cc of blood per liter of urine can produce a visible color change) to the uncommon event of life-threatening bleeding. It can present with no additional symptoms or a range of ancillary symptoms including dysuria, pain, obstruction, or hypotension. It is common, and as such the initial point of patient contact is often with a primary care doctor or an emergency medicine provider.

In a 2015 survey of internal medicine, family medicine, and emergency medicine practitioners, 87% were unaware of guidelines regarding the management hematuria, and 93% agreed that a clinical care pathway would be valuable in a primary care practice [1]. Gross hematuria represents a significant economic burden in particular because of emergency department (ED) use: a 2013 study using the National Emergency Department Sample (containing data from ED visits for over 950 hospitals) found that between 2006 and 2009, there were almost 720,000 visits with gross hematuria as the primary diagnosis. Total charges for patients with a primary diagnosis of hematuria who presented to a US ED were estimated at $238,000,000 a year [2].

In this chapter, we will discuss the most common etiologies of gross hematuria in adults, the management of the acute presentation, and the most common reasons for referral. Microscopic hematuria is outside the scope of this chapter: for further reference about this topic, please see the American Urological Association (AUA) guidelines on microscopic hematuria [3].

Gross Hematuria: Initial Management and Referral

While the initial presentation of gross hematuria may be alarming to both clinician and patient, it rarely requires acute intervention. In evaluating the patient, it is important to qualify the circumstances under which the hematuria started (with or without associated symptoms such as dysuria, flank pain, urinary retention, or fever) as well as whether it was provoked (in the setting of instrumentation, such as urologic surgery and Foley catheter placement, or recent trauma.)

It is also important to qualify the degree of hematuria. Referring to the color of urine as "frank blood" is rarely helpful: most patients and many clinicians will describe any red urine in that manner, and as previously noted, even a small amount of blood in the urine will produce visible discoloration. It is more helpful to elicit from the patient the translucency of their urine, as that helps determine the need for emergency room evaluation.

Mild hematuria may be described as clear pink or rose and moderate hematuria as cranberry juice or fruit punch colored. Urine that is translucent, mild, or moderate may be manageable in the outpatient setting in a patient who has no other symptoms such as urinary retention, fever, or flank pain. The patient must be able to keep themselves well hydrated to prevent the formation of large blood clots in the bladder that can result in urinary retention. Blood that is old may present as amber, tea, dark purple, or brown urine and may persist for long after the initial event has subsided due to the presence of small clots in the bladder.

Initial evaluation should also include a history of prior urologic or pelvic surgeries, pelvic radiation, chemotherapy, and anticoagulant use. According to the 2015 AUA Update on Gross Hematuria, all patients with a history of gross hematuria should have a urinalysis and urine cytology

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checked and undergo imaging of the entire urinary tract. They should also be referred for outpatient urology referral to complete their evaluation, including cystoscopy [4].

Imaging

The gold standard of imaging for evaluation of unprovoked gross hematuria remains a triphasic CT scan with noncontrast, parenchyma-enhanced, and delayed imaging (a CT urogram.) It may be performed prone to allow distal ureteral calculi to be distinguished from small bladder stones. The initial noncontrast phase allows for the evaluation of renal or ureteral stones that may be effaced by the administration of contrast. Iodinated intravenous (IV) contrast is then administered either with or without a bolus of IV fluid, and after approximately 100 s, the nephrographic phase scan of the kidney allows homogenous enhancement of the renal parenchyma to optimize the detection of small renal masses. The last, excretory phase scan from the kidney to pelvis is performed after 12–15 min to allow visualization of the collecting system, ureter, and bladder. This is the phase that is most prone to limited results, due to differences in peristalsis, and in the rate of contrast excretion into the ureters and bladder.

As this functionally represents three CT scans (one scan for each phase), the radiation dose may also be of concern and in some cases may be up to 66 mSv in an obese patient [5]. There is no good replacement for the noncontrast scan for the evaluation of ureteral or renal stones. Some centers lower the radiation dose by splitting the contrast bolus into two smaller, time-delayed doses before taking a second scan. This is referred to as a dual-phase or split-bolus CT urogram, and in an ideally timed situation, the earlier dose would provide excretory (ureteral and bladder) information, and the latter evaluates the vascular anatomy and renal parenchyma. In reality, this does produce less radiation exposure as it obviates the need for the third (delayed) scan, but ureteral opacification is also less reliable. The use of single-phase dual-energy CT (the acquisition of CT data at different tube settings) may provide a way to virtually reconstruct an "unenhanced" phase during a hematuria workup, but it is not as sensitive in the detection of stones <4 mm [6].

Intravenous pyelography (IVP) is rarely used today, and ultrasound is not as sensitive as multiphase CT scan in evaluating for nephrolithiasis [7] and renal or transitional cell lesions [8]. A contrast MR urogram provides the same evaluation of parenchyma, lumen, and collecting system as a CT urogram while limiting radiation exposure entirely, and this has been extensively studied in the pediatric population. However, this is not an option in patients with end-stage renal disease due to the risk of nephrogenic systemic fibrosis (NSF), claustrophobic patients, or patients with incompatible hardware. MR is also notably poor at diagnosing nephrolithiasis. A recent study notes that while CT urogram remains the best comprehensive examination of the upper urinary tract, one potential option in young patients to limit radiation exposure is a noncontrast CT scan followed by an MR urogram [9].

Emergency Department Referral and Evaluation

Mild or moderate hematuria may often be managed as an outpatient with a history, physical exam, labs, and outpatient urologic referral. Severe hematuria (urination with large clots or urine that resembles red wine or tomato juice), however, is more likely to result in clot obstruction or hemodynamic instability. Referral to the emergency room for urgent evaluation is indicated in patients who have severe hematuria, hematuria after a traumatic injury, inability to void or empty their bladder, fever, or severe flank pain.

Emergency Management of Hematuria

A physical exam to assess for hemodynamic instability and bladder distension is critical, as are labs to monitor creatinine, hemoglobin, and clotting factors, especially with patients on anticoagulation. Coagulopathies, both acquired and congenital, should be reversed if safe from a cardiac and vascular perspective. Urinary tract infection, if a concern either by history or laboratory results, should be treated.

The mainstay of the management of all severe hematuria, especially when presenting with clot obstruction, is bladder drainage with manual irrigation and removal of clot burden from the bladder. In general, mild or moderate hematuria in the setting of a patient who is able to empty their bladder without straining may not require bladder irrigation.

It is important to understand the design of a Foley catheter: the size, measured in "French" (Fr), refers not to the lumen but to overall circumference. A three-way urethral catheter allows for an irrigation port as well as a drainage port, but as a result has a smaller internal drainage lumen than an equivalent size two-way catheter. A whistle-tip catheter or other catheters without a balloon have the largest internal lumen and therefore can be the most effective for manual removal of clot (manual irrigation) [10].

Well-intended placement of a three-way urethral catheter in an attempt to "flush out clots" through the use of aggressive gravity irrigation is unlikely to succeed and moreover can lead to pain, bladder distension, or even perforation should clots obstruct the outflow. Clot can more effectively be extracted by gentle manual aspiration using a 60-cc catheter-tip syringe connected to the drainage port of a large-bore catheter. Irrigation with normal saline through the syringe then prevents bladder collapse and moves around the clot bur-

den so it can more easily be aspirated out. A whistle-tip catheter has the largest lumen for its circumferential size as well as an open tip to facilitate clot removal. However, it does not have a balloon and so cannot be left in the bladder for drainage, requiring placement of another catheter either for drainage or irrigation. A large-bore (22 Fr or greater) three-way catheter has a proportionally smaller lumen but has a vesical balloon as well as an irrigation port and as such can be used for either drainage or irrigation afterward. Some three-way catheters may also come with features such as a coude tip to allow passage through large prostate, reinforced coils to prevent lumen collapse during manual aspiration, or an open tip to facilitate clot removal. In vitro evidence as to the utility of these features in the various forms and brands of three-way catheters is conflicted [11], but several recent studies have shown differences in drainage lumen size, irrigation, and flow rate between the most commonly used three-way catheter brands even when marketed as being the same size [12, 13].

If urine clears with manual irrigation and removal of clots, aggressive oral and intravenous hydration should be instituted if medically tolerable, and in many cases may suffice. Depending on the patient's condition and color of the urine, the catheter may be discontinued before discharge. Continuous bladder irrigation with a three-way catheter and normal saline irrigation should be instituted if the urine does not clear, which can either be due to the continued presence of clot or continued bleeding. If the urine does not clear with irrigation alone, either ultrasound or CT imaging may be obtained to rule out the presence of continued clot in the bladder. In the setting of continued bleeding or persistent clot, urologic intervention may be considered.

The urologist may recommend a number of treatments depending on the etiology of the hematuria, including cystoscopy with clot evacuation or fulguration; hyperbaric oxygen; intravesical treatments such as alum, prostaglandin, silver nitrate, or even formalin; or endovascular procedures such as selective arterial embolization. The use of aminocaproic acid (Amicarα™), a competitive inhibitor of plasminogen and plasmin, has been described both orally and intravesically in small case series. It is rapidly absorbed orally and 80% is excreted unchanged in the urine. It presents an attractive option for the management of intractable hematuria as it is currently the only oral agent that has been shown to have some short-term success—up to 90% in cases of mild hematuria [14]. However, adverse systemic and ureteral thrombotic events have been reported in the literature [15]. Intravenous tranexamic acid (another reversible inhibitor of plasminogen) has been used to control intractable upper tract hematuria in some case studies [16]. However, it is more thrombogenic than Amicar and has been shown to cause both upper and lower tract clot obstruction, occasionally even in microscopic levels of hematuria [17]. It is not currently recommended as a treatment for the majority of gross hematuria [18] but is currently being studied in the setting of gross hematuria from cyst rupture in adult polycystic kidney disease [16, 19] and as another option for intravesical treatment in bladder-based hematuria [20].

Differential Diagnosis

The differential diagnosis for initial or recurrent gross hematuria is wide, and ultimately the workup must include a search for iatrogenic, infectious, inflammatory, traumatic, and neoplastic processes. The visible blood may originate from the upper tracts (kidney and ureter) or the lower tracts (bladder, prostate, and urethra.) It is also important to exclude other diagnoses that may masquerade as gross hematuria, including medicorenal disease such as acute tubular necrosis or glomerulonephritis (presenting with muddy brown urine with red cell or white cell casts), rhabdomyolysis (often visible discoloration presenting with a urine dipstick that is positive for blood but negative for microscopic red cells), and menstrual blood. Table 28.1 lists the various etiologies

Table 28.1 Select differential diagnosis for causes of hematuria

	Benign disease	Malignant disease	Vascular disease
Upper tract	Trauma Nephrolithiasis Ureteral stricture Fibroepithelial polyp Angiomyolipoma Polycystic kidney disease Endometriosis	Renal cell carcinoma Urothelial carcinoma (of ureter or renal pelvis) Other renal malignancy Invasion or metastasis by other malignancies	Pseudoaneurysm Ureteroileal fistula Nutcracker syndrome Arteriovenous malformation
Lower tract	Trauma Urinary tract infection Benign prostatic hyperplasia Papilloma/adenoma Bladder stone Endometriosis Placenta accreta/percreta Urethral caruncle/diverticulum	Urothelial carcinoma Squamous cell carcinoma Adenocarcinoma (urachal) Other bladder malignancies Invasion or metastasis by other malignancies	Hemorrhagic cystitis Arteriovenous malformation

of gross hematuria. The discussion covers in detail the most common causes.

The prevalence of most conditions varies by patient age, comorbidities, recent events such as trauma or recent surgery, and associated symptoms at presentation. While most gross hematuria can be managed in an outpatient setting and does not require an emergency room evaluation or urgent subspecialty referral, all gross hematuria should be referred to a urologist for an outpatient complete evaluation. Somewhat frustratingly, several large studies have shown that 50–75% of patients with gross hematuria will have no identifiable underlying etiology even after completion of urologic workup [21, 22]. The rate of recurrence in such patients is unknown.

Hematuria in Association with Trauma

Imaging remains the mainstay of diagnosis in gross hematuria in the setting of blunt and penetrating trauma in a stable patient, and dual-phase CT scan with delays to assess vasculature, renal, and ureteral integrity remains the gold standard (the noncontrast phase is omitted.) A one-shot IVP is typically limited to use intraoperatively and in order to determine that there is a functioning contralateral kidney prior to consideration for urgent renal exploration.

Ureteral injury from acute trauma is uncommon—80% of ureteral injuries are iatrogenic, which is important to consider after gynecologic, urologic, and bowel surgery [23]. Bladder evaluation is necessary after penetrating pelvic injury, pelvic surgery with gross hematuria, or blunt external trauma with pelvic fracture and gross hematuria. Imaging should be the first step in management, as bladder distension with manual or continuous bladder irrigation prior to ruling out a rupture could worsen a bladder injury and instill fluid, blood, and/or urine into the retroperitoneum or peritoneal cavity. Rupture is uncommon in the setting of patients with gross hematuria without pelvic fracture or pelvic fracture without gross hematuria. The bladder phase of a CT urogram is not sufficient even with a clamped indwelling catheter, as up to 29% of patients with both pelvic fracture and gross hematuria may have occult bladder rupture even in the presence of ability to void [24]. A formal cystogram should be performed, with the bladder filled retrograde to 350 cc, or in a cooperative and conscious patient, to a sense of discomfort. False negatives have been reported with instillation of 250 cc in the case of small tears [25]. If the cystogram is done by CT, the contrast must be diluted to 2–4% so that the CT quality is not compromised by scatter artifact, but in the presence of trauma spine boards and pelvic fracture fragments, this may at times be the preferred modality to best visualize the contrast [26]. If done under fluoroscopy rather than CT, drainage films must be taken to visualize posterior extravasation of contrast.

Indications for need for urethral evaluation in the trauma patient include pelvic or straddle injury with gross hematuria or inability to urinate with blood at the meatus. Occasionally, a complete posterior urethral disruption in a male may result in a catheter being placed into a pelvic hematoma rather than into the bladder. In a male, a retrograde urethrogram may be performed with a small-bore catheter placed 1 cm into the fossa navicularis and the balloon filled with 1 cc of water to seal off antegrade flow. With the patient in the lateral decubitus or oblique position, 25 cc of contrast is injected into the catheter under fluoroscopy. There is no radiologic substitute for visual inspection (urethroscopy) in a female [25]; however, traumatic urethral injuries in females are not common.

If renal, ureteral, bladder, or urethral injuries are suspected either through mechanism of injury, physical exam, or imaging, urgent urologic consultation is indicated.

Hematuria After Urologic Procedures

Gross hematuria is a feature after virtually all procedures with instrumentation of the urinary tract and in most cases is both expected and transient, requiring only timed voiding and the encouragement of hydration. In addition, recent instrumentation can make a urinalysis difficult to interpret. Pyuria can be due to either inflammation from recent instrumentation or an indwelling ureteral stent or due to infection, for which patients are at an increased risk shortly after urologic surgery. Severe gross hematuria, however, falls into a special category as the short-term and long-term management in many cases depends on the nature of the recent surgery.

Though both may exhibit severe hematuria and clot retention, severe gross hematuria in the setting of a recent transurethral resection of a bladder tumor (TURBT) is at higher risk for bladder perforation during manual irrigation than a recent transurethral resection of the prostate (TURP) or other similar cystoscopic procedures of the prostate (laser photovaporization; laser enucleation). The risk of bladder perforation during manual irrigation is especially high during recent surgical procedures where there is a fresh suture line in the bladder after a section of the bladder is opened and closed, such as a partial cystectomy, diverticulectomy, or ureteral reimplant. In these postoperative cases, manual irrigation should ideally only be performed by a urologist. It is important to note that it is not uncommon for patients to present with new or recurrent hematuria several weeks after an initial bladder or prostatic procedure due to the effects of urokinase on the old scab on the prior surgical site. Fortunately, many of these cases can be managed conservatively without intervention.

In general, lower tract hematuria (bladder or prostate) tends to be more severe than hematuria after upper tract surgery, such as ureteroscopy. However, while extremely infrequent, two potential causes of life-threatening upper tract

hemorrhage are the formation of renal arteriovenous malformations (AVMs)/pseudoaneurysms and ureteroiliac arterial fistula.

Renal AVMs and pseudoaneurysms are abnormal vascular communications, which are often unstable and prone to bleeding. Up to 75% are iatrogenic following partial nephrectomy, percutaneous nephrolithotomy, renal biopsy, or ablation of renal tumor [27]. Most commonly, patients present within 4–8 weeks after the procedure with flank pain and new-onset or recurrent hematuria. They may require interventional angiography and selective arterial embolization to control bleeding while maximizing preservation of normal perfusion to adjacent renal parenchyma. Identification of the responsible vessel during angioembolization can at times be a challenge, especially as such lesions may bleed intermittently and require provocative maneuvers to visualize the pseudoaneurysm or AVM [14].

Ureteroiliac arterial fistula is very rare, but may be suspected in a patient with pelvic radiation or previous iliac vascular procedure with a chronic long-term indwelling ureteral stent; they may present with life-threatening arterial hemorrhage due to partial pressure necrosis. A high index of suspicion is necessary, as patients require urgent angiographic evaluation and endovascular stenting [28].

Neoplasm

In patients with an initial presentation of gross hematuria, the rate of subsequently diagnosed urologic malignancy in several series is as high as 25% [22]. This is in contrast to microhematuria, where evaluation discovers malignancy in 2–4%. It is this risk of malignancy that prompts the recommendation for upper tract imaging of the kidney and ureter, as well as the bladder in all cases of gross hematuria. As discussed above cross-sectional imaging with triphasic CT scan may allow differentiation between benign and malignant masses of the kidney and may demonstrate a filling defect in the renal pelvis, ureter, or bladder, with associated changes such as wall thickening, lymphadenopathy, or invasion into perivesical or periureteral tissues.

The majority of cancer diagnosed in the setting of gross hematuria is urothelial, primarily the bladder; several large studies showed less than 3% of patients presenting with gross hematuria had upper tract urothelial carcinoma or renal cell carcinoma (RCC) [8, 22]. The classic triad of flank mass, hematuria, and pain is now overwhelmingly uncommon in RCC and presents in less than 10% of patients. Squamous cell carcinoma may be suspected in the setting of emigration from areas where *Schistosomiasis haematobium* colonization is endemic, or in the setting of chronic indwelling catheter or straight catheterization, and such patients should also complete their workup with a urologist.

In evaluating gross hematuria, one must also consider patient-specific risk factors. There is an especially strong causal association between cigarette smoking and risk of bladder cancer, with smokers having a threefold risk of invasive bladder cancer compared to nonsmokers [29]. One study found that of patients who present with gross hematuria, there was an association between meeting National Lung Screening Trial (NLST) criteria (55–75 years old with more than 30-pack-year smoking history and less than 15 years since smoking cessation) and the diagnosis of high grade and muscle invasive bladder cancer [30].

Patients who are on anticoagulant therapy are not exonerated from a necessary workup for gross hematuria. A retrospective analysis of ED visits suggests that patients on antiplatelet therapy or anticoagulant therapy may experience gross hematuria rather than microhematuria as their initial presenting symptom of malignancy more commonly than untreated patients [31]. Furthermore, a recent study demonstrated that patients on antithrombotic medications had an increased rate of hematuria-related complications [32]. Anticoagulants (particularly warfarin) may have a higher likelihood of contributing to gross hematuria events compared to antiplatelet agents, but the highest proportion of severe hematuria is associated with novel anticoagulant agents such as dabigatran [33].

While the immediate treatment for hematuria in the setting of malignancy is similar to other forms of hematuria, long-term treatment of the patient under the care of a urologist will ultimately depend on the grade, stage, and type of malignancy.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) remains the most common cause of gross hematuria in a male over 50 [34]. Prostatic hyperplasia may result in hypervascularity with fragile microvessels, in addition to the increase in acinar cells and stromal cells [35]. Rupture of the microvessels, often unprovoked, can cause transient hematuria that may then be worsened by clot retention and bladder distension.

Most BPH/prostatic bleeding can be managed conservatively. In the setting of suspected BPH/prostatic bleeding that is severe, if catheterization for removal of clots is necessary, a catheter with a large-volume balloon (30 cc) can be used and traction applied to the catheter to decrease prostatic blood flow and tamponade the area. 5α-reductase inhibitors such as finasteride or dutasteride have been associated with decreased prostatic blood flow, vascular endothelial growth factor (VEGF) expression, and microvessel density. This class of medications can be used in the setting of acute prostatic bleeding use, as well as prevention of future episodes when hematuria has been recurrent in nature. Several small prospective randomized control trials have shown a significant decrease in

BPH-related hematuria versus placebo at 1 year (14% vs. 63%) [36]. However, if 5α-reductase inhibitors are started for the purpose of hematuria prevention, it is important to keep in mind their effect on PSA: on average finasteride use halves the PSA in BPH in approximately 8 months [37].

Ultimately, if gross hematuria has been recurrent or persistent, cystoscopy with clot evacuation, fulguration, and possible electrocautery resection or laser photocoagulation/vaporization are often performed for prostatic debulking. Selective arterial prostatic angioembolization under interventional radiology was previously considered a means of last resort in the setting of continued hemorrhage [38] but more recently has been studied as a primary method of treating BPH, both with and without hematuria [39, 40].

Urinary Tract Calculi

Nephrolithiasis and ureterolithiasis often present with flank or abdominal pain, nausea, and vomiting in association with microscopic or gross hematuria, but occasionally may present with gross hematuria as the only presenting symptom. The presence of gross hematuria does not differentiate between renal calculi and passing ureteral calculi. It is rare for the hematuria from urinary tract calculi to produce severe hematuria or clots, even in the setting of anticoagulation. The management of nephrolithiasis itself is outside the course of this review, but the hematuria associated with nephrolithiasis almost never requires acute intervention.

Hemorrhagic Cystitis

Hemorrhagic cystitis (HC) has been associated with pelvic radiation (especially prostate or cervical cancer), oxazaphosphorine chemotherapy, and exposure to adenovirus or BK virus in transplant patients. The severity of it may vary from mild intermittent hematuria to life-threatening recurrent bleeding requiring transfusion and extirpative therapy. It remains one of the most pernicious and challenging clinical situations in urology.

The etiology of HC in pelvic radiation is thought to be due to pelvic radiation-induced edema, submucosal hemorrhage, and formation of abnormal fragile telangiectasias secondary to obliterative endarteritis. It is typically a delayed process that may present a median of 3 years after initial treatment [41]. Unlike the known use of hyperhydration and MESNA for chemoprevention in cyclophosphamide use, currently there is no preventative measure that has statistically been shown to prevent the development of radiation cystitis. Care must often be individualized to the individual patient's degree of hematuria at any particular moment, and hematuria is often recurrent. It is also important that these patients continue routine screening, as there remains the potential for diagnosis of a secondary urothelial malignancy [42].

Initial stabilization is determined by degree of hematuria and hemodynamic parameters, with catheterization avoided if possible due to the friability of the bladder mucosa. If bleeding persists, increasingly invasive measures may be pursued under the care of a urologist, including various forms of intravesical therapy with increasing levels of toxicity and long-term effects, laser fulguration of telangiectatic vessels, and the use of hyperbaric oxygen. In the acutely unstable patient, iliac artery embolization can be used as a method of hemorrhage stabilization. Diversion of the urine away from the bladder with bilateral percutaneous nephrostomy tubes is an option to help in the setting of recurrent HC. Surgical urinary diversion with or without cystectomy is a method of last resort, but has a high rate of perioperative morbidity (over 80%) [43]. Given the morbidity of recurrent presentation, current research focus is on the use of systemic therapies for the prevention of hemorrhagic emergencies rather than their acute treatment [44].

Conclusion

There are multiple etiologies for gross hematuria in the adult, but the presence of malignancy must always be excluded. While all gross hematuria should eventually result in referral to a urologist to complete the evaluation, most initial presentations of mild or moderate hematuria may be managed in an outpatient setting. Reasons for emergency room referral should include severe hematuria, inability to void, recent trauma, flank pain, or fever. Reasons for urgent urologic consultation include fever with ureterolithiasis or hydronephrosis, inability to establish bladder drainage, severe hematuria or clot retention after urologic surgery, severe hematuria that does not improve or resolve after irrigation, and suspicion for urologic system perforation or injury.

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Upper Gastrointestinal Bleeding

29

Nabeel Azeem and Martin L. Freeman

Introduction

By definition, upper gastrointestinal (GI) bleeding is any bleeding that occurs from the mouth to the ligament of Treitz. Upper GI bleeding is one of the most common reasons for admission to the hospital leading to nearly 300,000 hospitalizations per year in the United States [1]. For decades mortality from upper GI bleeding was as high as 5–10%, but recent data suggest a decrease to 2% from 1989 to 2009 associated with an increase in rates of endoscopy and endoscopic therapy [2].These findings suggest that there have been significant advances in medical and endoscopic management over the last few decades that are making a clear impact on outcomes. However, the economic burden for upper GI bleeding in the United States continues to increase from $3.3 billion to $7.6 billion over the same time period [2].The current chapter is an overview of upper GI bleeding management with a focus on recent endoscopic advances.

Upper GI bleeding can be divided into variceal (portal hypertensive) and nonvariceal. The most common cause of nonvariceal upper GI bleeding is peptic ulcer disease (Fig. 29.1), followed by erosive disease, esophagitis, malignancy, and Mallory-Weiss tears [3]. There are multiple less common causes of nonvariceal upper GI bleeding including Dieulafoy lesions, Cameron ulcers, gastric antral vascular ectasia (GAVE), angiodysplasias, gastrointestinal stromal tumors, hemobilia, hemosuccus pancreaticus, and vascular-enteric fistulas (see Table 29.1). Portal hypertension-related bleeding can be caused by esophageal, gastric, or ectopic varices and by portal hypertensive gastrointestinal enteropathy.

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Initial Assessment and Early Management

The initial assessment of patients with upper GI bleeding is critical as adequate risk stratification will lead to improved patient outcomes and reduced healthcare costs. Evaluation should start with assessment of airway and breathing status as brisk upper GI bleeding, especially in the setting of altered mental status, can quickly lead to aspiration of blood and respiratory arrest. The patient's intravascular status should also be quickly assessed as prompt volume resuscitation can treat or avoid shock. A focused history and physical exam will help determine the likely location of bleeding which will in turn help guide evaluation. It is also important to determine if the patient is at risk of portal hypertension-related bleeding as there are important differences in management.

Vital signs, including evaluation for orthostatic hypotension, should be obtained in all patients with upper GI bleeding. Tachycardia is a well-known response to volume loss and is one of the first indicators of hypovolemia [4]. Laboratory studies in the initial assessment of any patient with upper GI bleeding should include a complete blood count, complete metabolic panel, coagulation studies, and type and screen. It is important to note that early in upper GI bleeding, hemoglobin and hematocrit may be close to baseline and may not initially reflect the actual blood loss. Equilibration by extravascular fluid entering the vascular space and resuscitation with intravenous fluids may take a substantial amount of time such that leveling off of the hemoglobin may not occur for up to 72 hours, even after bleeding has stopped. Therefore, the hemoglobin and hematocrit should be checked periodically depending of the severity of the bleeding.

Once the initial assessment has been done, resulting information can be used to risk stratify the patient and help guide appropriate treatment. Most consensus guidelines recommend that patients with acute upper GI bleeding should undergo endoscopic evaluation within 24 hours of presentation unless they are at low risk for rebleeding [5, 6]. There are several pre-endoscopic risk assessment scores designed to risk

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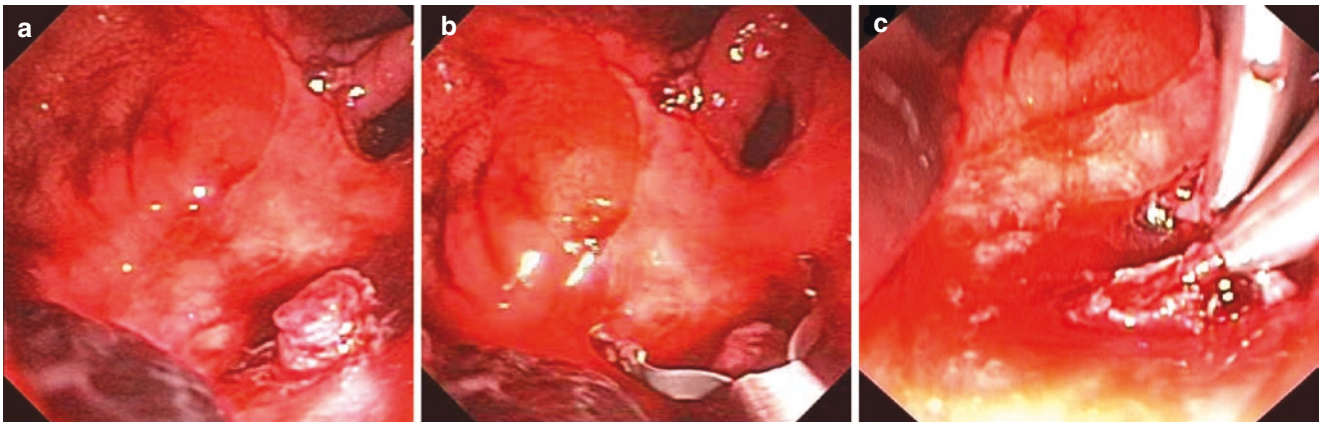

Fig. 29.1 (**a**) Duodenal peptic ulcer with a non-bleeding visible vessel (Forrest classification IIa). (**b**) Applying hemostatic clip. (**c**) After placement of two clips

Table 29.1 Causes of Upper Gastrointestinal Bleeding

Peptic ulcer disease
Erosive esophagitis/gastritis/duodenitis
Mallory-Weiss tear
Cameron's lesions
Dieulafoy lesions
Vascular malformations: angioectasias, arteriovenous malformations, GAVE
Malignancy
Iatrogenic: post-mucosal resection, post-sphincterotomy
Aortoenteric fistula
Arterial aneurysm/pseudoaneurysm
Hemosuccus pancreaticus/hemobilia
Esophageal varices
Ectopic varices: gastric varices, duodenal varices
Portal hypertensive gastropathy

stratify patients and determine risk of mortality, need for hospital admission, need for urgent endoscopy, need for blood transfusion, and risk of rebleeding. Among the best-studied are the AIMS65, the Glasgow-Blatchford Risk Score (GBRS), and the clinical Rockall score. These risk assessment scores are easy to calculate, as they take into consideration several parameters including comorbidities, vital signs, and laboratory values which are readily available at presentation.

A recently published large Danish cohort study of 12,601 patients with peptic ulcer bleeding assessed the relationship between the timing of endoscopy and mortality stratified by pre-endoscopic risk as defined by hemodynamic stability and American Society of Anesthesiologists (ASA) score [7]. This study showed that in hemodynamically stable patients with an ASA score of 3–5, there was a U-shaped association between timing of endoscopy and mortality where the nadir of in-hospital mortality was between 12 and 36 hours. This is one of the first studies to suggest worse outcomes with very early endoscopy, and the authors hypothesize that an initial period of optimizing resuscitation and managing comorbidities before endoscopy may improve outcomes. In patients with hemodynamic instability, the association between timing and mortality was less clear.

Two large-bore intravenous catheters, 18 gauge or larger, should be placed in patients with significant bleeding to allow for rapid fluid resuscitation and blood transfusions. The need for red blood cell transfusion is determined by the clinical presentation, vital signs, initial hemoglobin, and patient comorbidities. Consensus guidelines recommend blood transfusions for a hemoglobin less than or equal to 7 g/dL in patients who do not have coronary disease, evidence of organ hypoperfusion, or acute hemorrhage to maintain a target hemoglobin of 7–9 g/dL. Excessive transfusion has been associated with increased mortality [8]. Proton-pump inhibitors (PPI) should be started in all patients presenting with upper GI bleeding. PPI therapy has been proven to downgrade higher-risk stigmata of hemorrhage found at endoscopy (i.e., less active bleeding, visible vessels) (Fig. 29.1). PPIs have also been shown to reduce rates of rebleeding, need for surgical intervention, and mortality [9].

Erythromycin is an antibiotic with prokinetic effects, which when given prior to endoscopy has been shown to improve gastric emptying and increase visibility at endoscopy, leading to a decrease in second-look procedures, but has not translated to a decrease in blood transfusions, hospital stay, or surgery. It is still recommended in current guidelines and if no contraindications are found (hypokalemia, prolonged QT interval). A 250 mg bolus of erythromycin can be administered 30–45 min prior to emergency endoscopy [5]. The routine use of nasogastric lavage is no longer recommended. Recent studies have shown no difference in repeat blood transfusions or need for second-look endoscopy when comparing erythromycin to nasogastric lavage [10, 11].

If portal hypertensive bleeding is suspected, somatostatin or analogues (octreotide and vapreotide) and an antibiotic should

be started. Somatostatin and somatostatin analogues cause splanchnic vasoconstriction by inhibiting the release of glucagon. In practice, in the United States, octreotide, a somatostatin analogue, is the primary agent used to reduce the risk of portal hypertensive rebleeding. Antibiotics not only prevent infections such as spontaneous bacterial peritonitis but also decrease the burden of bacteria that produce vasodilating cytokines that lead to vasodilation and increase in portal pressures. All cirrhotic patients presenting with a GI bleed should be started on antibiotics as there is a clear mortality benefit [12, 13].

Traditional Endoscopic Therapies for Upper GI Bleeding

Upper endoscopy has both a diagnostic and therapeutic role in managing upper GI bleeding. Epinephrine injection in and around bleeding vessels leads to a transient vasoconstrictive effect and physical tamponade that allow temporary or sometimes permanent hemostasis. They may also improve visualization of the bleeding source. Epinephrine injection is generally a temporary measure and should not be used as monotherapy therapy in most circumstances due to high risk of rebleeding [14].

Thermal therapies includes coaptive coagulation probes such as bipolar and heater probes. These are effective at treating smaller caliber vessels in nonvariceal sources such as ulcers, Mallory-Weiss tears, and angiodysplasias (Fig. 29.2). Argon plasma coagulation (APC) is another type of thermal therapy, but it differs in that it is "noncontact." The probe uses monopolar energy that sends a current through a stream of ionized gas that coagulates mainly superficial tissue, although depth of thermal injury is dependent on power settings, duration of energy delivery, distance from the probe, and gas flow rate.

The most commonly used device for therapy of active bleeding and visible vessels are through-the-scope endoscopic clips placed through the endoscope channel (Fig. 29.1). These provide mechanical hemostasis and generally have low risk of complications even in the setting of maldeployment. There are multiple different types of clips now available that vary in their rotation ability, width of jaws, and ability to reopen and close.

Perforation can occur with any endoscopic procedure, but thermal therapy has a reported perforation rate of 1.8–3.0% [15]. Endoscopic injection with epinephrine rarely causes complications but has been associated with bleeding, cardiac arrhythmias, and hypertension [14]. Through-the-scope clips have rarely been associated with complications. A meta-analysis of 373 patients treated with clips and epinephrine showed no bleeding or perforation complications [14]. If bleeding recurs or persists after endoscopic therapy, then the options are to reattempt endoscopic therapy or involve interventional radiology to embolize the bleeding vessel during angiography. Rarely, persistent severe upper GI bleeding will require a surgical intervention to control the hemorrhage.

Band ligation is the treatment of choice for esophageal variceal bleeding. These devices attach on the end of a standard gastroscope, and multiple elastic bands can be deployed after visually targeting and suctioning in an esophageal varix into a cap. If endoscopic treatment has failed to stop variceal bleeding, traditional options to consider are temporary balloon tamponade or referral to interventional radiology for transjugular intrahepatic portosystemic shunt (TIPS). Balloon tamponade using the Sengstaken-Blakemore tube or Minnesota tube should be a temporary bridge to a more definitive therapy such as TIPS. Surgical shunts are mainly of historical interest.

Emerging Endoscopic Therapies

Over-the-Scope Clips

Originally, the first over-the-scope clip, OTSC (Ovesco, Tubingen, Germany), was developed for the purpose of closing fistulas and perforations, but since its introduction, it has become an important tool for gastrointestinal bleeding as both salvage and primary therapy (Fig. 29.3) [16–19]. The OTSC is a clipping system mounted like a cap to the tip of an endoscope that deploys a nitinol clip under direct endoscopic vision similar to endoscopic band ligation. During deployment, the clip closes itself and firmly anchors the tissue to be compressed. It is available in different diameters (11 mm, 12 mm, and 14 mm) that fit on different-sized endoscopes as well as three separate teeth shapes (a, t, gc) depending on therapeutic intent (hemostasis versus tissue approximation). There are several technical advantages to this type of system. All through-the-scope hemostatic devices have difficulty treating lesions that are opposite to the direction of the working channel (7 o'clock position for gastroscopes), making posterior duodenal bulb lesions and lesions located to the right of the endoscopic image difficult to treat with standard devices. The transparent cap design of OTSC devices allows the endoscope to come en face with lesions. As long as the lesion is within the center of the cap, it will then become entrapped by the clip after deployment. Similar to variceal banding, suction will help ensure the lesion or vessel will successfully be captured within the clip. With fibrotic ulcers, there may be some difficulty bringing the lesion into the cap, and an OTSC anchor may be helpful in pulling the lesion into the cap. An alternative over-the-scope clipping device has also recently became available, the Padlock Clip (Aponos Medical, Kingston, NH, USA) [20]. The deployment and principles of this clip are similar to the OTSC system, but this clip lays flatter after placement.

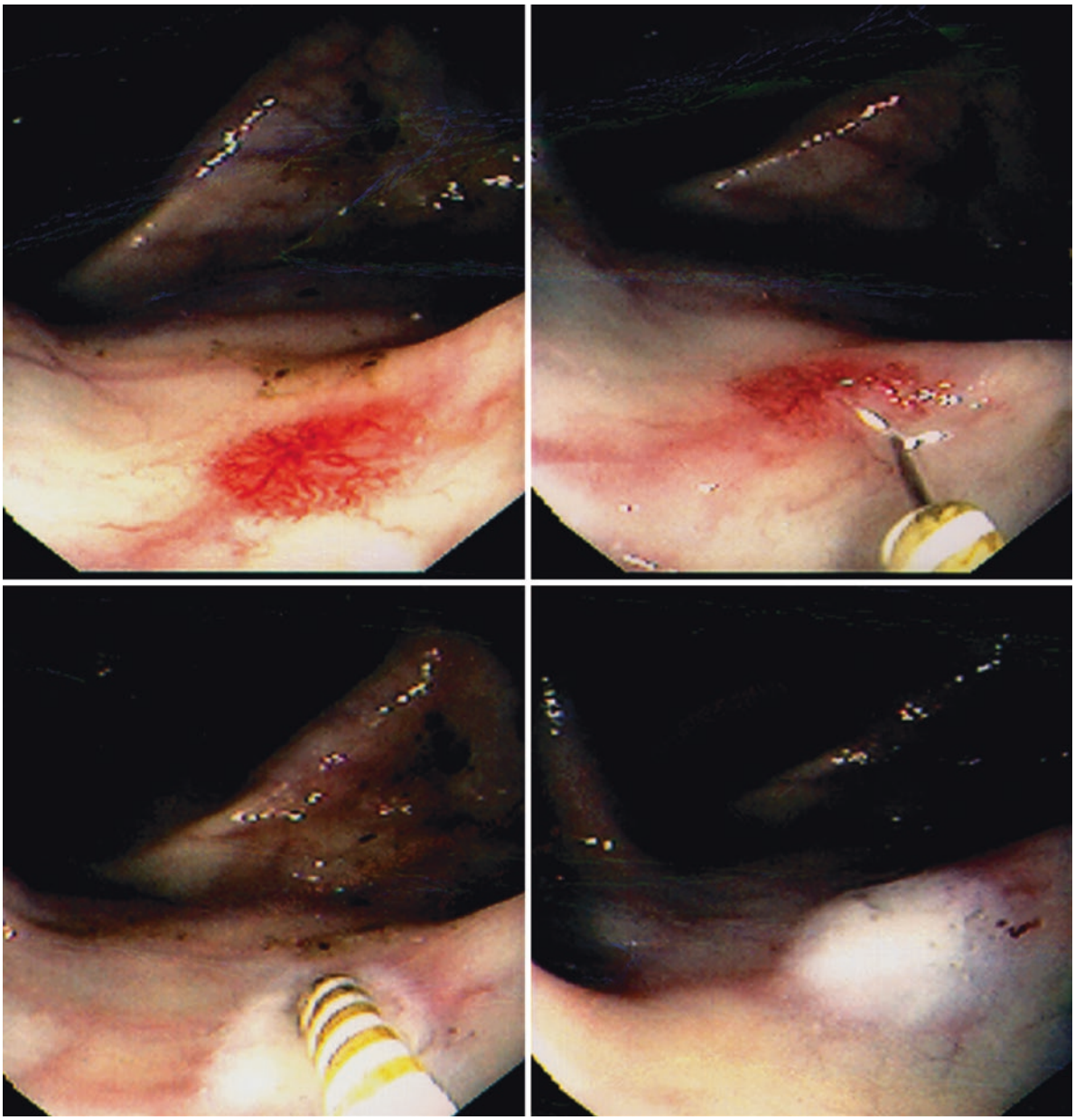

Fig. 29.2 Large angioectasia treated with injection-lift and bipolar coagulation

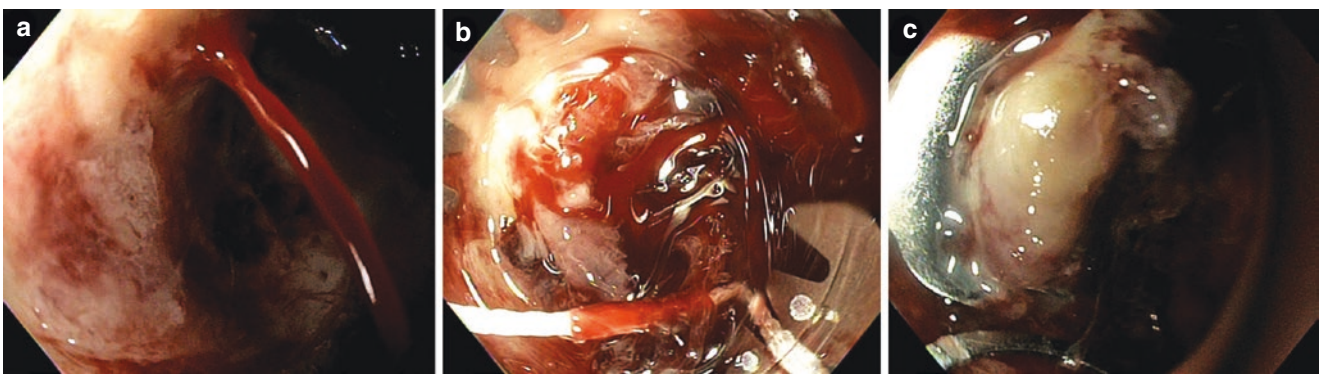

Fig. 29.3 (**a**) Duodenal ulcer with actively spurting bleeding from suspected gastroduodenal artery. (**b**) Over-the-scope clip with cap positioned over the bleeding vessel. (**c**) After deployment of over-the-scope clip, cessation of active bleeding with vessel seen entrapped within clip

Initial studies for the OTSC system for GI bleeding focused on rescue therapy for refractory nonvariceal upper GI bleeding. The first report was on 12 consecutive patients with ongoing bleeding despite traditional endoscopic therapy all of whom were critically ill with 75% in shock. Initial hemostasis with the OTSC was achieved in all patients. Rebleeding occurred in two subjects in 1 and 7 days later, which was stopped with an additional clip. No adverse events were reported [19]. A separate study published the same year of nine patients with refractory bleeding showed 100% technical success and 77.8% clinical effectiveness [21]. Finally, a third study of 23 patients showed immediate clinical success in 22 out of the 23 patients with OTSC as rescue therapy, and 2 of those patients had rebleeding at 12 and 24 hours later [22]. Eventually, a prospective multicenter randomized clinical trial (the STING study) was performed comparing OTSC to standard endoscopic therapy for rescue therapy in nonvariceal upper GI bleeding [23]. Sixty-six patients from nine academic centers in Germany, Switzerland, and Hong Kong with recurrent peptic ulcer bleeding were enrolled. Thirty-three patients were randomized to the OTSC arm, and 33 patients were randomized to the standard hemostasis arm (primarily hemoclips with epinephrine), although crossover to the OTSC arm was allowed. Persistent or recurrent bleeding occurred in 57.6% of the standard therapy group and in 15.2% of the OTSC group ($p = 0.001$). Moreover 10 patients crossed over from the standard endoscopic arm to the OTSC arm due to persistent bleeding, and all 10 patients had successful hemostasis. No mortality or differences in secondary endpoints were seen; however, the study was not powered to assess these findings. Taken together these studies showed a high clinical success rate with single clip deployment in a group of patients that have failed traditional endoscopic therapy.

Several nonrandomized studies have now examined the use of OTSC as primary therapy for nonvariceal upper GI bleeding. An Italian study of 40 consecutive patients showed a 100% technical success, immediate hemostasis, and clinical success (no rebleeding at 30 day follow-up) [24]. Another study from Germany looked at the use of OTSC for both first-line and second-line therapy. Clinical success was achieved in 88 out of 100 patients in the first-line and 78 out of 100 patients in the second-line groups. Overall failure rate was significantly lower when OTSC was used as first-line therapy compared to second-line therapy (4.9% vs 23%, $p = 0.008$) [16]. It should be noted that standard endoscopic therapy as a first-line intervention is quite effective when looked at overall with rebleed rates of 5–10%, so these findings are not all that surprising [25, 26]. However, another German study by Wedi et al. termed the FLETRock study risk stratified their subjects by Rockall score [17]. Similar to the previous studies, OTSC as primary therapy overall had a 92.4% clinical success rate among 118 patients. High-risk Rockall score patients were much more likely to rebleed or continue bleeding compared to low-risk Rockall scores (21.4% vs 4.9%). When comparing their data to the Rockall cohort, they demonstrated a significantly lower risk of rebleeding/persistent bleeding among the OTSC-treated patients who were intermediate risk (Rockall score 4–7) and high risk (Rockall score >8) with 4.9% vs 24% and 21.4% vs 53.2%, respectively ($p < 0.001$). This is one of the first studies to suggest superior outcomes when using OTSC as first-line hemostasis in nonvariceal upper GI bleeding among intermediate-to-high-risk patients. However, to date no prospective randomized trial has been performed on the use of OTSC as first-line hemostasis. Currently, such a study is ongoing by the same investigators as the STING trial.

Hemostatic Powders

Hemostatic powders have been available for several years and reported in the surgical and trauma literature. Mechanisms of action vary somewhat but all promote clot formation. Several powders have been used off-label to achieve temporary endoscopic hemostasis in case reports. Arista Absorbable Hemostat (Bard, Warwick, RI, USA) is a powder derived from plant starch within microporous polysaccharide hemospheres. It is indicated for bleeding during surgical procedures that cannot be controlled by standard means. Its high cost has limited its use for routine endoscopy for bleeding. Ankaferd Blood Stopper (ABS) is a traditional herbal mixture that has been approved and used in Turkey for many years with some limited data on endoscopic hemostasis [27].

Hemospray TC325 (Cook Medical Inc, Winston-Salem, NC, USA) is a hemostatic powder specifically developed for endoscopic use during gastrointestinal bleeding (Fig. 29.4).

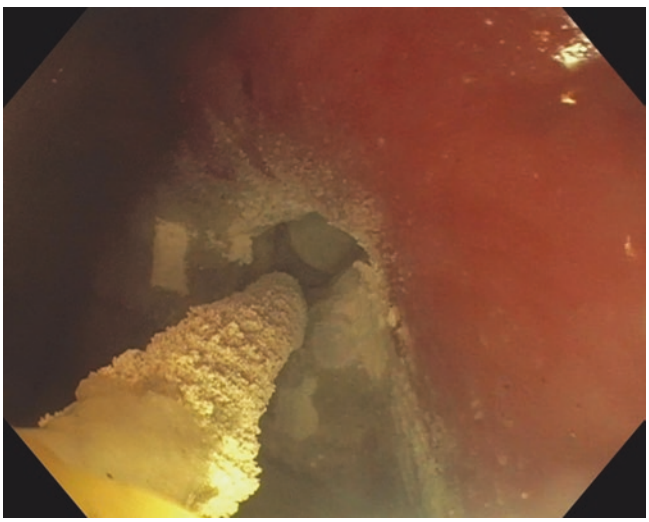

Fig. 29.4 Pyloric channel ulcer with associated pyloric stenosis and active bleeding treated with Hemospray with prompt cessation of active bleeding

The powder achieves hemostasis by concentrating clotting factors to create a plug on the injured blood vessel [28]. Hemospray has been available for some time now initially in Asia and later in Europe. It has only recently become commercially available in the United States. One of the initial pilot studies treated 20 reported Hemospray monotherapy within the first 24 hours of presentation for consecutive patients with Forrest classification Ia or Ib (active spurting or active oozing) peptic ulcer bleeding [29]. Acute hemostasis was achieved in 19/20 patients. Bleeding recurred in two subjects within 72 hours as described by a hemoglobin drop, but repeat upper endoscopy did not demonstrate active bleeding at 72 hours. No adverse events were reported. A separate study looked at hemostasis using Hemospray in patients with nonvariceal upper GI bleeding taking antithrombotics [30]. Initial hemostasis was achieved in five out of eight subjects taking antithrombotics compared to all eight subjects not taking antithrombotics. One of the first large multicenter studies reported 63 patients with nonvariceal upper GI bleeding treated with Hemospray, 33 with peptic ulcer, and 33 patients with nonpeptic ulcer bleeding [31]. Most patients were treated with Hemospray as monotherapy (87%) with 85.5% achieving initial hemostasis and 15% rebleeding at 7 days. Eight subjects who failed initial endoscopic therapy were retreated with Hemospray with all eight achieving hemostasis. The largest study on Hemospray enrolled 202 subjects in France [32]. The etiology of bleeding was ulcer in 37.1%, tumor in 30.2%, postendoscopic therapy in 17.3%, and other in 15.3%. Immediate hemostasis was achieved in 96.5%. Recurrence of upper GI bleeding occurred in 26.7% by day 8 and 33.5% by day 30. Factors that predicted rebleeding were melena at initial presentation, Hemospray as salvage therapy, and Forrest Ia ulcers (spurting arterial bleeding). Interestingly, hemostasis was achieved in 95.1% of patients with tumor bleeding, and only 25% rebled by day 8. Given the difficulty of treating tumor bleeding with other endoscopic modalities, Hemospray or other topical hemostatic powders may be the treatment of choice for this difficult indication.

Endoscopic Ultrasound (EUS)-Guided Vascular Therapy

Endosonographic guidance to treat GI bleeding has a few potential advantages over conventional endoscopic therapies. The bleeding vessel can be directly targeted with accuracy; active bleeding does not obscure the sonographic view of the source as it would visually. One can also confirm cessation of blood flow using color Doppler after delivering therapy. One of the first uses of endoscopic ultrasound (EUS)-guided therapy was by Fockens et al. in 1996 in the treatment of a Dieulafoy lesion in the upper GI tract [33]. Dieulafoy lesions not visible to endoscopy were localized endosonographically in three patients, a needle was advanced under EUS guidance into the vessel, and a sclerosant was injected into the vessel with subsequent obliteration. Several subsequent case series have reported EUS-guided treatment of nonvariceal GI bleeding using ethanol, cyanoacrylate (glue), epinephrine, thrombin, or coils to inject into lesions. Targeted lesions have included tumors (gastrointestinal stromal tumor [GISTs], pancreatic cancer), pseudoaneurysms, Dieulafoy lesions, and refractory peptic ulcer bleeding [34–37].

At select tertiary care centers, the most common use of EUS-guided therapy is in the setting of bleeding gastric varices. Traditionally, these were managed by interventional radiology via TIPS or balloon-occluded retrograde transvenous obliteration (BRTO). However, there are limitations to these interventions. Patients with high MELD (model for end-stage liver disease) scores are at high risk for liver failure and mortality following TIPS. TIPS is otherwise contraindicated in patients with hepatic encephalopathy, right heart failure, and other conditions. BRTO is only possible in patients with spontaneous splenorenal shunts in order to allow access to the gastric varices. Gastric varices can also form due to thrombosis of the portal vein or splenic vein (most commonly in the setting of acute pancreatitis or malignancy) in which case a TIPS would not be effective for decompression. Splenectomy has traditionally been recommended for such patients, but is associated with high operative risk. Soehendra et al. first described endoscopic injection of cyanoacrylate into bleeding gastric varices [38]. While quite effective, the risk of this procedure is embolization of the injected glue into the systemic circulation resulting in pulmonary embolism or an ischemic stroke. Binmoeller et al. described the use of EUS-delivered coils into gastric varices, followed by cyanoacrylate injection to reduce the risk of glue embolization [39]. Metal coils are covered with fibers which act as a scaffold for the glue to adhere. The coils, which are used by interventional radiology routinely for vascular embolization, come in a variety of sizes and can be passed through a standard EUS FNA (fine needle aspiration) needle using the stylet as a pusher. The coil diameter should be 1.25–1.5 times the diameter of the targeted vessel. Ideally, the "inflow" perforating vessels should be targeted to maximize obliteration (Fig. 29.5). A multicenter cohort study of 30 patients compared EUS-guided cyanoacrylate injection (n = 19) with EUS-guided coiling (n = 11) of gastric varices which showed no difference in the rate of obliteration (95% versus 91%, respectively); however, fewer sessions were needed in the coiling group (only one session in 82%). A post-procedure CT was obtained in all patients as part of the study protocol. Among the cyanoacrylate group, 58% of had asymptomatic pulmonary emboli post-procedure com-

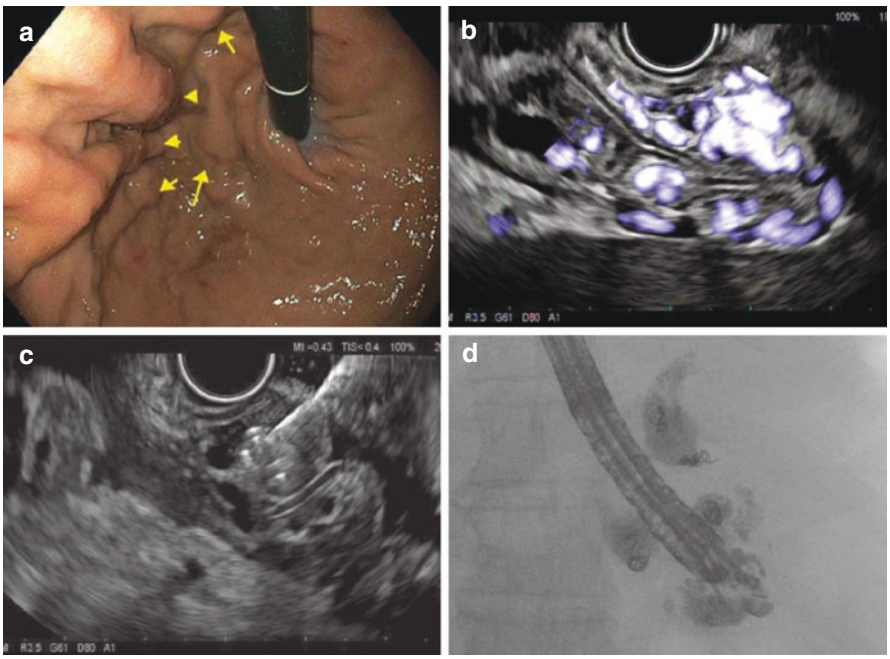

Fig. 29.5 (**a**) Endoscopic appearance of gastric varices (arrows) that recently bleed clinically. (**b**) Endosonographic power Doppler appearance of gastric varices. (**c**) EUS-guided puncture of a gastric varix, followed by delivery of coils, followed by cyanoacrylate glue. (**d**) Fluoroscopic image after treatment of multiple gastric varices with coil and gluing

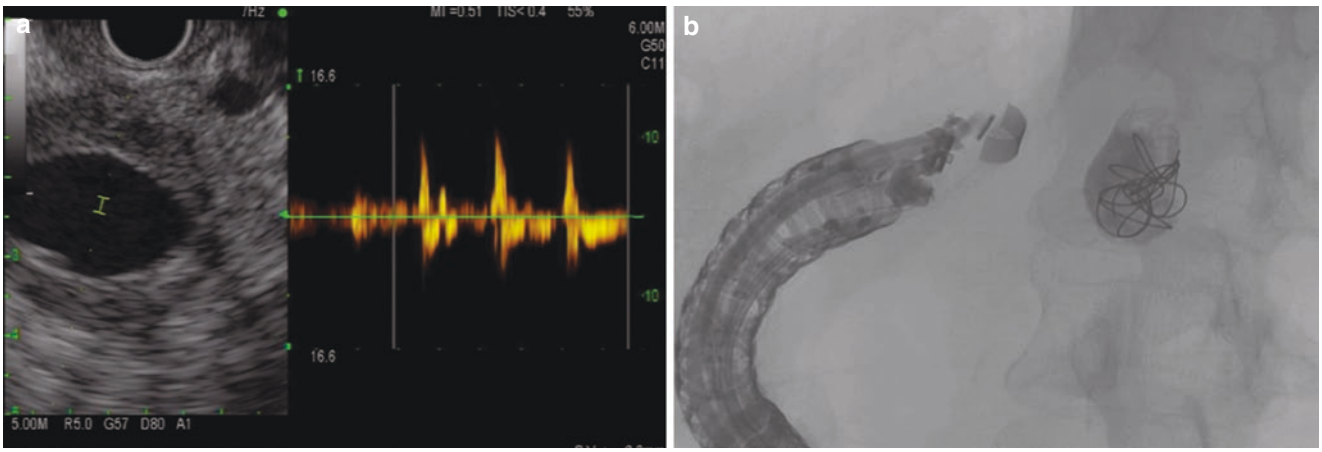

Fig. 29.6 (**a**) EUS appearance of a splenic artery pseudoaneurysm with pulsed wave Doppler confirming arterial flow within the pseudoaneurysm. (**b**) Successful EUS-guided coil and embolization of pseudoaneurysm

pared to 9% in the coiling group [40]. While all the pulmonary emboli were asymptomatic, it does confirm the significant risk of embolization when injecting cyanoacrylate alone. There are also a few reports of using EUS-guided coils to treat nonvariceal gastrointestinal bleeding (peptic ulcer disease, hepatic artery pseudoaneurysms, etc.) (Fig. 29.6) and ectopic varices [37, 41–43].

Radiofrequency Ablation

Radiofrequency ablation (RFA) during endoscopy is used frequently for the treatment of Barrett's esophagus with dysplasia. RFA delivers superficial but high-intensity thermal energy mainly localized to the mucosal and superficial submucosal layers. This characteristic has been used to also treat various GI bleeding but most commonly gastric antral vascular ectasias (GAVE) (Fig. 29.7). The primary mode of endoscopic therapy for GAVE has been argon plasma coagulation (APC) which is not universally effective. Comparative data are lacking, but a retrospective series of 24 patients with GAVE treated with RFA showed a significant reduction in transfusion requirements in all 23 transfusion-dependent patients with 15 patients not requiring transfusions at all during a 6-month period compared to a mean of 10.6 transfusions prior to treatment [44].

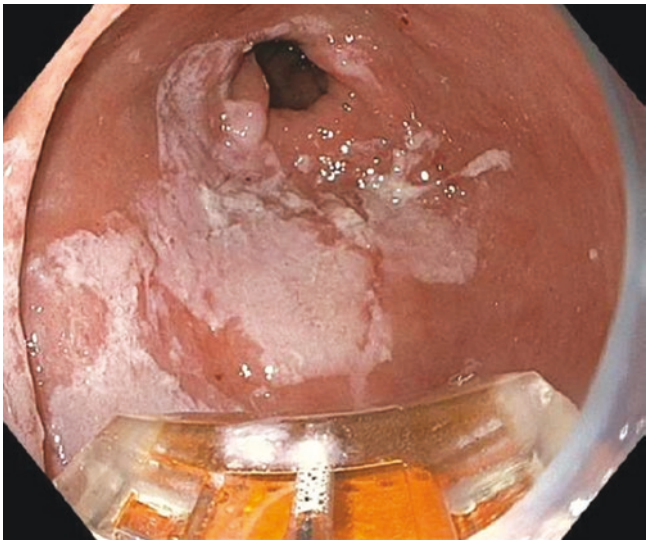

Fig. 29.7 Patient with iron deficiency anemia due to gastric antral vascular ectasias (GAVE) treated with radiofrequency ablation (RFA)

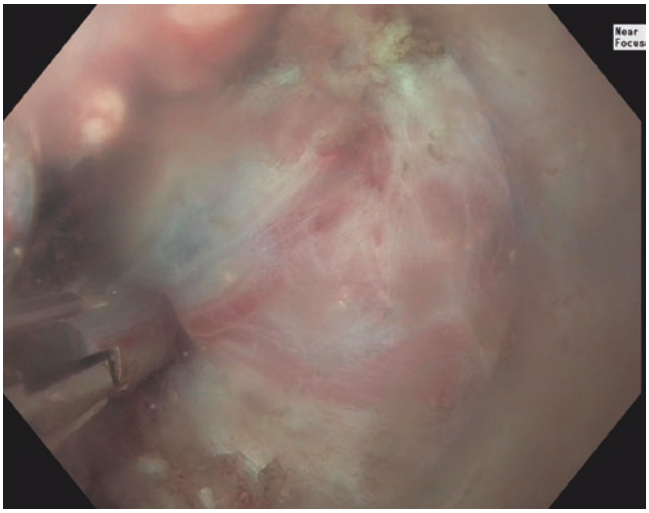

Fig. 29.8 Visible vessel encountered during endoscopic submucosal dissection treated prophylactically using a Coagrasper

Endoscopic Band Ligation

Endoscopic band ligation (EBL) is another well-known, well-studied technique for the management of esophageal varices which has also been used for a number of nonvariceal bleeding applications [45]. Conceptually, the rationale is similar to over-the-scope clipping described above, but it is likely cheaper, although probably less secure. One recent novel application of EBL is in the treatment of GAVE. One prospective study enrolled 21 patients with GAVE and applied multiple EBLs across the affected stomach. Clinical response was seen in 91% of patients with an improvement in hemoglobin and decrease in transfusion requirement with a mean follow-up of 10 months [46].

Monopolar Hemostatic Forceps

Monopolar hemostatic forceps have become a mainstay for hemostasis during endoscopic submucosal dissection (ESD) and peroral endoscopic myotomy (POEM) due to their ability to work within a small space without complicating further dissection, precise treatment of vessels, and minimal thermal damage to the muscle layer. There are two available types of monopolar hemostatic forceps: Coagrasper (Olympus, Tokyo, Japan) and hot biopsy forceps (various manufacturers). The Coagrasper was specifically designed for hemostatic applications during ESD, but some endoscopists use hot biopsy forceps for the same purposes due to their lower price. However, there are key differences that likely make the Coagrasper the more appropriate device for hemostasis (Fig. 29.8). Coagraspers are rotatable, the jaws completely appose, and are available in a 4 mm (esophageal or lower GI tract), 5 mm, or 6.5 mm (gastric) opening width as vessels in the stomach are typically larger than in other areas in the GI tract. Hot biopsy forceps were designed for polyp avulsion and have a cup shape, meaning that cautery is delivered along the edge of the forceps, which is not ideal when the goal is to apply mechanical tamponade and desiccate the isolated vessel. During ESD or POEM, visible vessels are prophylactically treated during dissection by grasping the vessel precisely with the hemostatic forceps, gently tenting away from the muscle layer, and applying low energy "soft coagulation" electrocautery until the vessel is obliterated, a technique applicable to active bleeding in which the bleeding point is precisely grasped. When the vessel is grasped, active bleeding should cease by mechanical tamponade alone, indicating that addition of "soft coagulation" is likely to be effective for permanent hemostasis.

While clearly effective for hemostasis during ESD and POEM, efficacy of monopolar hemostatic forceps for nonvariceal upper GI bleeding has only recently been reported. Toka et al. performed a randomized control trial comparing hemostatic forceps and hemoclip for the treatment of peptic ulcer disease (Forrest 1a, 1b, and 2a) bleeding [47]. Fifty-six patients were in each group. Initial hemostasis success rate was higher with hemostatic forceps compared to hemoclips (98.2% vs 80.4%; $p = .004$). Recurrent bleeding was detected in two patients in the hemostatic forceps group (3.6%) and eight patients in the hemoclip group (17.7%; $P = .04$). There were no adverse events in either group. Further confirmatory studies are needed to demonstrate superiority of hemostatic forceps, but clearly, they are an effective tool in the management in nonvariceal upper GI bleeding.

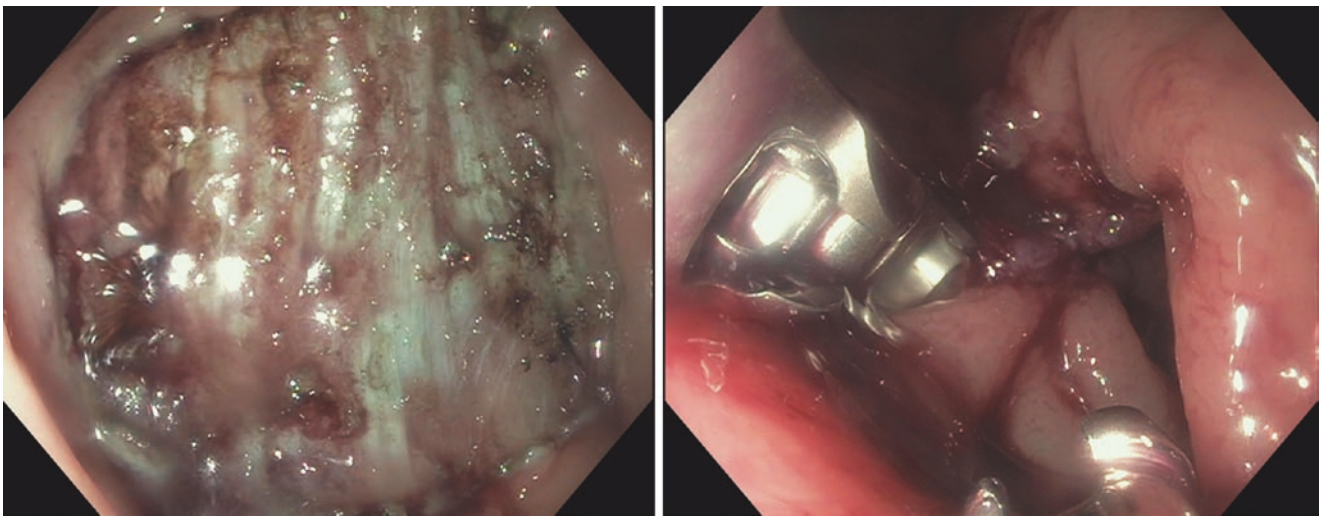

Fig. 29.9 (**a**) Mucosal defect after endoscopic submucosal dissection in the colon. (**b**) Defect completely closed using endoscopic suturing to prevent delayed bleeding

Endoscopic Suturing

Endoscopic suturing has obvious analogies to surgical techniques for tying off bleeding vessels, but clinical data are lacking. The OverStitch device (Apollo Endosurgery, Inc, Austin, TX) has been used to prevent delayed bleeding after ESD by closing the resulting defect/iatrogenic ulcer (Fig. 29.9) [48]. One retrospective international case series of 10 patients with bleeding peptic ulcer disease was recently published [49]. Nine patients had failed prior endoscopic therapy. Immediate hemostasis was achieved in all patients, and the rate of early or delayed rebleeding was 0% with a median follow-up of 11 months. No adverse events were noted. Nevertheless, this modality will likely have limited use given the technical complexity, restricted flexibility of a double-channel endoscope (required for the OverStitch device), and limited endoscopic visibility with the device in place in the setting of active bleeding.

Doppler Probe

The Doppler endoscopic probe was introduced years ago to predict the risk of rebleeding in a peptic ulcer, aid in targeting endoscopic therapy, and assess the success of endoscopic hemostasis. It is a 2 mm diameter catheter attached to a control unit that can be passed through the working channel of most any endoscope. The probe is then endoscopically placed adjacent to a stigma of recent bleeding such as a visible vessel, adherent clot, or pigmented spot typically associated with a peptic ulcer. The area should be washed to maximize tissue apposition with the probe. If an artery is associated with the stigmata, it should run as a straight line across the stigmata; therefore placing the probe systematically in four quadrants around the stigmata should help map out the directionality of the underlying vessel. The probe detects blood flow toward or away from the probe, and therefore the probe should be placed tangential to the suspected vessel and not perpendicular in order to detect the arterial blood flow. If an arterial vessel is present, then a characteristic pulsatile flow should be heard from the control unit. Using this information, the endoscopist can then determine if endoscopic therapy is needed at all, appropriate target for endoscopic hemostasis (mechanical or thermal), and if hemostasis stopped blood flow by re-examining with Doppler.

One randomized controlled trial performed by Jensen et al. compared standard endoscopically directed therapy for nonvariceal upper GI bleeding compared to Doppler-directed endoscopic therapy [50]. One-hundred and forty-eight patients were randomized. There was a significant difference in the rates of 30-day rebleeding in the control group (26.3%) vs the Doppler group (11.1%) ($p = 0.0214$). The odds ratio for rebleeding with Doppler monitoring was 0.35, and the number needed to treat was 7, providing strong evidence for the Doppler-guided approach to endoscopic hemostasis.

Summary

Upper GI bleeding continues to be a major reason for hospital admission. Significant advancements have been made over the last few decades leading to evidence-based risk stratification, medical management, and interventions that have objectively improved mortality and morbidity outcomes. Nevertheless, refractory bleeding cases still occur, and it is important for the practicing endoscopist to be able to utilize every available tool when needed.

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Part IV

Bleeding Associated with Medication

Antiplatelet and Anticoagulant Agents

30

Ibrahim F. Ibrahim and Lawrence Rice

Introduction

The management of anticoagulant and antiplatelet medications perioperatively and in the setting of acute hemorrhage is an increasingly complex problem faced by clinicians. With the rapid emergence of non-vitamin K antagonist, direct oral anticoagulants (DOACs), and newer and more potent antiplatelet drugs, questions about safety and practical use of these agents arise as they are incorporated into clinical practice (Table 30.1).

Anticoagulant medications are one of the most commonly prescribed medications in the United States, with 4.2 million Americans taking anticoagulants in 2007 [1]. This trend is increasing as familiarity and comfort among practitioners with DOACs increase and as indications for DOACs expand to include the treatment of peripheral artery disease and coronary artery disease [2]. Many patients receiving long-term antithrombotic therapy require temporary interruption of anticoagulation therapy before a procedure or surgery. The management of anticoagulation in these patients raises challenges in balancing the transient increase in risk of thromboembolism as well as the risk of bleeding. If the patient bleeds from the procedure, the anticoagulant may be discontinued for a longer period, and pro-hemostatic agents may be administered which could increase the risk of thromboembolism. Furthermore, a life-threatening hemorrhage while on anticoagulants or antiplatelet agents could develop. There is limited evidence to guide the physician in this frequently encountered clinical situation.

Bridging anticoagulation is often used to mitigate the risk of thrombosis in high bleeding risk scenarios such as in the perioperative setting. Bridging anticoagulation is defined as administration of a short-acting anticoagulant when a long-acting oral anticoagulant such as warfarin is interrupted and the anticoagulant effect is outside the therapeutic range. The short-acting anticoagulants are usually low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) given for several days around the time of a scheduled surgery or procedure. Generally, bridging therapies have a limited role with DOACs given their rapid onset and offset as compared to traditional vitamin K antagonists (VKAs). The purpose of periprocedural bridging (Tables 30.2 and 30.3) is to mitigate the risk of periprocedural thromboembolism. The evidence to guide clinical practice is lacking. Fortunately, some guidance has been provided by recent randomized trials answering the crucial question of whether bridging should occur at all in select clinical scenarios [3, 4]. More recent prospective studies evaluating the perioperative management of patients taking DOACs for atrial fibrillation who require interruption for elective procedures are being undertaken in a standardized and patient-tailored fashion [5].

The aims of this chapter are to (1) provide the reader with guidelines on the interruption and resumption of anticoagulation in the elective perioperative setting, (2) discuss the role of bridging anticoagulation, and (3) discuss strategies for reversal of bleeding for patients on antithrombotic therapy. The clinical guidance discussed in this chapter will incorporate the best available evidence, acknowledging the evidence can be weak or based on expert opinion.

Perioperative Management of Antithrombotic Therapy

Assessment of Risk

The determination to continue anticoagulation or withhold is made after assessing the risk of thromboembolism off anticoagulation weighed against the bleeding risk of the pro-

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Table 30.1 Anticoagulant agents: pharmacokinetic/pharmacodynamic properties [51, 55, 61]

Agent	Effect	Half-life (route)	Elimination	Antidote
Warfarin	Reduces factors II, VII, IX, and X	36–42 h (PO)	Renal (92%, primarily as metabolites)	Vitamin K, PCC
Heparin—unfractionated	Binds to AT and catalyzes the inactivation of thrombin and factors IIa, Xa, IXa, XIa, and XIIa	60–90 min (IV)	Combination of saturable process of binding to endothelial cell receptors and macrophages and slower non-saturable renal clearance	Protamine
Enoxaparin	Indirect factor Xa inhibitor	3–6 h (SC)	Renal	Protamine—partial effect[a]
Dalteparin	Indirect factor Xa inhibitor	2.4–4 h (SC)	Renal	Protamine—partial effect
Tinzaparin	Indirect factor Xa inhibitor	1–2 h (SC)	Renal	Protamine—partial effect
Fondaparinux	Indirect factor Xa inhibitor	13–21 h (SC)	Renal	No specific antidote[a]—(consider rFVIIa)
Idraparinux	Indirect factor Xa inhibitor	80–130 h (SC)	Renal	No specific antidote—(consider rFVIIa)
Danaparoid	Inhibits factor Xa and IIa	25 h (anti-Xa activity) 7 h (anti-IIa activity)	Renal	None
Rivaroxaban	Direct Xa inhibitor	7–11 h (PO)	Renal—60%	Andexanet alfa
Apixaban	Direct Xa inhibitor	8–15 h (PO)	Renal—25%, hepatic—75%	Andexanet alfa
Edoxaban	Direct Xa inhibitor	8–10 h (PO)	Renal—50%	None[a]
Betrixaban	Direct Xa inhibitor	20–27 h (PO)	Renal—10%	None[a]
Dabigatran	Direct thrombin inhibitor	12–17 h (PO)	Renal—80%	Idarucizumab
Bivalirudin	Direct thrombin inhibitor	~25 min (IV)	Proteolytic cleavage and renal (20%)	None
Argatroban	Direct thrombin inhibitor	39–51 min (IV)	Hepatic	None
Desirudin	Direct thrombin inhibitor	2 h (SC)	Renal	None

AT antithrombin, *IV* intravenous, *SC* subcutaneous, *rFVIIa* recombinant factor VIIa, *PCC* prothrombin complex concentrate
[a]Andexanet alfa is currently only FDA approved for the reversal of direct Xa inhibitors apixaban and rivaroxaban but has neutralizing activity against indirect Xa inhibitors fondaparinux and enoxaparin and other direct Xa inhibitors

Table 30.2 Risk stratification for perioperative thromboembolism [7]

		Indication for anticoagulant therapy		
Risk stratum for thrombotic events	Bridging recommendations	Mechanical heart valve	Atrial fibrillation	VTE
High (>10%/year risk of ATE or >10%/month risk of VTE)	Suggested bridging	Any mitral valve prosthesis Any caged ball or tilting disk aortic valve prosthesis Recent (within 6 months) stroke or TIA	$CHADS_2$ score of 5 or 6[a] Recent (within 3 months) stroke or TIA	Recent (within 3 months) VTE Severe thrombophilia (e.g., antiphospholipid antibody syndrome)
Intermediate (4–10%/year risk of ATE or 4–10%/month risk of VTE)	Optional bridging	Bileaflet aortic valve prosthesis and ≥1 of the following risk factors: atrial fibrillation, prior stroke or TIA, hypertension, diabetes, CHF, age >75 years	Rheumatic valvular heart disease $CHADS_2$ score of 3 or 4[a]	VTE within the past 3–12 months Recurrent VTE Active malignancy (treated within 6 months or palliative)
Low (<4%/year risk of ATE or <2%/month risk of VTE)	No bridging	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0–2[a] (assuming no prior stroke or transient attack)	VTE > 12 months previous and no other risk factors

Adapted from Spyropoulos et al. [7]
TIA transient ischemic attack, *ATE* arterial thromboembolism, *VTE* venous thromboembolism
[a]The $CHADS_2$ score is calculated by the cumulative score for congestive heart failure history (1 point), hypertension history (1 point), age ≥75 years (1 point), diabetes mellitus history (1 point), and previous stroke or TIA (2 points) [2]

Table 30.3 Perioperative anticoagulation and bridging protocol [6, 62]

Day	Intervention
Preoperative intervention	
−7 to −10	Assess for perioperative bridging anticoagulation; classify patients as undergoing high bleeding risk or low bleeding risk procedure; check baseline labs (hemoglobin, platelet count, creatinine, INR)
−7	Stop aspirin or other antiplatelet agents
−5	Stop warfarin
−3	Start LMWH or UFH at therapeutic dose
−1	Last procedural dose of LMWH administered no less than 24 h before the start of surgery; assess INR before the procedure; proceed with surgery in INR < 1.5; if INR > 1.5 and <1.8, consider low-dose oral vitamin K reversal (1–2.5 mg)
Day of intervention	
0 or +1	Resume maintenance dose of warfarin on evening of or morning after procedure
Postoperative intervention	
+1	Low bleeding risk: restart LMWH or UFH at previous dose; resume warfarin therapy High bleeding risk: no LMWH or UFH administration; resume warfarin therapy
+2 or +3	Low bleeding risk: LMWH administration continued High bleeding risk: restart LMWH or UFH (without bolus) at previous dose
+4	Discontinue LMWH or UFH if INR > 1.9
+7 to +10	INR testing

LMWH low-molecular-weight heparin (i.e., enoxaparin, dalteparin, tinzaparin, nadroparin), *UFH* unfractionated heparin

Table 30.4 Elective procedures by bleeding risk [7, 63]

Low bleeding risk		High bleeding risk
Anticoagulation could be continued	Anticoagulation discontinued	
Simple dental interventions	Endoscopy with biopsy	Thoracic surgery
Cataract or glaucoma surgery	Prostate biopsy	Transurethral prostate resection
Endoscopy without biopsy	Electrophysiology ablation	Spinal or epidural surgery Neuraxial anesthesia
Cutaneous biopsies	Angiography	Abdominal surgery
Pacemaker and cardiac defibrillator insertion	Minor orthopedic surgery	Major orthopedic surgery

cedure. Observational studies have suggested that brief interruption of warfarin therapy for a procedure is associated with a very low rate of postoperative thromboembolism [6, 7]. These findings appear to be validated with the publication of the BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) prospective trial which found the rates of arterial thromboembolism were noninferior in patients with atrial fibrillation who did not receive anticoagulation bridging for elective procedures. In fact, patients who did not undergo bridging had an incidence of major bleeding that was significantly less than the bridging group [3]. Importantly, the study did not include many patients with high $CHADS_2$ scores (>4) and left the use of antiplatelet medications to the discretion of the physician. $CHADS_2$ scores provide an estimated stroke risk in patients with atrial fibrillation only and are not otherwise applicable to patients with venous thromboembolic events. However, it is important to note that patients at highest risk for thrombotic events (Table 30.2) such as recent (within 3 months) venous thromboembolism (VTE), mechanical prosthetic heart valves, and recent stroke (within 3 months) will usually require bridging anticoagulation. Additionally, the BRIDGE study did not include high bleeding risk procedures such as cardiac surgeries and neurosurgical procedures (Table 30.4).

Generally, patients with a >10% annualized risk of thromboembolism are classified as high risk for a thromboembolic event. Patients on anticoagulation for VTE indications carry an estimated risk of recurrence of 40% after discontinuation in the first month and a risk of 15% in the first year after 3 months of anticoagulation [8]. For patients with arterial indications for anticoagulation, the $CHADS_2$ score (Table 30.2) is a validated clinical prediction score to estimate stroke risk in patients with non-valvular atrial fibrillation [9]. Additionally, data suggests that the $CHADS_2$ score may predict postsurgical stroke risk [10, 11]. In addition to patient-specific risk factors for thromboembolism, the type of surgery a patient undergoes is considered in assessing the risk of thromboembolism. For instance, neurologic and vascular surgeries are associated with a greater risk of stroke in patients with atrial fibrillation than other types of surgeries [12].

Individual bleeding risk evaluations are similarly needed in patients undergoing surgery on chronic anticoagulation. Risk prediction tools are used to estimate bleeding risk and are most helpful in identifying patients at lower risk for thromboembolism, where the net benefits of anticoagulation are smaller and the risk of bleeding may be more influential in clinical decision-making. Importantly, most risk assessment schemes were developed from cohorts of patient's newly prescribed anticoagulants or were already on chronic anticoagulation reflecting a population of patients already deemed suitable for systemic anticoagulation. Therefore, patients with very high bleeding risks are not well represented [13]. Patient-specific variables that are associated with an increased risk for bleeding include a history of bleeding, mechanical heart valve in the mitral position, the presence of an active malignancy, and thrombocytopenia. These four parameters are referred to as the "BleedMAP" and were shown to correlate with an increased risk for periprocedural bleeding [14]. In addition to the individual's characteristics,

the type of surgery and the location of the organ are important determinants for risk of bleeding, with more vascular organs (e.g., liver, kidney, spleen) associated with higher risks of bleeding. Assessing the relative bleeding risk between surgical procedures has been difficult to determine [8].

The patients' estimated thromboembolic risk is what determines an aggressive periprocedural antithrombotic strategy (such as bridging anticoagulation) versus a more conservative one (Table 30.2). Procedural bleeding risk determines how that strategy is utilized in the postoperative period. The clinical consequences of a thrombotic or bleeding event must be taken into consideration. For instance, mechanical heart valve thrombosis is fatal in 15% of patients, and embolic stroke results in death or major disability in 70% of patients. VTE has a case fatality rate of 5–9%, while major bleeding has a case fatality rate of 8–10%. The clinical consequences of an arterial thromboembolic event are more severe than major bleeding; therefore a strategy that incurs more major bleeds to prevent one stroke would, in theory, be more acceptable based on the trade-off between the consequences of a stroke as compared to a bleed [15–19].

The following sections describe management of various antithrombotic agents in the perioperative setting. Specifically, a discussion of the timing of anticoagulant discontinuation and the need for a bridging strategy is discussed for each category of antithrombotic agent.

Antiplatelet Drugs

Antiplatelet drugs include reversible and irreversible inhibitors of platelet function (Table 30.5). The thienopyridines, aspirin, dipyridamole, cilostazol, and nonsteroidal anti-inflammatory agents are irreversible inhibitors. Ticagrelor is a reversibly binding P2Y12 receptor antagonist that exhibits a rapid onset and offset of antiplatelet effect [20]. Vorapaxar is a novel protease-activated receptor-1 (PAR-1) antagonist that functions by inhibiting thrombin-associated platelet aggregation. Importantly, it is contraindicated in patients with a history of stroke, TIA, or intracranial hemorrhage. Cangrelor is an intravenous P2Y12 receptor antagonist that exhibits a rapid onset and offset of antiplatelet effect with a

Table 30.5 Antiplatelet drugs [7, 20–24, 64–67]

Name	Mechanism of action	Time to maximum level	Elimination half-life	Time to normalization of platelet function
Aspirin (non-enteric coated)	Irreversible inhibition of COX-1 and COX-2	30–40 min	15–30 min	Antiplatelet effect appears within 1 h and persists for at least 4 days after stopping therapy
Clopidogrel	Irreversible inhibition of P2Y12 ADP receptor	1 h for circulating drug; 3–7 days for maximal antiplatelet effect	8 h for circulating drug	More rapid inhibition of platelet function can be achieved with a loading dose; antiplatelet effect lasts up to 10 days
Ticlopidine	Irreversible inhibition of P2Y12 ADP receptor	1–3 h	24–36 h (after one dose)	Antiplatelet effects lasts for the life span of the platelet (5–7 days)
Prasugrel	Irreversible inhibition of P2Y12 ADP receptor	30 min	7 h	Antiplatelet effect lasts 5–7 days
Ticagrelor	Reversible inhibition of P2Y12 ADP receptor	1.5 h	7 h	Up to 5 days
Cangrelor	Reversible inhibition of P2Y12 ADP receptor	Seconds after IV administration	2–5 min	Normal platelet function returns by 60 min after infusion is stopped
Vorapaxar	PAR-1 antagonist	1–2 h	3–4 days	Due to very long half-life, effectively irreversible; displays significant inhibition of platelet aggregation that remains for up to 4 weeks after stopping
Dipyridamole	Inhibits adenosine deaminase and phosphodiesterase	2–2.5 h	10–12 h	3 days
Cilostazol	Inhibitor of phosphodiesterase III	3 h	11–13 h	3 days
Abciximab	Glycoprotein IIb/IIIa receptor blocker	<10 min	0.5 h	2 days
Eptifibatide	Glycoprotein IIb/IIIa receptor blocker	<5 min	2.5 h	0.4 days
Tirofiban	Glycoprotein IIb/IIIa receptor blocker	<10 min	2 h	4–8 h

COX cyclooxygenase, *PAR-1* protease-activated receptor-1

half-life of only minutes [21]. The intravenous glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide) will not be discussed in detail given the narrow clinical use of these medications and short plasma half-lives.

Antiplatelet medications are predominantly used for primary and secondary management of atherosclerotic thrombotic disease, specifically acute coronary syndromes, stroke, and peripheral arterial disease. Additionally, patients undergoing percutaneous coronary intervention or coronary surgery require antiplatelet therapy. Dual antiplatelet therapy (DAPT) with a thienopyridine and aspirin has been shown to markedly decrease the adverse events associated with coronary stents. Premature discontinuation of antiplatelet therapy is associated with an increased incidence of stent thrombosis, myocardial infarction, and death. This led the American Heart Association and the American College of Cardiology to issue an advisory in 2007 recommending adherence to 12 months of dual antiplatelet therapy after placement of drug-eluting stents. However, with advances in drug-eluting coronary stent technology, several more recent trials have tested the concept of shorter-course DAPT lasting 3–6 months. Lower rates of bleeding complications were universally observed with a modest increase in ischemic events, especially in patients who presented with an acute coronary event. Therefore, based on currently available data and guidelines, it is reasonable to defer elective surgery for at least 3–6 months after a drug-eluting stent in patients with stable coronary artery disease and longer in those with percutaneous coronary intervention (PCI) after an acute coronary event [5, 22, 23].

Most antiplatelet medications have short half-lives; however the most frequently used agents (aspirin, clopidogrel) irreversibly inhibit platelet function (Table 30.5). This necessitates withholding their administration for 7–10 days prior to an invasive procedure or surgery. No randomized trials have determined whether a shorter interval would be just as safe. For low bleeding risk procedures, antiplatelet therapies do not need to be held, similar to recommendations for anticoagulants [12]. Procedures associated with higher risk of bleeding need to account for an individual patient's cardiovascular event risk. For low cardiovascular risk patients, stopping antiplatelet therapy before a procedure is reasonable, while for high cardiovascular risk patients, consideration should be given to either continuing aspirin or delaying the procedure until the patient is at lower risk [12]. For patients undergoing coronary artery bypass grafting (CABG), continuing aspirin would be appropriate, although guidelines from the American College of Chest Physicians suggest that thienopyridine therapy should be held before CABG [12].

Perioperative bridging strategies for antiplatelet agents have been developed similar to perioperative management strategies with warfarin for patients at high risk for thromboembolism. The short-acting intravenous glycoprotein IIb/IIIa receptor inhibitors (GPI) eptifibatide and tirofiban have been used in small case series as "bridging" antiplatelet therapy in patients requiring temporary withdrawal of clopidogrel, given its longer onset and offset of action (Table 30.5). Cangrelor, a nonthienopyridine adenosine triphosphate analogue, was investigated as a bridging agent in a prospective trial involving patients receiving a thienopyridine who underwent CABG [24]. No increase in major bleeding before surgery or an increase in CABG-related bleeding was observed despite a greater rate of platelet inhibition in the cangrelor group. However, a recent weighted meta-analysis showed that preoperative bridging therapy with GPI did not eliminate the risk of postoperative stent thrombosis in patients with drug-eluting stents [25]. An alternative strategy for temporary reversal of antiplatelet effect for patients on dual antiplatelet therapy is to use specifically timed platelet transfusions based on the half-life of aspirin and clopidogrel [26]. However, the use of platelet transfusion in reversing newer antiplatelet agents such as ticagrelor has recently been called into question [27]. Clinical trials are needed to ascertain the efficacy of this strategy as the current literature shows insufficient evidence to make concrete clinical practice decisions.

Vitamin K Antagonists and Bridging Anticoagulation

Deciding if warfarin interruption is needed is based on the bleeding risk of the surgery/procedure. Most major procedures require warfarin interruption, but some such as dental, cataract surgery, and minor skin procedures do not need interruption of warfarin (Table 30.4). Once a decision of interruption of warfarin has been made, a careful decision regarding the use of bridging therapy should be decided. As detailed earlier in this chapter, bridging anticoagulation carries substantial risk of major and minor bleeding, and for low thrombotic risk and some intermediate thrombotic risk indications, the use of bridging anticoagulation carries little additional antithrombotic benefit [3, 4].

The approach to perioperative warfarin cessation and bridging anticoagulation is detailed in Table 30.3. The protocol is as follows. Stop warfarin 5 days before a high bleeding risk procedure, and when the INR falls below the therapeutic range, begin LMWH at a therapeutic dose. The final dose should be administered 24 h before the procedure. Check the INR on the morning of the procedure. Restart warfarin therapy immediately after the procedure if hemostasis is secured. For high bleeding risk procedures, reinstitute treatment with subcutaneous LMWH or intravenous UFH at a therapeutic dose (without bolus) 48 h after the procedure if no bleeding has occurred, with the exception that for patients undergoing endoscopic sphincterotomy, heparin therapy should be initi-

ated after 72 h [28]. Discontinue heparin therapy when the INR is in the therapeutic range.

In high thrombotic risk patients who require bridging therapy with renal impairment (creatinine clearance of less than 30 mL/min), the use of UFH is preferred. Therapeutic dose or high-dose UFH is commonly used, with monitoring of the activated partial thromboplastin time (aPTT) or anti-factor Xa levels. For low-risk patients, such as those with an episode of VTE more than 3 months before the planned procedure, prophylactic low-dose heparin can be used for bridging. In moderate-risk patients, the decision to use bridging therapy and the degree of intensity of bridging therapy should be individualized [12, 29].

Some special considerations should be taken for certain minor and diagnostic procedures. In patients having one to two dental extractions or endodontic procedures, warfarin can usually be safely continued. Antifibrinolytics such as tranexamic acid mouthwash can be taken prior to the procedure to reduce the incidence of gingival bleeding. Alternatively, warfarin can be held for 2 days prior to the procedure. Warfarin interruption is usually needed for endoscopy as there is a potential for biopsy or polyp removal. Caution is required after removal of large (>1 cm) polyps since bleeding can occur 2–7 days after polypectomy due to dislodgement of eschar. Caution is also warranted with renal biopsy, liver biopsy, prostate biopsy, endoscopic sphincterotomy, and pacemaker placement given the higher bleeding risk association with these minor procedures [29].

Direct Oral Anticoagulants

The DOACs include direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, and betrixaban) and the direct thrombin inhibitor dabigatran (Table 30.6). The timing of discontinuation of these agents before high-risk procedures depends on the creatinine clearance and half-life of the particular agent (Fig. 30.1) with dabigatran being the most renally dependent and betrixaban being least renally dependent [12, 30]. It is important to caution that edoxaban should not be used in patients with a creatinine clearance greater than 95 mL/min due to the results of a subgroup analysis suggesting patients with normal renal function developed higher rates of stroke when treated with edoxaban versus warfarin [31].

Resumption of antithrombotic therapy after a procedure, as previously discussed, must take into account the risk of thrombosis and bleeding. For low bleeding risk procedures, DOACs can be safely held 24 h preoperatively and resumed 24 h postoperatively. Higher bleeding risk procedures may require 48–72 h. Importantly, an assessment of the stability of renal function is critical given its impact on drug clearance [12, 32]. Thus far, prospective studies involving the perioperative management of DOACs have been limited and involve DOACs such as dabigatran, rivaroxaban, and apixaban [33]. A large prospective study known as the PAUSE (Perioperative Anticoagulant Use for Surgery Evaluation) study is the first study to demonstrate the safety of a standardized perioperative management approach in patients with AF who are taking a DOAC [34].

Bridging therapies have a limited role with DOACs given their rapid onset and offset as compared to traditional VKAs. However, bridging anticoagulation is not completely obviated, specifically in postoperative patients who are unable to take oral medications. In addition, an extended period of bridging anticoagulation may be warranted in patients who have undergone major abdominal surgeries (i.e., gastric resection or postoperative ileus) in whom DOAC bioavailability may be affected over a prolonged period. Several randomized trials involving DOACs in atrial fibrillation did have a small subset of patients who received bridging therapy during periods of temporary interruption. No increase in the rate of bleeding was observed. Interestingly, in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, trial

Table 30.6 FDA-approved indications for DOACs [42, 51]

Condition	Dabigatran[a] (Pradaxa™)	Rivaroxaban[b] (Xarelto™)	Apixaban (Eliquis™)	Edoxaban[a] (Savaysa™)	Betrixaban (Bevyxxa™)
Stroke prevention in atrial fibrillation	☑	☑	☑	☑	–
Cardiovascular risk reduction in patients with chronic CAD or PAD	–	☑	–	–	–
VTE treatment	☑[a]	☑	☑	☑[a]	–
VTE prophylaxis in knee and hip arthroplasty	–	☑	☑	–	–
VTE prophylaxis in hospitalized acutely ill patients	–	☑	–	–	☑

FDA Food and Drug Administration, as of October 2019, *VTE* venous thromboembolism, *CAD* coronary artery disease, *PAD* peripheral artery disease

[a]Edoxaban and dabigatran are approved for the acute treatment of VTE only after an initial 5-day course of treatment with a parenteral anticoagulant

[b]Rivaroxaban has an expanded FDA indication for the prevention of major cardiovascular events in patients with stable coronary artery disease and peripheral artery disease and acutely ill hospitalized patients, but expert opinion varies due to excess risk of major bleeding

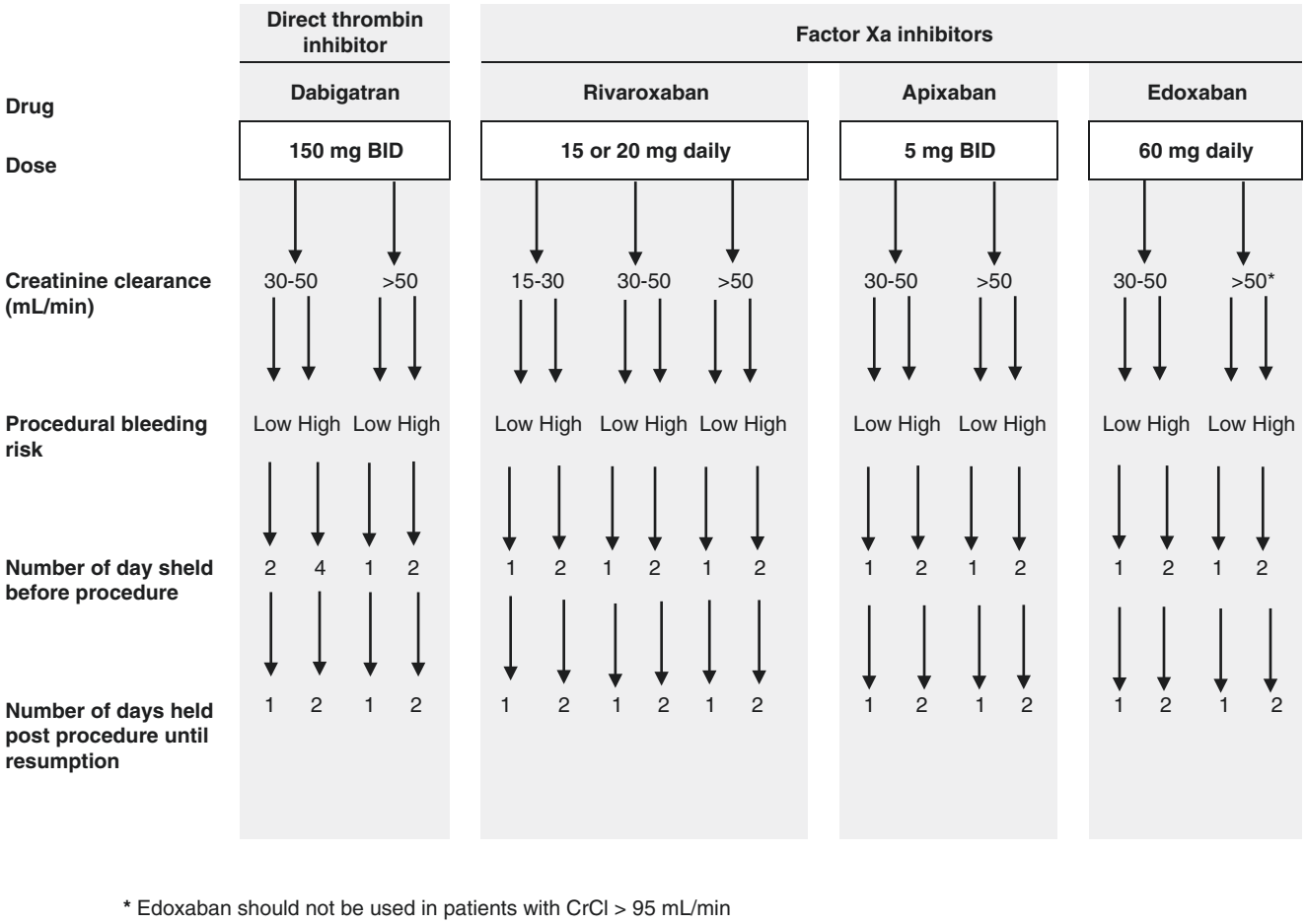

Fig. 30.1 Perioperative interruption and resumption of DOACs. (Adapted from the PAUSE study [12, 30, 34, 68])

patients who were continued on apixaban for procedures did not have an increase in bleeding compared to those in which the drug was held. Although the BRIDGE trial examined bridging therapy in patients taking VKAs, its conclusions regarding the safety of interruption of oral anticoagulation in patients with atrial fibrillation undergoing procedures without bridging therapy are likely applicable to the DOACs as well [3, 33].

Parenteral Anticoagulants: Heparin, Heparin Derivatives, and Direct Thrombin Inhibitors

Intravenous UFH has a half-life of 60–90 min (Table 30.1), with its anticoagulant effects dissipating 3–4 h after discontinuation. For high bleeding risk procedures, heparin infusions are held approximately 4–6 h prior to the procedure. Low-molecular-weight heparin (e.g., enoxaparin, dalteparin, tinzaparin) is administered subcutaneously for bridging and for the treatment of VTE. The half-life of these agents is approximately 4 h (Table 30.1), and the last dose should be given 24 h before the anticipated procedure [3]. Fondaparinux is subcutaneously administered with a half-life of 17 h. It has been shown to be associated with acceptable rates of bleeding when discontinued more than 36 h before CABG [35].

Parenteral direct thrombin inhibitors include bivalirudin, argatroban, lepirudin, and desirudin. Lepirudin is no longer manufactured. Bivalirudin is used primarily during acute coronary interventions and in heparin-induced thrombocytopenia and has a half-life measured in minutes and should be discontinued 90 min before high bleeding risk procedures. It can be safely used in patients with renal failure or combined renal and hepatic failure. Argatroban is used for the treatment of HEPARIN-induced thrombocytopenia and should be avoided in patients with hepatic dysfunction. Infusions of argatroban should be held 4 h prior to a procedure. Desirudin is used postoperatively for prophylaxis against deep vein thrombosis in patients undergoing hip replacement. It has a half-life of 2 h and should be discontinued 10 h before high-risk procedures [7].

Pharmacological Reversal of Antithrombotic Therapy: Emergency Procedures and the Bleeding Patient

Major bleeding events can occur in patients taking anticoagulants and originate from anatomical sites leading to rapid blood loss. The location and size of the lesion along with the coexisting conditions may have a greater effect on hemostasis (and prognosis) than the ability to rapidly neutralize an anticoagulant. Additionally, the previously discussed direct anticoagulants are associated with less severe bleeding episodes than warfarin [6]. Nonetheless, numerous agents are available and are in development to aid in the rapid reversal of anticoagulants in the setting of life-threatening bleeding and emergent surgery (Table 30.7 and Fig. 30.2). Despite the ability to neutralize anticoagulants, factor concentrates and plasma will have a vital role in achieving hemostasis given the complexity of the underlying hemostatic defects.

Table 30.7 Interventions for bleeding cessation [52–57]

Agent	Dose	Comments
Blood product derivatives		
Platelets	1 apheresis unit 5–8 whole blood-derived units	Used in patients receiving antiplatelet therapy Raise platelet count by 30×10^9/L
Fresh frozen plasma (FFP)	10–15 mL/kg IV	Cannot fully correct all coagulation factors, especially factor IX Short half-life with repeat dosing needed in 4–6 h Large volume
Prothrombin complex concentrates	25–50 units/kg IV	Rapid, complete INR correction in warfarin-treated patients Requires coadministration with vitamin K to sustain warfarin reversal Risk of thrombosis 1.4% Short half-life Consider concurrent FFP or rVIIa if three-factor PCC used; four-factor PCC is preferred Most PCC preparations contain heparin and are contraindicated in heparin-induced thrombocytopenia
Activated prothrombin complex concentrates	25–100 units/kg IV	Use may be associated with a higher risk of thrombosis compared to nonactivated PCCs especially with higher doses Monitor closely for arterial and venous thrombosis
Reversal agents		
Vitamin K	1–10 mg IV/PO	Takes 6 h (IV) to 24 h (PO) to reverse warfarin Subcutaneous administration not recommended
Protamine sulfate	12.5–50 mg IV	Full reversal of unfractionated heparin 60–80% reversal of LMWH No reversal of fondaparinux
Idarucizumab	5 g IV	Full reversal of dabigatran Administered as two separate 2.5 g doses no more than 15 min apart If coagulation parameters re-elevate (aPTT), may consider additional 5 g dose
Andexanet alfa	Dose depends on the dose and timing of the last dose of the factor Xa inhibitor *Low dose*: 400 mg intravenous bolus at 30 mg/min, followed by infusion of 480 mg at 4 mg/min for up to 2 h *High dose:* 800 mg intravenous bolus at 30 mg/min, followed by infusion of 960 mg at 8 mg/min for up to 2 h	FDA approved for the reversal of rivaroxaban and apixaban Reversal effects on indirect and direct Xa inhibitors Cost prohibitive with limitations in availability
Hemostatic agents		
Aminocaproic acid	4–5 g IV/PO over 1 h and then 1 g/h × 8 h (max dose 30 g/24 h)	May increase risk of thrombosis May accumulate in patients with renal impairment Caution use in hematuria
Tranexamic acid	1300 mg PO q8 h	Labeled indication for menorrhagia
Desmopressin (DDVAP)	0.3 μg/kg IV	Tachyphylaxis develops after the second dose Rare thrombotic events
Recombinant factor VIIa (rFVIIa)	15–90 μg/kg	Rapid infusion of small volume Rapid correction of INR but may not restore hemostasis Risk of thrombosis 5–10% Short half-life, may need repeat dose after 2 h

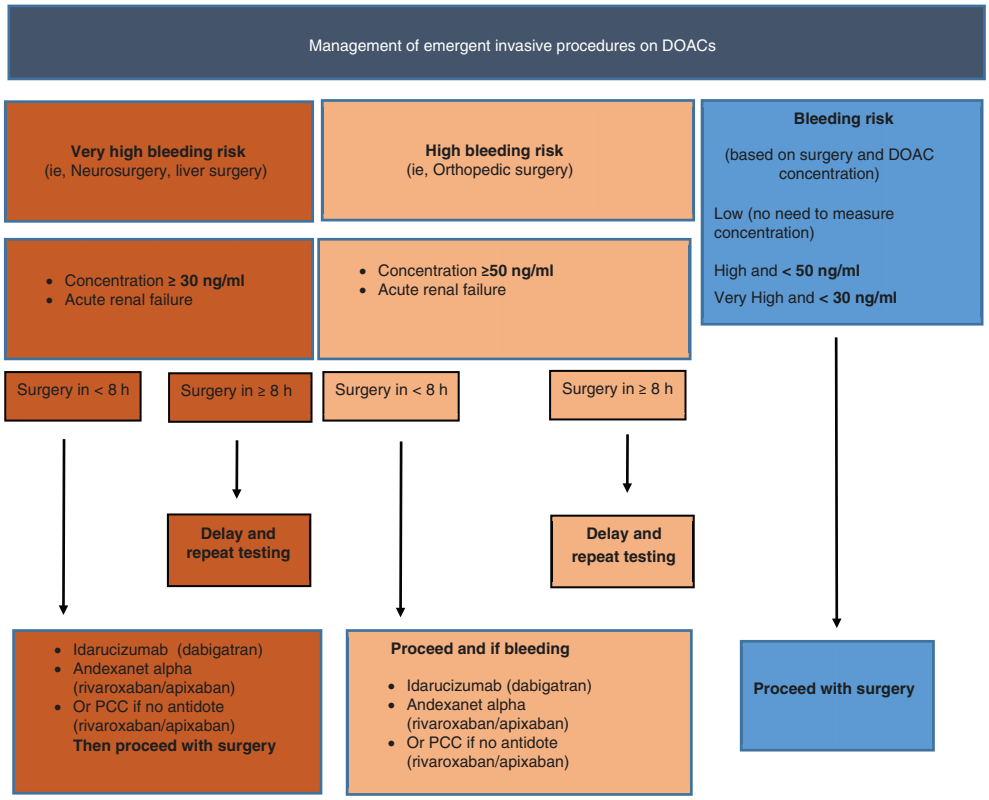

Fig. 30.2 Management of emergency surgery on DOACs [52–54]

Antiplatelet Drugs

Aspirin, nonsteroidal anti-inflammatory drugs, dipyridamole, ADP receptor (P2Y12) inhibitors, and PAR-1 antagonists (Table 30.5) are used to prevent thrombosis by interfering with normal platelet function. The antiplatelet effects of these agents are weakest with aspirin and more potent with the P2Y12 inhibitors and PAR-1 antagonists.

In patients with mild bleeding, discontinuation of the antiplatelet agent is the typical approach. Limited data are available for the management of patients with severe bleeding, but platelet transfusion is a common strategy [36]. The role of platelet transfusion is even less clearly defined in patients requiring emergent surgery. Some clinicians give prophylactic platelet transfusions to patients taking antiplatelet drugs who require major surgery, while other clinicians use platelet transfusion only to treat excessive surgical bleeding [37]. Previously published studies suggest there is often no benefit to administering platelet transfusions, and there may be transfusion-related harms. A more recent systematic review and meta-analysis demonstrates uncertainty regarding the effect of platelet transfusion for reversal of pre-injury antiplatelet agents after traumatic brain injury [38].

The use of desmopressin (DDVAP) in patients with normal renal function who have active bleeding on antiplatelet agents has limited data. However, randomized data is available in the setting of patients requiring urgent cardiovascular surgery [39, 40]. Nonetheless, these cases can be complex, and an individualized approach based on the complete clinical picture is required.

Certain antiplatelet agents, specifically P2Y12 receptor antagonists like ticagrelor, cannot be reversed with platelet transfusion as the free drug binds to fresh platelets. Newer agents in development may offer targeted reversal of the antiplatelet effects of ticagrelor, but none are yet approved [41].

Heparin and Derivatives

Protamine sulfate, a protein derived from fish, can fully neutralize heparin effect. Because of the relatively short half-life of intravenously administered heparin (Table 30.1), the dose of protamine sulfate is calculated by estimating the amount of heparin remaining in the plasma at the time that reversal is required. If this information is not immediately available, administration of a single dose of 25–50 mg can be given and the aPTT rechecked. Importantly, if heparin has been given by subcutaneous injection, repeated small doses of protamine may be required because of prolonged heparin absorption from the various subcutaneous sites. Additionally, given protamine's derivation from fish, it carries a small risk of anaphylaxis.

No drug currently available is completely effective in reversing enoxaparin or other LMWHs. Protamine sulfate can only partially reverse 60–75% of enoxaparin, and it has no effect on fondaparinux [42]. However, andexanet alfa and aripazine (PER-977, ciraparantag), the latter of which is still under study, may have a future role in the reversal of heparin derivatives [43].

Vitamin K Antagonist Therapy

For patients with serious bleeding or those who require emergent surgery, the combination of intravenous vitamin K and four-factor prothrombin complex concentrate (PCC) should be administered for warfarin reversal [44, 45]. PCC is lyophilized and therefore preferred over fresh frozen plasma (FFP). This allows PCC to be reconstituted, as opposed to thawing, providing a significant advantage in time to administration. In terms of clotting factor concentration, 2000 mL of FFP is comparable to a dose of PCC. In patients where volume may be a confounding problem, PCC's smaller volume provides an additional advantage. It should be noted that PCC products typically contain heparin and therefore should not be used in patients with a history of heparin-induced thrombocytopenia.

Direct Oral Anticoagulants: Dabigatran and Direct Xa Inhibitors

Given the short half-lives of DOACs, the anticoagulant effect of these medications can dissipate in a matter of hours. However, any underlying renal dysfunction can prolong the anticoagulant effect depending on the DOAC used and the degree of renal impairment (Table 30.1). Additionally, severe hepatic impairment could result in bioaccumulation of most of these agents except dabigatran.

Although routine testing of coagulation parameters is not necessary and unreliable in patients taking DOACs, coagulation studies could aid in determining the presence of residual anticoagulant effect. A normal thrombin time virtually eliminates the possibility of residual dabigatran in a patient. For the direct factor Xa inhibitors, the absence of anti-factor Xa activity indicates that no clinically relevant anti-factor Xa drug effect is present. Increased anti-factor Xa activity may reflect the presence of continued anti-factor Xa anticoagulant effect; however, unless the assay used has been calibrated for the specific anticoagulant, the amount of anticoagulant effect present cannot be reliably determined. Therefore, it is important to consult with laboratory personnel regarding how the assay behaves in the presence of each of the different factor Xa inhibitors.

The bleeding profile of DOACs, as compared with VKAs, demonstrates lower rates of intracranial and fatal hemorrhage [46]. However, more recent observational data indicate higher levels of gastrointestinal- and menstrual-associated bleeding. There are currently two FDA-approved reversal agents for DOACs: (1) idarucizumab for the direct thrombin inhibitor dabigatran and (2) andexanet alfa for the direct factor Xa inhibitors, apixaban and rivaroxaban [47, 48].

Idarucizumab is a humanized, monoclonal, antibody fragment that reverses the direct thrombin inhibitor dabigatran with demonstrated efficacy. In the RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study, interim analysis of the first 90 patients (51 with bleeding, 39 requiring a procedure) showed normalization of coagulation tests within minutes of infusion. Among patients requiring an emergent procedure, 92% were judged to have normal surgical hemostasis. Clinical outcomes, including cessation of bleeding, were more difficult to assess in the group with serious hemorrhage. Idarucizumab was well tolerated with only one patient experiencing a thrombotic event within 72 h of administration [47, 49]. Later a full cohort analysis of 503 patients showed similar results with rates of thrombosis approaching 7%. Criticism of the trial centers around the lack of a control arm in the study.

Andexanet alfa is a modified recombinant factor Xa decoy molecule that reverses direct oral anticoagulants and parenteral indirect factor Xa inhibitors like enoxaparin and fondaparinux (Table 30.8). At the time of publication, it is approved only for the reversal of rivaroxaban and apixaban. In a single-group trial, 352 patients with acute major bleeding while taking a factor Xa inhibitor were treated with andexanet. Andexanet alfa markedly reduced anti-factor Xa activity, and 82% of the patients had excellent or good hemostatic efficacy at 12 h [48, 50].

Prothrombin complex concentrate (PCC) has also demonstrated hemostatic efficacy in patients with bleeding associated with VKAs and DOACs, although the latter is based on

Table 30.8 Doses of andexanet alfa according to different factor Xa inhibitors in ANNEXA-4 trial [48]

Drug	Bolus IV	2-h infusion
Apixaban	400 mg	480 mg
Rivaroxaban, last administration >7 h before	400 mg	480 mg
Rivaroxaban, last administration <7 h before	800 mg	960 mg
Edoxaban[a]	800 mg	960 mg
Betrixaban[a]	NA	NA
Enoxaparin[a]	800 mg	960 mg
Fondaparinux[a]	NA	NA

[a]Andexanet alfa is currently only FDA approved for the reversal of direct Xa inhibitors apixaban and rivaroxaban but has neutralizing activity against indirect Xa inhibitors fondaparinux and enoxaparin and other direct Xa inhibitors

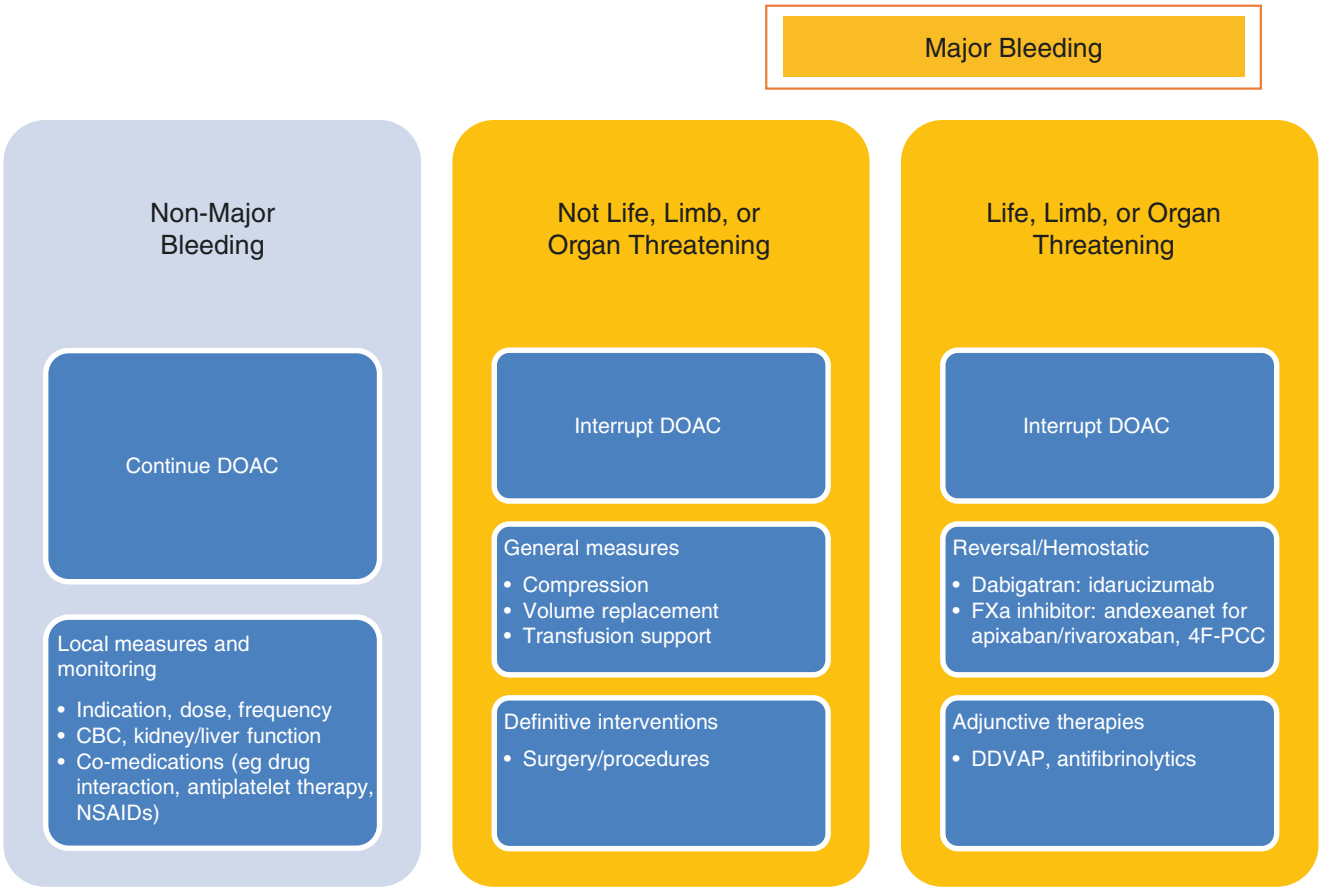

Fig. 30.3 Management of DOAC-associated bleeding [69]

healthy subjects and retrospective institutional studies. A small prospective trial demonstrated efficacy in patients who suffered a major bleed while on rivaroxaban or apixaban. The rate of major thromboembolic events was noted at 8%. While both PCC and andexanet alfa have demonstrated efficacy in bleeding associated with anti-Xa inhibitors, no head-to-head study between andexanet alfa and PCC has been undertaken. The cost discrepancy between these agents is also quite high with andexanet alfa costing nearly 10–20-fold higher than PCC at up to $55,000 per dose. This has called into question the optimal utilization of this reversal agent. Several authors and international hemostasis organizations have attempted to provide guidelines for the optimal use of these reversal agents in the setting of emergent scenarios including surgery (Fig. 30.2) and life-threatening bleeding (Fig. 30.3) [51–56].

Non-pharmacological strategies have become less relevant in the era of targeted reversal agents. Activated charcoal and hemodialysis have demonstrated some reversal effect in dabigatran-associated bleeding. Conversely, rivaroxaban and apixaban are too highly protein bound and therefore not readily dialyzable. With the advent of targeted reversal agents and antidotes, hemodialysis or activated charcoal have a limited role but offer a reversal strategy in resource-limited facilities which encounter a bleeding patient on dabigatran [57].

Future Directions

The reversal agent aripazine (PER-977, ciraparantag) is in an earlier stage of development. It is a small, synthetic molecule with potentially universal anticoagulant reversal activity. There is data demonstrating the efficacy of this compound with normalization of laboratory parameters in healthy edoxaban-treated volunteers within minutes of administration [58].

Other novel reversal agents have also being evaluated in vitro and in animal studies including monoclonal antibodies in development for the reversal of antiplatelet agents [41, 59, 60]. It is clear additional research is needed to assess long-term safety and efficacy of these agents with specific attention paid to the risk of rebound thrombosis after efficacy of the drug wanes and any possible procoagulant effects of the reversal agents. Ultimately, clear guidance will need to be developed to determine their impact on clinical practice and incorporation with other hemostatic agents.

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Thrombolytic Therapy: tPA-Induced Bleeding

31

Jennifer Erklauer

Tissue plasminogen activator (tPA) is one of the most influential advancements in the treatment of acute arterial ischemic stroke, myocardial infarction, and pulmonary embolism in the past century. It is frequently known as a miracle "clot buster" medication that has revolutionized management and improved outcomes in patients with these conditions. The FDA first approved tPA in 1984 for the use in acute myocardial infarction [1]. Following publication of the landmark study by the National Institute for Neurological Diseases (NINDS) in 1996, tPA was approved in acute ischemic stroke after investigators showed a clear improvement in clinical outcome if tPA was received within 3 hours of stroke symptom onset [2]. tPA now holds FDA approval for acute arterial stroke, ST elevation myocardial infarction (MI), and massive pulmonary embolism. Additionally, it is frequently used off-label for acute ischemic stroke within 3–4 and a half hours [3], sub-massive pulmonary embolism [4], acute peripheral arterial occlusion [5], frostbite [6], and para-pneumonic effusions [7]. With expanding clinical use, complications may become more prominent. Prompt recognition and treatment of bleeding complications after receiving tPA is essential and can be lifesaving.

tPA is a serine protease found naturally in the endothelial lining of the blood vessels. Its main role is to cleave plasminogen to plasmin acting to disrupt fibrin cross-linking leading to clot breakdown into fibrin degradation products [8]. This process serves to help regulate the coagulation system in the body minimizing inappropriate clot formation. tPA may also play a role in lowering systemic levels of fibrinogen [9]. More recently, tPA has been identified as a signaling molecule in the brain, assisting in regulation of brain development via extracellular matrix remodeling [10]. It may also play a role in neurometabolic coupling [11] and vascular permeability with suggestion that its effect may be mediated via regulation of the blood-brain barrier [12]. After injury to the brain such as ischemia, tPA is thought to potentially upregulate excitotoxic signaling in the brain which may increase neurotoxic injury [10]. tPA has great potential to improve outcome in high-risk clot formation, but balancing its protective and toxic effects, particularly in the brain, is of the utmost importance. Recombinant tPA used in clinical practice is derived using recombinant DNA technique obtaining native tPA found in human cell lines [1].

Acute Ischemic Stroke

Bleeding complications occur with all indications for recombinant tPA. In general, the most dreaded complication is intracranial bleeding. Acute arterial ischemic stroke carries the highest risk of this most concerning complication because the brain is already undergoing ischemic injury from stroke resulting in neuronal cell death prior to tPA administration. This process triggers an inflammatory reaction, worsening acute brain injury and contributing to breakdown of the blood-brain barrier by which bleeding into the brain occurs. Additionally, the brain loses the ability to autoregulate blood flow, and coupled with a sympathetic hypertensive response, this exposes the brain to a higher risk of bleeding [10]. Recently, matrix metalloproteinases (MMPs) have been identified as contributors to the neurotoxicity that occurs after stroke, ultimately affecting blood-brain barrier integrity and neuronal injury. One study showed that baseline levels of MMP-9 in acute stroke prior to treatment with tPA were predictive of risk of intracranial hemorrhage following tPA administration [13]. tPA itself may play a role in worsening or triggering some of these processes via its proteolytic properties affecting the neurovascular matrix [14].

The goal of recombinant tPA is to re-perfuse the brain and restore adequate oxygen delivery. Restoration of blood flow to the brain is necessary to save the penumbra; however, reperfusion itself after a period of ischemia can increase the risk of

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hemorrhagic transformation, particularly if there has been loss of cerebral autoregulation. The more quickly blood flow is restored to the injured tissue, the less the chance for hemorrhagic transformation after tPA [8]. The original NINDS trial in 1996 evaluating the role of tPA in ischemic stroke showed that risk of symptomatic intracerebral hemorrhage (ICH) within 36 h of administration of tPA was 6.4% [2]. Other serious systemic bleeding complications occurred in 1.6% of patients who received tPA compared with 0% in the placebo groups. Symptomatic ICH was therefore the most common serious bleeding complication of tPA and resulted in fatality in 45% of patients who experienced this complication [2]. tPA is often administered up to 4 and a half hours after the ECASS III trial in 2008 showed that more patients had improved outcomes at 90 days compared to those treated with placebo in this time window. Risk of ICH increased to 7.9% [3].

ST Elevation Myocardial Infarction (MI)

Recombinant tPA is frequently used in the treatment of ST elevation MI within 12 h of symptom onset when percutaneous coronary intervention cannot be performed within 120 min of arrival to the hospital [15]. Bleeding complications after the use of tPA for ST elevation MI were evaluated in the GUSTO trial. Here, patients with ST elevation MI were given one of four different treatment regimens: streptokinase with SQ or with intravenous (IV) heparin, tPA with IV heparin, or tPA and streptokinase combined together. Out of the four different treatment groups, the overall risk of moderate to severe bleeding was lowest in the tPA group plus IV heparin. The rate of ICH was 0.6%. Intracerebral hemorrhages that occurred were most commonly large, solitary, lobar hemorrhages with some degree of mass effect; however, hemorrhages of all varieties, locations, and sizes were seen [16].

Massive Pulmonary Embolism

Use of tPA is FDA-approved for massive pulmonary embolism. According to the American Heart Association (AHA), this includes patients with evidence of shock, respiratory distress, or moderate to severe right ventricular strain [4]. Interestingly in the studies examining the use of thrombolysis in massive pulmonary embolism, 0.4% of patients in both the tPA-treated group and placebo group experienced intracerebral hemorrhage [4].

Overall, the use of recombinant tPA is associated with bleeding complications. Significant bleeding tends to happen at a fairly low rate overall; however, it can have serious complications necessitating prompt recognition and urgent intervention. Serious systemic bleeding will be managed in general with immediate cessation of the tPA infusion and emergent correction of the coagulopathy. In life-threatening hemorrhage resulting in intravascular volume loss and hemodynamic instability such as severe bleeding in the gastrointestinal tract, management will include treatment of hypovolemic shock with massive transfusion protocol, volume replacement, and vasoactive medications. Other serious hemorrhages such as bleeding into the pericardial space will necessitate intervention including pericardial drainage to relieve tamponade physiology. Arguably, the most concerning location of hemorrhage with high morbidity and mortality is intracerebral hemorrhage. Due to severity of this complication, further discussion will focus on the management of intracerebral hemorrhage from which the same principles can be applied to other locations of serious bleeding complications.

Management of Intracerebral Hemorrhage Associated with tPA

Prevention of intracerebral hemorrhage after tPA is extremely important as mortality from symptomatic ICH after tPA has been reported at 45% [3]. Determining patient risk for intracerebral hemorrhage after IV tPA has become an area of much interest. Various prediction scores have been developed to determine risk; however, the best way to use these scores is unclear as the patients at highest risk for intracerebral hemorrhage are also most likely to have a poor prognosis without the use of IV tPA [17]. A recent systematic review and meta-analysis by Cheng et al. considered dose adjustments for IV tPA to minimize the risk of bleeding. They found that low-dose tPA (0.6 mg/kg) reduced the risk of symptomatic intracerebral hemorrhage compared to treatment with standard-dose tPA (0.9 mg/kg) while still showing benefit in mortality and improved functional neurologic outcome in survivors [18]. Dose adjustments are not currently recommended, but this may be a potential target for preventing hemorrhage in high-risk patients in the future. In 2010, there was a national initiative to decrease door to needle time for tPA administration in acute stroke. With this initiative, there was an improvement in the number of patients treated in less than 60 min from arrival to the hospital, and this translated to a statistically significant decrease in the number of intracerebral hemorrhages seen within 36 h of receiving tPA [19]. Risk evaluation, close adherence to current guidelines for administration of tPA, and delivery of treatment as soon as possible may help prevent this life-threatening complication.

Initial Management and Supportive Care

Guidelines for the management of hemorrhagic transformation after IV tPA have been developed by the American Heart Association/American Stroke Association (AHA/ASA) and

should be applied to this unique situation [17]. Goals of treatment should include minimizing risk of hematoma expansion, monitoring for and treating increased intracranial pressure or signs of herniation, and decreasing risk for secondary brain injury [17]. Ideally, all patients receiving tPA should be admitted to a neurosciences intensive care unit or acute stroke unit for close neurologic and hemodynamic monitoring [17, 20]. This has been associated with improved clinical outcomes [21–22]. If during the administration of IV tPA there is an acute neurologic change, hemorrhage should be suspected, and the infusion should be stopped immediately. The patient should be assessed emergently and stabilized if necessary. Neurologic exam including level of consciousness, cranial nerves, and brainstem function should be performed swiftly. Therapy for increased intracranial pressure should be instituted if indicated based on clinical exam. STAT non-contrast head CT should be obtained to evaluate and confirm hemorrhage.

There are limited data to support best practice for tPA-related intracranial hemorrhage. However, having a treatment protocol in place and readily available is important for rapid evaluation and treatment of this potentially lethal complication. Once hemorrhage is confirmed, neurosurgery should be consulted. Initial screening blood tests should be drawn including prothrombin time, activated partial thromboplastin time, fibrinogen levels, complete blood count, PFA-100™, and ABO/Rh typing and red cell antibody screening test. Normal blood glucose and normal body temperature should be maintained. Clinical seizures should be treated with antiepileptic medication. If the patient has depressed mental status, continuous EEG should be performed to assess for subclinical seizures, and electrographic seizures should be treated. Prophylactic treatment of seizures has been associated with higher rates of death and disability in the past and is typically not recommended [23]. All patients should be monitored closely for any signs of increased intracranial pressure. If present, increased intracranial pressure monitor, external ventricular device, and maintenance of adequate cerebral perfusion pressure should be considered [20].

Blood pressure control after thrombolysis-induced ICH has been a topic of debate. During tPA infusion, guidelines recommend maintaining blood pressure <180/105 mmHg in an attempt to minimize risk of hemorrhagic conversion. If bleeding occurs, AHA/ASA guidelines for spontaneous ICH from 2015 propose that it is safe to lower systolic blood pressure <140 mmHg suggesting it may improve functional outcome and reduce chances of hemorrhage expansion [20]. Newer studies showed that while it is safe, lowering the systolic blood pressure <140 mmHg in ICH did not improve outcome compared with systolic blood pressure of <180 mmHg [24]. In spontaneous ICH, the ischemic penumbra is limited in size, and maintaining perfusion to it may not make a significant difference clinically [25]. However, in patients with ischemic stroke and hemorrhagic transformation, maintaining adequate cerebral perfusion pressure and adequate blood flow to the ischemic penumbra may be more important to prevent the tissue from progressing to irreversible ischemia. New AHA/ASA guidelines on the management of hemorrhage after thrombolysis suggest that maintaining cerebral perfusion pressure to the penumbra may be particularly important in patients with incomplete recanalization of the affected vessel in ischemic stroke and that those patients with full recanalization may benefit from more aggressive blood pressure control. Treatment should be individualized weighing the risks and benefits [17].

Management of Coagulopathy

Management of coagulopathy after thrombolysis is variable. Goldstein et al. reviewed practice at their institution finding great variation with 55% of patients receiving some type of pro-coagulant therapy. Therapies included fresh frozen plasma (35%), cryoprecipitate (25%), vitamin K (20%), platelets (15%), and ε-aminocaproic acid (5%) [26]. Alderazi et al. found that 42% of their patients with tPA-related ICH received clotting factors including fresh frozen plasma and cryoprecipitate. Mortality was high in both treated and placebo groups, and there was no statistically significant difference in outcome [27]. Due to sample size limitations in both studies, no one treatment was found to be associated with improved clinical outcome.

Management guidelines for the treatment of spontaneous and anticoagulation-related ICH have previously been used to establish protocols for bleeding after thrombolysis. However, the mechanism for hemorrhagic transformation after tPA is different, and these treatment options may not be optimal. tPA has multiple means of inducing coagulopathy. tPA converts plasminogen to its active form of plasmin that ultimately breaks up fibrin clot. tPA is known to decrease systemic levels of fibrinogen, likely minimizing new clot formation [9]. Lower fibrinogen levels have been associated with hemorrhagic transformation [28]. tPA may also affect platelet activation and function [29]. Therefore, treatment modalities that target these mechanisms of hemorrhagic transformation may be most beneficial in this setting.

The Neurocritical Care Society (NCS) and the Society of Critical Care Medicine (SCCM) previously developed an evidence-based guideline to aid in the management of ICH after tPA [30]. This was closely followed by the evidence-based statement by the AHA/ASA in 2017 [17]. Both guidelines recommend treating patients immediately with 10 units of cryoprecipitate [17, 30]. However, the quality of evidence supporting this recommendation was reported as low. Due to the association of low fibrinogen level and hemorrhagic

transformation, it is also recommended to recheck the fibrinogen level after the patient receives the reversal agent. Additional cryoprecipitate should be given if fibrinogen level remains <150 mg/dL [30].

Cryoprecipitate has several advantages over other means of correcting coagulopathy after tPA. Cryoprecipitate is made from donor plasma and is high in fibrinogen. Donor plasma is thawed, and the higher molecular weight proteins are precipitated out and collected to make cryoprecipitate. These proteins include factor VIII, von Willebrand factor, factor XIII, fibronectin, and fibrinogen [31]. The intrinsic pathway of the coagulation system is also activated by cryoprecipitate as it contains factor VIII [32]. Activation of the intrinsic pathway ultimately leads to the conversion of fibrinogen to fibrin leading to improved clot formation. Cryoprecipitate works quickly to correct coagulopathy and may provide advantage over other blood products in that a lower volume of fluid will be necessary to achieve this. FFP, from which cryoprecipitate is made, has been used itself to correct coagulopathy in this setting. FFP contains all of the components of donor plasma including factors from both the intrinsic and extrinsic pathways of the coagulation system [31]. A large volume of FFP is typically required to provide clinically significant improvement in coagulation parameters; thus it may take over 24 h to correct INR. The large volume of fluid may not be well-tolerated in all patients and can lead to increased blood pressure, cardiac dysfunction, pleural effusions, or pulmonary edema.

Tranexamic acid and ε-aminocaproic acid are important choices for targets in the management of tPA-induced bleeding as they directly act to prevent the conversion of plasminogen to plasmin. These agents are lysine analogues that appear to work by the very mechanism that tPA targets, yet very little research has been done examining their use in tPA-associated hemorrhage. There are two case reports of these agents being used. The first was in a patient who developed ICH after receiving tPA for what was thought to be an acute left mid-cerebral artery stroke. After tPA administration, it was noted that the suspected clot might have been a septic embolism. This patient refused blood products and was administered tranexamic acid for his ICH, after which his hematoma did not expand further. Ultimately, he did die from his stroke after redirection to comfort care by family [33]. The second case was reported in a patient who received aminocaproic acid in addition to FFP, cryoprecipitate, and platelets for his hemorrhage following tPA administration. Follow-up imaging to assess hemorrhage progression was not done [26]. A recent meta-analysis and systematic review was completed evaluating the use of tranexamic acid in cerebral hemorrhage showing a decrease in the rate of hematoma expansion and rebleeding. However, there was no difference in rate of mortality or poor neurologic outcome [34]. Although the mechanism of action of these agents remains promising, quality of evidence for the clinical use of these products remains very low. NCS/SCCM Guideline in 2016 stated that if cryoprecipitate is contraindicated or not available, tranexamic acid at a dose of 10–15 mg/kg IV over 20 min or ε-aminocaproic acid at a dose of 4–5 g IV can be considered [30]. The quality of evidence supporting this recommendation was reported as very low. The newer AHA/ASA guidelines suggest that these agents may be considered, especially in patients who do not wish to receive blood products [17].

There is limited data examining platelet function in the setting of tPA, but it is thought that a complex interaction exists between platelets, plasminogen, and tPA that is not completely understood [29]. There are studies that suggest both increase and decrease in platelet aggregation and functional activity via effect on the GPIIb/IIIa receptor and interaction with ADP, though exact mechanisms have not been elucidated [29]. Data in spontaneous ICH suggests that decreased platelet function may be associated with early hematoma expansion and worse functional clinical outcome at 3 months based on modified Rankin scores [35]. It is known that many patients receiving tPA are taking antiplatelet medication, resulting in known baseline platelet dysfunction. There is some evidence that receiving a platelet transfusion after antiplatelet-related intracerebral hemorrhage is associated with worse outcomes at 3 months after the stroke [36]. The NCS and the SCCM report it is unclear if platelet administration is beneficial in the management of ICH after tPA and no recommendation has been made at this time [30]. However, the AHA/ASA guideline suggests consideration for platelet transfusion if platelet level is <100,000/μL [17].

Recombinant activated factor VII (rFVIIa) was included as an option for treating acute ICH after tPA administration in the algorithm for emergency management of acute stroke previously developed by the Neurocritical Care Society [37]. However, it is no longer recommended in the newest guideline. rFVIIa binds to factor X on activated platelets initiating a cascade of events resulting in thrombin formation and clot formation at the site of bleeding [38]. Phase II trials in spontaneous ICH were initially promising; however, phase III trials found that although rFVIIa minimized hematoma expansion, there was no clear difference in clinical outcome between patients who received rFVIIa and those who did not. There were also higher numbers of arterial thrombotic events in the group treated with rFVIIa compared to placebo [39]. Subgroup analysis suggested an improved outcome with rFVIIa in patients less than 70 years of age, with ICH

volume less than 60 mL, IVH less than 5 mL, and time from onset of treatment less than 2.5 h [40]. Overall, due to high risk of serious thrombotic complications, rFVIIa is not currently recommended for bleeding after tPA [30].

Prothrombin complex concentrates (PCC) have been considered in the treatment of tPA-related ICH. PCC are either three or four factor combination hemostatic agents. In general, the three factor agents contain factors II, IX, and X along with proteins C and S, and the four factor agents also contain factor VII. These agents have recently been developed with the goal of quickly replacing all vitamin K-dependent coagulation factors. The use of PCC agents has been studied in patients on oral anticoagulants with one study showing that by 30 min, 93% of patients had reversal of their INR less than or equal to 1.3 [41]. The rapid correction of INR and the low volume of product required make this an attractive choice. However, PCC agents lack fibrinogen which is particularly important to replace in the setting of tPA. Side effects include thrombotic complications such as stroke, myocardial ischemia, pulmonary embolism, and DIC [42]. PCC agents have not been adequately studied and they remain controversial for this use. Consideration can be given for use in patients who have been on warfarin prior to receiving tPA [17].

Finally, vitamin K needed for the ɣ-carboxylation of factors II, VII, IX, and X should be considered [43]. Vitamin K is effective but does take a few hours to achieve clinical effect, so it is not generally used urgently in the setting of hemorrhage. Vitamin K can be considered in all patients with ICH as it promotes coagulation but should definitely be used in patients receiving tPA who had been on oral anticoagulant therapy prior to administration of tPA [32].

Surgery

Surgical intervention is often considered a potential option in this patient population. In general after receiving tPA, surgery is considered risky due to the prolonged fibrinolytic effect of tPA which may last up to 24 h despite its short half-life [44, 45]. Smaller retrospective studies indicate there may not be an increased risk of hemorrhage with decompressive craniectomy surgery after receiving tPA [46]. However, large-scale studies evaluating surgical intervention after tPA have not been done. In myocardial infarction data, however, ICH after tPA has been treated successfully with surgical evacuation of hematoma. Patients in the GUSTO trial showed that 30-day mortality was decreased and there was a trend toward better functional outcome in the group treated surgically [47].

For spontaneous ICH, two major studies showed no difference in outcome between surgical versus conservative management of ICH. Subgroup analysis of the STICH I trial suggested that lobar hemorrhages within 1 cm of the surface of the brain could benefit from surgical evacuation [48]. STICH II was then undertaken to clarify this, and again there was no clear benefit from surgery [49]. In both studies, however, there were high rates of crossover from the medical management to the surgical management arm. For hemorrhage in the posterior fossa that is 3 cm or greater, it is considered standard of care to surgically evacuate the hematoma [20]. Trials are currently evaluating the benefit of minimally invasive surgical techniques [17, 50–52].

Neuroprotection

Finally, it has been shown that MMP contributes to destruction after ischemic stroke in hemorrhagic transformation. MMP, a large zinc endopeptidase, is active in the maintenance of the brain extracellular matrix. Initially, it is thought that MMPs are detrimental in the acute phase of brain injury, worsening injury in the setting of stroke and ICH [14]. There are some data that suggests that MMPs may be beneficial in the recovery phase through improved brain remodeling [53, 54]. It has been shown that in the setting of focal embolic ischemic stroke, MMPs are elevated. This elevation may be involved in hemorrhagic transformation in brain tissue after tPA. Giving MMP inhibitors in animal studies has been associated with decreased hemorrhage volume offering an agent that could confer neuroprotection [55]. Other potential therapeutic targets include reactive oxygen species, the vascular endothelial growth factor pathway, progranulin, kallikrein, and the adenosine receptor [56–58].

Conclusion

tPA has benefited many patients with acute stroke, myocardial infarction, and pulmonary embolism. However, its use is not without great risk. Practitioners administering tPA must be prepared to quickly respond to bleeding complications. Although there is a lack of evidence supporting best practice guidelines, preparation with readily available management protocols is essential in order to minimize life-threatening consequences and improve functional outcome of surviving patients (Table. 31.1).

Table 31.1 Management of thrombolysis-related bleeding concern for symptomatic intracerebral hemorrhage [17, 30]

Stop tPA infusion
Immediately assess and stabilize patient
Consider emergent intervention for increased intracranial pressure if exam necessitates including trial of hypertonic saline or mannitol until definitive treatment measures can be undertaken
STAT head CT
Call for neurosurgical consultation
Obtain labs including prothrombin time, activated partial thromboplastin time, fibrinogen, complete blood count, PFA-100™, ABO/Rh typing, and red cell antibody screening test
Order 2–4 units red blood cells on hold
Correct coagulopathy
10 units of cryoprecipitate
If cryoprecipitate is contraindicated or not readily available, consider either:
Tranexamic acid 10–15 mg/kg mg IV over 20 min
ε-Aminocaproic acid 4–5 g IV
Recheck fibrinogen after administration of reversal agent. If fibrinogen <150 mg/dL, give additional cryoprecipitate
Admit to neurosciences ICU if available
Maintain normothermia and normocarbia
Monitor blood pressure
Maintain normal glucose levels
Monitor closely for seizures and if clinical seizure present, treat with antiepileptic medication
If depressed mental status, consider continuous EEG

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Part V

Bleeding Associated with Procedure

Bleeding Associated with ECMO

32

Jun Teruya and Cole Burgman

Overview of Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) has been more and more commonly utilized for patients with respiratory failure and cardiorespiratory failure. Extracorporeal cardiopulmonary resuscitation (ECPR) is also performed in many hospitals. Recent improvements in technology have made the circuit, oxygenator, and pump more biocompatible. However, bleeding and thrombotic complications are still ongoing problems, especially for patients requiring extended ECMO support.

ECMO can be used to support both the circulatory and/or the respiratory systems. The two modalities are veno–venous (VV) used to support the lungs and veno–arterial (VA) used to support the heart and the lungs.

In 1976, Dr. RH Bartlett was the first person to successfully support a baby with lung disease on ECMO for 3 days using VA ECMO [1]. Today VA ECMO is used in patients that have circulatory failure or respiratory failure with compromised cardiac function, such as in pulmonary hypertension. Besides pulmonary hypertension, current indications for cardiac ECMO support are congenital heart disease, cardiac arrest, sepsis, cardiomyopathy, myocarditis, and other miscellaneous cardiac diseases. When considering ECMO support, the cardiac failure must be reversible, or the patient on ECMO must be a candidate to be bridged to a ventricular assist device, or to heart transplantation. Cardiac repair, whether in the catheterization laboratory or cardiac operating room, can cause the heart to have poor function postoperatively. ECMO can be used to stabilize these patients until heart function has returned to normal or near normal.

VV ECMO was unavailable for respiratory support until the last decade. With improvements in catheter technology, i.e., double lumen catheter, VV ECMO has become a primary modality to support patients of all ages with respiratory failure. Indications for VV ECMO support are severe pneumonia (viral, bacterial, or combined), end-stage chronic lung diseases awaiting a lung transplant, pneumonitis, and respiratory failure caused by a foreign body obstruction in the airway. Since VV ECMO only supports the respiratory system, a patient must have good cardiac function and may still need inotropic support during ECMO. The goal of VV ECMO is to increase O_2 and decrease CO_2 to maintain an appropriate acid/base balance. Respiratory support has allowed patients to remain on ECMO for much longer time than they ever had when using VA support. Due to the increasing length of time patients may remain on ECMO, the management of these critical patients has needed to evolve. Physical and physiological therapies are now becoming very important, especially since recovery can take weeks to months.

Along with the new VV catheter, other technology innovations have improved the ability to support a patient on ECMO. Improvements in the oxygenator, the biocompatibility of the tubing, cannula design, and the type of pump used have helped minimize blood usage, reduce circuit pressures, and reduce clotting. Prior to these advancements, all of these were major complications. Manufacturers have designed tubing that is bonded with biocompatible coatings. The coatings range from heparin, albumin, and charged ions to help reduce tubing surface tension. The purpose of the coating is to help reduce contact activation which happens within the first hours of initiation of ECMO. Factor XII, one of contact factors, is activated by negatively charged surfaces. By reducing inflammation, patients have less early clotting and less third spacing of volume into their tissues. Manufactures are still working to improve tubing coatings. The goal is to make the circuit appear invisible to the body's defense mechanisms.

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Other developments that have improved the ECMO circuitry are cannula strength, more efficient oxygenators, and pumps that are less traumatic to the blood. The catheters used for ECMO are now designed to be non-collapsible. Wire reinforcing or heavy plastics are now being used to prevent blood flow interruption. Older cannulas had a tendency to collapse over time which would decrease circuit flow and increase negative pressures within the circuit. These pressures would cause turbulent flow which caused stress to the blood. Turbulent flow within the ECMO circuit is a source for clot and hemolysis. The oxygenator used to be the primary source of turbulent flow causing clotting, hemolysis, and increased pressures within the circuit. It was not until the new polymethylpentene hollow-fiber oxygenator that the ECMO circuit had a reduction in internal pressures. This helped reduce hemolysis and clotting within the membrane. This reduction in pressures allowed the use of centrifugal pumps to last longer than the traditional roller pump. New-generation centrifugal pumps have very little heat production, decreasing clotting within the ECMO circuit. The centrifugal pump has definitely improved in pediatric and adult ECMO, but in neonatal ECMO there are still many questions about its performance. The centrifugal pump is less traumatic to the blood cells, but the concern is at low flows for neonatal ECMO the trauma could be worse. The theory is at low flows the pump is not able to be continuously levitated which can generate heat. The heat can create clotting in the cone which creates hemolysis. For adults that have higher flows, the pump works much better than the roller pump which would break down blood cells and tubing by trauma. Overall the centrifugal pump is a safer and less traumatic way to pump blood to the patient. Only with more experience will we know if the centrifugal pump is the best option for neonates.

Finally, renal support devices are routinely used during ECMO. These devices include porous membranes that cannot have biocompatible coatings and are a source of clotting within the ECMO circuit. The membrane has a large surface area which can cause contact activation and turbulence. Different strategies of renal management require different styles of renal replacement. Some centers use a free flow system and others use an integrated pump system. Both are effective in renal clearance, but both filter systems need to be changed routinely to prevent clot.

In all types of ECMO support, the risk of mortality without ECMO versus with ECMO should be taken into consideration. Even with improved equipment, the risks of bleeding and clotting in ECMO still remain although they have some improvements at high-volume institutions.

How to Monitor Coagulation and Anticoagulation During ECMO

Unfractionated heparin (heparin hereafter) is used as an anticoagulant in most cases. When the patient has heparin-induced thrombocytopenia or continuous clot formation despite adequate heparin dose, thrombin inhibitors, such as argatroban or bivalirudin, may be used. Coagulation and anticoagulation are monitored by activated clotting time (ACT), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, anti-Xa, and platelet count. Monitoring methods and target ranges vary among hospitals. ACT has been used for many years; however, the utility in monitoring coagulation and heparin effect in the setting of ECMO has been criticized. It has no or little correlation with aPTT or anti-Xa [2]. Therefore, ACT alone is not enough to monitor heparin effect [3, 4]. Table 32.1 shows an example of a monitoring panel. There is always debate which test is the best to monitor the heparin effect. When ACT, aPTT, and anti-Xa are performed at the same time and show discrepant results, questions remain about which result is most reliable. In other words, how should the heparin dose be changed based on three different results? ACT and aPTT are affected not only by heparin but also the underlying coagulable state, moderate to strongly positive C-reactive protein and lupus anticoagulant. Anti-Xa values represent the overall anticoagulant effect of heparin, which are similar to anti-IIa values. High bilirubin and plasma hemoglobin levels can cause interference, but it is not affected by the underlying coagulable state. Therefore, once underlying hypocoagulable state is appropriately corrected, heparin dose should be adjusted based on anti-Xa values. Table 32.2 shows the advantages and disadvantages of anti-Xa, aPTT, and ACT. Of note, some

Table 32.1 Monitoring hemostasis parameters at Texas Children's Hospital (PT and aPTT values depend on reagents)

Test	Desired target/range	Comments
PT INR	≤1.6	To assess underlying coagulable state
aPTT Hepzyme	<38.0 s	
Fibrinogen	>200 mg/dL	
aPTT	70–90 s	To monitor heparin effect
D-dimer		To monitor fibrin formation and fibrinolysis in the circuit and patient's circulation
Platelet count	>100,000/mm^3 [21]	
Anti-Xa	0.2–0.5 units/mL	To monitor heparin activity
Antithrombin	>60% (or higher if heparin resistance is encountered)	To maximize heparin therapy

Table 32.2 Monitoring methods for unfractionated heparin

Lab test	Advantages	Disadvantages
Anti-Xa	Automated assay—relatively easy to perform Overall anti-Xa action with the patient's own antithrombin Good correlation with anti-IIa	Affected by high bilirubin and free hemoglobin Not available at all hospitals
aPTT	Global test for intrinsic coagulation factors Readily available at most hospitals By removing heparin using heparinase (Hepzyme™), baseline aPTT can be measured Evaluate heparin's overall activity	Affected by lupus anticoagulant, bilirubin, plasma hemoglobin, C-reactive protein, etc. Not precise to monitor heparin effect
ACT	Uses fresh whole blood Performed at bedside	Neither precise nor accurate Affected by coagulation factors, heparin, lupus anticoagulant, and many others

Table 32.3 Other markers that need to be monitored during ECMO

	Desired value	Frequency of monitoring
Plasma-free hemoglobin	<150 mg/dL	Daily
von Willebrand panel (factor VIII, VWF activity, VWF antigen, VWF multimer)		Weekly

VWF von Willebrand factor

reputable hospitals in the USA and Europe have stopped using ACT to monitor anticoagulant effect in ECMO (personal communication). Table 32.3 shows other important parameters that affect hemostasis during ECMO. See below for individual explanations.

Etiology of Bleeding and Management

Heparin Overdose

Overall, the anticoagulant action of heparin occurs via inhibition of factors Xa and IIa, involving proteins such as antithrombin, heparin cofactor II, and tissue factor pathway inhibitor (TFPI). Heparin overdose is definitely one of the common causes of bleeding during ECMO. Heparin forms a complex with antithrombin and inhibits mainly factor Xa and thrombin. Heparin also makes a complex with heparin cofactor II and inhibits thrombin. Heparin increases plasma level of free and total TFPI released by endothelial cells by two- to fourfold [5]. TFPI is synthesized in endothelial cells with a half-life of 60–120 min. It is cleared from the kidney and liver. Once factor VIIa activates factor X to factor Xa, the process is inhibited by TFPI. TFPI also inhibits factor Xa and factor VIIa. More than 50% of TFPI binds to lipoprotein. Congenital deficiency of TFPI has not been reported; however, low levels of TFPI or low heparin-releasable TFPI was found to be associated with venous and arterial thrombosis [6, 7]. On the other hand, increased level of TFPI, associated with mutation of factor V, can cause persistent bleeding [8, 9]. Children have more sustained increase of TFPI after heparin infusion, which may contribute to bleeding due to over-anticoagulation [10]. Prolonged release of TFPI may be a risk for bleeding.

The response to heparin widely varies among patients. Usually heparin is started at 20–25 units/kg/h to attain the goal anti-Xa of 0.2–0.5 units/mL, which depends on every institutional protocol; however, some patients may require 50–60 units/kg/h or more to attain the goal. Since heparin is known to bind to many plasma proteins other than antithrombin and heparin cofactor II, its bioavailability depends on individual patients and conditions. In the setting of ongoing bleeding, the goal anti-Xa may need to be reduced such as 0.15–0.20 units/mL or 0.10–0.15 units/mL. If bleeding is continuous, heparin may be stopped until bleeding stops.

Coagulopathy

Immediately after initiation of ECMO, dilutional coagulopathy and thrombocytopenia develop if the ECMO circuit is primed by only saline or red cells. Fresh frozen plasma is needed to correct dilutional coagulopathy. Data show that even if anti-Xa level is within the target range, there is a significant increase in coagulation activation markers such as thrombin–antithrombin complex and prothrombin fragment 1.2 [11].

Due to the constant thrombin formation, fibrinogen level may be decreased due to consumption. Transfusion of cryoprecipitate or infusion of fibrinogen concentrate is needed to correct low fibrinogen levels. It is recommended to maintain the fibrinogen level >200 mg/dL. However, in the setting of severe pneumonia or sepsis, the fibrinogen level may go up as an acute phase reactant, which is a risk factor for thrombo-

sis. There are reports of decreases in factor XIII levels during ECMO [12]. Therefore, if the patient is bleeding during ECMO, factor XIII assay may be needed. If the factor XIII level is >50%, it is enough for normal hemostasis. However, it is not known if the factor XIII level of 40–50% in the setting of ECMO with heparin can be a cause of bleeding. Potentially factor XIII concentrate, recombinant factor XIII, or cryoprecipitate may be given if bleeding persists despite treatment with an antifibrinolytic and/or VWF (concentrate or recombinant).

Thrombocytopenia/Platelet Dysfunction

Thrombocytopenia is a common finding during ECMO. Platelet dysfunction is also seen due to the constant shear force caused by the pump. In the presence of thrombocytopenia, platelet function cannot be accurately assessed. The platelet function may be impaired even 15 min after starting ECMO and throughout ECMO until it is discontinued [13]. Target platelet counts vary from institution to institution, such as 50,000–100,000/mm^3. However, if the patient has bleeding symptoms, platelet count should be >150,000/mm^3 or even higher for suspected concurrent platelet dysfunction.

Hyperfibrinolysis

During ECMO, the fibrinolytic system is activated mainly due to increase in tissue plasminogen activator (tPA). It was reported that tPA and plasmin–antiplasmin complex levels increased and tissue plasminogen activator inhibitor 1 level decreased [11]. Although infusion of Amicar™ did not alter the rate of neonatal intracranial bleeding, it reduced the incidence of surgical bleeding [14].

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AVWS) is seen in virtually all patients on ECMO. Large multimers are lost due to the high shear force. This occurs within 24 h after ECMO initiation [15]. Laboratory findings show decreased VWF activity/antigen ratio and loss of large multimers despite normal or increased VWF activity and antigen [16, 17]. The diagnosis of AVWS is based on VWF activity/VWF antigen ratio and VWF multimer studies (Figs. 32.1 and 32.2). In the setting of ECMO, VWF activity may be normal or only mildly decreased [18]. Table 32.4 shows an

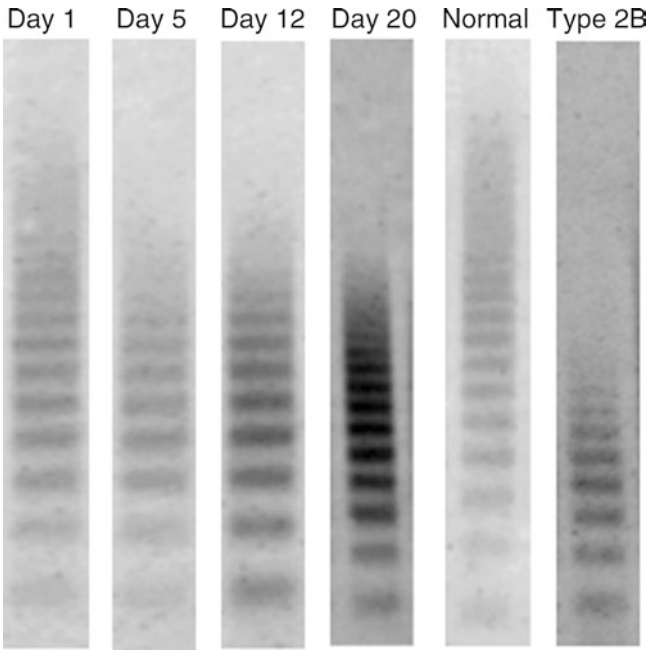

Fig. 32.1 von Willebrand factor multimer pattern during ECMO

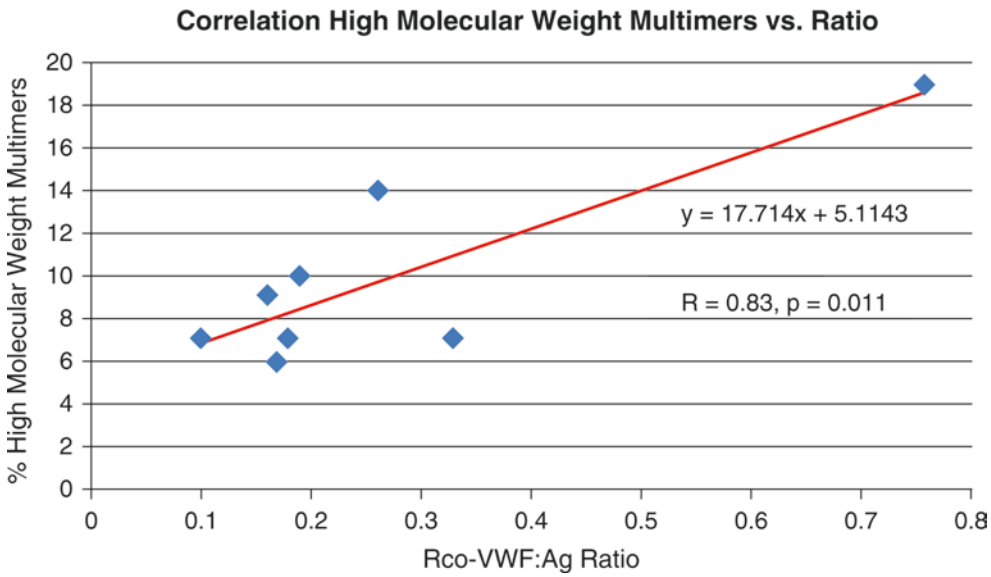

Fig. 32.2 VWF:RCo/VWF:Ag ratio with high molecular weight multimers. *VWF:RCo* von Willebrand factor ristocetin cofactor activity

Table 32.4 Example of von Willebrand panel in a patient on ECMO

ECMO day	Day 1	Day 5	Day 12	Day 20
Factor VIII (%)	162	156	56	56
VWF:Act (%)	27	31	47	40
VWF:Ag (%)	81	302	278	225
VWF:Act/ VWF:Ag	0.33	0.1	0.17	0.18
High:Medium:Low multimer band (%)	7:51:43	7:58:35	7:56:37	7:56:37

example of laboratory results of AVWS. The management of AVWS includes transfusion of cryoprecipitate or infusion of Humate-P™. While cryoprecipitate has almost intact large VWF multimers, Humate-P™ has a borderline level of large VWF multimers since some of those large VWF multimers are lost during the purification process. Recombinant VWF (Vonvendi™) contains more large VWF multimers. However, since the cause of AVWS, i.e., high shear force, persists while the patient is on ECMO or VAD, efficacy of cryoprecipitate or Humate-P™ is temporary. Therefore, it may need to be given repeatedly. It should be noted that cryoprecipitate also contains fibrinogen and factor VIII, which are acute phase reactants. If the levels of factor VIII and fibrinogen are increased, transfusion of cryoprecipitate may cause a risk of thrombosis. Likewise, Humate-P™ contains substantial amount of factor VIII, which may increase the risk for thrombosis if factor VIII is already increased.

Hemolysis

Intravascular hemolysis is another cause of derangement of hemostasis and renal damage. Plasma-free hemoglobin (≥50 mg/dL) increases VWF-mediated platelet adhesion in vitro. It also augments microthrombi formation on fibrin(ogen), extracellular matrix, and collagen at high shear stress [19]. In addition, plasma-free hemoglobin competes A2 domain of VWF with ADAMTS13 [20]. Once clots are formed in the circuit, it consumes coagulation factors and platelets, leading to bleeding. Intravascular hemolysis may be attributed to clot formation in the circuit or the position of the cannula. That is the reason plasma hemoglobin should be monitored daily during ECMO. Decreasing the pump flow is not recommended since stasis caused by lower flow rate may cause more clot formation. Changing the oxygenator or entire circuit may be considered first. If plasma hemoglobin is increased such as >150 mg/dL, plasma exchange using plasma as replacement fluid should be performed to remove it in order to prevent renal damage and thrombosis.

Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is performed to correct coagulopathy, remove plasma-free hemoglobin, and remove lupus anticoagulant [22, 23].

Anti-Xa assay is interfered with significantly elevated plasma-free hemoglobin due to the red color of plasma. When lupus anticoagulant is present, aPTT is usually prolonged. When direct thrombin inhibitors such as bivalirudin or argatroban are used, the anticoagulant effect cannot be reliably monitored using the aPTT, which is currently most commonly used method for monitoring, in this setting. Since presence of lupus anticoagulant is a risk factor for thrombosis, it should be removed. However, because the efficacy of TPE may not last for a long time, it has to be repeated every few days. TPE is also used for newborns to remove unconjugated bilirubin in order to prevent kernicterus. Overall, TPE can "reset hemostasis" although the efficacy is transient.

Bleeding from Organs and Cannula Insertion Site

It is not uncommon to have bleeding in the brain, lung, chest cavity, genitourinary tract, gastrointestinal tract, and cannula insertion sites. It should be noted that red urine does not always indicate hematuria. It can be hemoglobinuria or simultaneous hematuria and hemoglobinuria. Therefore, testing using urinalysis with microscopic examination and plasma-free hemoglobin is necessary to distinguish hematuria from hemoglobinuria. In case of hematuria, administration of antifibrinolytics such as tranexamic acid or Ɛ-aminocaproic acid is a relative contraindication. Antifibrinolytics may cause clotting in the ureter or bladder, which can occlude the urinary tract leading to hydronephrosis or urinary obstruction (see Chapter 28, "Gross Hematuria"). In this chapter, hemorrhage in the brain and cannula insertion site will be addressed. Refer to other chapters from other organs (Part III).

Intracranial Bleeding

Interventricular hemorrhage (IVH) in neonates is not uncommon especially when neonates are premature. If IVH is not severe, i.e., grade I or II, ECMO does not need to be discontinued [24].

Heparin anticoagulation may have to be stopped, or dose may be decreased with a target anti-Xa of 0.1–0.2 units/mL. Unless patient has disseminated intravascular coagulation predisposed by underlying condition such as sepsis or severe pneumonia, patients can usually tolerate ECMO

without anticoagulation for hours or sometimes days, especially when tubing is coated by heparin or albumin which is less thrombogenic materials. However, if the cannula size is small, sudden onset of clotting in the circuit can happen. Therefore, the entire circuit has to be carefully and frequently examined for clots. Head ultrasound should be repeated to monitor if the grade of IVH remains the same. Small intracranial bleeding may not have symptoms such as changes in vital signs, seizure, paralysis, or anisocoria. Continuous monitoring of electroencephalogram (EEG) is useful in order to detect small intracranial bleeding. If intracranial bleeding is suspected in EEG, a head CT scan needs to be performed. If the patient has impending herniation or mid-line shift, risks and benefits of stopping ECMO and/or surgical intervention have to be carefully assessed. Use of antifibrinolytics may be beneficial in order to prevent expansion of hematoma [25].

However, the potential side effect of clotting has to be considered if antifibrinolytic agents are given. There are reports of using recombinant activated factor VII in life-threatening bleeding in the setting of ECMO, but it should be the last option due to its strong thrombogenicity.

Bleeding from Cannula Insertion Sites

If bleeding from cannula insertion sites is the only bleeding symptom, it may not be due to systemic coagulopathy. Rather, it is accounted for by anatomical or surgical etiology, which has to be managed by surgical intervention such as tighter suture or topical hemostatic agents.

Summary

Management of bleeding is an ongoing problem for patients on ECMO. The bleeding etiology is multifactorial. It includes, but is not limited to, coagulation factor deficiencies, thrombocytopenia, platelet dysfunction, hyperfibrinolysis, and AVWS. Regular monitoring and targeted management are needed to prevent major fatal bleeding such as in the brain or lung (Figs. 32.3 and 32.4).

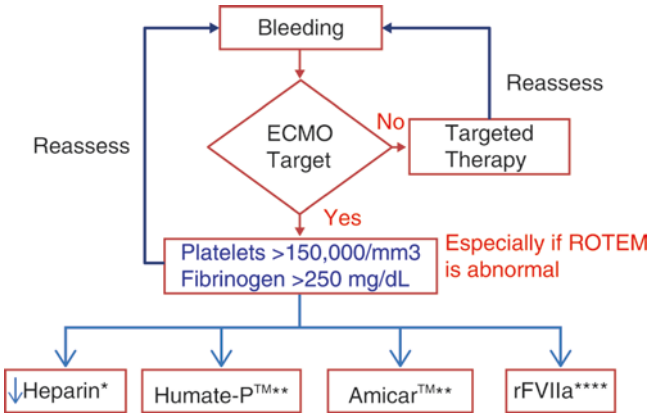

Fig. 32.3 Algorithm-based management. *anti-Xa 0.1–0.2 units/mL or hold heparin up to 12 h; **15–25 units/kg; ***10–30 mg/kg/h until bleeding improved; ****although there are reports of using recombinant activated factor VII, it induces a significant risk of thrombosis and clotting the circuit. Humate-P™ is von Willebrand factor/factor VIII concentrate. Amicar is ε-aminocaproic acid. Courtesy of ShiuKi Rocky Hui, MD, modified

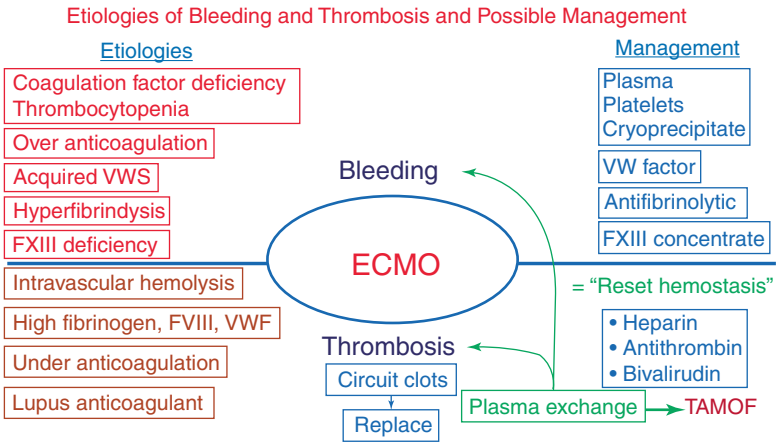

Fig. 32.4 Etiology and management of bleeding and thrombosis during ECMO. *VWS* von Willebrand syndrome, *tPA* tissue plasminogen activator, *PAI-1* plasminogen activator inhibitor 1, *FXIII* factor XIII, *FVIII* factor VIII, *VWF* von Willebrand factor, *TAMOF* thrombocytopenia-associated multiorgan failure

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33 Management of Bleeding Associated with Durable Mechanical Circulatory Support

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Mechanical Circulatory Support and Ventricular Assist Devices

Heart failure is a worldwide epidemic that affects nearly 6.5 million adults in the United States. Projections estimate that this number will rise to greater than eight million by 2030, representing a 46% increase from 2012 [1]. Although survival after onset of heart failure has improved with targeted interventions, 1-year mortality remains high at 20–30% [1]. From 1989 to 2012, only 67% of the 40,000 people awaiting heart transplants were able to undergo transplantation due to a disparity between the supply and demand of donor organs [1]. Mechanical circulatory support (MCS) devices have become a viable option for patients with advanced heart failure and help facilitate unloading of the heart, maintenance of cardiac output, and organ perfusion [2]. These devices can be used as bridge-to-transplant (BTT), bridge-to-decision (BTD), or destination therapy (DT) [3]. By the end of 2016, more than 22,000 MCS device implants had been reported to the INTERMACs registry (not including devices placed through investigational trials) at an estimated rate of more than 2500 implants annually across 185 centers in the United States [4]. The introduction and continued advancement of MCS has led to improved prognosis, functional status, and quality of life in patients with advanced heart failure but continues to be associated with serious complications including thrombotic and bleeding events due to the location of the device and complex interplay with the native vasculature [5].

Table 33.1 Types of durable mechanical circulatory support devices [9]

Device type	Key design features	Examples	Support type
Total artificial heart	The native ventricles and valves are removed and replaced by a pneumatically powered artificial heart with four single leaflet mechanical valves	Syncardia TAH	BT
Pulsatile flow devices (LVAD +/− RVAD)	Designed to mimic the pulsatile nature of the native heart with systolic and diastolic unidirectional flow	HeartMate XVE	BTT, DT
Continuous flow device (LVAD +/− RVAD)	Continuous flow design with only one moving part and are available as either an axial or centrifugal flow; smaller size	HeartMate II, HVAD, HeartMate 3	BTT, DT

TAH total artificial heart, *LVAD* left ventricular assist device, *RVAD* right ventricular assist device, *BTT* Bridge-to-transplant, *DT* destination therapy

There are three broad types of durable MCS including the (1) total artificial heart (TAH), (2) pulsatile flow left ventricular assist devices (PF-VAD) such as HeartMate XVE, and (3) continuous flow VADs (CF-VAD) such as HeartMate II, HeartWare, and HeartMate 3 (Table 33.1). The TAH is indicated for patients who have irreversible biventricular heart failure awaiting heart transplant (ongoing trial and FDA approval for DT) [6]. The native ventricles and valves are removed and replaced by a pneumatically powered artificial heart with four single leaflet mechanical valves [7, 8]. Durable VADs can be used as left ventricular assist devices (LVADs) in patients with isolated left ventricle heart failure.

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For patients who have both left and right ventricular failure, LVADs and right ventricular assist devices (RVADs) can be used simultaneously to provide bi-ventricular support.

Older generation pulsatile flow VADs were designed to mimic the pulsatile nature of the native heart with systolic and diastolic unidirectional flow. One proposed benefit of this design was to reduce the risk of thromboembolism without requiring systemic anticoagulation [9, 10]. Due to the complex design of these devices, there was a high incidence of device failure [10]. Newer generation devices use a continuous flow design with only one moving part and are available as either an axial or centrifugal flow [10, 11]. The design, placement, and duration of MCS affect the incidence of bleeding and thromboembolic events. Of the approximately 19,000 MCS devices placed primarily for left ventricular support between 2006 and 2016, 2% were TAH, 5% were pulsatile flow VADs (LVAD +/− RVAD), and the remaining 93% were continuous flow VADs (LVAD +/− RVAD) [4]. Since the majority of LVADs implanted now are continuous flow devices, the discussion regarding bleeding and management of bleeding will focus on this population.

Effect of Mechanical Circulatory Support on Hemostasis

Placement of MCS devices within the vasculature result in constant interaction of non-biologic surfaces with blood flow, which can have profound effects on hematologic, inflammatory, and immunologic parameters [12, 13]. Variables that influence bleeding complications in patients with MCS include patient factors, management factors, and specific device characteristics (Table 33.2) [14]. Patient factors include critical illness, advanced age, renal failure, diabetes, and other comorbidities. Patients may also have inherited or acquired coagulopathies [14, 15]. Additionally, a HAS-BLED score (*h*ypertension, *a*bnormal renal and liver function, *s*troke, *b*leeding, *l*abile INR, *e*lderly, *d*rugs or alcohol) of ≥3 has been associated with a significantly higher risk of bleeding events in one study of VAD patients [16].

Table 33.2 Factors influencing bleeding incidence and severity [14, 15, 16]

Patient characteristics	Comorbidities such as critical illness, advanced age, renal failure, diabetes	
	Inherited or acquired coagulopathy	
	HAS-BLED score of ≥3	
Device management factors	Type of device: continuous-flow, pulsatile, TAH	
	Pump speed (RPM)	
Antithrombotic therapy	Anticoagulation	Target INR range
		Time in therapeutic range
	Antiplatelet therapy	Aspirin 81 mg to 325 mg
		Dual antiplatelet therapy with clopidogrel or dipyridamole

HAS-BLED (*h*ypertension, *a*bnormal renal and liver function, *s*troke, *b*leeding, *l*abile INR, *e*lderly, *d*rugs or alcohol)
TAH Total artificial heart
INR International normalized ratio

Management factors such as pump speed and intensity of antithrombotic therapy can influence the hemodynamic balance and bleeding risk. The incorporation of a rotary pump to drive blood flow and the non-pulsatile nature of these newer devices can lead to damaged blood cells, induction of hemolysis, and platelet activation [14, 17]. The degree of shear stress on platelets and von Willebrand factor (vWF) multimers is variable depending on the device implanted and pump speed. Shear stress leads to loss of high-molecular weight vWF multimers by inducing a conformational change that leaves these proteins susceptible to cleavage by proteolytic enzymes (ADAMTS13) [12, 14]. In their normal state, high-molecular weight vWF multimers allow for appropriate platelet binding; their destruction may lead to increased risk of bleeding. However, studies have shown that this loss of high-molecular weight vWF multimers cannot solely account for the high rates of bleeding in this population and may only be one contributing factor. The low pulse pressure of continuous flow VADs may also contribute to the high degree of gastrointestinal (GI) bleeding and formation of arteriovenous malformations (AVMs) by allowing for a decrease in intraluminal pressure and dilatation of the mucosal veins [14].

These hematologic alterations, along with the requirement for indefinite anticoagulation with or without concomitant antiplatelet agents to mitigate thromboembolic events, can lead to significant hemorrhagic complications [18]. Despite consensus guidelines and device-specific manufacturer recommendations, practice across institutions varies widely based on real-world experience with thrombotic and hemorrhagic outcomes [13].

Antithrombotic Medications in Mechanical Circulatory Support Management

Patients supported by MCS have an indefinite requirement for antithrombotic therapy, but the exact regimen will vary depending on the clinical scenario. The bleeding risk varies with the type and intensity of antithrombotic therapy in addition to other factors such as drug-drug interactions, fluctuations in volume status, critical illness, and interruptions/bridging of anticoagulation. Practice varies between institutions and between different devices. Therapy has historically been adjusted based on published rates of both thrombotic and bleeding events as more information

becomes available as well as site specific experience with such events [19].

In the immediate post-operative period, patients are commonly started on low dose aspirin and a short-acting titratable intravenous (IV) anticoagulant such as heparin or bivalirudin [18]. Anticoagulation is generally started at a lower intensity (e.g., goal PTT 40–60) and increased after the patient is considered hemodynamically stable. Once platelets have recovered, aspirin doses may be increased to 325 mg to optimize the antithrombotic benefits. When clinically appropriate (chest tubes removed and no planned invasive procedures), oral anticoagulation with a vitamin K antagonist (VKA) is initiated and IV anticoagulation is discontinued once the INR is therapeutic. The management of anticoagulation in the periprocedural period can be influenced by drug interactions, the nutritional status of the patient, clinical status post-operatively, and previous anticoagulation requirements. Alternative anticoagulation strategies have been evaluated in the immediate post-operative period and include the use of low molecular weight heparin (LMWH), delaying anticoagulation until post-op day 3, and starting oral VKA without a lead-in bridging agent [20, 21].

In the outpatient setting, patients are maintained on a VKA indefinitely. Despite the improved bleeding outcomes in the general population with the direct oral anticoagulants (DOACs), there are limited data available for their use in the VAD population. One trial of patients randomized to dabigatran versus VKA was halted early when four of the eight patients treated with dabigatran developed thromboembolic strokes [22]. For this reason, VKAs remain the oral anticoagulant class of choice for VAD patients despite the known bleeding risk, required INR monitoring, and frequent medication titration.

The risk of bleeding for patients on VKAs is closely associated with the time in therapeutic range (TTR) and target INR goal. The TTR for patients with MCS is typically much lower than the general venous thromboembolism or atrial fibrillation populations at around 31–52% [23–27]; however higher TTRs of up to 66% have been reported [28]. One study found that in the 30 days preceding a bleeding event, patients were more likely to have spent a higher percentage of time above the therapeutic range [24]. Typically an INR range of 2.0–3.0 is standard for patients with MCS, although this has been evaluated and adjusted over time due to increased bleeding and thrombosis seen with different devices. Two small studies evaluated the effect of lowering the target INR range to 1.5–2.5 in HeartMate II patients due to a noted increase in bleeding [21, 29]. When evaluating studies of anticoagulation control and outcomes in MCS patients, it is important to understand the historical timeframe of the study, the type of implanted device, and concomitant antithrombotic therapy utilized throughout the study. These factors vary widely between institutions over different periods of time and can have a direct impact on the outcomes.

In addition to anticoagulation, patients are frequently prescribed concomitant antiplatelet therapy due to the role of platelet dysfunction in the disruption of hemostasis leading to bleeding and thrombosis. Most patients are maintained on aspirin monotherapy at a dose ranging from 81 mg to 325 mg daily and adjusted based on the occurrence of bleeding and thromboembolic events. For patients who experience a thromboembolic event, such as LVAD thrombosis, a second antiplatelet agent (usually dipyridamole or clopidogrel) may be added to the antithrombotic regimen. This change may also be accompanied by an increase in target INR range. For patients who experience bleeding events, aspirin may be decreased to 81 mg daily or discontinued completely and the target INR range may be lowered. These alternations in the antithrombotic strategy are based on clinical judgment and supported by limited evidence-based guidelines. Guidelines recommend that chronic therapy with aspirin (81 mg to 325 mg) may be used in addition to a VKA and that additional antiplatelet therapy may be utilized according to recommendations from manufacturers of the specific device [18].

In the outpatient setting, patients with MCS may also require "bridging" with an injectable agent either to facilitate an interruption in oral therapy for a procedure (e.g., colonoscopy or heart catheterization) or to provide adequate anticoagulation when an INR is below the target range. This is more commonly done in patients who are at high risk or have a history of thromboembolic events in the past. In these cases, patients are typically bridged with either full or half-dose LMWH depending on the clinical scenario [30]. Fondaparinux may be used in patients with a documented history of heparin-induced thrombocytopenia. The use of LMWH agents, especially during the transitional periods between injectable and oral anticoagulants, has been found to be associated with an increased risk of bleeding [31].

Finally, patients may also require re-admission to the hospital, interruption of oral anticoagulation therapy, and temporary bridging with either IV unfractionated heparin or bivalirudin to facilitate a procedure or in the case of threatened or confirmed pump thrombosis. After the acute event has resolved, patients are typically bridged back to oral VKA therapy. Close management of this overlap period to prevent over anticoagulation is required.

Bleeding in the Ventricular Assist Device Population

Most of the available data detailing the incidence of major bleeding events in the VAD patient population uses the INTERMACS database definition of major bleeding that

includes any bleed resulting in death, reoperation, hospitalization, or the requirement of red blood cell transfusion outside of the first week after device placement [4]. The information regarding adverse event rate and incidence discussed throughout this chapter is primarily derived from the CF-VAD population, most of which have had HeartMate II or HeartWare devices implanted. As mentioned previously, CF-VADs have become the standard of care over PF-VAD in patients requiring MCS due to their smaller size, increased durability, and increased reliability [32]. The information relating specifically to the incidence of adverse events in the PF-VAD population will not be discussed.

Overview of Ventricular Assist Device Bleeding

Bleeding is the most common adverse event experienced by patients on CF-VAD support. Major bleeding (using the INTERMACS definition described above) occurs at a rate of around 0.95 events per patient year during the first 12 months after device placement [33]. The highest risk for major bleeding is experienced in the immediate post-operative period due to complications related to the surgical placement of the device. The bleeding rate is four times higher during the first 3 months of CF-VAD therapy compared with the remainder of the duration of MCS therapy. The risk of procedure-related major bleeding differs between specific CF-VAD devices due to the variations in surgical technique required for placement. For example, the HeartWare device (HVAD) can be placed entirely within the intrapericardial space and does not require upper abdominal pump pocket creation that is needed with other devices such as the HeartMate II (HMII). As a result, the surgical time for implantation is shorter and the rate of bleeding requiring reoperation is almost cut in half (0.26 events per patient year for HVAD versus 0.45 events per patient year for HMII) [11].

The severity of a bleeding episode is dependent upon multiple patient-specific factors including bleeding history, antithrombotic regimen, and the location of the bleed. When dealing with such a high-risk patient population, each bleeding event must be managed appropriately to avoid potentially devastating consequences.

Gastrointestinal Bleeding

GI bleeding is the most common type of bleeding event experienced by CF-VAD patients. The cumulative risk of GI bleeding has been shown to be 21% at 1 year post-VAD placement, 27% at 3 years, and 31% at 5 years [3]. Possible mechanisms that may explain this high incidence include acquired von Willebrand disease and the formation of angiodysplastic lesions within the gastrointestinal tract caused by the non-pulsatile flow of the CF-VADs [34]. These lesions typically form within the upper GI tract and are the source for around 44% of all GI bleeding events [35].

Acute GI bleeding usually requires hospitalization and supportive use of blood products, making it a complication with a high medical and financial burden. In the CF-VAD patient population, GI bleeds account for half of the bleeding events that require transfusion of red blood cells [36]. The biggest independent risk factors for GI bleeding include history of GI bleed (odds ratio of 22.7) and an elevated INR for patients on warfarin (odds ratio of 3.9) [36]. It is important to assess the GI bleeding risk of each patient individually before and during their VAD treatment course.

Recurrent bleeding from sources within the GI tract is also a large issue. Around 60% of patients who rebleed do so from the same source as their index event. This risk increases with advanced patient age. While the average age of a VAD patient who experiences a GI bleed is around 60 years, the average age of patients with recurrent GI bleeding is around 70 years. It is important that INR values are maintained below the upper limit of the therapeutic range to reduce the risk of bleeding, especially for older patients with a documented history of GI bleeding.

Hemorrhagic Cerebral Vascular Accident

Hemorrhagic cerebral vascular accidents (HCVA) are the leading cause of death within the VAD population, with a mortality rate between 46% and 56% [37]. Approximately 11% of patients will experience a HCVA within the first 2 years following VAD placement [3].

Factors that have a direct impact on HCVA incidence include supratherapeutic INR, VAD type, and specific antithrombotic regimen. Compared to the overall occurrence rate of around 0.03 events per patient year [32], the rate of HCVA can increase to as high as 0.14 events per patient year when the INR is supratherapeutic (>3.0) [36]. INRs above the therapeutic range can increase the risk of any type of bleeding event, but the severity and mortality of HCVA makes this particular complication more concerning.

Antithrombotic regimens need to be optimized to reduce the incidence of HCVA, and device type must be considered. In general, HeartWare patients have a higher incidence of HCVA compared to those implanted with a HeartMate device [38]. In the HeartWare patients, using an expanded INR range of 2.0–3.0 (versus a lower or tighter intensity range) paired with high dose aspirin resulted in decreased thrombotic events without increasing the risk of HCVA [37]. However, in the HeartMate II patients, using a high dose aspirin resulted in a higher incidence of HCVA than those on aspirin and dipyridamole or low dose aspirin alone. This increase in HCVA incidence was not accompanied by a reduction in thrombotic

events [37]. The decision to use high dose or low dose antiplatelet therapy must be made on a case-by-case basis.

Epistaxis

Although epistaxis may seem less threatening than the previously mentioned complications, there is still significant morbidity and mortality associated with these events. The incidence of epistaxis in the VAD population is around 9.2% with a rate of around 0.06 events per patient year [11, 39]. The majority of patients who experience epistaxis require an emergency room visit or hospitalization, with 16% of events requiring invasive interventions such as embolization or cauterization [39]. Independent risk factors associated with a higher risk of epistaxis include HeartWare device use (versus HeartMate II), current tobacco use, and insulin-dependent diabetes.

Downstream effects of epistaxis-related hospitalizations are also important to consider. There is a 2.4 times higher chance of death and a 1.8 times higher chance of experiencing another type of bleed for VAD patients who experience epistaxis (such as GI hemorrhage) [39].

Other Types of Bleeding

Although GI bleeding, HCVA, and epistaxis are the most common and notable types of bleeding experienced by VAD patients, there are also bleeds that fall outside those definitions. In many cases, the source or site of bleeding cannot be identified. Anemia of unknown source that is severe enough to require blood transfusions account for about 20% of all bleeding events [3]. In these cases, a complete inpatient work up may need to be carried out to ensure the patient is stable and appropriate for outpatient management.

Treatment and Management of Bleeding

Once a bleeding event has been identified, it must be managed quickly and effectively to avoid serious complications. All inpatient institutions should create standard operating protocols and guidelines to assist providers in managing VAD bleeding events in a standardized and rapid manner.

Management of bleeding in the VAD population is complex because anticoagulation therapy withdrawal or reversal leaves the patient unprotected and at risk for thrombotic complications. Approximately 35% of patients who present with GI bleeding experience a subsequent thromboembolic event, which is almost three times higher than the rate in patients who do not experience bleeding [35]. Bleeding needs to be managed in a way that mitigates risk of thromboembolic complications and downstream negative clinical outcomes.

General Bleeding Management

Strategies for bleeding management are centered around identifying the source of the bleed, providing supportive therapy during the bleeding episode, and administering procoagulant therapy if needed to urgently stop the hemorrhage. In the perioperative setting, bleeding usually occurs due to inadequate heparin neutralization, surgical bleeding related to device placement, or hemostatic abnormalities secondary to liver or kidney dysfunction caused by chronic heart failure or end organ dysfunction [13]. Heparin products should be fully reversed using protamine prior to initiation of device placement. Surgical bleeding typically requires additional procedural interventions for resolution.

Supportive therapy typically consists of blood product replacement as needed depending on rate and quantity of blood loss. Blood product transfusion must be used selectively in patients who are candidates for transplant, as there is an inherent risk of alloimmunization that could lead to prevention of listing for a subsequent heart transplant. If immediate reversal of anticoagulation therapy is required, 4-factor prothrombin complex concentrate should be considered due to its quick INR normalization time and small infusion volume [33].

If life-threatening bleeding continues despite initial treatment attempts, procoagulant therapy such as recombinant activated factor VII can be considered [13]. The safety of aminocaproic acid, tranexamic acid, and other antifibrinolytic therapies has not been extensively studied in the VAD population. Hemorrhage that is refractory to medical management can be an indication for urgent heart transplantation in bridge to transplant patients and can qualify a patient to have their United Network for Organ Sharing (UNOS) status updated.

Once the patient has been stabilized after the acute phase of the bleed, changes to the patient's antithrombotic regimen are typically made to reduce the chances of rebleeding. Options include the lowering or narrowing of the target INR range and reduction or removal of antiplatelet therapy [3]. After a patient's first minor bleeding event, aspirin may be decreased from full dose to low dose. If a patient experiences a first major bleed or a second minor bleed, discontinuing antiplatelet therapy completely or decreasing the target INR range by 0.5 are possible treatment adjustments.

Management of Gastrointestinal Bleeding

Since GI hemorrhage is the most common type of bleed experienced by VAD patients, there is more information available on how to best manage this complication.

Treatment hinges on whether not the patient is hemodynamically stable or not at the time of the bleed. For all patients, strategies for treating GI hemorrhage frequently include withholding or reversing anticoagulation therapy and initiating GI protective medications such as proton pump inhibitors (Fig. 33.1) [18].

If the patient is hemodynamically stable, upper endoscopy and colonoscopy can be utilized to help identify the source of the bleed [35]. These procedures can be safely performed while a patient is anticoagulated if the INR is <3.0. If no source can be identified, video capsule endoscopy (VCE) can be used to provide further diagnostic information about the bleeding area. The most common site of bleeding identified by VCE is the small intestines, with over 75% of events originating from this area [18]. Unfortunately, no source of bleeding is identified in approximately half of the patients who undergo VCE.

Once the area of bleeding has been identified, deep enteroscopy can be used to assist with localized treatment of the area to resolve bleeding [35]. Medical therapy is initiated in patients who are unable to undergo enteroscopy, who have bleeding recurrence, or who have unidentifiable sources of bleeding. Blood counts should be checked twice daily during acute bleeding and transfusion can be considered if hematocrit drops below 21%. Decision to transfuse red blood cells is influenced by the patient's transplant status, baseline blood levels, and clinical state. All patients with GI bleeding should also undergo *H. pylori* screening to rule out infection as a causative factor.

Patients are considered hemodynamically unstable if they exhibit tachycardia, tachypnea, hypotension, large volume hematemesis, require inotropic support, or other symptoms of bleeding or volume reduction. Fluid resuscitation should begin immediately with IV fluids until red blood cells can be

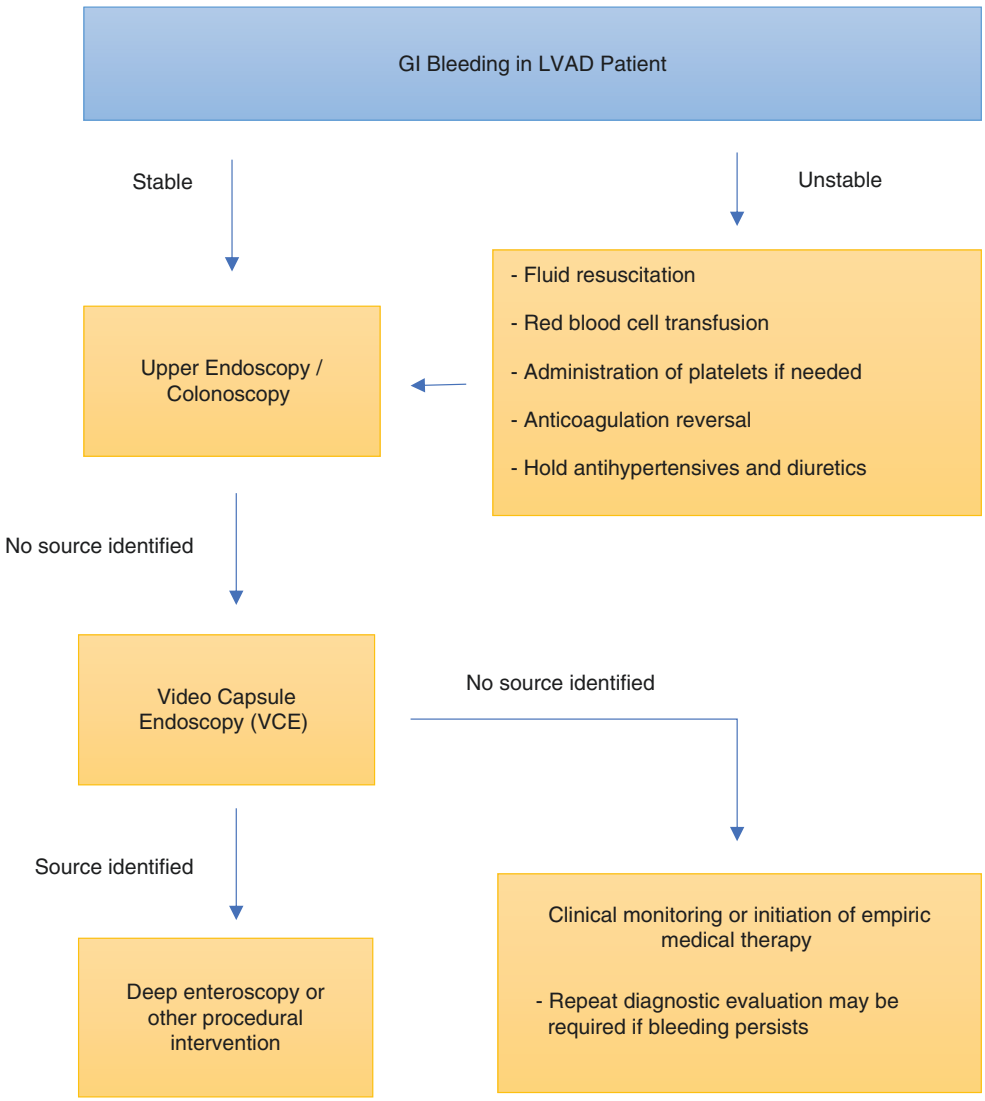

Fig. 33.1 Management of GI bleeding in the LVAD patient

Table 33.3 Strategies to prevent recurrent GI bleeding

Medical therapy [20]	*Octreotide*	Somatostatin analog
	Danazol	Suppresses FSH and LH; increases complement C4
	Thalidomide	Immunomodulatory and antiangiogenic effects
Treatment modifications	Maintain lowest possible VAD speed	
	Tighten or reduce target INR range	
	Frequent monitoring of complete blood count and other appropriate lab values	
	Low threshold for gastrointestinal evaluation of high-risk patients	

transfused. Platelets should also be given if the patient was on antiplatelet agents upon admission. Anticoagulation therapy should be reversed for life-threatening bleeding with 4-factor prothrombin complex concentrate (Kcentra™). Diuretics and antihypertensives should all be held during the acute period to avoid pharmacologic exacerbation of hypotension or hypovolemia.

Recurrent bleeding usually requires medical therapy in addition to the work up outlined above (Table 33.3). Treatment options include octreotide, danazol, and thalidomide. Octreotide is somatostatin analog that is used to reduce portal pressure and assist with reduction in variceal bleeding. However, there is limited data regarding the use in this context with no reported improvement of transfusion requirement, rebleeding rates, or mortality. Thalidomide is reserved for very refractory cases in patients who have failed octreotide and can only be given after authorization by the gastroenterology specialists.

For patients with recurrent bleeding events, VAD speed can also be reduced in order to increase pulsatility and improve the bleeding profile for the patient. This should be considered especially if the bleeding is secondary to AVMs. VAD patients with a high pulsatility are four times less likely to develop a bleeding complication compared to those with a low pulsatility [3]. Individual patient characteristics must be evaluated prior to making changes to device pulsatility as risk for thromboembolic events is greatly increased [32].

Other strategies for prevention of recurrent GI bleeding are focused on maintaining the VAD speed at the lowest possible safe RPM range, maintaining INR at the lower end of therapeutic range, frequent follow-up of appropriate laboratory values, and setting a low threshold for diagnostic evaluation for patients at high risk of rebleeding.

Anticoagulation Management

Management of bleeding in the VAD population is especially difficult because essentially all patients are on anticoagulation and antiplatelet agents at the time of the acute event. Both anticoagulation and antiplatelet therapy should be withheld during clinically significant bleeding, but reversal should only be used in the setting of elevated anticoagulation parameters or in the context of life-threatening bleeding. Warfarin can be reversed if INR >3.0, and the patient requires an invasive intervention to manage or diagnose bleeding or they are experiencing a life-threatening bleed. Antithrombotic therapy should continue to be withheld until bleeding resolves as long as there is no evidence of VAD pump dysfunction. It is very important to monitor device parameters and alarms during this period as the risk for thromboembolic events is very high.

After acute bleeding has resolved, providers should consider withholding antiplatelet agents indefinitely if the bleeding occurred while INR was within or below the therapeutic range, if there are no further indications for antiplatelet therapy besides the presence of VAD device. If the bleeding event happened while the INR was supratherapeutic, antiplatelet agents can be re-introduced slowly after the patient has been stabilized until the required intensity of therapy is reached. INR control is extremely important during the first few weeks after the bleeding event, and the INR level should be maintained in the lower end of the therapeutic range if possible.

Conclusion

As the number of patients with heart failure worldwide continues to rise without a concurrent rise in the availability of donor hearts, the number of patients supported with MCS as either BTT, DT, or BTD will also be expected to rise. Despite the improvement of prognosis, functional status, and quality of life in patients with advanced heart failure who are supported with MCS, a significant portion of these patients will experience one or more bleeding events in their course of therapy due to the complex interplay of the VAD within the vasculature. The number and severity of bleeding events is affected by patient, device, and management-specific factors and is exacerbated by the requirement for lifelong anticoagulation with or without concomitant antiplatelet therapy. Anticoagulation and antiplatelet therapy should be managed closely throughout their course of therapy to ensure patients are maintained within their target therapeutic INR range. In the event of a bleeding event, standardized protocols should be used to assist clinicians in determining how to treat the immediate bleed while supporting the VAD, when and how to reverse anticoagulation and when to restart in order to minimize the risk for a subsequent thrombotic event.

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Bleeding Related to Cardiac Surgery

34

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Introduction and History of Transfusion in Cardiac Surgery

Remarkably, cardiac surgery has been performed for over 100 years. The first description of a successful cardiac surgery was by Dr. Ludwig Rehm in which he repaired a stab wound to the right ventricle in 1896 [1]. During the same year, Dr. Stephen Paget wrote that "surgery of the heart has probably reached the limits set by nature to all surgery" [2]. Not until pioneering work by Dr. John Gibbon led to the development of the heart-lung machine was cardiopulmonary bypass feasible, thereby allowing him to perform the first successful open heart surgery [3]. This single innovation allowed for tremendous expansion in the field of cardiac surgery in the 1950s and 1960s. With this expansion came the realization of major complications related to bleeding in patients undergoing cardiac surgery.

In patients undergoing cardiac surgery, approximately 5% of patients will have major bleeding complications, and this patient population accounts for up to 25% of the blood products transfused annually in the United States [4]. There are many factors contributing to bleeding complications in cardiac surgery patients, related not only to the technically difficult surgical procedures at hand but also to non-surgical coagulopathic bleeding. Notably, alterations in coagulation experienced during cardiopulmonary bypass were initially described by Dr. Gibbon, who observed bleeding complications with prolonged pump runs on the heart-lung machine [3]. In addition to intraoperative events that contribute to clinical bleeding in cardiac surgery patient, there are also preoperative and postoperative factors to consider that could lead to excessive bleeding during the perioperative period. In this chapter we will discuss the major risk factors that influence bleeding in patients undergoing cardiac surgery and discuss the various strategies that can be utilized in managing and preventing bleeding in these complex patients.

Risk Factors for Bleeding in Cardiac Surgery

Anticoagulants

The underlying conditions for which a patient may need cardiac surgery often require anticoagulation. All anticoagulant agents are risk factors for bleeding.

Warfarin

Warfarin competitively inhibits the subunit 1 of the multiunit vitamin K epoxide reductase (VKOR) complex and depleting functional vitamin K reserves and reduces synthesis of active clotting factors (factors II, VII, IX, and X as well as proteins C and S). Commonly encountered in the preoperative setting due to historical use, and reversible, warfarin is FDA approved for prophylaxis and treatment of thromboembolic disorders, embolic complications arising from atrial fibrillation or cardiac valve replacement, and as an adjunct to reduce risk of systemic embolism after myocardial infarction [5–8].

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Unfractionated Heparin (UFH) and Low-Molecular-Weight Heparin (LMWH)

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) bind antithrombin inducing a conformational change and inhibit factors Xa and IIa. Due to a short, predictable half-life and ease of titration, UFH is still the drug of choice for patients on extracorporal membrane oxygenation and cardiopulmonary bypass and for bridging therapy in patients with other mechanical circulatory support (MCS) devices and thus is also commonly encountered in the preoperative setting. UFH is more readily reversible than LMWH. Both are frequently used in the postoperative setting as well as for venous thromboembolism (VTE) prophylaxis and bridging therapy in valve replacement patients [5–8].

Bivalirudin

Bivalirudin acts as a specific and reversible direct thrombin inhibitor. Bivalirudin binds both circulating and clot-bound thrombin and inhibits coagulant effects by preventing thrombin-mediated cleavage of fibrinogen to fibrin monomers and activation of factors V, VIII, XI, and XIII. Encountered in urgent surgeries following cardiac catheterization procedures, but irreversible, bivalirudin is FDA approved for use in conjunction with aspirin for patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) with provisional glycoprotein IIb/IIIa inhibitor, as well as in conjunction with aspirin for patients undergoing PCI with (or at risk of) heparin-induced thrombocytopenia (HIT)/thrombosis syndrome (HITTS) [5–8].

Dabigatran

Dabigatran is a direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Dabigatran inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers; activation of factors V, VIII, XI, and XIII; and inhibition of thrombin-induced platelet aggregation. Dabigatran is FDA approved for stroke prevention in patients with atrial fibrillation, VTE treatment, and prophylaxis. Dabigatran is one of the direct oral anticoagulants (DOACs). Idarucizumab is a humanized monoclonal antibody fragment indicated in reversal of dabigatran for emergency surgery and in life-threatening or uncontrolled bleeding [5–9].

Rivaroxaban, Apixaban, Betrixaban, and Edoxaban

These drugs are factor Xa inhibitors and known as direct oral anticoagulants (DOACs). These were designed not to require routine monitoring, with the aim of making them more desirable choices than warfarin. Rivaroxaban and apixaban are FDA approved for VTE prophylaxis after hip and knee surgery, risk reduction for VTE occurrence in those with recurrent VTE, treatment of VTE, and risk reduction of stroke in nonvalvular AF. *Betrixaban is used for VTE primary prophylaxis. Edoxaban is used for VTE treatment and for risk reduction of stroke in nonvalvular AF. Andexanet alfa is a recombinant modified human factor Xa protein indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding* [5–8, 10].

Antiplatelet Agents

As with anticoagulant agents, cardiac patients are often candidates for antiplatelet therapy. All antiplatelet agents are risk factors for bleeding.

Aspirin

Aspirin reduces platelet aggregation by non-selectively and irreversibly inhibiting cyclooxygenase, reducing prostaglandin and thromboxane A2 synthesis. Aspirin decreases mortality and ischemic events in coronary artery bypass surgery patients. Aspirin is also shown to improve coronary artery bypass graft patency and decrease the incidence of stroke, renal failure, and bowel infarction. However, five of six randomized controlled trials determined that preoperative aspirin increases blood loss as measured by chest tube drainage, increased blood transfusion rates, or increased the frequency of mediastinal re-exploration [11–16]. In patients undergoing coronary artery bypass graft (CABG), preoperative aspirin administration resulted in 200–400 mL of increased chest tube drainage, and between 0.5 and 1 unit of increased red blood cell (RBC) transfusion, when compared to controls. The Society of Thoracic Surgeons (STS) practice guidelines recommend stopping aspirin therapy 3–5 days before elective CABG surgery [5, 7], but risks and benefits of discontinuation of preoperative aspirin should be carefully assessed for complicated cases.

Clopidogrel

Clopidogrel inhibits platelet aggregation by blocking the effects of adenosine diphosphate at its receptor, which inhibits adenosine diphosphate-mediated activation of the glycoprotein IIb/IIIa receptor. Clopidogrel is FDA approved to decrease thrombotic events after acute MI, cerebrovascular accident, established peripheral arterial disease, non-ST segment elevation MI, and acute ST segment elevation MI. Most studies demonstrate that when clopidogrel is given within 5 days of surgery, there is an increased risk of bleeding, an increase in blood transfusions, and an increase in the need for re-exploration for bleeding [5, 7].

Ticagrelor

Ticagrelor, a cyclopentyl-triazolopyrimidine, inhibits platelet aggregation by blocking the effects of adenosine diphosphate at its receptor, which inhibits adenosine diphosphate-mediated activation of the glycoprotein IIb/IIIa receptor, similar to clopidogrel [5, 7]. However, ticagrelor exhibits reversible binding, resulting in greater difficulty overcoming drug effect with platelet transfusion alone.

Epoprostenol

Epoprostenol (Flolan™), also known as prostacyclin, is a strong vasodilator of all vascular beds. Epoprostenol is a potent endogenous inhibitor of platelet aggregation, activating intracellular adenylate cyclase and increasing cyclic adenosine monophosphate concentration and thus decreasing thrombogenesis and platelet clumping in the lungs. Epoprostenol is used for pulmonary arterial hypertension, including intraoperative pulmonary hypertension during cardiac surgery with cardiopulmonary bypass [17, 18], and thus may contribute to intraoperative and postoperative bleeding.

Cangrelor

Cangrelor, a nonthienopyridine adenosine triphosphate analogue, is a direct $P2Y_{12}$ platelet receptor inhibitor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor binds selectively and reversibly to the P2Y12 receptor, preventing further signaling and platelet activation. Cangrelor is used for percutaneous coronary intervention and bridging prior to cardiac surgery. For bridging therapy prior to cardiac surgery, cangrelor may be started following thienopyridine discontinuation for up to 7 days prior to surgery and then discontinued 1 to 6 hours prior to surgical incision [19].

Renal Insufficiency

Renal insufficiency may accompany cardiac disease, especially in advanced stages. Chronic renal insufficiency has been associated with a bleeding diathesis consisting mostly of bruising, nasal and oral mucosal bleeding, and gastrointestinal bleeding. The risk for major bleeding episodes in hemodialysis patients increases significantly while on aspirin and/or warfarin. Renal insufficiency also presents an increased bleeding risk secondary to acquired platelet dysfunction, abnormal platelet-vessel wall interaction, and anemia [20–22].

Hepatic Dysfunction

The cardiac causes of hepatic dysfunction include constrictive pericarditis, severe pulmonary arterial hypertension, mitral stenosis, tricuspid regurgitation, cor pulmonale, and ischemic cardiomyopathy. All of these lead to passive congestion due to elevated right ventricular pressure and right-sided heart failure. Untreated, longstanding congestion can lead to chronic congestive hepatopathy. Acute ischemic hepatitis can also result from instances of severe hypoxemia and profound systemic hypotension due to cardiac failure. Impairment of liver function will decrease the production of most coagulation factors, as the hepatocyte is the exclusive source of all clotting factors except for factor VIII and VWF. Vitamin K-dependent clotting factors (factors II, VII, IX, and X) may be defective in function as a result of decreased γ-carboxylation. VWF, factor VIII and fibrinogen are acute phase reactants that tend to arise in the early phase of liver failure; however, decreased level of fibrinogen is found with advanced liver failure [20, 21, 23–25]. Decreased baseline factors will increase the likelihood of intraoperative dilutional coagulopathy.

Previous Chest Radiation

Radiation has important early and delayed effects on skin and connective tissues. The early responses are predominantly due to cytotoxic effects of radiation on the epithelium. The mechanisms underlying the delayed responses are more complex; all layers of the skin are involved, and vascular damage and fibrosis are prominent features. The vasomotor properties of irradiated blood vessels are abnormal, and bleeding and hematoma formation may occur. Cardiac surgery on previous irradiated tissue is associated with increased risk of wound infection and dehiscence [20, 26].

Reoperation

Cardiac reoperation represents one of the main challenges in cardiac surgery. The reoperation rate for CABG is approximately 3% at 5 years and 11% at 10 years. The number of patients undergoing reoperation for valvular heart disease is increasing as the general population ages. Resternotomy is associated with risks of cardiac injury and catastrophic hemorrhage [20].

Hypothermia

Therapeutic hypothermia, the intentional reduction of the body core temperature, has been applied as a neuroprotective measure during cardiac surgeries. Hypothermia has been loosely categorized as mild (33–36 °C), modest (32–34 °C), moderate (28–32 °C), and severe(16–28 °C). Hypothermia-induced coagulopathy is multifactorial. Platelet dysfunc-

tion, increased fibrinolytic activity, and decreased activity of coagulation cascade enzymes all contribute to bleeding during hypothermia as well as during rewarming. Coagulopathy and thrombocytopenia appear to occur more frequently in spontaneous hypothermia after trauma than after medically induced hypothermia [20, 27, 28].

Hyperfibrinolysis

Deposition of fibrin within the vascular system converts the proenzyme plasminogen into the active enzyme plasmin, which in turn degrades fibrin. Under normal circumstances, plasminogen-to-plasmin conversion is regulated by activators such as tissue plasminogen activator (t-PA), urokinase plasminogen activator, and activated factor XII. These profibrinolytic activators are opposed by plasminogen activator inhibitor (PAI), α2 antiplasmin, and thrombin-activatable fibrinolysis inhibitor (TAFI). Hyperfibrinolysis may result if there is imbalance among these regulators and increases the risk of hemorrhage. Hyperfibrinolysis is increased in cardiopulmonary bypass, hepatic dysfunction, and trauma patients [20, 23].

Dilutional Coagulopathy

Patients with massive blood loss through surgery or trauma are resuscitated with fluids to restore blood volume and prevent hemorrhagic shock. Infusion of fluids often starts with crystalloids and colloids due to availability and then follows with red blood cells to prevent tissue hypoperfusion and hypoxia. An operative definition of massive transfusion is transfusion of more than 10 units of RBCs within 24 hours, or more than 4 units of RBCs within 1 hour. Unless accompanied by plasma and platelets, massive transfusion of RBCs results in dilution of coagulation factors as well as platelets and lowering of the hemostatic potential with subsequent increased bleeding. This may be clinically observed as prolonged bleeding from wound surfaces after surgical control or as spontaneous bleeding from uninjured surfaces [20, 29, 30].

Hypocalcemia

Acute hypocalcemia <0.9 mmol/L is a common complication of colloid-induced hemodilution in severe trauma patients. Citrate is a primary component of blood additive solutions, binding calcium and thereby reducing serum levels of the ionized calcium fraction. Fresh frozen plasma contains a greater concentration of citrate than RBCs. The vitamin K-dependent factors II, VII, IX, and X and phospholipids are negatively charged; positively charged ionized calcium acts as a bridge between these surfaces and serves to enhance coagulation factors at the site of damaged endothelium. Intracellular calcium mobilization is also required for platelet incorporation into the developing thrombus and platelet aggregation. Furthermore, calcium plays an important role in conversion of fibrinogen to fibrin [20, 28]. If massive transfusion is required during cardiac surgery, ionized calcium levels should be frequently monitored, and calcium adequately replaced, usually with intravenous administration of calcium chloride.

Management of Bleeding in Cardiac Surgery

Risk Assessment

Assessment of the risk of major perioperative bleeding should include an understanding of the type of surgery, including use of cardiopulmonary bypass and hypothermia, a comprehensive history and physical, including noting of personal or family history of bleeding, personal history of renal dysfunction, hepatic dysfunction, active cancer and chemotherapy, and, if available, laboratory evaluation of residual effects of antithrombotic agents, as well as an understanding of any need for reinitiation of antithrombotic therapy within 24 hours after the surgery. To some degree, all cardiac surgeries must be considered high risk for bleeding [31].

More than six million patients in the United State receive long-term anticoagulation therapy for the prevention of thromboembolism due to atrial fibrillation, placement of a mechanical heart-valve prosthesis, venous thromboembolism, or mechanical circulatory support device. After the placement of a coronary-artery stent, use of dual antiplatelet therapy (combination treatment with aspirin and a thienopyridine) has dramatically increased [32]. Annually, approximately 10% of patients taking antithrombotic agents undergo surgical or other invasive procedure [33]. The goal in these patients is to minimize both thromboembolic events and major hemorrhage in the perioperative period [21]. Management involves balancing the risk of perioperative bleeding with continued treatment or use of bridging anticoagulation therapy against the thrombotic risk with suspension of treatment [5]. Guidelines from scientific societies with graded levels of evidence, as well as prior review articles, provide direction for perioperative management of antithrombotic medications [5, 6]. Bridging anticoagulation therapy is considered standard of care in patients who are at high risk for thromboembolism when anticoagulation therapy is suspended and to minimize the risk of bleeding after high-risk surgery. In most cases, bridging anticoagula-

tion therapy is used in patients receiving warfarin [5, 6, 8], and cangrelor, a reversible P2Y12 inhibitor, may be used as a bridging antiplatelet agent in cardiac surgery patients receiving a thienopyridine [19, 34]. Laboratory assays to assess residual drug effect may include prothrombin time/international normalized ratio (INR), activated partial thromboplastin time, thrombin time, anti-Xa, and platelet aggregometry or other platelet function assays. Delaying surgery to allow drug clearance on complex cases requires a multidisciplinary discussion (Table 34.1).

Reversal of Antithrombotic Agents

When urgent or emergent surgeries are required, there are various option for the management of antithrombotic agents. The administration of reversal agents may be considered if the risk of bleeding outweighs the risk of thrombotic events (Table 34.2).

Massive Transfusion

Of all blood transfusion in the United States, 20% were associated with cardiac surgery, with 13% of those going to patients undergoing combined CABG and valve replacement surgery [20]. Uncontrolled hemorrhage and, by way of consequence, massive transfusion are a frequent complication of trauma and surgery [30]. After transfusion of more than four units of RBCs within 1 hour, transfusion of blood products has been advocated to be kept as plasma, platelets, and red blood cells in a 1:1:1 ratio. *A 1:1:1 ratio achieved better hemostasis and had fewer deaths by exsanguination at 24 hours*, although overall mortality rate at 24 hours and at 30 days did not differ from a 1:1:2 ratio [36]. Rapid turnaround time for laboratory testing can improve management of massive bleeding by more appropriately targeting blood components therapy and/or pharmacologic augmentation of the hemostatic system according to identified abnormalities in coagulation system [37]. Calcium supplementation to

Table 34.1 Overview of antithrombotic agents [5–10, 29]

Agent	Mechanism of action	Recommended interval between last dose and surgery
Anticoagulant agents		
Warfarin	Inhibition of vitamin K dependent factors for γ carboxylation and proteins C and S	1–8 days, depending on INR and patient characteristics: INR decreases to ≤1.5 in approximately 93% of patients within 5 days
Unfractionated heparin	Complex formation with antithrombin and heparin cofactor II and release of tissue factor pathway inhibitor (inhibition of factors IIa, VIIa, IXa, XIa, and XIIa)	IV, 2–6 hr., depending on dose. Subcutaneous, 12–24 hr., depending on dose
LMWH	Complex formation with antithrombin and heparin cofactor II and release of tissue factor pathway inhibitor (inhibition of factors IIa, VIIa, IXa, XIa, and XIIa)	12–24 hr
Fondaparinux	Antithrombin activation(factor Xa inhibitor)	36–24 hr
Bivalirudin	Direct thrombin inhibitor	2–6 hr., depending on dose and creatinine clearance
Dabigatran	Direct thrombin inhibitor	1 or 2 days with creatinine clearance rate of ≥50 ml/min; 3–5 days with creatinine clearance rate of <50 mL/min
Apixaban	Direct factor Xa inhibitor	1 or 2 days with creatinine clearance of >60 mL/min; 3–5 days with creatinine clearance of <60 mL/min
Betrixaban	Direct factor Xa inhibitor	3–4 days depending on dose and creatinine clearance
Edoxaban	Direct factor Xa inhibitor	1–2 days depending on dose and creatinine clearance
Rivaroxaban	Direct factor Xa inhibitor	≥1 day with normal renal function; 2–4 days with creatinine clearance rate of <90 ml/min
Desirudin	Direct thrombin inhibitor	2 hr
Antiplatelet agents		
Aspirin	Irreversible cyclooxygenase inhibitor	7–10 days
Dipyridamole	Phosphodiesterase inhibitor	7–10 days
Cilostazol	Phosphodiesterase inhibitor	7–10 days
Thienopyridine agents (clopidogrel, prasugrel, ticlopidine)	P2Y12 receptor antagonist	5 days (clopidogrel), 7 days (prasugrel), or 10–14 days (ticlopidine)
Ticagrelor	Reversible P2Y12 receptor antagonist	5–7 days
Cangrelor	Direct P2Y12 receptor antagonist	1 to 6 hr

Table 34.2 Reversal of antithrombotic agents [5–9, 35]

Agents	Laboratory monitoring	Reversal agents	Comments
Anticoagulant agents			
Warfarin	INR	Oral or intravenous vitamin K, fresh frozen plasma; 4-factor PCCs	Compared to FFP, PCC requires less volume
Unfractionated heparin	PTT, anti-Xa, TEG™, or ROTEM™	Protamine sulfate	If time permits, hold intervention for 4 hr. to avoid the need for protamine
LMWH	Anti-Xa	Protamine sulfate (partial neutralization)	Protamine is only partially effective. LMWH clearance should be gauged with GFR in mind
Fondaparinux	None, consider fondaparinux-specific anti-Xa assays	None, rFVIIa in patients with major bleeding	Elimination is impaired in stage IV/V chronic kidney disease
Bivalirudin	PTT, thrombin time for residual effect, dilute thrombin time, ecarin chromogenic assay	None, rFVIIa in patients with major bleeding	Clearance is impaired with renal dysfunction
Dabigatran	PTT, thrombin time for residual effect	Idarucizumab (Praxbind)	Reversal agent not widely available
DOACs (rivaroxaban, Apixaban, edoxaban, Betrixaban)	Anti-factor Xa activity (using specific drug calibrator curve, or if unavailable, LMWH curve)	Andexanet alfa, if unavailable, PCC	Reversal agent not widely available, PCC higher risk of thrombosis
Antiplatelet agents			
Aspirin	LTA-arachidonic acid, PFA-100™, VerifyNow™	Platelet transfusion, desmopressin	Laboratory assays need clinical validation
P2Y12 receptor antagonists (clopidogrel, prasugrel, ticlopidine, ticagrelor)	LTA-ADP, VerifyNow™	Platelet transfusion, consider rFVIIa in patients with major bleeding	Precise FDA indications vary according to specific drug

FFP fresh frozen plasma, *PCC* prothrombin complex concentrate, *LMWH* low molecular weight heparin, *GFR* glomerular filtration rate, *LTA* light transmittance aggregation

keep ionized calcium >1.00 mmol/L and avoidance or correction of hypothermia may be critical in patients receiving massive transfusion [30].

Hemostatic Agents

Antifibrinolytic Drugs

A degree of fibrinolysis is to be expected after cardiac surgery. In current clinical practice, true hyperfibrinolysis apparent in vitro by TEG™ or ROTEM™ is a rare occurrence. Tranexamic acid (TXA) and epsilon aminocaproic acid (Amicar™) are synthetic lysine-analogues that reversibly block the lysine binding site of plasminogen, which inhibits the lysis of polymerized fibrin. These agents have a plasma half-life of around 2 hr. and are excreted in urine. The most commonly used regimen for TXA is 10 mg/kg bolus followed by 1 mg/kg/hr. as a continuous infusion, whereas for Amicar™ a 5 g bolus is followed by 1 g/hr. as a continuous infusion. Seizures are the main reported adverse event with TXA. Both agents have been shown to reduce blood loss when used prophylactically in cardiac surgery [21, 29, 38].

Aprotinin was a bovine-derived serine protease inhibitor which has powerful antiplasmin and anti-kallikrein effects. In high doses, it reduces bleeding in cardiac surgery. Despite a positive effect on RBC transfusion and reduction in blood loss, a retrospective analysis of 4000 patients by Mangano et al. detected an increase in the incidence of renal failure, myocardial infarction, and heart failure in the aprotinin group compared with TXA, Amicar™, and placebo. This was confirmed in the randomized controlled BART trial. The trial was terminated early due to excess mortality in patients who received aprotinin, despite decreased blood loss and transfusion. This led to withdrawal of aprotinin from the market [29].

Desmopressin

Desmopressin (DDAVP) is a vasopressin analogue which triggers release of endogenous VWF stored in the Weibel-Palade bodies of endothelial cells, as well as factor VIII, prostacyclin, and tissue plasminogen activator. The drug is typically administered no more frequently than once in 24 hr. and is useful as an adjunct in uremic and cirrhotic bleeding. Rapid administration can lead to hypotension, and the antidiuretic hormone-like effect can lead to fluid retention and potentially hyponatremia [20, 29, 39].

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) can be used as a rescue therapy for severe, intractable bleeding without an identifiable surgical source that is unresponsive to routine approaches after cardiac procedures on cardiopulmonary bypass [6]. rFVIIa may lead to thrombotic complications, especially in patients at high risk [39–42]. Patients undergoing routine cardiac surgery may be at substantially higher risk for development of thrombotic complications with rFVIIa because of elevated systemic levels of tissue factor and thrombin that occur during CPB [37]. However, patients receiving lower doses (10–20 μg/kg) may have a lower incidence of thromboembolic events [43].

Prothrombin Complex Concentrate (PCC)

4-factor PCCs contain a high concentration of lyophilized clotting factors II, VII, IX, and X and proteins C and S [44]. These compounds are currently licensed in Europe and the United States for the treatment of congenital or acquired deficiency of these clotting factors and for the emergency reversal of vitamin K antagonists, such as warfarin, for patients who are bleeding or when urgent surgery is planned [6, 45]. Compared with FFP, 4-factor PCC is administered in much smaller volumes without consideration of blood groups, is free of many safety issues of plasma as an allogeneic blood component, and has a shorter time to efficacy [6]. 4-factor PCCs may be an alternative to FFP in patients who are coagulopathic and bleeding after cardiac surgery, particularly when intravascular administration of fluid must be limited due to concern of right ventricular dysfunction and the risk of lung injury [45, 46]. PCC use may be associated with increased risk for thromboembolic events, usually in patients with other prothrombotic risk factors [43]. Analysis of a pharmacovigilance report after 15 years of clinical use of a 4-factor PCC showed a low risk of thromboembolic events (1:31,000) [47].

Summary and Recommendations

- Cardiac surgery includes a subpopulation of surgical patients that account for nearly 25% of all blood products transfused in the United States.
- Bleeding complications seen during cardiac surgery can be broadly divided into risk factors related to medication effect, previous medical illness, technical surgical issues, and physiologic changes related to cardiopulmonary bypass (CPB).
- Medications that prevent coagulation such as heparin (unfractionated heparin, low molecular weight heparin), vitamin K antagonist (warfarin), direct thrombin inhibitors (bivalirudin, dabigatran), and factor Xa inhibitors (rivaroxaban, apixaban), as well as medications that decrease platelet aggregation such as cyclooxygenase inhibitors (aspirin), P2Y12 receptor inhibitors (clopidogrel, prasugrel, ticagrelor), and prostacyclin (epoprostenol) increase significantly the risk for bleeding complications.
- A history of liver disease which can lead to impairment of coagulation factors, thrombocytopenia, and/or hyperfibrinolysis, as well as renal disease which can result in an acquired platelet dysfunction, are established risk factors for increased bleeding.
- Technical surgical issues including resternotomy and previous chest irradiation are associated with increased risk for cardiac injury, bleeding, wound infection and dehiscence.
- Physiologic changes seen with CPB include dilutional effect, hypocalcemia, and hypothermia, which can result in intraoperative coagulopathy. Additionally, hypothermia and the bypass circuit itself can result in platelet dysfunction. Finally, hyperfibrinolysis can occur during CPB and disrupt the balance of hemostasis leading to an increased risk for bleeding.
- Management for bleeding during cardiac surgery includes risk assessment and delay of surgery if necessary, reversal of anticoagulation, massive transfusion including calcium supplementation, and use of hemostatic agents.
- Reversal of antithrombotic agents is typically seen with protamine sulfate for unfractionated heparin and use of oral/IV vitamin K, fresh frozen plasma, or 4-factor prothrombin complex concentrate for reversal of the effects of warfarin. Reversal agents for other anticoagulants, like idarucizumab and andexanet alfa, are now available but may be challenging to obtain.
- Desmopressin can be utilized for those patients with an increased risk for bleeding secondary to platelet dysfunction related to renal disease.
- Antifibrinolytic agents, such as tranexamic acid and aminocaproic acid, have been shown to decrease bleeding and use of blood products during cardiac surgery.
- For patients with severe bleeding during cardiac surgery, use of prothrombin complex concentrate and/or recombinant factor VIIa can be utilized. However, use of these agents may be associated with an increased risk for thromboembolic complications. Judicious use of these agents at doses less than manufacturers' recommendations has been shown to decrease bleeding while reducing the risk for thromboembolic complications.

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Bleeding Related to Liver Transplant

35

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Hemostasis in Cirrhosis and Liver Failure: Model of "Rebalanced" Hemostasis

Hemostasis is based on complex interactions between blood cells, endothelial cells, hepatocytes, and plasmatic coagulation factors, with complex feedback mechanisms including amplification and inhibition loops. The term "hemostasis" highlights the sensible equilibrium between pro- and anticoagulants as well as fibrinolytic and antifibrinolytic factors [1–4].

Since most coagulation factors are produced in the liver, their plasma levels are decreased in cases of chronic or acute liver disease. The vitamin K-dependent coagulation factors II, VII, IX, and X—as well as factor V—and the vitamin K-dependent coagulation inhibitors proteins C and S, as well as antithrombin, are affected particularly [1–4]. In contrast, von Willebrand factor (VWF) and coagulation factor VIII, which are synthesized in the vascular endothelium, are normal or increased significantly in cirrhosis and compensate for the low level of vitamin K-dependent factors and low platelet count. Furthermore, the activity of the VWF cleaving enzyme ADAMTS13—a metalloprotease exclusively produced in hepatic stellate cells—is reduced in cirrhosis. This deficiency of ADAMTS13, in particular 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. Eventually, this can result in multiple organ failure [5–7]. 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. Therefore, it may be useful in predicting long-term survival of cirrhotic patients [8]. Accordingly, some patients with end-stage cirrhosis show conditions similar to thrombotic thrombocytopenic purpura (TTP). Besides sequestration of platelets in the spleen due to portal hypertension and subsequent hypersplenism, this mechanism may substantially contribute to thrombocytopenia in cirrhosis [9, 10]. Thrombocytopenia seems to rebalance the increased platelet adhesion and aggregation resulting from increased levels of large VWF multimers in plasma and decreased ADAMTS13 activity [4]. Therefore, platelet transfusion should be restricted to bleeding complications since it may result in further liver damage and exacerbated portal and portopulmonary hypertension [11–13]. Notably, platelet dysfunction and acquired dysfibrinogenemia may also occur in cirrhosis [1, 14, 15]. Furthermore, changes in pro- and antifibrinolytic drivers have been reported. Plasminogen and alpha$_2$-antiplasmin levels decrease, while tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) levels simultaneously increase [1, 2]. Endotoxemia and subsequent tissue factor expression on monocytes are common in patients with cirrhosis or during and after liver transplantation [11]. Therefore, infection and sepsis can quickly result

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in alterations in hemostasis in cirrhotic patients by inducing disseminated intravascular coagulation (DIC) [16, 17]. Similar but more pronounced changes of pro- and anticoagulant factors are observed in acute liver injury and failure [18]. However, data regarding fibrinolysis in acute liver dysfunction are inconclusive [18, 19]. Recent studies showed evidence for a shutdown of fibrinolysis rather than hyperfibrinolysis in acute liver failure, similar to the early phase of sepsis [19–21]. In conclusion, hemostasis in cirrhosis is rebalanced at a low level, but can result in thrombosis or hemorrhage, depending on concomitant risk factors and the clinical situation (Fig. 35.1) [1–4, 22]. Nevertheless, patients with cirrhosis seem to be more at risk for thrombosis than bleeding, even if limitations of standard laboratory coagulation tests suggest hypocoagulability [1, 23]. Therefore, prophylactic correction of laboratory results by transfusion of blood products may have a deleterious effect on cirrhotic patients [1, 2, 24–28].

"Car-Based Model of Hemostasis" in Cirrhosis

Hemostasis in cirrhosis can also be described like an old car with a starter issue. Here, the starter issue reflects the impaired extrinsic system with low levels of factors VII, X, V, and II. However, if the system is once started, thrombin generation is amplified by high factor VIII activities, which means that the "engine" is running well. The main issue in cirrhosis is that the "brakes" are not working due to low antithrombin and activated protein C levels. Accordingly, patients with cirrhosis can on the one hand present a high international normalized ratio (INR) (reflecting the "starter" issue) but on the other hand may develop thrombosis (reflecting the "brakes" issue) (Fig. 35.2).

Coagulation Tests in Cirrhosis and Liver Failure

In order to understand the concept of rebalanced hemostasis in cirrhosis, knowledge of the scope and limitations of standard laboratory coagulation tests, viscoelastic hemostatic tests (VHT), and point-of-care (POC) platelet function testing is essential [29–31].

Standard Laboratory Coagulation Testing

The prothrombin time (PT) test, first described in 1935, was developed and implemented to monitor anticoagulation with vitamin K antagonists (VKA) [32]. 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 extrinsic procoagulant factors in plasma, but it is neither capable of measuring the activity of the vitamin K-dependent anticoagulant proteins C and S nor the complex interaction of cells and coagulation factors in whole blood [1–4]. Due to the use of different thromboplastins, results from different laboratories and reagents are not comparable. The INR was established—and is indeed useful—to monitor anticoagulation in patients on VKA. Later,

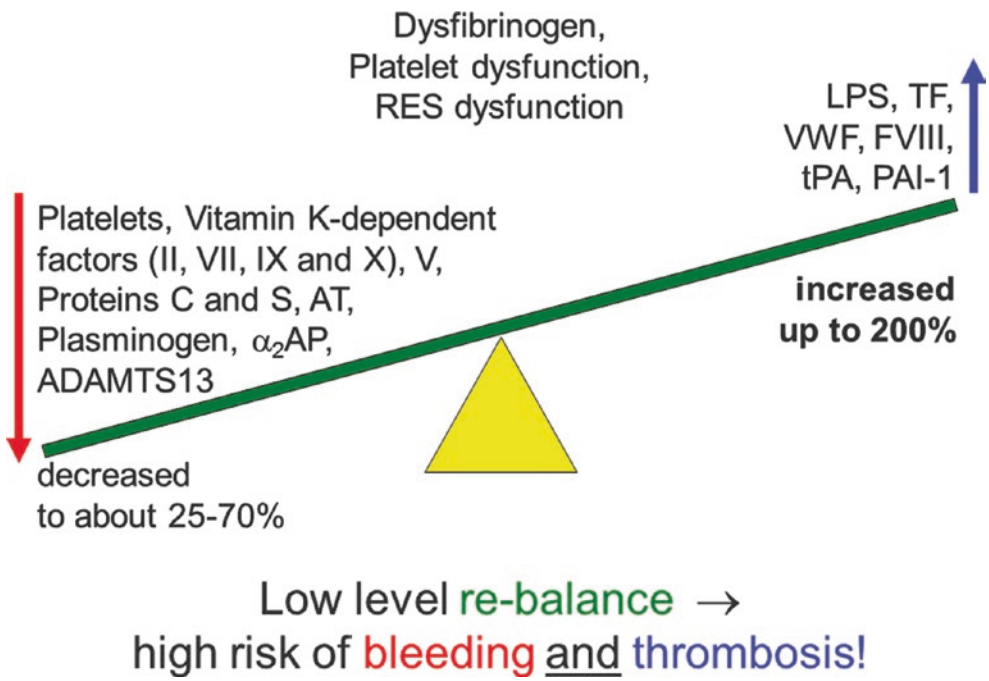

Fig. 35.1 Hemostasis in cirrhosis. In cirrhosis hemostasis is rebalanced at a low level associated with a high risk of bleeding and thrombosis. RES, Reticuloendothelial system; LPS, lipopolysaccharide, TF; tissue factor; AT, antithrombin; α2 AP, α2 antiplasmin; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. Courtesy of Klaus Görlinger, Essen, Germany

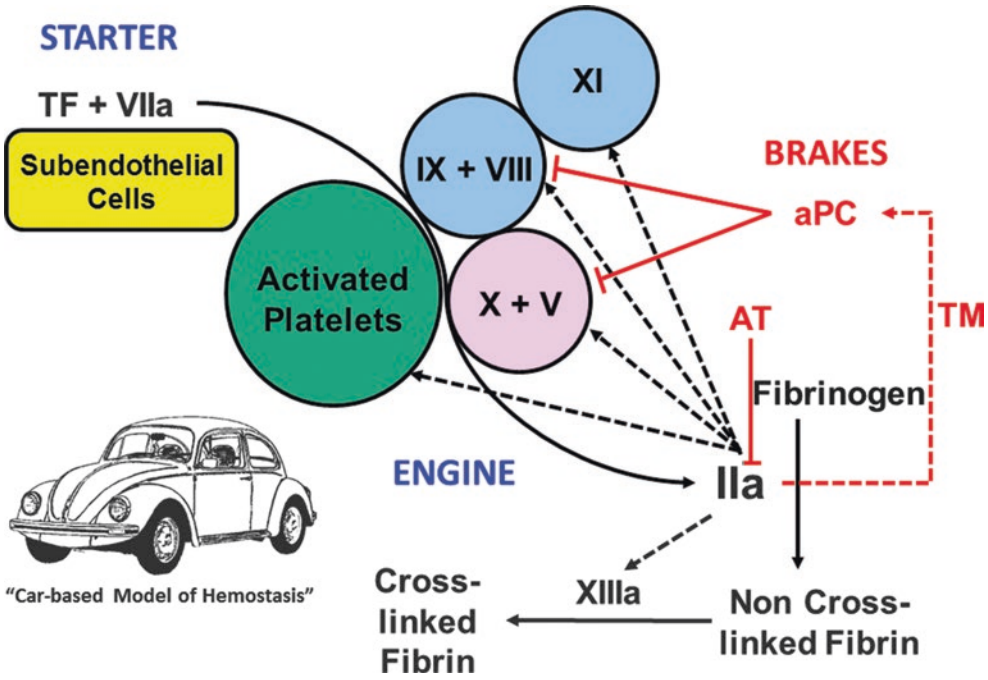

Fig. 35.2 "Car-based model of hemostasis" in patients with cirrhosis. aPC, Activated protein C; AT, antithrombin; TF, tissue factor; TM, thrombomodulin; V, VIII, IX, X, and XI, coagulation factors V, VIII, IX, X, and XI; VIIa, activated coagulation factor VII; XIIIa, activated coagulation factor XIII. Courtesy of Klaus Görlinger, Essen, Germany

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 or invasive interventions is poor [29, 33–35]. This has been demonstrated in patients with cirrhosis and patients undergoing liver transplant as well [1, 24, 36–44]. In particular, no correlation could be observed between PT and the bleeding time observed directly on the liver surface during laparoscopic liver biopsy [45, 46]. However, the validity of the INR as a prognostic parameter in liver dysfunction is not affected by this finding [36, 42].

Thrombin Generation Assays

Thrombin generation (TG) assays measure the endogenous thrombin potential (ETP) by adding phospholipids and thromboplastin to platelet-poor plasma (PPP) or platelet-rich plasma (PRP): the main parameters are the lag time, velocity, and area under the reaction curve. According to the TG assay in PPP, 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 cirrhotic patients—cannot be reflected by this basic TG assay performed in the absence of platelets and thrombomodulin. Notably, the thrombin-thrombomodulin complex is essential for the activation of the protein C system [1]. The thrombin-thrombomodulin-protein C system on intact endothelial cell shuts down thrombin generation by inactivating the accelerators factors V and VIII and activates fibrinolysis by inactivation of PAI-1. This keeps clotting localized at the site of injury and prevents DIC and thrombosis. In patients with acute and chronic liver disease, results of TG assays were indistinguishable from those in healthy volunteers and may even show higher thrombin generation in the presence of soluble thrombomodulin [1, 19, 46]. Similar results can be achieved by the addition of Protac™ (Pentapharm, Basel, Switzerland), a snake venom that activates protein C in a manner similar to thrombomodulin [18, 47–49]. Furthermore, the results of TG assays are modified by the presence or absence of platelets [50–52]. 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 [53]. In summary, modified TG assays can be useful for the determination of hemostatic function in patients with liver dysfunction and cirrhosis, but they have the major drawback of not being timely available as standard laboratory tests.

Viscoelastic Hemostatic Testing (Thromboelastometry/ Thromboelastography)

Viscoelastic hemostatic testing (VHT) such as thromboelastometry (ROTEM™, Tem Innovations GmbH, Munich, Germany) and thromboelastography (TEG™, Haemonetics,

Niles, IL) is 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, CLI30, CLI60) [43, 54, 55]. 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. Therefore, they can be used to guide hemostatic therapy in severe bleeding, including patients undergoing liver transplantation [56–60]. 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 [61–63]. 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 [64–68]. 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 [64, 65, 69]. On the other hand, algorithms based on a panel of ROTEM™ reagents may avoid platelet transfusion when goal-directed fibrinogen substitution is more appropriate (Fig. 35.3 and Chapter 7, Figs. 7.4a–c) [54, 57, 63, 64, 70–76]. 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 [77–79]. The negative effect of platelet activation, platelet consumption, and platelet transfusion on outcome in patients with liver failure and/or undergoing liver transplant has been confirmed by other authors [11, 12, 80, 81]. Notably, viscoelastic tests showed normo- [36, 82–86] or even hypercoagulability [18, 87–93] in patients after liver resection or liver transplantation or with hepatic malignancies or acute liver failure, further challenging the bleeding tendency concept in liver dysfunction. Hypercoagulability seems to be better detected by whole blood thromboelastometry than by TG tests using platelet-poor plasma (see Chapter 7) [51]. Furthermore, tissue factor expression on monocytes, detected by thromboelastometry in septic patients as well as in patients undergoing liver transplantation or extracorporeal organ support, as well as fibrinolytic shutdown may play an important role in hypercoagulability and thrombosis in liver cirrhotic patients (see Chapter 7) [11, 19–22, 94–98].

Due to the higher diagnostic performance, higher predictive value for bleeding and thrombosis compared to limitations of standard laboratory coagulation tests, and the ability to guide hemostatic therapy during and after liver transplantation and major liver resections, viscoelastic testing is increasingly used in high-volume liver transplant and surgery centers and is recommended as the standard of care in this setting [26, 54, 55, 60, 99–113]. For more details on thromboelastometry, see Chapters 6 and 7 [54].

Platelet Function Testing

Perioperative platelet function testing—in particular in combination with viscoelastic hemostatic testing (VHT)—has been shown to be effective in reducing blood loss and transfusion requirements in cardiac surgery [114–117]. Here impedance aggregometry has been shown to be the most reliable and reproducible POC test, providing a high predictive value for bleeding and thrombosis [118–121]. In patients undergoing liver transplantation, rapid changes of platelet function—in particular by using ADP as an activator—have been shown to be associated with liver graft damage and worse patient outcomes as it is proven for platelet transfusion in this setting [5, 11–13, 81]. Furthermore, platelet adhesion and aggregation seem to be increased in cirrhosis due to a disbalance of high VWF and low ADAMTS13 levels [5–7]. In liver transplant patients at risk of hepatic artery thrombosis, impedance aggregometry can be used to assess the effect of antiplatelet drugs [122–127]. Notably, impedance aggregometry results may be influenced by platelet counts $<150 \times 10^3/mm^3$ [128]. This may limit the value of platelet function testing in patients with cirrhosis and severe thrombocytopenia $<50 \times 10^3/mm^3$. Notably, 3-month non-survivors showed a drop in TRAPTEM AUC 2–3 weeks after liver transplantation after an initial recovery of platelet function [129]. Therefore, TRAPTEM might be an important biomarker to identify patients at risk for serious complications after liver transplantations such as liver rejection and portal vein and hepatic artery thrombosis and may allow for identification of these patients before hospital discharge. For more details on impedance aggregometry, see Chapter 6 [54].

Bleeding Management in Patients with Cirrhosis/Liver Dysfunction

Bleeding management should always also consider the risk of thrombotic events—in particular in patients with cirrhosis. A "therapeutic window" concept seems to be able to reduce both bleeding and thrombotic events as described in Chapter 7 [54].

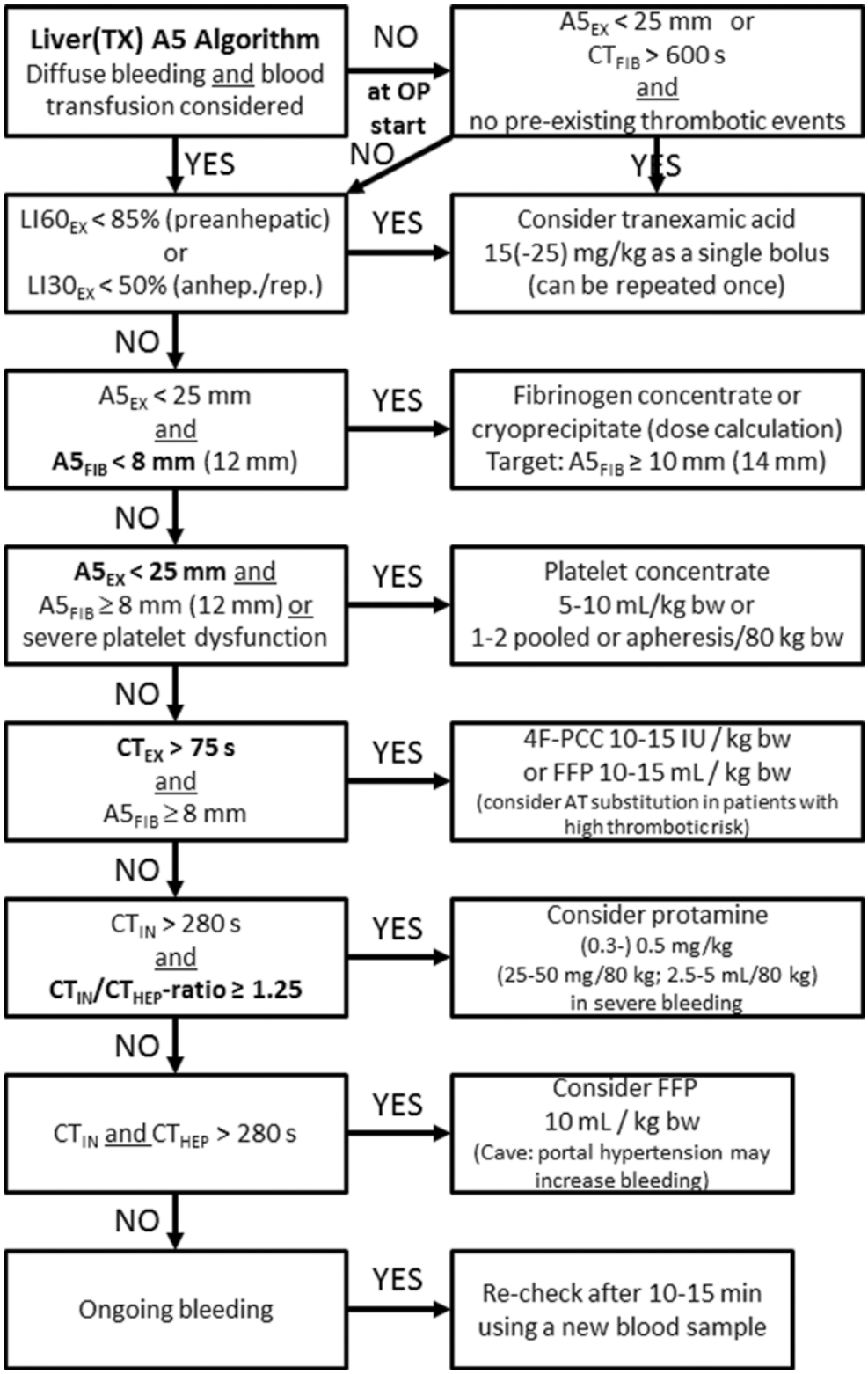

Fig. 35.3 Evidence-based ROTEM™ A5 bleeding management algorithm in liver disease and transplantation. $A5_{EX}$ Amplitude of clot firmness 5 min after CT in EXTEM; $A5_{FIB}$ amplitude of clot firmness 5 min after CT in FIBTEM; *bw* body weight in kg; CT_{EX} coagulation time in EXTEM; CT_{FIB} coagulation time in FIBTEM (CT_{FIB} > 600 s reflects a flat-line in FIBTEM); CT_{HEP} coagulation time in HEPTEM; CT_{IN} coagulation time in INTEM; *FFP* fresh frozen plasma; *IU* international units; $LI30_{EX}$ $(LI60_{EX})$ lysis index described as remaining clot firmness in percentage of maximum clot firmness (MCF) 30 (60) minutes after CT; *4F-PCC* 4-factor prothrombin complex concentrate. Courtesy of Klaus Görlinger, Essen, Germany

Bleeding Management in Patients with Cirrhosis/Liver Dysfunction Suffering from Acute Gastrointestinal Bleeding

Severity of acute gastrointestinal bleeding correlates well with portal hypertension and transfusion-associated circulatory overload (TACO). Therefore, a restrictive transfusion strategy has been shown to be superior compared to a liberal transfusion concept in this setting [24, 130–132]. Notably, gastrointestinal bleeding is the only setting where a restrictive transfusion strategy was not only equally effective but superior regarding 6-week mortality, TACO, cardiac complications, and pulmonary edema [131]. Notably, TACO is a leading cause of transfusion-related fatalities in the USA and UK with an incidence of 3–5.5% of transfused patients [133–135]. Furthermore, therapy with prothrombin complex concentrate (PCC) was superior to plasma transfusion in gastrointestinal hemorrhage due to warfarin therapy [132]. Time to INR correction and bleeding control was significantly shorter and length of stay in the emergency department significantly shorter in the PCC compared to the plasma-treated group. However, therapy with coagulation factor concentrates should not be done blindly but guided by timely available and meaningful hemostatic assays such as thromboelastometry [24, 43, 109, 110, 136, 137].

Bleeding Management in Patients with Cirrhosis/Liver Dysfunction Undergoing Invasive Interventions

According to the concept of balanced hemostasis in cirrhosis and liver dysfunction, the administration of blood products and coagulation factors in order to correct laboratory values, e.g., prior to invasive interventions, is inappropriate [1, 2, 18]. Nevertheless, plasma and platelet transfusions are still used for pre-procedural prophylaxis in cirrhosis patients [34, 35, 138–140], and in the UK, cirrhosis is one of the factors associated with a greater use of prophylactic plasma transfusion [141]. However, a high proportion of current plasma transfusion is of unproven clinical benefit and has to be considered as inappropriate [34, 35, 140–149]. Notably, several recently published studies have proven that using a restrictive, thromboelastometry-/thromboelastography-guided strategy is able to reduce prophylactic hemostatic interventions significantly without any increase in bleeding or thrombotic complications [24, 38–41, 87]. One randomized controlled trial (POCKET-RCT) is actually running to compare efficacy and safety of three transfusion strategies (standard coagulation test-based vs. ROTEM™-based vs. restrictive protocol) for central venous catheterization in cirrhotic patients [150].

Bleeding Management in Patients Undergoing Liver Transplantation: Impact on Transfusion Requirements, Patient Outcomes, and Health-Care Costs

As mentioned before, viscoelastic testing is increasingly used in high-volume liver transplant and surgery centers and is recommended as the standard of care due to their higher diagnostic performance, higher predictive value for bleeding and thrombosis compared to standard coagulation laboratory tests, and their ability to guide hemostatic therapy during and after liver transplantation and major liver resections [3, 55, 99–106]. Several studies could demonstrate a significant reduction in bleeding and transfusion requirements, massive transfusion rate, and transfusion-associated costs without an increase in thrombotic/thromboembolic complication rates [3, 26, 60, 71–74, 80, 100, 109–113, 151–159]. In these studies, the transfusion requirements for red blood cells (RBC), plasma, and platelets could be reduced by up to 62%, 95%, and 66%, respectively, and the incidence of massive transfusion (≥10 units of RBC) by up to 66% [155]. The need for an off-label use of recombinant activated factor VII (rFVIIa) could be eliminated completely after implementation of a ROTEM™-guided bleeding management algorithm in several studies [155]. Furthermore, Leon-Justel et al. demonstrated a significant reduction in the incidence of postoperative complications, such as reoperation for bleeding, acute kidney failure, or hemodynamic instability (5% vs. 13.0%, $p = 0.048$, 2% vs. 17%, $p = 0.001$, and 16% vs. 29%, $p = 0.028$, respectively), in the POC group (mobile laboratory unit including ROTEM™) [156]. Accordingly, Zamper et al. demonstrated a reduction of any transfusion from 58 to 37% ($p = 0.019$), of any thromboembolic event from 6.0 to 3.7%, of arterial thrombosis from 3.5 to 1.9%, of in-hospital mortality from 6.0 to 1.9%, and of hospital length of stay in survivors from 16.3 to 11.3 days [112]. Only one small ($n = 60$) prospective before-and-after cohort study reported a trend to more plasma transfusion in the ROTEM™-guided compared to the control group. However, the transfusion of plasma was not guided by the ROTEM™ algorithm used in this study but was based on anesthetist's discretion, estimated blood loss (>60 mL/kg), and/or number of transfused RBC (>4 units), solely [160]. The trend to more plasma transfusion can be explained by the change in the plasma transfusion trigger between the two cohorts. In the first (without ROTEM™) cohort, plasma was transfused not earlier than an estimated blood loss of at least 60 mL/kg in a dose of 10–15 mL/kg body weight, whereas in the second (with ROTEM™) cohort, plasma transfusion was started already after the transfusion of the fourth unit RBC in a dose of 15–20 mL/kg, independent from the ROTEM™ results. This resulted in a lower incidence (23% vs. 40%) but higher

amount of plasma transfusion (8 vs. 5 units per patient) in the second cohort. This clearly demonstrates that ROTEM™ diagnostics should always be implemented in conjunction with a reasonable bleeding management algorithm [109]. Actually, at least one prospective observational study (Massicotte L, Montreal, Canada, NCT02356068, 2015), one prospective interventional study (Blasi A, Barcelona, Spain, NCT03011827, 2017), and one randomized controlled trial (RCT) (Bonnet A, Lyon, France, NCT02352181, 2015) are running to assess the predictivity, efficacy, and safety of a ROTEM™-guided bleeding management algorithm in patients undergoing liver transplantation.

Algorithm for Thromboelastometry-Guided Bleeding Management in Patients Undergoing Liver Transplantation

The Essen University algorithm for thromboelastometry-guided bleeding management in liver transplantation, first published in 2006, clearly defines the indication, dose, and sequence of each hemostatic intervention in bleeding patients during or after liver transplantation [3, 70–72, 109]. This algorithm is used in cirrhotic patients with bleeding complications and patients undergoing major visceral surgery such as liver resection, too. It is also used to avoid unnecessary prophylactic interventions prior to invasive interventions such as liver biopsy in cirrhotic patients [38, 39]. The algorithm has been shown to reduce transfusion requirements in patients undergoing liver transplantation and major visceral surgery without increasing the incidence of thrombotic/thromboembolic events [60, 71–74, 109, 110, 112]. Our evidence-based ROTEM™ A5 liver transplant bleeding management algorithm is displayed in Fig. 35.3 and discussed in the following paragraphs. In the USA, the algorithm is actually guided by the amplitude of clot firmness 10 min after CT (A10 in EXTEM and FIBTEM). A ROTEM™ A5 FDA-approval study is actually running.

Since the amount of blood transfusion and need for massive transfusion are the best predictor of morbidity and mortality in patients undergoing liver transplantation, all therapeutic interventions which might reduce the need for allogeneic blood transfusion and might help to avoid thrombotic/thromboembolic complications should be included in such a liver transplant bleeding management protocol. This includes cell salvage, restrictive volume therapy, implementation of a reasonable thromboelastometry-/thromboelastography-guided liver transplant bleeding management algorithm, and implementation of a dedicated liver transplant anesthesia team [35, 44, 77, 156, 161–169].

Timing of Blood Sampling During Liver Transplant

During liver transplantation, ROTEM™ analysis should be performed at the following time point:

1. At baseline (to assess preexisting hemostatic disorders and to predict transfusion requirements) [170].
2. Recheck after 60 min or in case of bleeding during preanhepatic phase.
3. 5–10 min after cava clamping (early anhepatic phase).
4. 30–45 mm after cava clamping (late anhepatic phase).
5. 5–10 min after reperfusion.
6. 30–45 min after reperfusion.
7. At skin closure.
8. Always in case of diffuse bleeding as well as 10–15 min after a specific hemostatic intervention (in particular if the intervention failed to stop bleeding).

Hemostatic Preconditions

Hypothermia (<35 °C), acidosis (pH <7.2), hypocalcemia (Ca_i^{++} < 1 mmol/L), and severe anemia (Hb < 7 g/dL) can impair thrombin generation and primary hemostasis [171]. Therefore, blood gas analysis should be checked in addition to ROTEM™ analysis in particular during the anhepatic and reperfusion phase. The risk of hypothermia is particularly high in infants due to their small body weight and high body surface. In combination with acidosis, hyperkalemia, and hypocalcemia after reperfusion, hypothermia can aggravate coagulopathy and can result in severe hypotension, bradycardia, and even cardiac arrest [172, 173]. Acidosis can also enhance fibrinolysis [174]. In particular during the anhepatic phase, rapid transfusion of high amounts of plasma can result in citrate intoxication and anticoagulation [175–177]. High amounts of calcium gluconate or calcium chloride may be needed to antagonize this effect [172, 178]. This issue can be avoided by using coagulation factor concentrates (fibrinogen concentrate and/or PCC) instead of plasma for correcting coagulopathy.

Management of Fibrinolysis (Aprotinin, Epsilon-Aminocaproic Acid, and Tranexamic Acid)

In the 1980s and 1990s, most liver transplant centers treated their patients prophylactically with antifibrinolytic drugs such as aprotinin, epsilon-aminocaproic acid (EACA), or tranexamic acid (TXA). At that time, transfusion requirements in patients undergoing liver transplantation were very

high, and the administration of antifibrinolytic drugs reduced these transfusion requirements significantly [179–186]. During the last 10–15 years, more and more concerns about the efficacy and safety of a prophylactic administration of antifibrinolytic drugs have arisen—boosted by the marketing dispensation of aprotinin [187–192]. Furthermore, implementation of POC VHT allowed for a timely and specific detection of hyperfibrinolysis in this setting [70, 102, 127, 190–195]. Several studies demonstrated that the ROTEM™- or TEG™-guided therapy with antifibrinolytic drugs is as effective as a prophylactic administration in patients undergoing liver transplantation but avoids potential thromboembolic complications [71, 196].

The incidence of hyperfibrinolysis in patients undergoing liver transplantation has been reported between 6.7% and 84.1% during liver transplantation and depends on the cutoff value used to define severe fibrinolysis/hyperfibrinolysis (from 15 to 50% within 1 h) [66, 70, 191, 195–197]. Furthermore, fibrinolysis can be aggravated by acidosis, fibrinogen deficiency, colloids (HES > gelatin > albumin), factor XIII deficiency, platelet factor 4 liberation, and platelet dysfunction (in particular in the ADP pathway) [53, 174, 198–200]. Accordingly, this complex interaction can only be assessed by VHA but not by plasmatic coagulation tests.

Notably, patients with acute liver failure present with a fibrinolytic shutdown rather than hyperfibrinolysis as shown for patients with sepsis, too [19, 20]. Therefore, prophylactic administration of antifibrinolytic drug might rather be harmful than beneficial in this patient population.

According to our algorithm, TXA (15–25 mg/kg as a single bolus which can be repeated once if hyperfibrinolysis is detected later on during liver transplantation) is only given prophylactically at the beginning of surgery if the patient has a significantly increased risk of hyperfibrinolysis of about 90%. This has been reported for patients with a baseline TEG™ MA ≤ 35 mm or a ROTEM™ $A5_{EX}$ < 25 mm [194, 201]. Furthermore, a flat-line in FIBTEM (CT_{FIB} > 600 s) seems to be associated with a very high incidence of hyperfibrinolysis during liver transplantation (Fig. 35.3) [202]. Notably, the viscoelastic hemostatic fibrinogen assays FIBTEM (ROTEM™) and TEG™ Functional Fibrinogen are about five times more sensitive to fibrinolysis than the standard EXTEM or kaolin-TEG™ assays [197, 203]. However, the prophylactic administration of antifibrinolytics should strictly be avoided in patients with preexisting thrombotic events [188–192].

Notably, tPA activity is increased during the anhepatic phase, whereas PAI-1 activity is decreased. Accordingly, the fibrinolytic activity achieves a peak level after reperfusion of the liver graft [193, 204]. However, hyperfibrinolysis developed during the anhepatic phase or reperfusion is self-limiting in most cases after reperfusion and not associated with increased mortality (in contrast to hyperfibrinolysis during the pre-anhepatic/resection phase or in severe trauma) [70, 191, 195, 205, 206]. Therefore, hyperfibrinolysis is only treated with TXA according to our algorithm in case of severe bleeding and a $LI60_{EX}$ < 85% during the pre-anhepatic phase or a $LI30_{EX}$ < 50% during the anhepatic phase or after reperfusion (Fig. 35.3 and Chap. 7, Fig. 7.5b). In the absence of severe bleeding during the anhepatic or reperfusion phase, ROTEM™ is rechecked after detection of hyperfibrinolysis and not treated with TXA if it is self-limiting. A continuous infusion of antifibrinolytic drugs is generally avoided, but a second bolus can be administered in case of recurrence of hyperfibrinolysis (incidence < 0.1%).

Management of Clot Firmness (Fibrinogen and Platelets)

Early variables of clot firmness (A5 and A10) in EXTEM and FIBTEM are rapid available and reliable thromboelastometric parameters to identify thrombocytopenia and hypofibrinogenemia in patients undergoing liver transplantation [58–60]. This is crucial in the management of bleeding in liver transplant and other settings. EXTEM A5 can reliably identify a platelet count below 50 × 10^3/mm^3 and 30 × 10^3/mm^3 with a cutoff value of 19 mm and 15 mm, a sensitivity of 82.1% and 86.3%, a specificity of 77.5% and 76.5%, and a ROC AUC of 0.871 and 0.9, respectively. The cutoff values of EXTEM A10 are about 10 mm higher (see Chapter 6, Table 6.4) [56, 63]. FIBTEM A5 and A10 can identify a plasma fibrinogen concentration below 100 mg/dL with a cutoff value of 4 and 5 mm, a sensitivity of 81.3% and 76.2%, a specificity of 76.5% and 82.0%, and a ROC AUC of 0.857 and 0.866, respectively [57]. EXTEM and FIBTEM A5 show an excellent correlation to A10 (r = 0.99 and 1.0, respectively) and MCF (r = 0.97 and 0.99, respectively). The difference in A5 (A10) between EXTEM and FIBTEM—the so-called A5 (A10) PLTEM (platelet contribution to clot firmness)—even correlates better with platelet count compared to A5 (A10) in EXTEM (r = 0.85 and 0.74; p = 0.04) [63]. However, clot firmness in FIBTEM, EXTEM, and PLTEM does not only reflect plasma fibrinogen concentration and platelet count but provide additional information about fibrin polymerization disorders, e.g., due to dysfibrinogens produced by the liver in cirrhosis, colloid effects, and factor XIII deficiency [131, 149], as well as about platelet dysfunction affecting the thrombin receptor (PAR = protease activatable receptor) pathway [129]. Accordingly, EXTEM and FIBTEM A5 (A10) have been shown to better predict bleeding than platelet count and plasma fibrinogen concentration [33, 207] and therefore have to be considered as the best predictors for bleeding and blood transfusion in patients undergoing liver transplantation besides detection of severe hyperfibrinolysis [60, 70, 170, 208]. Blasi et al.

identified an EXTEM A10 value of 35 mm and a FIBTEM value of 8 mm as the best cutoff value for the need of platelet transfusion and fibrinogen administration, respectively [208]. This is in line with our experience and data published by other authors in this setting [3, 60, 70, 152, 153, 156, 209–211]. Whereas EXTEM A5 (A10) gives information whether bleeding is most probably based on a clot strength issue, FIBTEM A5 (A10) can further differentiate between a fibrinogen deficiency/fibrin polymerization issue and a low platelet count/platelet dysfunction issue. Since standard viscoelastic hemostatic assays can only detect platelet dysfunction related to the thrombin receptor pathway, thromboelastometry (ROTEM™ *delta*) is complemented by whole blood impedance aggregometry (ROTEM™ *platelet* module) assessing the cyclooxygenase (ARATEM), ADP receptor (ADPTEM), and PAR-1 pathway (TRAPTEM) (further detail is provided in Chapter 7) [54]. Using the before mentioned ROTEM™, cutoff values in interventional trials resulted in a significant reduction in transfusion requirements in patients undergoing liver transplantation [60, 71–74, 110, 112, 154–156]. Accordingly, these cutoff values for EXTEM and FIBTEM A5 (A10) are used in our algorithm (Fig. 35.3), too, and management of clot firmness is considered as the second most important step of the liver transplant bleeding management algorithm. Here, clot firmness will be increased by fibrinogen substitution in case of bleeding, EXTEM A5 (A10) < 25 (35) mm, and FIBTEM A5 (A10) < 8 (9) mm. The dose of fibrinogen concentrate (Haemocomplettan™ P, CSL Behring GmbH, Marburg, Germany, marketed in the USA under the tradename RiaSTAP™, or Fibryga™, Octapharma AG, Lachen, Switzerland) or cryoprecipitate can be calculated based on the targeted increase in FIBTEM A5 or A10 (Table 35.1) [73, 212]. Instead of the table presented in Table 29.1, the following formula can be used for fibrinogen dose calculation [213, 214]:

$$\text{Fibrinogen dose}\,(\text{g}) = \text{targeted increase in FIBTEM A5}\,(\text{mm}) \times \text{bogy weight}\,(\text{kg})\,/\,160$$

Here, the correction factor (140–160 mm kg g^{-1}) is dependent on the actual plasma volume, and it has to be considered that the FIBTEM A5 (A10) increase reached finally can be lower than the calculated increase in severe bleeding.

Here, fibrinogen dose calculation is based on the targeted increase in FIBTEM A5 (A10) in mm [65, 190]. In case of severe bleeding, the achieved increase in FIBTEM A5 (A10) may be lower than the calculated increase. Courtesy of Klaus Görlinger, Essen, Germany

Since fibrinogen concentrate has a well-defined fibrinogen concentration (a 1 g vial contains 0.9–1.3 g to be dissolved in 50 mL aqua ad injectabile resulting in a final fibrinogen concentration of 20 g/L), dose calculation is much more precise compared to cryoprecipitate which usually contains a fibrinogen concentration between 8 and 16 g/L [212]. Accordingly, a pool of 10 units of cryoprecipitate contains about 2 g fibrinogen. Fibrinogen concentrate is approved in Germany since 1985 for hereditary hypo-, dys-, and afibrinogenemia, as well as for any case of acquired hypofibrinogenemia, whereas it is actually FDA approved for hereditary fibrinogen deficiency, solely. In cirrhosis, the high factor VIII and VWF content of cryoprecipitate might be an issue in patients with cirrhosis setting since these compounds are considered as important factor for a progress in liver fibrosis [7]. However, there are actually no data comparing the efficacy and safety of fibrinogen concentrate versus cryoprecipitate available in this setting.

According to our algorithm, platelet transfusion is considered in case of bleeding, if EXTEM A5 (A10) < 25 (35) mm and FIBTEM A5 (A10) ≥ 8 (9) mm (Fig. 35.3 and Chap. 7, Fig. 7.5d). Here, one pooled or apheresis platelet concentrate can increase EXTEM A5 (A10) by at maximum 8 mm [52, 215, 216]. Therefore, transfusion of one platelet concentrate (or 5 mL/kg body weight in infants and children) may be sufficient to reach an EXTEM A5 target of >25 mm if EXTEM A5 was between 17 and 24 mm before platelet transfusion. In case of a pre-transfusion EXTEM A5 between 10 and 16 mm, usually two platelet concentrates (or 10 mL/kg body weight in infants and children) are necessary to reach this target, whereas a pre-transfusion EXTEM A5 < 10 mm usually requires the combined administration of platelets (two pooled units or apheresis unit of 10 mL/kg body weight) and fibrinogen (25–50 mg/kg body weight). ROTEM™-guided platelet transfusion in patients undergoing liver transplantation has been shown to be able to avoid 75% of platelet transfusion without excessive bleeding compared to an approach with prophylactic platelet transfusion in case of a platelet count below 50 × 10^3/mm^3 [80]. This concept has a high

Table 35.1 FIBTEM-guided fibrinogen substitution

Targeted increase in FIBTEM A5 (A10) (mm)	Fibrinogen dose (mg/kg bw)	Fibrinogen concentrate (mL/kg bw)	Cryoprecipitate (mL/kg bw)
2	12.5	0.6 (1 g/80 kg)	1 (5 U/80 kg)
4	25	1.2 (2 g/80 kg)	2 (10 U/80 kg)
6	37.5	1.9 (3 g/80 kg)	3 (15 U/80 kg)
8	50	2.5 (4 g/80 kg)	4 (20 U/80 kg)
10	62.5	3.1 (5 g/80 kg)	5 (25 U/80 kg)
12	75	3.8 (6 g/80 kg)	6 (30 U/80 kg)

potential to reduce platelet transfusion-related complications in patients undergoing liver transplantation [24, 74, 77–79].

Furthermore, a shift to higher fibrinogen levels in case of bleeding after reperfusion by using a higher FIBTEM A5 (A10) cutoff (<12 mm) and targeted value (≥14 mm) might be reasonable to avoid potential harmful platelet transfusion and is considered in our algorithm (Fig. 35.3) since platelet transfusion is in general the hemostatic intervention with the highest complication rate and in particular during reperfusion has been shown to reduce 1-year survival rate in patients undergoing liver transplantation significantly [77–79]. Several studies could prove the concept that higher fibrinogen levels can compensate for low platelet counts [213, 214, 217]. However, this has still to be confirmed for the liver transplant setting by prospective randomized trials.

Management of Thrombin Generation (Prothrombin Complex Concentrate, Plasma, and Recombinant Activated Factor VII)

A prolonged EXTEM CT should only be considered as an indicator for impaired thrombin generation in the presence of a normal A5 (A10) in FIBTEM since fibrinogen deficiency results in a EXTEM CT prolongation, too [197, 218]. In bleeding patients undergoing liver transplantation, an EXTEM CT > 75 s seems to be the best cutoff value to trigger a therapeutic intervention [60, 170]. Potential therapeutic options to increase the activity of enzymatic coagulation factors and subsequent thrombin generation are plasma transfusion or the administration of four-factor PCC (4F-PCC) or rFVIIa. Since the activity of factor VIII—synthesized by the endothelium—is significantly elevated in cirrhosis, the vitamin K-dependent coagulation factors II, VII, IX, and X as well as factor V are the most limiting factors for thrombin generation in this setting [1–4].

Accordingly, we primarily use in our algorithm 4F-PCCs (Beriplex™ P/N, CSL Behring GmbH, Marburg, Germany, or Octaplex™, Octapharma AG, Lachen, Switzerland) in a dose of 10–15 IU/kg body weight in this constellation without an increase in thrombotic/thromboembolic events (Fig. 35.3) [24, 70–74, 110, 219]. In cardiovascular surgery, the incidence of thrombotic/thromboembolic events could even be significantly increased by implementing a bleeding management algorithm based on ROTEM-guided therapy with coagulation factor concentrates [114, 115, 220]. 4F-PCCs 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 and therefore provide a very good safety profile [74, 221–223]. Notably, these 4F-PCCs are already approved in Germany since 1996 for the prophylaxis and therapy of bleeding in patients with a hereditary or acquired deficiency of vitamin K-dependent coagulation factors. Our first study, reporting about the efficacy of 4F-PCCs to correct coagulopathy in patients with cirrhosis has been published in 1994 and later has been confirmed by other authors [24, 25, 38, 39, 74, 112, 132, 224–229]. In the first years, the administration of 4F-PCC was complemented by antithrombin; however, this seems not to be necessary to prevent thrombotic/thromboembolic complications when guided by thromboelastometry and may be also based on the high proteins C and S content of these products [24, 70–74, 219]. In patients undergoing liver transplantation, the administration of antithrombin might even increase bleeding due to the liberation of heparinoids during liver graft reperfusion (see Section Management of Endogenous (Auto-)Heparinization). On the other hand, antithrombin administration may be considered in patients presenting hypercoagulability (increased EXTEM clot firmness and decreased EXTEM CT) and a significant hemostatic disbalance based on a normal activity of procoagulants but a severe antithrombin deficiency. However, the evidence for this approach is low. Notably, 4F-PCC (Kcentra™, CSL Behring GmbH) is actually FDA approved for warfarin reversal, solely, whereas Octaplex™ (Octapharma AG) is licensed in Canada for the same broad spectrum of indications as in Europe [230–233]. Nevertheless, broader use of 4F-PCC is under debate in the USA, too [116, 212, 234–236].

Whereas PT and INR were designed and perform well to monitor the effect of oral anticoagulation with VKA, they overestimate coagulopathy in cirrhosis. Accordingly, INR and EXTEM CT—but not INTEM CT or kaolin-TEG™ or rapid-TEG™ r-time—correlate very well in patients treated with warfarin but not in patients suffering from cirrhosis [74, 219, 237–239]. Accordingly, administration of PCCs guided by INR bares a high risk of overtreatment and thrombosis in patients with cirrhosis—in particular if given prophylactically [1, 24, 34, 35, 38, 39]. An RCT (PROTON trial; EudraCTN 2011-005650-54) comparing prophylactic PCC administration to placebo in patients with increased INR (≥1.5) before liver transplantation has stopped recruiting patients [240].

Even high amounts of plasma (10–20 mL/kg body weight) are quite ineffective to correct coagulopathy in cirrhosis [140, 241]. Therefore, the potential benefits of plasma transfusion have to be balanced against their real risks. In order to avoid TACO with portal hypertension, transfusion-related lung injury (TRALI), and transfusion-related immunomodulation (TRIM) with nosocomial infection and sepsis, we restricted plasma transfusion in our algorithm to bleeding based on a deficiency of coagulation factors not provided by fibrinogen concentrate or 4F-PCC, e.g., factors V, VIII, and XI [122, 130, 133, 162, 163, 165–168, 242–244]. This is

indicated by a normal CT in EXTEM but a prolonged CT in INTEM, not corrected in HEPTEM. Plasma should only be transfused in case of bleeding because INTEM and HEPTEM CT can also be prolonged due to the presence of lupus anticoagulant or low factor XII levels which are not associated with bleeding.

Of note, rFVIIa (NovoSeven™, Novo Nordisk A/S, Bagsværd, Denmark) is not labeled for the use in cirrhosis and liver transplantation, and studies failed to demonstrate a significant benefit in bleeding of the upper gastrointestinal tract or in liver transplantation but showed a significant increase in arterial thromboembolic events [244–247]. Keeping the increased risk of thrombosis in mind, the off-label use of rFVIIa (45–90 μg/kg body weight) in patients with severe bleeding unresponsive to other hemostatic interventions (cryoprecipitate, platelet, and plasma transfusion) might be considered—in particular if 4F-PCCs are not available [101, 116, 248, 249]. However, the off-label use of rFVIIa was not any more necessary after implementation of our ROTEM™-guided liver transplant bleeding management algorithm [71–74].

Management of Endogenous Heparin-Like Effects (HLE) (with Protamine)

During liver graft reperfusion, liberation of heparinoids (glycosaminoglycans) from the glycocalyx of the damaged liver endothelium often occurs [16, 250–252]. This is associated with a prolongation of the activated partial thromboplastin time (aPTT), the kaolin-TEG™ r-time, and the INTEM CT. Here, a heparin-like effect (HLE) can be confirmed by a shortening of the r-time in the heparinase-TEG™ or of the CT in HEPTEM, respectively (Fig. 35.3) [70, 102, 193, 202, 250, 253–256]. The HLE can be quantified by the INTEM/HEPTEM CT ratio, and a significant effect is considered at ratios ≥1.25 (mild HLE) [257]. INTEM/HEPTEM CT ratios >2.0 (severe HLE) have been shown to be associated with increased 3-month mortality after liver transplantation [258]. In severe bleeding, a HLE can be antagonized by small amounts of protamine (25–50 mg in an adult) (Fig. 35.3) [193, 259, 260]. However, this is rarely necessary since the effect is most often short acting and self-limiting. Of note, a protamine overdose itself can prolong coagulation times (INTEM and EXTEM) and furthermore can result in severe platelet dysfunction and bleeding [261–263]. Therefore, the administration of protamine should be considered carefully, and an overdose should strictly be avoided. Similar endogenous HLE have been recently reported in severe trauma [263, 264].

ROTEM™ Reassessment

10–15 min after a therapeutic intervention which failed to stop bleeding, ROTEM™ analysis should be reassessed using a new blood sample and running the algorithm again.

Thrombotic Complications in Patients with Cirrhosis/Liver Dysfunction

Patients with cirrhosis and liver dysfunction are not "auto-anticoagulated" [2, 265, 266]. In contrast, global coagulation assays such as thromboelastometry and ETP show more hypercoagulability with an inherent risk of thrombosis [18]. Several studies demonstrated that thromboelastometry/thromboelastography (EXTEM MCF > 68 mm) can identify thrombosis in patients with cardiovascular diseases with a sensitivity and specificity of 94% and can predict thrombosis in patients undergoing major noncardiac surgery with a ROC AUC of 0.751 (INTEM and EXTEM A10), whereas standard laboratory coagulation tests have no predictive value. FIBTEM values below 24 mm are not predictive for thrombosis [92, 267–269]. However, FIBTEM MCF results >25 mm have been shown to be associated with a fivefold increased risk of portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma [93, 270]. Furthermore, FIBTEM MCF results >23 mm on day 3 after liver transplantation have been predictive for thromboembolic complications in patients with preexisting thrombophilic factors (low protein C, low protein S, low antithrombin, increased homocysteine, increased antiphospholipid IgG/IgM antibodies, increased lupus anticoagulant, and positive factor V Leiden) [91].

Besides deep vein thrombosis (DVT), 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 due to high factor VIII and VWF and low protein C and ADAMTS13 levels [5–8, 266]. Furthermore, 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 [271]. Accordingly, venous thromboembolism (VTE) prophylaxis is required during the hospitalization of patients with liver dysfunction—in particular in patients with malignancies or other preexisting thrombophilic factors [90, 272–275]. Nevertheless, 75% of these patients do not receive any VTE prophylaxis [276, 277].

Thromboprophylaxis in Patients with Cirrhosis/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 [278]. Notably, 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. The recently published European guidelines on perioperative venous thromboembolism prophylaxis suggested that the use of pharmacological prophylaxis in patients with severe liver dysfunction should be carefully balanced against the risk of bleeding. If a treatment is administered, the use of LDUH (low-dose unfractionated heparin) or LMWH (low molecular weight heparin) is suggested (Grade 2C) [279].

Notably, a study investigating the prevention of portal vein thrombosis in patients with chronic liver disease proved the efficacy and safety of enoxaparin application (4000 U subcutaneously once daily) in cirrhotic patients [280]. Prophylactic use of LMWH in patients with cirrhosis appears to be safe [281]. However, 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 antithrombin, due to reduced hepatic synthesis, is the most likely cause of this phenomenon [281].

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 [282, 283]. Since argatroban is mainly metabolized in the liver, it should be used with caution in patients with liver dysfunction and/or hyperbilirubinemia [284, 285]. Despite some absolute contraindications (e.g., peripheral vascular disease), mechanical 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 [286].

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36 Percutaneous Image-Guided Interventions Including Solid Organ Biopsies

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Introduction

Management of bleeding in patients undergoing interventional procedures is complex owing to the wide range of comorbidities and anticoagulants currently involved in hemostatic dynamics. The field is further complicated by a paucity of data providing guidelines on how to manage patients' bleeding risks. Many studies used to guide bleeding management are provided by surgical literature; however, interventional procedures differ from open invasive procedures by the inability to see and directly control sources of bleeding during the procedures. Complications related to bleeding from interventional procedures are often delayed [1, 2]. It is therefore important to reduce the pre-procedural risk when performing interventional procedures.

Bleeding Parameters

Although a full discussion of the coagulation cascade and mechanism of coagulopathies is beyond the scope of this chapter, a brief discussion of the most important parameters used to guide pre-procedural risk is detailed here.

Table 36.1 Coagulation marker thresholds [1]

	Low risk	Moderate risk	High risk
INR	Correct to less than 2	Correct to less than 1.5	Correct to less than 1.5
Platelets	Transfuse under 50,000/mm^3	Transfuse under 50,000/mm^3	Transfuse under 50,000/mm^3
PTT	No consensus	No consensus	Correct so value is less than 1.5× control unless lupus anticoagulant without coagulopathy

International Normalized Ratio

The coagulation cascade is composed of two distinct components: the extrinsic and intrinsic pathways which converge into a common pathway. Activation of clotting factors within these pathways leads to the final product of producing a fibrin clot that forms a barrier over breaks within the endothelium from which blood can escape [3, 4]. Prothrombin time (PT) is a measure of the extrinsic and common pathways with international normalized ratio (INR) being a standardized calculation of the PT that negates the effects of laboratory variation. An elevated INR confers an increased risk of bleeding. INR is elevated from warfarin therapy, vitamin K deficiency, disseminated intravascular coagulation (DIC), severe liver injury, and other causes such as congenital extrinsic coagulation factor deficiency (factor VII, X, V, II, or I) or coagulation factor inhibitor [5].

Activated Partial Thromboplastin Time

Activated partial thromboplastin time (PTT) measures the intrinsic pathway and can be elevated by liver disease, intrinsic factor deficiency such hemophilia A and B, lupus anticoagulant, and anticoagulants such as heparin, warfarin, some direct oral anticoagulants (DOAC), and direct thrombin inhibitor such as bivalirudin and argatroban. Certain causes

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of an elevated PTT can increase bleeding risk, such as intrinsic factor deficiency or the use of heparin. A single elevated lab value may revert to a normal value on repeated testing in the presence of lupus anticoagulant. Of note, lupus anticoagulant is a risk factor for thrombosis, not bleeding even if PTT is prolonged unless there is a concurrent factor deficiency. A single elevated value therefore is not always associated with an increased bleeding risk [6, 7].

Platelet Count

A low number of platelets and platelet dysfunction both confer an increased bleeding risk in interventional procedures. A low platelet count is defined as less than 150,000/mm^3 [3]. Although guidelines on appropriate platelet count vary based on procedure and physician preference, a platelet count less than 20,000 confers a high risk of life-threatening spontaneous bleeding and requires transfusion [8]. A level greater than 50,000/mm^3 is sufficient for interventional procedures assuming normal platelet function [9]. Normal platelet count may still confer bleeding risk if the platelets are dysfunctional as may occur in renal failure with uremia.

Pre-procedural Risk Reduction

Adequately screening patients for bleeding risk prior to performing a procedure is a major part of managing bleeding in interventional procedures. The most important piece of information from a patient that dictates risk and the need for pre-procedural management is a positive history of severe or life-threatening bleeding. In the absence of such a history, the risk of bleeding, regardless of the use of anticoagulants or other comorbidities, is relatively low.

To further reduce this risk, physicians should be aware of the medications a patient is taking and how to alter procedures being performed based on that risk. The risk of a bleeding complication must also be weighed against the benefit conferred by the procedure. It is generally accepted that emergency procedures where the patient's life is imminently in danger, such as controlling hemodynamically unstable gastrointestinal bleeding, have a benefit that outweighs the risk of bleeding due to altered coagulation parameters. Further, elective procedures that can be deferred until the patient has improved INR or platelet count are also a more straightforward situation. The following sections are meant to provide guidance when procedures are not imminently necessary and cannot be fully postponed until bleeding risk is ideal.

Anticoagulants

The most common reason for altered preoperative risk is due to the use of anticoagulants, so the following section deals with the most commonly used drugs and the current research discussing their management. A full discussion about these therapies in terms of their pharmacokinetics is outside the scope of this chapter and can be found in alternative sources [3, 10].

Warfarin

Warfarin (Coumadin™) is one of the most commonly used anticoagulants prescribed to patients presenting to interventional radiology. Warfarin causes an elevated INR and prolongation of PTT due to its effects on factors II, VII, IX, and X. A normal INR is stated as being less than 1.1; however, the degree of elevation that can be tolerated for a pro-

Table 36.2 Management recommendations by the Society of Interventional Radiology for anticoagulation [41]

	Low-risk procedure	Medium-risk procedure	High-risk procedure
Coumadin™	Withhold 3–5 days	Withhold 5 days	Withhold 5 days
Plavix™	Withhold 0–5 days	Withhold 5 days	Withhold 5 days
Aspirin™	Do not withhold	Do not withhold	Withhold 5–10 days
NSAIDs	Do not withhold	Do not withhold	Withhold 24 h–10 days (depending on medication half-life)
LMW heparin	Withhold 1 dose	Withhold 1 dose	Withhold 2 doses or 24 h prior
Unfractionated heparin	No consensus	No consensus	Withhold 2–4 h
GPIIb/GPIIIa inhibitors	Withhold 12–24 h	Withhold 24 h	Withhold 24 h
Argatroban	Do not withhold	Defer until off medication. If not possible, withhold 4 h	Defer until off medication. If not possible, withhold 4 h
Dabigatran	Do not withhold	Defer until off medication. If not possible, withhold 2–5 days depending on renal function	Defer until off medication. If not possible, withhold 2–5 days depending on renal function

See original paper [41] for full details and more management recommendations

cedure is procedure and physician dependent. Most studies looking at bleeding risk with warfarin use INR cutoffs of 1.5, over which the INR is considered to confer additional bleeding risk. The half-life of warfarin is around 37 h, although this is dependent on the levels of circulating clotting factors, heart function, renal status, nutritional status, and use of concomitant medications that can alter warfarin metabolism [3, 11].

Management of patients undergoing interventional procedures with warfarin centers on the level of INR elevation. There are two options with an elevated INR from warfarin: postponing the procedure to allow warfarin levels to decrease or reversing the effects of warfarin. The drug takes approximately 5–7 days to clear the bloodstream and for the INR to revert back to a normal range. Procedures that can therefore be postponed for this period of time promote the lowest bleeding risk.

If the procedure cannot be postponed, or if warfarin cannot be discontinued, the effects of warfarin can be temporarily reversed with fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC). FFP works by providing the clotting factors that have been downregulated by warfarin. Two units or 10–15 mL/kg of FFP will, in general, be effective in normalizing an INR of 2.5. Larger quantities are required for larger patients or for patients with higher INR elevations or with severe liver disease [12].

Studies looking at (FFP)efficacy, however, have shown insufficient data to recommend or refute use of the blood product prophylactically when undergoing interventional procedures [13]. Studies have traditionally looked at more invasive procedures when evaluating FFP's efficacy, with little data available specifically for imaging-guided procedures. A review of 25 studies looking specifically at coagulation parameters in interventional radiology procedures such as lumbar punctures, thoracentesis, and kidney biopsy showed little predictive value of altered coagulation parameters predicting bleeding complications. Prophylactic FFP or clotting factor transfusions should therefore be weighed against the risks associated with transfusion, such as transfusion-related acute lung injury, volume overload, anaphylaxis, and transmission of infectious agents [14].

FFP's other main limitation in management of bleeding is its slow availability. FFP is stored frozen and involves a time period of thawing before it is ready for use unless the blood bank carries liquid plasma. In patients with life-threatening warfarin-induced bleeding, this delay may not be appropriate. PCCs, however, do not require this preparation and have been shown to effectively reverse warfarin with equal efficacy [15]. PCCs work within 20 min of administration compared to FFP which can take 1–2 h for maximal effect. The downsides of the use of PCCs are that they are associated with thrombotic events which can precipitate DIC as well as lack of adequate research describing an established effective dose.

Warfarin acts to downregulate clotting factors by competitively inhibiting vitamin K, a key component of γ-carboxylation of factors II, VII, IX, and X and proteins C, S, and Z. Providing vitamin K can help reverse this effect and lead to production of the clotting factors that will effectively lower the INR and help reverse the bleeding risk of warfarin. This process, however, can take 2–3 days before working and is only used in interventional procedure preoperative management when the procedure can be postponed and the effectives of warfarin safely reversed. In this situation, vitamin K plays a role in reducing the time to achieve an acceptable INR range and plays less of a role in emergent intervention. Intravascular and subcutaneous administration of vitamin K has been issued a "black box" warning from the Food and Drug Administration due to high risk of anaphylactoid reactions [16, 17].

Heparin

Heparin is a commonly used anticoagulant, particularly in the treatment of acute coronary syndromes. There are two types commonly used, both of which work by inhibiting factor Xa and factor IIa (thrombin). The first, unfractionated heparin (UFH), is administered as a continuous intravenous infusion. PTT is used to monitor the level of anticoagulation and adjust the medication dosage. The second, low-molecular-weight heparin (LMWH), is administered subcutaneously. LMWH has higher anti-Xa effect than anti-IIa. LMWH does not prolong PTT much, and monitoring levels is not required unless renal failure, pregnancy, or infants. Both types have a half-life of only a few hours (UFH 1–2 h, LMWH 4 h), so performing interventional procedures in patients on heparin can be safely done by stopping heparin for several hours [18].

Performance of emergency procedures can be accomplished by the use of protamine which can rapidly reverse the effects of UFH and LMWH to a lesser extent. Protamine has a rapid onset of 10 min but only lasts up to 7.5 min, which requires frequent readministration. A neutralizing dose of protamine is 2 mg/kg with a total of 50 mg as an adequate dose to reverse the most common intraprocedural UFH doses. Multiple side effects limit the effectiveness of protamine, including hypotension, bradycardia, and pulmonary artery hypertension. Its use should therefore be limited to emergency situations [1, 19, 20].

Fondaparinux

Fondaparinux is a selective inhibitor of factor Xa and works similar to LWMH. It is more commonly used in cases where heparin-like anticoagulation is necessary as it can be dosed once per day. It is excreted by the kidneys, resulting in a heightened bleeding risk in patients with acute renal failure [21]. Fondaparinux also has a significant lower risk of heparin-induced thrombocytopenia (HIT) compared to UFH and LMWH [22].

Direct Thrombin Inhibitors

Hirudin, bivalirudin, argatroban, dabigatran, and lepirudin (withdrawn from US market) block thrombin directly, allowing for more predictable anticoagulation compared to indirect inhibition from medications like heparin. Other than dabigatran, there is no effective antidote to these anticoagulants in patients presenting with bleeding. For patients taking dabigatran, idarucizumab is approved for reversal in the setting of emergency/urgent procedure (see Chapter 41, "Evaluation of Bleeding Risk Prior to Invasive Procedures"). It is therefore recommended that patients undergoing interventional procedures who are on these medications should have their procedures postponed, if possible, until at least four half-lives have passed and the drug levels within the blood are negligible [23].

Direct Oral Anticoagulants (DOAC)

Dabigatran (Pradaxa™) is a direct thrombin inhibitor similar to the ones described above [24]. Rivaroxaban (Xarelto™) and apixaban (Eliquis™) are direct factor Xa inhibitors [25]. They are approved for deep vein thrombosis prophylaxis in patients undergoing orthopedic procedures [26]. These medications are being more frequently prescribed for risk reduction in patients with atrial fibrillation due to the lack of needing to monitor blood levels to ensure therapeutic anticoagulation [27]. As mentioned above, idarucizumab is a specific antidote for dabigatran, and andexanet alfa is a specific antidote for rivaroxaban and apixaban. Alternatively, PCCs have been shown to assist in treating refractory bleeding associated with these medications [28–30]. Kcentra™, a type of PCC, has shown some efficacy in clinical trials for the treatment of hemorrhages associated with rivaroxaban when given as an intravenous injection at 50 units/kg for a one time dose [29]. An activated PCC called FEIBA™ has been shown to assist with treatment of dabigatran-related bleeding at a 50 units/kg intravenous injection [31]. Dabigatran can also be partially removed from the blood using dialysis which may assist in treating refractory bleeding associated with interventional procedures or may be considered prior to the procedure to reduce risk [30]. New research is currently underway to determine the effects of different types of reversal agents, including targeted monoclonal antibodies, against these newer anticoagulants to help provide treatment options in cases of life-threatening bleeding.

A special note should be made about recombinant activated factor VII, which is being studied for the use of refractory bleeding. This agent has been shown to be minimally effective in treatment of severe bleeding such as in trauma, in patients with hemophilia, and in refractory cases of rivaroxaban and dabigatran bleeding when PCCs do not adequately control hemorrhage [32]. Research into its efficacy has been mixed, with studies showing a high risk of arterial thrombosis. It is therefore the last resource or in cases of hemophilia where the risk of bleeding is significant [33].

Antiplatelet Agents

Aspirin works by inhibiting cyclooxygenase, thereby decreasing platelet activation and aggregation. Aspirin is a key component in the treatment of many cardiac pathologies as well as treatment of coronary stents. Its discontinuation should therefore involve discussion with the patient's cardiologist to assess if stopping the medication for an interventional procedure can be done. If the patient is able to temporarily stop aspirin, a 10-day cessation will allow new platelets with normal function to be produced. In general, a 5-day period without aspirin will allow approximately 50% of platelets to be renewed and will be adequate to proceed with intervention [34]. The degree of inhibition and bleeding risk with aspirin is lower than other antiplatelet agents, so continuation of the medication for low-risk procedures is often safe. In one study, the incidence of bleeding with solid organ biopsy was 0.4% without aspirin and 0.6% with aspirin [35]. Another retrospective study looked at biopsies in patients taking antiplatelet agents and found that minor complications occurred at a lower rate when patients were taken off the medications but that there was no difference in the rate of major bleeding, defined as needing transfusion or causing hemodynamic instability [36]. High bleeding risk procedures, such as those involving direct arterial access or kidney-related procedures, may necessitate stopping aspirin for at least 5 days prior to the procedure.

Thienopyridines, such as clopidogrel (Plavix™), ticlopidine, and prasugrel, all work by binding to platelet receptors and inhibiting platelet aggregation for the entire life span of the platelet. Achieving completely normal platelet levels to proceed with intervention will therefore require stopping medications, as with aspirin, for the entire life span of a

platelet (roughly 10 days). Stopping the medication for 5 days, as with aspirin, will allow roughly 50% of platelets to be renewed and should be adequate for most procedures [34]. Studies looking at the risk of bleeding with clopidogrel are extrapolated from surgical literature where 5.6% of patients undergoing coronary artery bypass grafting experienced life-threatening hemorrhage with this medication compared to 4.2% of patients on placebo. There was no statistically significant difference between the two groups [37]. In emergent cases or in cases where clopidogrel cannot be safely discontinued due to recent cardiac treatment, it may be possible to proceed with certain types of procedures.

With aspirin and thienopyridines, management of bleeding in patients undergoing intervention will require platelet transfusions. As the half-life of the thienopyridines is around 4 h, waiting up to 6 h after the last dose to begin platelet transfusion can decrease the chances of the newly transfused platelets from being affected by the drug [38].

An alternative approach is to use the medication desmopressin (DDAVP). This medication is a synthetic analog of antidiuretic hormone and enhances plasma levels of factor VIII and von Willebrand factor. These factors are involved in the aggregation and adherence of platelets to breaks in the endothelial lining. Increasing their levels allows for improved platelet function. Desmopressin can be used in patients with antiplatelet medications and renal disease where uremia causes platelet dysfunction [39] (refer to Chapter 42, "Hemostatic Agents and Blood Components Used to Stop Bleeding").

Glycoprotein IIb/IIIa inhibitors should be mentioned in a complete discussion of management of bleeding, although they are rarely used in clinical practice due to short half-life and intravenous form of administration. The medications include abciximab, eptifibatide, and tirofiban. These medications act as antagonists to the glycoprotein IIb/IIIa complex on platelets and prevent aggregation. This can increase bleeding risk for emergent procedures [40]. Performing interventional procedures on patients with these medications can be safely performed by withholding the medication for 24 h prior [41].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are another extremely commonly used medication which affects coagulation. NSAIDs cause decreased platelet aggregation by the same mechanism as aspirin; however, the effect is reversible. Bleeding risk from NSAIDs is therefore significantly lower than other previously mentioned medications and only becomes an issue when combined with other severe coagulopathies, such as hemophilia or thrombocytopenia [42, 43]. In general, NSAIDs do not need to be withheld for the majority of interventional procedures, especially if the procedure is more emergent. If the procedure has a very high risk of bleeding, the medications can be withheld to allow for four half-lives to pass [1, 41].

Thrombocytopenia

Along with inhibition of platelet function, a low platelet count also confers bleeding risk and requires correction prior to procedures. Platelet transfusion decisions are based on the degree and etiology of thrombocytopenia, the type of procedure being performed, and concurrent comorbidities or coagulopathies. Patients with uremia, for instance, have variable platelet counts but will often have nonfunctional platelets and may require transfusions regardless of the measured platelet count. A platelet count of 40,000/mm^3 is generally safe for more interventional procedures. Certain procedures with low risk of vascular injury, such as bone marrow aspiration and certain types of superficial biopsies, can be performed with platelet count of 20,000/mm^3 [1].

A special note should be made about HIT which is a side effect of heparin administration. This entity is defined as having a 50% decrease in the platelet count approximately 5–10 days after the start of heparin therapy. The rate of HIT is more common with UFH than with LMWH. There are two types: type 1 is a self-limited disorder where the platelet count is usually above 100,000/mm^3; type 2 is more life-threatening with platelet counts typically lower than 75,000/mm^3. As this entity involves an immune response that destroys platelets, further administration of platelets will cause the newly transfused platelets to be destroyed as well. Management of bleeding patients with HIT therefore centers on cessation of heparin. Platelet count will generally rebound after this and allow the patient to continue with the interventional procedure [1, 10].

Altering Pre-procedural Planning

Although management of patients on medications that increase bleeding risk is highly important when performing interventional procedures, bleeding risk can further be decreased by planning different approaches to a procedure. Most arterial-based procedures involve puncturing the femoral artery; however, the femoral artery can be a deep structure, making it difficult to apply pressure to achieve hemostasis. Switching to a radial artery approach has been shown to decrease incidence of bleeding events and makes it easier for clinicians to monitor the puncture site for delayed complications and to apply pressure when necessary. Mapping out the intended site of the procedure can be used to minimize bleeding risk. In patients undergoing random liver biopsy, for instance, many patients present with ascites. The presence of fluid can dilute clotting factors at the site of vascular puncture and prevent adequate hemostasis. Changing the biopsy site to the left, nondependent portion of the liver can decrease the amount of fluid in the area and reduce bleeding risk. Alternatively, the interventionalist can

opt to perform a transjugular biopsy which avoids the intraperitoneal fluid and reduces the risk of hemodynamically unstable bleeding by allowing postoperative bleeding to flow directly back into the vasculature.

Another issue to consider when decreasing bleeding risk involves the equipment used for the procedure. Ultrasound can be used to localize needles when attempting puncture of the femoral artery and leads to greater success in cannulating the appropriate vessel and in avoiding other structures that can cause serious bleeding. The choice of biopsy needle also plays a role in bleeding as larger diameter needles, such as 14 gauge needles versus smaller gauges, increase the risk of bleeding by increasing the probability of hitting a vascular structure in the course of the biopsy tract. Which size biopsy needle to use to lower bleeding risk has to be weighed against the smaller amount of diagnostic tissue acquired from a smaller needle size.

Post-procedural Management of Bleeding

Post-procedural management should also include adequate patient positioning. In patients undergoing organ biopsies, for instance, the patient should lay on the biopsy site for 1–4 h depending on the type of procedure. This technique allows for the weight of the body to provide a natural tamponade effect on the biopsy site and promotes hemostasis. Organs which are more vascular, such as the kidney, will require longer periods of lying on the biopsy site [44].

Although management of bleeding patients focuses on medications, the interventionalist can use several devices and techniques to reduce the bleeding associated with the procedure. Tracts created when using needles can be injected with FFP or Gelfoam (a type of synthetic fibrin) to help promote hemostasis within the needle tract [45, 46]. When arterial punctures are performed, clinicians can also choose to use special vascular closure devices that can seal the holes in the endothelium created in the procedure. Many of these devices have been shown to be efficacious in reducing postoperative delayed bleeding [47–49].

Procedure-Specific Management

Although the previous sections discussed commonly used anticoagulants and the general approach to management of bleeding on these agents, there are several procedure-specific approaches to treatment of bleeding risk.

Table 36.3 Bleeding risk with types of procedures [1]

Low risk of bleeding	Moderate risk of bleeding	Significant risk of bleeding
IVC filter placement	Chemoembolization	Transjugular intrahepatic portosystemic shunt
PICC/catheter placement (non-tunneled)	Central venous catheter placement (tunneled)	Renal biopsy
Venography	Angiography	Nephrostomy tube placement
Collection drainage (not within the peritoneal or pleural cavities)	Collection drainage (intra-abdominal, intrapleural, retroperitoneal)	Biliary interventions involving creation of a new tract
Thoracentesis	Radio frequency ablation	
Paracentesis	Spinal procedures	
Dialysis access	Transabdominal and transjugular liver biopsy	
Procedures in the subcutaneous tissues	Lung biopsy	
Thyroid biopsy	Gastrostomy tube placement	
Joint aspiration/ injection	Percutaneous cholecystostomy	

Angiography

Angiographic procedures involve direct cannulation of the common femoral artery or radial artery in certain approaches. A study to assess bleeding risk with angiography looked at PT and PTT as pre-procedural risk stratification tools. The study found that the rate of major bleeding, defined as groin hematoma over 4 cm, was 1.2% with abnormal coagulation markers and 1.6% with normal coagulation markers [50]. Pre-procedural testing for coagulopathy with PT and PTT was therefore of no benefit. Instead, a low platelet count, less than 100,000/mm^3, was more associated with bleeding risk and should be used to guide pre-procedural risk management.

Paracentesis and Thoracentesis

These procedures involve small needle punctures through the skin without entry into major blood vessels or puncture of solid organs. The major sources of bleeding in these procedures involve superficial small vessels where bleeding can easily be visualized and controlled with direct compression.

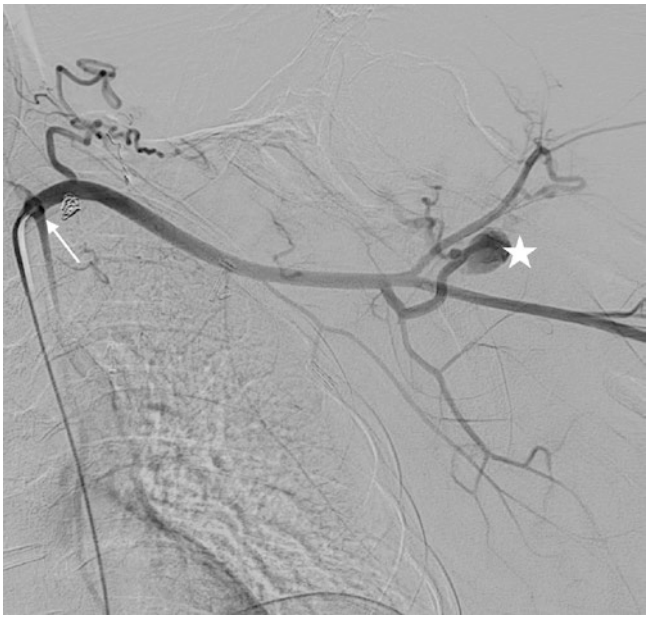

Fig. 36.1 Angiography of the left subclavian artery. A catheter was threaded into the femoral artery, is passed up through the abdominal and thoracic aorta, and is seen ending in the left subclavian artery (*white arrow*). After contrast opacification of the artery, a pseudoaneurysm is visualized in the artery (*white star*)

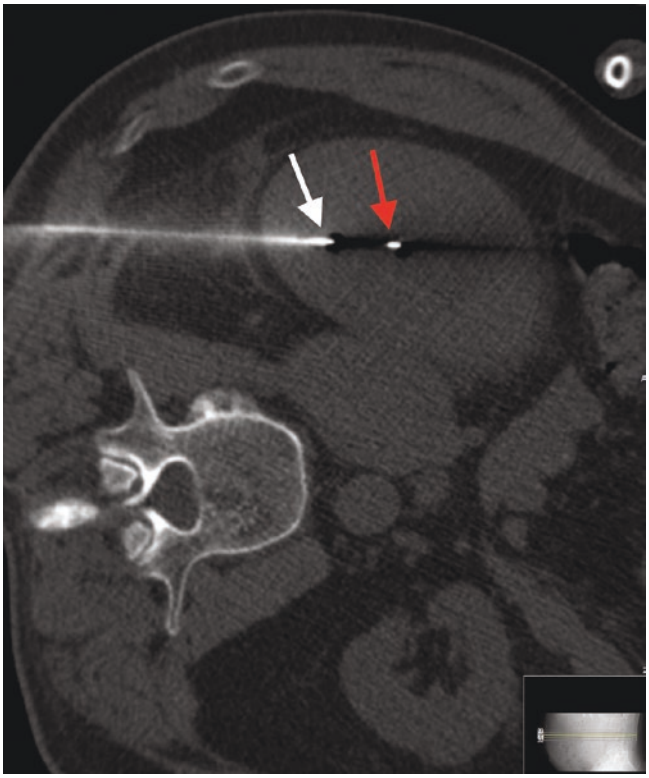

Fig. 36.2 CT-guided renal biopsy. The image demonstrates a biopsy needle being placed percutaneously through the right posterior of the patient and into the inferior pole of the right kidney. The red arrow denotes the end of the biopsy needle. Note the dark spot between the part of the needle denoted by the red arrow and the white arrow. This indicates the section of tissue that will be biopsied

Damage to vessels on the inner abdominal wall can be difficult to control, however, where contact with underlying fluid within the pleural or peritoneal cavity causes dilution of clotting factors. Risk of perforation of major vessels can be significantly decreased by utilizing ultrasound guidance to map skin vasculature. Despite these techniques, thoracentesis and paracentesis can be performed without correction of coagulopathy or withholding of anticoagulant medications [51, 52]. A study by Puchalski showed that bleeding risk from multiple factors, whether that be medications such as heparin and clopidogrel or other coagulopathies like renal disease, did not contribute to increased bleeding rates compared to patients with normal coagulation parameters for thoracentesis [53].

Kidney Biopsy and Nephrostomy Tube Placement

The kidney is one of the most vascular organs and thus holds a high bleeding risk for all interventional procedures [54, 55].

Kidney biopsy bleeding complications fall into two major categories, with major bleeding being something that requires intervention and minor bleeding being amenable to conservative treatment. The frequency of minor bleeding after percutaneous kidney biopsy ranges from 2% to 35% [54]. The most common mild complications are hematuria or small perinephric hematoma without kidney injury. The most common major complications include hematomas requiring transfusion, outlet obstruction, and acute kidney injury. The major complication rate is 1–7%. Ninety percent of complications occur within the first 24 h and can dictate post-procedural management [56, 57].

Recommendations to reduce bleeding risk with kidney biopsy suggest withholding warfarin until the INR is below 1.5. Further, if the patient is on heparin, this anticoagulant should be stopped at least 6 h prior to the procedure and not be restarted until at least 24 h afterward [58]. When evaluating patients who have other risk factors for bleeding, such as high blood pressure, elevated creatinine, amyloidosis, or end-stage renal disease, studies have shown that there is no increased rate of complications in patients undergoing biopsy

[59–61]. One study looked at 160 patients undergoing nephrostomy tube placement and found that of the 7 patients with abnormal coagulation parameters, no patients had bleeding complications [62]. Continuing the use of antiplatelet agents has also not been associated with clinically significant bleeding and only decreases rates of minor bleeding such as postoperative limited hematuria [63].

A platelet function analyzer (PFA-100™) is an alternative method of measuring bleeding time and has started to be studied as a method of predicting bleeding complications. A PFA-100™ measures closure time of undergoing a normal platelet and von Willebrand factor interaction in vitro. PFA-100™ can therefore identify clinically relevant platelet-binding disorders and deficiencies of platelet membrane receptors. Closure times are measured using a PFA-100™ device composed of either collagen and epinephrine or collagen and ADP. A large prospective study in patients undergoing percutaneous renal biopsy showed that closure time of either or both collagen/epinephrine and collagen/ADP was >170 s or >120 s, respectively. 51.3% patients with elevated closure times had clinically significant bleeding events, while 26.0% of patients with normal closure times had bleeding events, allowing for PFA-100™ to serve as a useful screening tool to predict hemostasis in renal biopsy [64]. However, further research is needed into the usefulness of the PFA-100™ as other retrospective studies have found no correlation between the use of the test and bleeding complications [65].

Studies to look at ways to reduce bleeding complications included research looking at administration of desmopressin, a medication that can cause vasoconstriction and thus decrease the rate of blood loss from vascular injury. The study found that there was a decreased rate of silent hematomas with desmopressin versus placebo in patients with otherwise normal renal function; however, the complication rate was not affected [66]. In patients with high bleeding risk undergoing biopsy, such as those with kidney injury resulting in uremia and platelet dysfunction, multiple treatments can reduce bleeding time including desmopressin, cryoprecipitate, and erythropoietin [39, 67]. However, studies have not conclusively shown a reduction in bleeding risk in patients undergoing kidney biopsy from any of these agents.

Liver Biopsy

Like the kidney, the liver is a highly vascular organ that has a high bleeding risk from biopsy. There are two main approaches to biopsy the liver, either through the skin (percutaneous) or by cannulating the internal jugular vein and passing a catheter to the liver (transjugular).

A study by McVay showed that there was no statistical difference in bleeding rates between patients with mild thrombocytopenia (defined as platelet counts between 50,000 and 99,000/mm^3) and normal platelet count [68]. Another study looked at severe thrombocytopenia in patients undergoing transjugular biopsy. Patients received an average of 11 units of platelets for a mean pre-procedural platelet count of 17,000/mm^3 and mean post-procedural count of 38,000/mm^3. Patients exhibited no major bleeding complications, leading to a conclusion that a pre-procedural platelet count of greater than 30,000/mm^3 was safe for transjugular liver biopsies [69]. A similar study looking at INR showed that there was no difference in complications between patients with an INR above or below 1.5 in patients undergoing transjugular biopsies. The bleeding risk is significantly reduced due to the fact that bleeding from the biopsy site flows back into the vascular system without causing loss of intravascular volume [70].

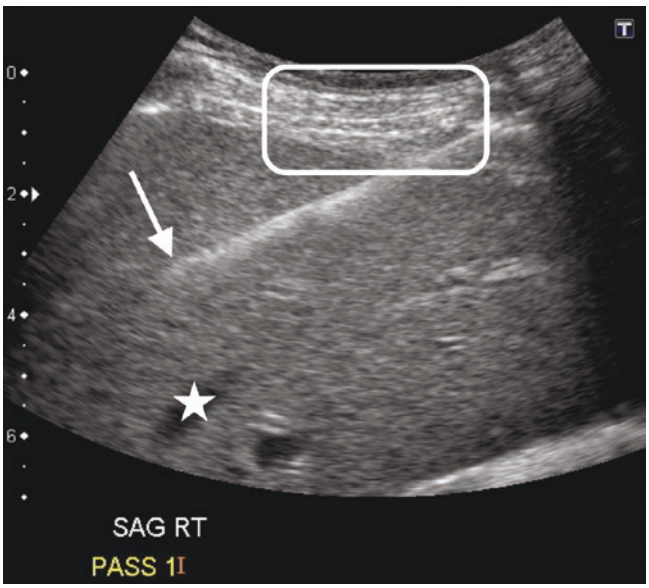

Fig. 36.3 Ultrasound-guided liver biopsy. The image shows a bright echogenic needle being guided under a curved array ultrasound transducer for a random liver biopsy. The needle tip is denoted by the white arrow. This was a random liver biopsy. Ultrasound allows the radiologist to visualize the needle tip live during placement to avoid structures such as large blood vessels (*white star*). Ultrasound is useful for liver biopsies because of the proximity of the organ to the skin (the white box denotes the subcutaneous tissues and measures roughly 1–2 cm)

In patients undergoing percutaneous biopsy, a path of 1–2 cm deep to the capsule should be used during percutaneous biopsy as the dense surrounding parenchyma can provide a theoretical tamponade effect [71].

Post-procedural management should include scanning the entire liver as bleeding may not be visible in the immediate area of the biopsy. The liver has two vascular supplies, with arterial injury being the most common source of clinically significant hemorrhage. Angiography with Gelfoam or coil embolization can be performed to evaluate for and control suspected post-procedure bleeding. A superior mesenteric artery angiogram should be performed prior to embolization

of liver hemorrhage to confirm portal venous potency as blockage of this vein can lead to more ischemic complications [72].

Lung Biopsy

The most common complication of lung biopsy is pneumothorax, with life-threatening hemorrhage a rare occurrence [73]. However, microhemorrhage is a very common complication, occurring in 4–27% of percutaneous biopsy cases [74]. The bleeding risk is related to lesion size, with smaller lesions having a higher rate of bleeding due to more movement of the needle to achieve correct positioning. Depth of the needle tract also increases the probability of hitting a vascular structure. Despite the risk of bleeding, 86% of bleeding cases are minimal alveolar hemorrhage and require no further intervention. Bleeding risk can further be reduced by withholding anticoagulant medications and rigid pre-procedural planning to avoid the central major pulmonary arteries or veins [75].

Soft Tissue, Breast, and Lymph Node Biopsies

The Society of Interventional Radiology classifies these procedures as moderate risk of bleeding and thus suggests withholding clopidogrel for 5 days and ensuring INR is lower than 1.5. The incidence of major bleeding, defined as requiring transfusion or other intervention, is listed in the literature as ranging between 0.1% and 8.3% [1, 41]. Hemostasis can, however, often be achieved with direct compression as a majority of these procedures are superficial. Three studies looking at breast biopsies in patients on anticoagulation showed no clinically significant bleeding and showed similar rates of small hematoma formation in patients with and without anticoagulant medications [76–78].

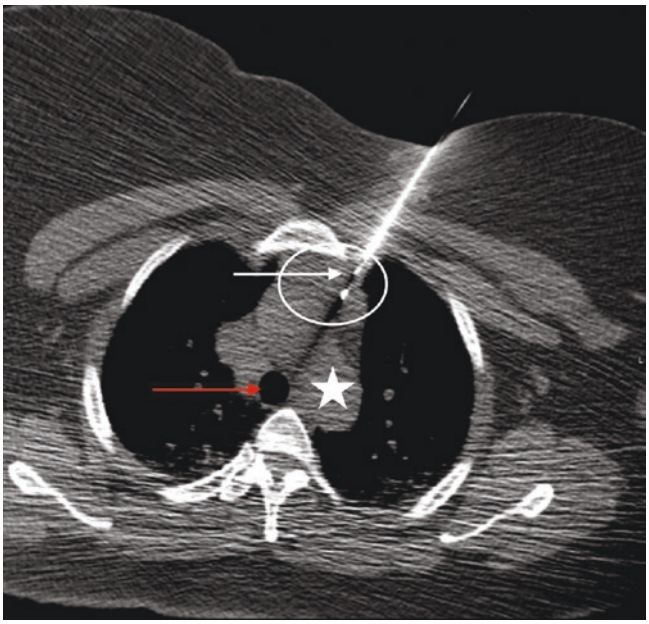

Fig. 36.4 CT-guided mediastinal mass biopsy. This image shows needle (*white arrow*) placement within an anterior mediastinal mass (*white circle*). Note the proximity of the mass and the needle to the aortic arch (*white star*) and the trachea (*red arrow*). Active imaging guidance during such a procedure reduces risk of injury to such vital structures

Central Venous Catheterization

Bleeding rates with central venous catheterization (CVC) are reported as 0.5–1.6% of cases, with the procedure rarely having fatal bleeding. The majority of cases of bleeding can be directly visualized and controlled with direct pressure. Although elevated INR and a low platelet count have been linked to higher rates of bleeding in general, the bleeding risk can be reduced by choosing a vessel to cannulate that can be more easily compressed [79]. The internal jugular vein, for instance, is more easily identified and can be compressed compared to the deeper subclavian vein [80]. The use of ultrasound guidance can also increase the changes of cannulating the appropriate vessel and reduce bleeding risk [81–83]. Studies have shown that insertion of tunneled catheters can be performed safely with platelet count above 25,000/mm^3 and INR up to 2.0 [84].

For non-tunneled catheters, some studies showed that platelet count less than 50,000/mm^3 and INR above 1.8 have been shown to have a higher risk of any type of bleeding [85]. However, a study by Fisher looked at patients undergoing CVC with an INR over 1.5 with normal platelet count [86]. The study found only one case of major bleeding due to accidental puncture of the carotid artery and stated that CVC could be safely performed with coagulopathy. Other studies have looked at the rate of bleeding with isolated thrombocytopenia as well as thrombocytopenia with elevated INR. These studies have shown low incidence of bleeding complications ranging from 1% to 6% with no life-threatening bleeding requiring intervention. Pre-procedural testing for central venous catheter placement is therefore not routinely necessary [87].

Some studies have looked at the case of hemophilia with CVC. In a pediatric study group of 34 catheter insertions, 6 patients showed bleeding that required treatment [88]. Although there is not a significant amount of data regarding this particular situation, factor replacement may be a useful adjunct to periprocedural management of bleeding risk.

Special note should be made about bleeding risk with removal of catheters. Although there is a paucity of information regarding this topic, one study looked at risk factors for continued puncture site bleeding after removal of tunneled

venous catheters. The study showed that platelet dysfunction due to renal disease and antiplatelet agents contributed to a longer time of compression at the puncture site necessary to control visible bleeding. Pre-procedural coagulation testing and platelet count did not correlate with the amount of compression time needed and are therefore not routinely necessary [89].

Lumbar Puncture and Interventional Spinal Pain Procedures

Bleeding during spinal interventional procedures occurs due to damage to vasculature within the epidural and subdural spaces of the spinal column and is usually due to venous bleeding. One study quotes a 4.5% incidence of minor hemorrhagic complications related to epidural injections. The risk of bleeding from such procedures is generally low; however, a significant epidural hematoma can result in spinal cord compression. Evaluation of bleeding risk prior to the procedure is therefore of utmost importance. Procedures which can be safely deferred until appropriate coagulation parameters are met should be postponed [90].

Multiple studies, mostly from literature in anesthesiology with epidural anesthesia injections, have looked at the risks of spinal intervention causing bleeding. Studies have shown that antiplatelet agents do not confer a significant bleeding risk in these procedures [91, 92]. Another study showed that patients undergoing epidural steroid injections showed no spinal hematomas or major hemorrhagic events within the spinal cord when on aspirin or NSAIDs [93]. This author also showed that NSAIDs did not lead to an increase in minor hemorrhagic events either, described as bleeding that was not interspinal [94]. Despite these studies, many physicians discontinue medications due to personal comfort. The American Society of Regional Anesthesia and Pain Medicine and the Society of Interventional Radiology (SIR) recommend discontinuation of warfarin for 5 days prior to the procedure to achieve an INR within the normal range (less than 1.5) and discontinuation of clopidogrel for 5 days to improve platelet function [95]. The decision to discontinue medications should be weighed against the risk of discontinuation. One study showed that the rate of thromboembolic events after discontinuing antiplatelet medication was three times higher than those continuing these agents. The rate of epidural hematomas in these patients where antiplatelet medications were continued versus discontinued was the same [96].

The platelet count is very important in patients undergoing interventional spinal procedures as well. In two studies looking at lumbar punctures, subdural hematomas and subarachnoid hematomas occurred more frequently in patients with platelet counts less than 20,000/mm^3 [97, 98]. Studies looking at patients with acute leukemia undergoing lumbar puncture showed patients with thrombocytopenia lower than 25,000/mm^3 had a higher rate of traumatic puncture, although there were no significant bleeding events in any patient [99, 100]. A recommended threshold of 20,000/mm^3 is therefore set for platelet transfusion prior to lumbar puncture in order to minimize bleeding risk.

The most common symptoms of major interspinal bleeding include back pain and neurologic dysfunction including sensorimotor loss and incontinence. The presentation can be immediate or delayed as much as several days. The management of these patients involves rapid reversal of coagulopathy, high-dose corticosteroids, and consultation with a neurosurgeon to evaluate if decompressive surgery is necessary. Favorable outcomes generally occur with intervention within 36–48 h.

Bone Biopsies and Musculoskeletal Intervention

Bone is not a very vascular structure, especially when compared to the previously discussed liver and kidney biopsies. Despite this fact, bone biopsies are usually not urgent procedures, so withholding anticoagulant medication prior to the procedure is reasonable in order to minimize bleeding risk as far as possible. In rare instances when anticoagulation cannot be withheld or when the need for the procedure is more urgent, proceeding with the procedure is likely reasonable. A few studies have utilized large numbers of patients to assess true bleeding risk. In a small look at 11 cervical bone biopsies, no bleeding complications were seen, although the small sample size makes this observation difficult to extrapo-

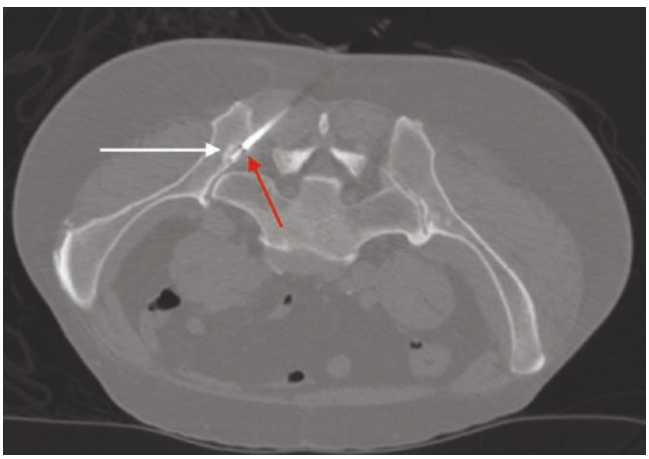

Fig. 36.5 CT-guided bone biopsy. This figure shows biopsy of the right ischial tuberosity with an 18 gauge biopsy needle. The white arrow denotes a sclerotic lesion within the bone. The red arrow points to the needle. As in Fig. 30.2, there is a gap between the end of the needle and the area of the needle denoted by the red arrow. This is the portion of the needle that procures the sample tissue

late. In another study looking at CT-guided vertebral body biopsies, anticoagulation led to several cases of retroperitoneal hematomas, none of which were severe requiring treatment or impacting patient care [101].

Injection and aspiration of fluid into the muscles are associated with an even lower rate of bleeding complications. Generally very small needles (around 25 gauge) are used in muscular, bursal, or peritendinous injections. A study looking at patients with anticoagulants including warfarin, aspirin, and clopidogrel undergoing electromyography, which mimics intra-articular and bursal injections in technique and risk, showed 3 subclinical hematomas out of 158 patients, none of whom required treatment or experienced symptoms [102].

Guidelines from the American College of Chest Physicians suggest continuation of warfarin at a low dose, where the INR goal is 1.3–1.5 and is safe for low-risk orthopedic procedures, of which interventional radiologic procedures is a subset [16, 58]. Other studies have looked specifically at arthrocentesis and found that warfarin was safe to continue even to INR up to 3 (therapeutic INR) due to the higher risk of thromboembolic events from subtherapeutic INR compared to the minimal risk of hematoma [103, 104]. Bone marrow biopsy is similarly low risk with a bleeding incidence rate of 0.05%. The majority of patients undergoing bone marrow biopsy have some form of hematologic derangement that contributes to coagulopathy; however, despite this the literature states that clinically significant bleeding is rare and that a majority of physicians would proceed with the procedure without correction of abnormal coagulation parameters as long as the INR was not supratherapeutic (INR >3) [1, 95].

Kyphoplasty and vertebroplasty are defined as more high-risk procedures and have hemorrhagic complication rates around 1.4% [105]. The risk of thromboembolic events in such patients is listed as 1.2%, however, so the risks of thrombotic events when withholding anticoagulant medications should be weighed with the risk of bleeding.

New Guidelines

The relative lack of definitive and comprehensive studies assessing bleeding risk with minimally invasive procedures became the impetus for societies to create guidelines to help proceduralists in the care of coagulopathic patients. In 2019, the Society of Interventional Radiology (SIR) released its revised consensus guidelines to help create a more unified and evidence-based approach for the management of coagulopathy [106, 107]. The guidelines outline the existing and updated science behind various topics in the coagulation literature including mechanisms of actions for newer anticoagulant medications as well as emerging research on the use of different laboratory tests such as fibrinogen in the true assessment of bleeding risk in patients with chronic liver disease. The goal of the guidelines is to provide a tool for interventionalists to understand and reduce bleeding risk and complications and appropriately triage patients for different forms of pre-procedural planning and post-procedure monitoring. The rationale for the update from the previous SIR guidelines is that multiple new studies have since been published in the hematology, cardiology, and surgical literature that better define risk management strategies for coagulopathic patients. Additionally, newer anticoagulants as well as new reversal agents have been released to the market without the proper research conducted to guide physicians on how to handle patients on these new therapies.

The cornerstone of the new SIR guidelines centers on trying to avoid performing procedures while patients are on anticoagulation whenever possible or to reverse the anticoagulation when appropriate and possible. If patients are on anticoagulation for which there is no rapid reversal agent such as the newer direct oral anticoagulants, waiting for these medications to naturally decay in the body can help reduce risk to sufficient levels to make a procedure safer to perform. The guidelines outline discrete recommended waiting times before and after procedures for each medication. In cases where procedures cannot be delayed until anticoagulation can be terminated or reversed, the guidelines classify procedures based on low and high risk of bleeding modeled on bleeding risk scores developed in the surgical literature such as the HAS-BLED and Bleed MAP scores. These scores are weighed against the risk of thrombosis in patients taking anticoagulation for indications such as hypercoagulable state, stent placement, cardiac disease, etc. to arrive at a total risk assessment of bleeding versus thrombotic risk. Based on these, the interventionalist is encouraged to proceed or not proceed with a procedure, with the knowledge of risk reduction tools available in various clinical scenarios.

The guidelines reclassify many interventional procedures into high- and low-risk groups. Low-risk procedures are those that are expected to rarely have hemorrhagic complications or occur in areas where bleeding is easy to diagnose and control. High-risk procedures are those that are expected to have hemorrhagic complications, occur in areas where bleeding is difficult to diagnose/treat, or occur in areas where even minor amounts of bleeding have devastating consequences, such as the eye, spine, and brain.

Based on the risk of the procedure, the guidelines further suggest laboratory parameters that should be pursued when possible with regard to INR and platelet goals, which have traditionally been provider- or institution-specific goals and varied across the spectrum of interventional practices. The goal is to provide a standardized cutoff for lab markers that can be used to help guide providers when referring their

patients to an interventional radiologist. The guidelines provide more flexibility in cases where thrombotic risk of anticoagulation cessation may outweigh bleeding risk reduction and allows proceduralists more freedom to do lower-risk procedures on patients who cannot have their anticoagulation stopped or reversed. The guidelines further provide information on how to manage patients on various types of anticoagulation with specific guidelines for the type of procedure being performed (high versus low risk). An example of this is the guideline to not withhold heparin or Lovenox in cases of low bleeding risk procedures in patients whose thrombosis risk is high. The guidelines also suggest ways to reverse these medications in emergencies and how long to hold medications for higher-risk procedures. Finally, the guidelines relax previous societal cutoffs for INR and platelets to allow more flexibility in performing procedures in general by raising these cutoffs to account for improvements in procedural techniques and equipment that can reduce bleeding risk.

Aside from providing more standardized ways to approach a patient with coagulopathy, the new guidelines provide a tool for interventional radiologists to progress in SIR's goal of promoting clinical knowledge and management skills among radiologists. The guidelines provide more information for radiologists to understand how various factors in patient's comorbidities play into the true risks that should be addressed with those patients by the proceduralists before and after intervention. An additional goal of the guidelines is to help interventional radiologists practice cost-effective care in an era of exponentially rising medical costs. In this goal, one of the recommendations of the guidelines is to not routinely obtain bloodwork for preoperative coagulation markers and blood counts prior to performing low-risk procedures on patients without certain comorbidities (such as liver and renal disease). Due to large gaps in the literature surrounding these risks, large parts of the guidelines are formed by consensus among the SIR committee and voted to be incorporated into the official guidelines. The committee was formed by a combination of interventional radiologists and vascular medicine/hematology specialists to provide the most robust and well-rounded consensus possible while incorporating as much evidence-based information as possible across multiple medical societies and specialties.

A complete discussion of the nuances of the guidelines is outside the scope of this chapter, so the reader is referred to the original manuscripts for further information. Part 1 of the guidelines addresses the science, updated literature, and advances in techniques and medications relating to coagulopathy. Part 2 provides medication and procedure-specific guidelines for daily use. By creating these guidelines in an algorithmic approach using all considerations of bleeding and thrombotic risks for the procedure, interventionalists can create more patient-specific decision-making processes. The new guidelines attempt to provide some guidance on previous grey areas in clinical care based on updates in research and consensus among various experts while still keeping language and recommendations vague enough to allow for provider deviation in specific cases.

Conclusion

Based on the previous discussion, it is clear that there is a lack of consensus on management of bleeding in many situations, with a lack of robust research limiting creation of widespread guidelines for periprocedural care. Based on the available research, however, decisions on how to manage and reduce risks of bleeding can be extrapolated to many different clinical scenarios. When possible, anticoagulation should be stopped, and procedures should be postponed as this confers the lowest possible risk. When procedures are more urgent, anticoagulation cannot be postponed, or the procedure carries a significant bleeding risk; clinical judgment should always weigh the risks, benefits, and findings of evidence-based research to determine the proper course of care.

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Dental Extractions in Patients with Congenital and Acquired Bleeding Disorders

37

Julia A. M. Anderson and Andrew Brewer

Preventive Care

With a few exceptions including the loss of deciduous teeth, orthodontic extractions, and the removal of impacted wisdom teeth, a dental extraction represents a treatment failure. A retrospective audit of the dental health status of 31 consecutively referred hematology patients attending a Scottish dental hospital, compared to the normal population, demonstrated that untreated decay and numbers of missing teeth increase significantly with age and delays in intervention result in extractions becoming the chosen treatment [1]. Preventive treatment including good dental hygiene and regular tooth brushing with fluoride toothpaste is of paramount importance and should be promoted in all patient groups [2].

Dental Extractions in Patients with Congenital Bleeding Disorders

Individuals with hemophilia do not bleed more profusely than an individual with normal coagulation but may bleed for a longer period of time and may experience delayed bleeding due to clot instability. Patients with congenital bleeding disorders hold an increased risk of significant bleeding from invasive dental and oral surgery procedures. A major anxiety held by patients with inherited bleeding disorders is the risk of bleeding peri- or postprocedurally, as well as concerns about dentists' knowledge of their bleeding condition and its management. Preventive dentistry may be difficult to access in a non-hospital setting, and in the past a significant number of patients have experienced the refusal of treatment by general dental practices. As a result, individuals may avoid the dentist until extensive treatment needs arise. This group of patients requires the same level of routine dental care as any other patient, and good preventive practice is essential to avoid dental extraction [2].

Congenital Bleeding Disorders

There are many congenital bleeding disorders and the same first principles apply to the dental management of all these disorders in the community. In the United Kingdom, patients with congenital bleeding disorders are provided with a hemorrhagic states card that outlines the nature of their factor deficiency and main treatment strategy [2].

von Willebrand disease (vWD) is mainly an autosomal dominant condition, affecting males and females, and is the commonest congenital bleeding disorder. It is characterized by a deficiency or abnormally functional von Willebrand factor (vWF) that leads to mucocutaneous bleeding and gingival bleeding. Bleeding after dental extractions may be a presenting feature of this condition. There are three subtypes of vWD and patients in each subtype may be categorized into mild, moderate, and severe phenotypes at the time of diagnosis. In the majority of patients with type 1 vWD, treatment with desmopressin is used; in type 2 and type 3 vWD, the administration of coagulation factor replacement therapy with a factor VIII concentrate rich in vWF is necessary [2]. Currently both plasma-derived and recombinant vWF are available.

Hemophilia A and B are X-linked recessive conditions with identical clinical manifestations [3]. Depending on the plasma levels of factor VIII or factor IX activity, hemophilia is defined as "mild," "moderate," or "severe" (see Table 37.1). Mild hemophilia may not be diagnosed until a procedure such as a dental extraction causes prolonged bleeding [4]. It should be noted that female carriers of hemophilia may have low factor levels and may be at risk of bleeding [2]. Although it is important to measure clotting factor levels before dental

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Table 37.1 The severity of hemophilia, clinical manifestations, and recommendations for dental procedures

Severity of hemophilia	Factor percentage (normal range 50–150%)	Clinical features	Dental treatment
Severe	<1%	Frequent spontaneous bleeds	Enhanced preventive advice and treatment with a dental practitioner with the support of the hemophilia center Should have all dental treatments except for prosthodontics carried out in a hospital setting with specialist dental unit, unless prior arrangements made with the hemophilia center and the dental practitioner.
Moderate	2–5%	May have spontaneous bleeds	Enhanced preventive advice and treatment provided by a dental practitioner Manage as for severe hemophilia
Mild	6–40%	Bleed after trauma or surgery	Enhanced preventive advice and treatment with a dental practitioner Do not require all treatments carried out at the hospital; ideally they should be reviewed every 2 years by the specialist dental team at the hemophilia center. Close liaison between dentist and the hemophilia center is necessary; some procedures may require prophylactic cover, and this will be arranged and provided by the hemophilia unit
Carrier	Factor level may vary		If the factor level is <50%, carriers should be treated as mild hemophilia

Adapted from Anderson et al. [2]

procedures in all carriers and potential carriers of hemophilia, the factor levels have weak correlation with clinical bleeding in hemophilia carriers [5, 6].

There are a number of congenital platelet disorders, the most common being Glanzmann thrombasthenia and Hermansky-Pudlak syndrome. These conditions are extremely difficult to manage and any surgical procedures need to be carefully planned with the hemophilia center.

Patients with severe hemophilia may be placed on prophylactic factor regimens, the administration of factor replacement therapy prescribed on an individual basis, usually on alternate days or three times weekly, to minimize spontaneous bleeding. Dental treatment should be scheduled at times of factor administration to minimize the risks of therapies and reduce overall treatment costs [2]. Several extended half-life products have been introduced [7] requiring less frequent infusions compared with standard products. Top-up treatments might be necessary before dental procedures.

The development of antibodies or "inhibitors" to factor therapies is a serious complication, and patients previously required concentrates known as "by-passing therapies" to enable hemostasis to be achieved [8]. Recombinant factor VIIa (rfVIIa, NovoSeven™) is administered as a bolus injection and a treatment consists of 90 μg/kg every 2 h for three doses. With a short half-life of only 2 h, it is vital that the rfVIIa is given on time, and the time of administration should be agreed by the dental surgeon. An alternative therapy is an activated prothrombin complex concentrate, FEIBA™. This is a plasma-derived product and is given at a dose of 70–100 units/kg, to a maximum daily dose of 200 units/kg. As these treatments are highly costly, patients with inhibitors to factor VIII or factor IX therapy should be managed by good prevention and minimally invasive techniques since the administration of local anesthesia is almost never required.

A new therapy, a humanized bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing or dysfunctional activated factor VIII, known as Emicizumab™ has recently been introduced for the management of patients with chronic inhibitors. Given once weekly by subcutaneous injection, it has been shown to reduce bleeding episodes in people with hemophilia A complicated by a factor VIII inhibitor [9, 10].

Factor XI deficiency causes an unpredictable bleeding tendency that may be provoked by surgery in areas with high fibrinolytic activity such as tonsillectomy and dental procedures. The inheritance is autosomal and may occur in either sex. Therapeutic options include incrementing factor XI levels by administration of fresh frozen plasma or factor XI concentrate and by the use of antifibrinolytic agents [11]. Factor XI concentrate is not currently available in the United States.

Dental Extractions in Congenital Bleeding Patients: Basic First Principles

Treatment Planning

An overall treatment plan should take account of the patient's bleeding risk: the type and severity of the congenital bleeding disorder, the location and extent of dental surgery, and the experience of the dentist. This will involve detailed liaison with the hemophilia center and discussion with the patient regarding the overall steps required for effective hemostasis [2, 12]. Factor concentrate replacement therapy should be administered as close to the time of the dental pro-

cedure as possible. Patients with severe hemophilia, or with inhibitors, may require post-procedural assessment by the hemophilia team and may require hospital admission for 24-h monitoring to ensure no late bleeding complications occur. If the patient is managed as an outpatient, contact numbers should be provided by the hemophilia center in case of any questions or concerns following discharge home [2].

Implant Placement

A dental implant can be placed in either the upper or lower jaw providing there is sufficient bone support. This should not be any more traumatic than a dental extraction. If the bone depth is inadequate for implant placement, mainly in the maxilla due to the proximity of the sinus, bone augmentation procedures can be performed. This is a separate procedure which will need to be carefully planned with the hemophilia unit.

Wisdom Teeth

The removal of wisdom teeth is a more complex problem since although many teeth are relatively easy to remove, extraction of a number of teeth may pose a significant surgical problem. Radiographic examination is an essential part of planning, and the difficulty of the extraction should be discussed with an experienced oral surgeon.

Local Anesthesia

In adults, local anesthetic infiltration using modern fine-gauge single-use needles and a slow injection technique can usually be used without the need for factor replacement therapy [13, 14]. Augmentation of factor levels with or without tranexamic acid is required when inferior alveolar and posterior superior alveolar dental nerve blocks are given as there is a risk of muscle hematoma, in addition to potential airway compromise due to hematoma formation in the retromolar or pterygoid space. Factor replacement therapy is also necessary for lingual infiltration and floor-of-mouth injections as there may be a significant risk of hematoma. Intraligamentous or intrapapillary injections do not require hemostatic cover; however it would be advised to give buccal infiltration at the time of the injection to avoid pain [2, 13, 14] (see Table 37.2).

Table 37.2 Use of local anesthesia in patients with congenital bleeding disorders (CBDs)

Procedures that do not require factor cover	Procedures that require factor cover
Buccal infiltration	Inferior dental block
Intrapapillary injection	Lingual infiltration
Intraligamentary injections	
Single tooth anesthesia (STA)	
Buccal infiltration of articaine and adrenaline	

Adapted from Anderson et al. [2]

A new computer controlled anesthetic delivery system, Single Tooth Anesthesia (STA) has been introduced that does not require factor cover [15].

There are no restrictions regarding the type of local anesthetic used, and 2% lidocaine with 1 in 80,000 epinephrine is routinely used in restorative dentistry; the use of a vasoconstrictor improves local hemostasis [13]. There have been reports that the use of articaine with 1:100,000 epinephrine may achieve more optimal bone penetration, and this local anesthetic has been suggested as a buccal infiltration to provide local anesthetic, instead of an inferior dental nerve block, thus removing the need for preoperative factor cover [16, 17].

Analgesia

The use of aspirin and aspirin-containing medications should be avoided in patients with inherited bleeding disorders due to their effect on platelet function. The use of nonsteroidal anti-inflammatory drugs should be discussed with the hemophilia treater as they may increase the risk of bleeding but can be beneficial postprocedurally to control pain. Overall, paracetamol and codeine-based analgesia are recommended [2].

Other Issues

At present there is insufficient evidence to support the administration of topical antiseptics and antibiotics prior to extraction. Cautery may be required following the removal of granulation tissue from areas of chronic inflammation and should be considered on an individual basis.

Augmentation of Factor Levels

The management options to increment factor levels depend on the type of hemophilia and vWD and include coagulation factor replacement therapy as well as the release of endogenous factor VIII stores using desmopressin (DDAVP).

Factor Concentrates Coagulation factor replacement therapy is the main form of therapy for patients with moderate and severe hemophilia A and B and may be prescribed on a prophylactic basis to prevent bleeds or may be administered "on demand" when a bleed occurs. In the past, factor concentrates were plasma-derived and held the possible complication of transfusion-transmitted infections, but recombinant factor replacement therapy has since reduced this risk [18]. Recent modifications to optimize the half-life of factor products have become the focus of product development, and several extended half-life products have been introduced offering the patients the possibility of less frequent infusions [7].

Concentrates are administered by intravenous infusion, either by the individual or by a hemophilia treater, and are costly so it is important that as much dental work as possible is performed on a given occasion to avoid the need for fur-

ther factor concentrate administration. Dental procedures should be performed as close to the time of administration of factor concentrate, normally within 30 min to an hour, as levels slowly decline thereafter [2].

In terms of optimal factor levels to achieve periprocedurally, the European Hemophilia Standardisation Board noted that most studies in the literature are based on replacement with a single dose of factor concentrate to a minimum preoperative factor level of 30–50% for individuals undergoing dental extraction. However a survey of 26 European Hemophilia Comprehensive Care Centres, representing 15 different European countries, recommended the administration of concentrate to raise factor levels to 60–80%, with one third of centers administering repeat doses [19]. In 2009, the UKHCDO (United Kingdom Haemophilia Centre Doctors' Organization) Dental Working Party Survey noted a similar variation in practice, with the majority of UK hemophilia centers aiming for a minimum single factor level of 50%, but with a range of preoperative factor levels from 30% to 60%, and with some centers giving repeat doses on a second day. All UK centers responding to the UKHCDO Dental Working Party Survey used a combination of factor therapy with some form of antifibrinolytic therapy (unpublished data) [2].

Desmopressin (Deamino-8-D-arginine Vasopressin (DDAVP)) *Desmopressin stimulates release of endogenous factor VIII and vWF from stores in patients with mild hemophilia A and vWD and is an established therapy for the control of bleeding around the time of dental and oral surgical procedures [20]. Patients with hemophilia B do not respond to DDAVP.*

DDAVP is administered 1 h pre-procedure subcutaneously (0.3 μg/kg using a 15 μg/mL concentration) or intravenously (0.3 μg/kg of a 4 μg/mL concentration in 50 ml of normal saline) as a slow intravenous infusion (over 20–30 min 1 h pre-procedure. DDAVP can also be given intranasally; the intranasal dose is 150 μg to one nostril for patients weighing <50 kg and to both nostrils for those weighing >50 kg. An elective trial of DDAVP is usually undertaken at the hemophilia center to assess an individual's responsiveness prior to the procedure. Repeated treatments cause a diminished response, most likely due to exhaustion of the endothelial stores, and have side effects of fluid retention and symptomatic hyponatremia. Patients should be advised to limit fluid intake for 24 h following DDAVP. Adverse reactions to DDAVP given intravenously include mild tachycardia, hypotension and facial flushing, and headache, nausea and abdominal cramps have also been reported. DDAVP should be avoided in patients with ischemic heart disease and hyponatremia of <130 mEq/L [2].

Antifibrinolytic Agents Tranexamic acid (Cyklokapron™) binds to plasminogen and inhibits fibrin clot lysis. It is available in intravenous and oral tablet form as well as in the form of a mouthwash. In patients with hereditary bleeding disorders, the use of systemic tranexamic acid and epsilon aminocaproic acid has been demonstrated in two small randomized controlled studies in the early 1970s to control hemorrhage following dental extraction [21, 22]. There is a limited body of evidence to support the combined use of oral tranexamic acid and tranexamic mouthwash together. A combination of systemic plus local tranexamic acid has been demonstrated to be associated with a reduced amount of bleeding compared to monotherapy in retrospective single-center observational and case-control studies of dental extraction in patients with hemophilia [23, 24].

Oral tranexamic acid is given at a dose of 15–25 mg/kg which approximates to 1 g for the majority of adults every 6–8 h. This is usually given 2 h preoperatively and continued for 7–10 days postprocedure. There is no evidence to support a 10-day over a 7-day course [2].

Tranexamic acid mouthwash (10 mL of a 5% solution) should be commenced just prior to the dental procedure to increase salivary levels and continued 6 hourly for 7–10 days. For adults the mouthwash should be gently swilled inside the mouth for 2–3 min and then swallowed or gently expelled. In the hospital setting, tranexamic acid mouthwash can be prepared from the solution used for intravenous injection as a "special order" or can be bought as a ready-made solution from the manufacturer. Special-order formulations hold a limited short shelf life of 5–14 days, are variable in cost, and are reported to be bitter and unpalatable.

Adjunctive Measures. In adult patients the use of sutures and local hemostatic measures such as oxidized cellulose (Surgicel™), resorbable gelatin sponges (Spongostan™), collagen sponges (Haemocollagel™), Gelfoam™, cyanoacrylate tissue adhesives, and surgical splints is a useful adjunctive therapy [2, 13, 25]. Resorbable and non-resorbable sutures are acceptable.

Dental Extractions in Patients with Inhibitors to Factor VIII and Factor IX With the possibility of increased difficulty in controlling bleeding, it is advisable to avoid multiple extractions if a patient has an inhibitor and to hospitalize the patient for 24 h post-extraction. For those individuals taking by-passing agents, a written regimen outlining the administration times for the bypassing agents are necessary prior to and after the extraction. In advance of the extraction, a soft vacuum-formed splint may be constructed for postprocedural socket coverage. Hemostasis can be aided by local hemostatic agents such as packing with Gelfoam™ rolled in thrombin powder (Thrombostat™). The use of tranexamic

acid may pose an increased risk of thromboembolic complications when patients are treated with by-passing agents and must be discussed with the hemophilia treater [2].

For those taking Emicizumab™ Interim guidance from the UKHCDO Inhibitor Working Party and Executive Committee advises consideration to undertaking dental extraction using tranexamic acid with no additional hemostatic cover. There should be close clinical review for bleeding, and rFVIIa should be used to manage surgical related bleeding if necessary [10].

As co-administration of Emicizumab and activated prothrombin complex concentrate (aPCC, FEIBA) has been associated with thrombotic microangiopathy (TMA), venous thrombosis, and skin necrosis, this bypassing agent must be avoided [10].

Gene Therapy There have now been gene therapy studies reporting achievement of sustained factor VIII and IX levels with efficacy and safety data available for over 6 years [26]. Dental procedures in patients who have undergone gene therapy should be performed in close liaison with the hemophilia treater.

Dental Extractions in Patients with Acquired Bleeding Disorders

Anticoagulants

Warfarin and the oral VKAs (e.g., acenocoumarol (Sintrom™)) were the mainstay of oral anticoagulation for several decades and are still used, yet hold a number of limitations including an unpredictable anticoagulant effect leading to a requirement for regular monitoring, numerous food and drug interactions, and a long half-life. The activity of warfarin is expressed using the international normalized ratio (INR); for an individual not taking warfarin, a normal coagulation profile is represented by an INR of 1.0. Low-molecular-weight heparins were previously the optimal antithrombotic treatment in patients with active malignancy undergoing treatment for venous thromboembolism, although there is emerging clinical trial evidence in favor of the use of DOACs in this setting [27]. Low-molecular-weight-heparins are the anticoagulant of choice in pregnant women and in breastfeeding [28].

Direct oral anticoagulants (DOACs) are now available that act by direct inhibition of thrombin or by direct inhibition of activated factor X, key pivotal coagulation factors responsible for the formation of a fibrin clot. Each DOAC holds desirable pharmacokinetic characteristics with predictable dose response and rapid onset and offset of effect with no need for routine anticoagulant monitoring and with few drug and food interactions [29].

Treatment Planning and Basic First Principles

Close liaison between clinician and dentist is important for satisfactory outcome and focuses on the assessment of bleeding risk, including how many extractions are necessary, the technical difficulty and expectation for bleeding, and the distance the patient lives from the treating center in case of complications. It is important to take into account the indication for anticoagulation and other medical comorbidities such as recent placement of a cardiac stent (as the patient may be on dual antiplatelet therapy in addition to an anticoagulant), liver or renal impairment, alcohol problems, and if the patient is receiving cytotoxic drugs (as the patient may have thrombocytopenia), or those with a known bleeding disorder. Patients requiring major surgery should not be treated in a primary care setting. Good soft tissue management is important to avoid excessive trauma, and it is generally recommended that surgery is performed in the morning and at the start of the week in order to adequately deal with any possible bleeding complications.

As for patients with congenital bleeding disorders, nonsteroidal anti-inflammatory analgesia and aspirin-containing medications should be avoided due to their antiplatelet action and risk of over anticoagulation and hemorrhage; paracetamol and codeine-based preparations are recommended.

Postoperative bleeding can be avoided by the use of resorbable and non-resorbable sutures. Resorbable sutures are preferable as they attract less plaque; if non-resorbable sutures are used, they should be removed after 4–7 days. Local hemostatic measures are also useful. The use of locally applied tranexamic acid for the prevention of oral bleeding in people using warfarin and VKAs undergoing minor oral surgery or dental extractions has been shown to be effective [30]. The use of tranexamic acid mouthwash in primary care has been recommended in some guidelines [31] but is felt by others to be expensive, difficult to obtain, and of no more benefit than other local hemostatic measures [30, 32].

The use of antifibrinolytic agents in people undergoing dental extractions on DOACs is being evaluated in clinical trials.

Patients should be given written instructions on their postoperative management including avoidance of rinsing the mouth for 24 h and avoidance of disturbance of the tooth socket in any way such as by chewing on the affected side [33]. If bleeding restarts pressure should be applied over the socket using a gauze pad with the instructions to bite down for 20 min firmly. If the bleeding continues, the dentist should be recontacted to repack and resuture the socket. For this reason, emergency contact numbers and out-of-hours arrangements should always be provided.

Local Anesthesia

Local anesthetic containing a vasoconstrictor should be administered by infiltration or intraligamentary injection and

regional nerve blocks avoided if at all possible; if no alternative, then local anesthetic should be cautiously administered using an aspirating syringe.

Warfarin and Oral VKAs

Published reviews of the available literature advise that VKAs including warfarin should not be stopped prior to dental extraction and other dental procedures [31, 32]. The incidence of postoperative bleeding not controlled by local measures varies from 0% to 3.5%, and the estimated risk of thromboembolic events if the anticoagulant is stopped varies between studies but is estimated to be from 0.02% to 1%. Patients with an INR greater than 4.0 should not undergo dental extraction without advice from the clinician responsible for their anticoagulation, when the warfarin/VKA dose requires adjustment prior to the extraction. Patients with erratic INR control may need to be referred to a dental hospital or a hospital-based oral/maxillofacial surgeon. A general consensus view is that minor dental surgical procedures such as extractions can be performed without alteration to the warfarin if the INR is between 2.0 and 4.0. If multiple (more than 3) extractions are necessary, then several visits may be necessary with planned removal of 2–3 teeth at a time.

Low-Molecular-Weight Heparins (LMWHs)

Patients may be on a once daily or twice daily subcutaneous regimen. For those on once daily regimens, the dental extraction should be scheduled at the time of minimal (trough) anticoagulant activity, and in practical terms this equates to when the next dose of anticoagulant would be given. At the time of the extraction, the authors advise that the dose of LMWH should be withheld and a lower prophylactic dose given later, with a view to full treatment dose being given the next day, or the dose of LMWH simply withheld on the day of extraction.

In the United Kingdom, patients on twice daily regimens will likely either be pregnant women or patients with an underlying malignancy who have experienced breakthrough thrombosis; in these patients, discussion with the treating clinician is necessary as the anticoagulant intensity may be higher than with once daily regimens.

Direct Oral Anticoagulants (DOACs)

Rivaroxaban (Xarelto™), apixaban (Eliquis™), and edoxaban (Lixiana™) are oral anti-factor Xa inhibitors, and dabigatran (Pradaxa™) is an oral direct thrombin inhibitor. These drugs are now licensed for the prevention of stroke and systemic embolism in adult patients nonvalvular atrial fibrillation with one or more known risk factors of congestive heart failure, hypertension, age over 75 years, diabetes mellitus, prior stroke, or transient ischemic attack and for the treatment and prevention of venous thromboembolism. A licensed reversal agent, Idarucizumab, has been developed for the immediate reversal of dabigatran (Pradaxa™) [34] and a reversal agent, Andexanet alfa, is licensed in the United States, but not yet in Europe, for the reversal of factor Xa inhibitors [35]. The role of prothrombin complex concentrates and activated prothrombin complex concentrates remains unclear but are often given in emergency situations if antidotes are not available, with little strong evidence of efficacy.

There is evidence emerging in the literature to guide us on the management of people taking DOACs at the time of dental extractions. An analysis of the periprocedural bleeding risk of patients in the RE-LY trial treated with dabigatran and warfarin revealed 10% of the study group undergoing dental procedures [36]. The study protocol involved cessation of the study drug with patients assigned to dabigatran taking the last dose of drug 49 (range of 35–85) hours before the procedure compared with 114 (range of 87–144) hours in patients receiving warfarin. The analysis showed no difference in the rates of periprocedural bleeding between the dabigatran and warfarin patients [36].

The prospective Dresden NOAC registry categorized dental extraction as a "minor procedure" and reported the experience of 641 patients undergoing such procedures. Outcome at 30 days reported 3 patients with major bleeding and 6 with minor bleeding but did not specify the type of procedures the patients had undergone, with 22% of patients undergoing invasive procedures without interruption of the DOAC [37]. There are also general surveillance reports and communications that advise interruption of DOACs for patients with minor bleeding risk is not necessary [38].

Based on this limited evidence, differing approaches have been suggested and there remains controversy about best practice [39]. One approach recommends withholding the DOAC for 24 h in the setting of normal renal function prior to the extraction. This approach takes into consideration the low thromboembolic risk associated with discontinuation of the DOAC for a short period of time alongside the bleeding risk that can sometimes be difficult to gauge, that antidotes for the factor Xa inhibitors may not be universally available, and may be relevant for people living geographically distant from access to emergency dental or medical advice. The next dose of anticoagulant should not be given until at least 4 h postprocedure, or longer if hemostasis has been difficult to achieve [39]. It is important to note that oral absorption takes around 4 h for time to peak effect.

Others recommend performing dental extractions at the time of trough level, but this can be difficult to arrange in

busy dental surgeries. A recent small prospective case-control study has demonstrated a standardized approach of DOAC interruption, where omitting the dose on the morning of the extraction, regardless of the drug regimen, renal function, and the time of the extraction, is feasible and safe in terms of procedural bleeding. However, it was noted that delayed bleeding tended to occur more frequently in the anticoagulated group than the matched control group [40].

An alternative approach for those with minor bleeding risk (defined as less than a total of three simple dental extractions, and surgery lasting less than 45 minutes) is to continue the DOAC without interruption, as long as the individual does not have additional medical comorbidities or is taking antiplatelet agents. Hemostasis should be facilitated with local measures to minimize the risk of post-extraction bleeding [41]. However, an increase in bleeding during the first postoperative week was observed in a retrospective observational study in patients undergoing dental extraction with continued rivaroxaban therapy [42].

For those requiring multiple extractions (more than three) and surgery lasting more than 45 minutes, or if requiring significant oral maxillofacial surgical procedures, the DOAC may be withheld at least 24–48 h prior to surgery, with the exact timing dependent on the bleeding risk of the procedure and the patient's renal function [41].

Consensus guidelines have been published [43], but the optimal strategy is currently uncertain. Further research and audit is necessary to validate these approaches.

Other Acquired Bleeding Disorders

Bone Marrow Failure Syndromes and Patients Receiving Cytotoxic Medications

Patients undergoing chemotherapy for solid tumors or for hematological malignancies may have transient low platelet counts. If a dental extraction is necessary, it should be planned following liaison with the patients' clinician to avoid the nadir of the thrombocytopenia and preferably be undertaken when the patient has no cytopenias and a platelet count over 50,000/mm^3.

Liver Cirrhosis

Patients with liver cirrhosis may have a significant coagulopathy. It is very important that this group of patients receive optimal preventive care in the early stages of the disease to reduce the risk of extractions and surgery being required in the later stages.

The management of this group of patients requires close liaison with the clinicians caring for the patient. In our opinion, it is probably easiest to divide patients into three groups depending on the results of the platelet count and the prothrombin time ratio (Table 37.3).

Table 37.3 Management of patients undergoing dental extraction with liver cirrhosis: patient classification

Classification	Hematological parameters
Mild	Platelet count over 100,000/mm^3 No change in the PT ratio[a]
Moderate	Platelet count over 100,000/mm^3 PT ratio <1.7
Severe	Platelet count less than 100,000/mm^3 PT ratio >1.7

[a]Prothrombin time (PT)

Patients who are classified as mild or moderate can usually receive a full range of dental treatment without any significant problems. Bleeding in these patients is relatively easily controlled using local measures. A small prospective observational trial of 23 pre-liver transplant patients requiring 35 procedures and 84 teeth removed has shown a low rate of bleeding complications. Patients were included in the study with platelet counts 31–160,000/mm^3, and INR ≤3·0 (mean 1.50, SD 0.39; range, 0.98–2.59), and were randomized to gauze with or without tranexamic acid to apply local pressure post-extraction. A third of the patients had a platelet count <50,000/mm^3. Postoperative bleeding was noted in one procedure (2.9%) and local pressure with gauze enabled hemostasis [44, 45].

Patients with severe cirrhosis may have an unpredictable significant risk of bleeding following a dental extraction. The extraction should be planned with the appropriate clinician, and blood product support may be required in conjunction with local hemostatic measures.

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Part VI

Specific Issues in Neonates and Pediatrics

Neonatal Thrombocytopenia

38

Rebecca Barton and Paul Monagle

Introduction

Thrombocytopenia, defined as a confirmed platelet count of less than $150 \times 10^3/mm^3L$, is a relatively common haematological abnormality in the newborn population, occurring in 1–2% of healthy term neonates, with an increase in the incidence to 15–20% in unwell, low-birth weight or premature infants [1–3]. Thrombocytopenia is further classified as severe if the platelet count is less than $50 \times 10^3/mm^3$.

The causes of thrombocytopenia can be divided into acquired or congenital or based on their mechanism of action which includes decreased production, increased destruction/consumption or both (see Table 38.1 below).

In addition, the causes can be distinguished based on time of onset, either early or late. Early onset is either related to pregnancy-associated conditions and is usually mild or it is severe and is most commonly caused by alloimmune thrombocytopenia. Late-onset thrombocytopenia is usually related to neonatal sepsis or necrotising enterocolitis (NEC) [3].

The majority of neonatal thrombocytopenia is mild to moderate, does not cause any bleeding and resolves without treatment or intervention.

Table 38.1 Causes of neonatal thrombocytopenia

Acquired	Congenital
Immune mediated Neonatal alloimmune Maternal autoimmune	No or minor platelet dysfunction Fanconi anaemia Thrombocytopenia with absent radii syndrome (TAR) Congenital amegakaryocytic thrombocytopenia Von Willebrand disease Type 2B Thrombotic thrombocytopenic purpura (ADAMTS13 deficiency) Aneuploidy (Trisomies 18, 13, 21 or triploidy) Platelet dysfunction Wiskott-Aldrich syndrome X-linked macrothrombocytopenia Chediak-Higashi syndrome
Congenital/perinatal infection Cytomegalovirus Rubella Parvovirus Toxoplasma Group B streptococcus Human immunodeficiency virus	
Postnatally acquired infection	
Disseminated intravascular coagulation (DIC)	
Chronic fetal hypoxia Placental insufficiency Maternal hypertension Maternal diabetes IUGR	
Kasabach-Merritt syndrome	
Thromboembolism	
Liver failure	
Hypersplenism	

Fetal/Neonatal Alloimmune Thrombocytopenia (FNAIT)

Fetal and neonatal alloimmune thrombocytopenia, also known as *fetomaternal alloimmune thrombocytopenia (FMAIT)*or *alloimmune thrombocytopenia of the newborn (AITN)*, is characterised by the presence of antibodies, produced by the mother, against paternal antigens present on fetal platelets. It is one of the major causes of severe thrombocytopenia and subsequent intracranial haemorrhages within the neonatal population and was first recognised more than 50 years ago when it was first described by Harrington and colleagues in 1953.

Incidence

The incidence of thrombocytopenia within the Caucasian population has been estimated to be 1 in 1000–2000 live births; however many studies suggest that the true incidence is underestimated [1, 4].The mortality rate has been estimated to be up to 15% with the majority of this due to intracranial haemorrhages [5].

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Pathogenesis

Fetal platelets expressing specific platelet antigens, which are not present on maternal platelets, cross the placenta and enter the maternal circulation, where alloimmunisation occurs and platelet specific antibodies are produced. Maternal platelet antibodies (immunoglobulin G alloantibodies) then cross the placenta and act via the human platelet alloantigens (HPA) on fetal platelets causing destruction and subsequent thrombocytopenia [6, 7].

Fetal HPAs which are the target of the maternal immunoglobulins are expressed from the first trimester, with transplacental passage of maternal antibodies occurring around 14 weeks, the transfer of which continues to increase until a maximum is reached late in the third trimester [8]. The resultant severe thrombocytopenia can present from as early as 14 weeks gestation in at least 50% of first pregnancies [1, 3, 6]. There is no spontaneous correction or recovery of the platelet count throughout pregnancy, and it will usually continue to fall as the pregnancy progresses unless appropriate therapy is initiated.

The nomenclature for HPA was designed by the *Platelet Working Party of the International Society of Blood Transfusion* in 1990, with each of the antigens named in order of discovery, and the alleles labelled alphabetically in order of serological frequency from more to less common [9, 10]. Current research has identified the glycoproteins on which the antigens are located, the single nucleotide polymorphism and amino acid changes for more than 20 of the common HPAs found in FNAIT. Antigen expression and frequency appear to vary according to race and ethnic origin; however, there is a paucity of comprehensive population-based data, both in regard to HPA frequency in the general population and within the FNAIT population. A number of reviews have demonstrated that within the Caucasian population HPA-1a is the most common HPA accounting for approximately 79–90% of FNAIT cases, followed by HPA-5b [4, 5, 10, 11] (see Table 38.2 below). Population studies have demonstrated that 2% of the female population are HPA-1a negative; however, only 10% of these women will develop an antibody during pregnancy [12, 13].

Table 38.2 Comparison between two large case series of the most common single HPA-specific alloantibodies identified in the mother of patients with FNAIT. Listed in order of frequency

HPA-specific alloantibodies	Davoren et al. (%)	Mueller-Eckhardt et al. (%)
HPA-1a	79	90
HPA-5b	9	8
HPA-1b	4	<1
HPA-3a	2	<1

Adapted from Davoren et al. [10]

The development of this alloantibody appears to be human leukocyte antigen (HLA) restricted, and studies have shown that 95% of these are positive for HLA class II DRB3*0101 (DR52a) type [11, 13–17]. Further research has suggested there is no association between gene dose and neonatal platelet count or incidence of intracranial haemorrhage; however, additional studies have produced inconclusive results regarding compound heterozygosity with other HLA alleles and clinical outcome [17–19].

Initially HPAs were thought to be platelet specific; however, they have since been identified on smooth muscle cells and fibroblasts, which Kay and colleagues have postulated potentiates the severity of the haemorrhage by causing endothelial damage [20].

The mechanism by which FNAIT causes thrombocytopenia is considered to be the platelet equivalent of haemolytic disease of the fetus and newborn (HDFN) [7, 21]; however, in contrast, FNAIT frequently affects the first pregnancy, which has been reported in over 50% of cases [4, 6]. The clinical phenotype of FNAIT usually worsens with each subsequent pregnancy.

Clinical Presentation

The diagnosis of FNAIT is rarely made during pregnancy and is usually made after birth with the identification of minor bleeding or bruising, in an otherwise healthy child [7, 22]. The majority of newborns with FNAIT present with signs of thrombocytopenia and bleeding, with occasional incidental diagnosis on routine full blood examination for other diagnostic purposes. The most common bleeding signs include petechiae, haematomas, melena, haemoptysis, retinal bleeding and haematuria [4].

However, 10–20% of patients present with an intracranial haemorrhage (ICH), with 25–50% of these events occurring in utero, and the remainder intrapartum and postnatally [5, 22, 23]. Intraparenchymal haemorrhages are the most common site of ICH; however, intraventricular and extra-axial haemorrhages are reported [4, 23], and if intrauterine death does not occur, then subsequent porencephaly or hydranencephaly and ventriculomegaly develops with resulting neurodevelopmental sequelae of intellectual disability, cortical blindness, seizures and cerebral palsy. There is currently a lack of long-term data and neurodevelopmental outcomes of affected children; however, it is generally assumed that the outcome is directly related to the extent of haemorrhage.

There is currently limited evidence to conclude what additional factors are present for an ICH to occur, with severe thrombocytopenia not routinely being a good predictor of haemorrhage [24].

Diagnosis

Platelet counts should be performed on blood samples collected in tubes containing EDTA and run through an appropriate cell counter. The count should always be confirmed on a subsequent blood sample and further confirmation with examination of the blood film to exclude pseudothrombocytopenia.

In addition to those with a strong clinical suspicion of alloimmune thrombocytopenia, FNAIT testing should be performed on all neonates with thrombocytopenia of unclear aetiology, as well as those with an unexplained ICH. Testing involves collection of both maternal and paternal blood samples and serological demonstration of maternal alloantibody directed against a paternal platelet antigen, as well as cross-match between samples to identify rare antigens, and lastly antigen detection by polymerase chain reaction (PCR) techniques [24]. Alloantibody testing is performed by antigen capture assays, for example, the monoclonal antibody-specific immobilisation of platelet antigens (MAIPA) or modified antigen capture enzyme-linked immunosorbent assay (MACE) [25]. Maternal serum is tested against both the paternal platelets and a panel of blood group typed O platelets [6] (see Table 38.3 below for suggested diagnostic work-up).

The presence of rare antigens, difficulties in testing procedures and changes in maternal alloantibody levels make the laboratory diagnosis of FNAIT difficult. In a published series by Mueller-Eckhardt and colleagues, there was a positive serological identification in only 40% of their cases. As such FNAIT often remains a diagnosis of exclusion.

To date prospective studies have failed to find a consistent link between maternal alloantibody concentration and the fetal status or risk of haemorrhage. Some groups have shown a correlation between higher maternal alloantibody levels and the more severe cases of NAIT. However, these studies have failed to be replicated and are thought to be due to issues with small sample sizes, methodology of antibody titration and timing of levels [12, 25]. The maternal alloantibody concentration appears to fluctuate during pregnancy, both from a physiological level and from therapy-related changes; therefore serial measurements may be an essential component in monitoring patients [12, 25]. Bertrand and colleagues have found that the maternal alloantibody concentration may rise following delivery, postulated to be as a result of the termination of the fetal circulation, which may affect postnatal testing and therefore prediction of fetal status.

Table 38.3 Suggested diagnostic work-up of suspected FNAIT cases

FNAIT investigations	Sample source
HPA genotyping	Maternal sample Paternal sample
HLA typing	Maternal sample Paternal sample
Platelet autoantibody (PIFT)	Maternal serum vs. maternal platelets
Platelet cross-match (MAIPA)	Maternal serum vs. paternal platelets Maternal serum vs. donor group O matched platelets
HLA cross-match (CDC assay)	Maternal serum vs. paternal sample

PIFT platelet immunofluorescence test, *MAIPA* monoclonal antibody-specific immobilisation of platelet antigens, *CDC* complement dependent cytotoxicity

Treatment

There is currently significant variation in the management strategies of affected women and their offspring, primarily around the specific gestational age for commencement of treatment and target neonatal platelet count postdelivery. As such optimal management may vary from country to country until further research can elucidate a gold standard of treatment and management. A recent systemic review, which included four randomised controlled trials and 22 nonrandomised studies, found comparable outcomes regarding intracranial haemorrhage, irrespective of the antenatal strategy utilised, with all studies showing increased complication rates with fetal blood sampling and intrauterine platelet transfusion [26].

Risk Stratification

Recurrence rates of FNAIT have been reported to range from 75% to 90% in subsequent pregnancies [3, 4, 27].

With the addition of new maternal noninvasive techniques for the identification of fetal HPA-1a genotype, not only has the need for invasive techniques such as amniocentesis been reduced, but it has allowed for enhanced risk stratification for subsequent fetuses. If the fetus is identified as carrying the specific HPA and the mother is positive for the corresponding HPA antibody, the child is considered 'at risk' for the development of low platelets and subsequent bleeding complications. Further risk stratification remains unclear; however, if in the previously affected child there was an antenatal ICH or a platelet count $<20 \times 10^3/mm^3$, then the fetus is considered to be 'high risk' [22, 28]. A proposed treatment algorithm based on this risk stratification is shown in Fig. 38.1.

The data pertaining to outcomes and natural history of FNAIT in both at risk and high-risk patients remain unclear, but given the devastating complications associated with FNAIT and bleeding, treatment is initiated in all patients.

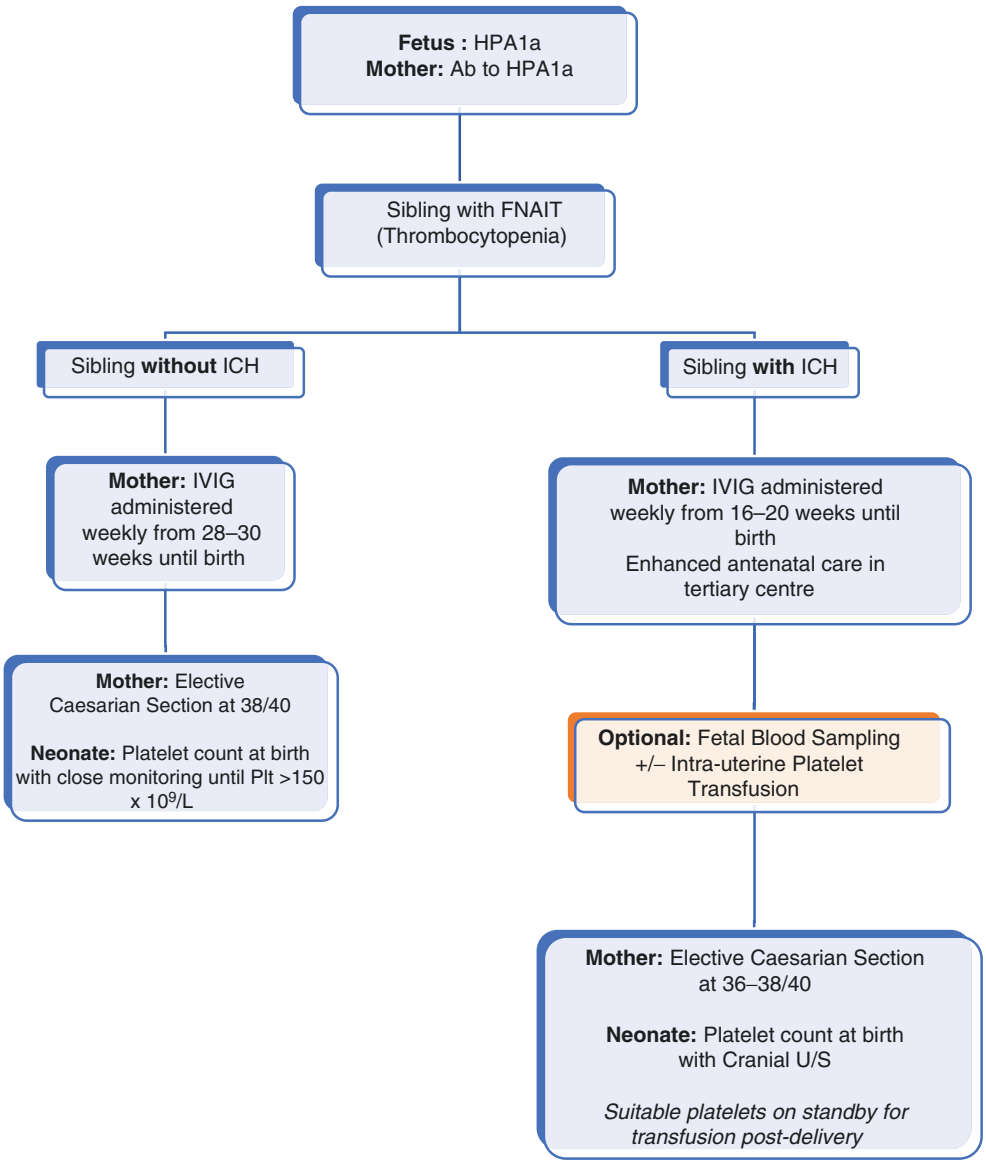

Fig. 38.1 Proposed treatment algorithm. (Adapted from Porcelijn et al. [28])

Fetal Blood Sampling

Fetal blood sampling (FBS) is an invasive procedure that is used to obtain a fetal platelet count and also monitor the status of the fetus. The procedure has a rate of fetal loss of 0.5–1% per procedure, largely due to haemorrhage, with additional risks associated with premature delivery [14, 25, 29].

Maternal Therapy

Current maternal antenatal therapy is largely based on risk stratification and includes the use of high-dose intravenous immunoglobulin (IVIG), with or without the use of corticosteroids [26, 30, 31]. Aggressive treatment of pregnant women who have previously had an affected child, with high-dose IVIG, has demonstrated a reduced incidence of ICH and subsequent neurological sequelae [8, 23, 32].

Intrauterine Platelet Transfusion

Previous aggressive treatment strategies included intrauterine platelet transfusion (IUPT), with transfusion compatible allogeneic or washed maternal platelets. Unfortunately, IUPT has a high fetal loss rate, is often required multiple times throughout pregnancy and is therefore largely reserved as a high-risk rescue strategy only.

Delivery

Clinicians experienced in this field generally recommend that a fetus with FNAIT is delivered via caesarean section, to prevent complications related to trauma to the head and subsequent bleeding. However, a vaginal delivery may be considered if the platelet count is confirmed via FBS. In addition to careful consideration of the mode of the delivery, it may be prudent to ensure there are appropriate platelets for transfusion available at delivery.

Neonatal Therapy

Any infant with signs of clinical bleeding or a platelet count below 30,000–50,000/mm^3 in the first 24 hours of life should be promptly transfused with platelets. Platelet options include random donor platelets, antigen-negative platelets from phenotype-matched donors or apheresed maternal platelets [11, 33]. The choice of which may depend on the prevailing HPA genotypes in the community and the subsequent availability of antigen-negative platelets. Maternal washed platelets may be used; however, for practical reasons and medical condition of the mother, especially if the baby was born by caesarean section, these are not always available [11]. In an emergency situation, transfusion of HPA-1a/HPa-5b-negative platelets if available, or random donor platelets if the former is unavailable, is recommended in neonates with a presumptive diagnosis of FNAIT, with some studies showing that antigen-matched platelets give larger platelet increments than random donor platelets [34].

If only random donor platelets are available, the addition of IVIG, at a dose of 1 g per kg of body weight, may be considered.

The use of IVIG alone remains controversial because of the delay in increase of the platelet count of 24–48 hours following transfusion; however, it is often recommended as a complementary treatment strategy [35].

Regardless of the treatment, monitoring the neonate closely for any clinical signs of bleeding, routine regular cranial ultrasounds and regular platelet counts are required, as the relationship between platelet count and bleeding risk remains unclear, as well as the efficacy of platelet transfusions [36, 37]Furthermore, in the context of both thrombocytopenia and platelet transfusions, the non-haemostatic role of platelets as a mediator within the inflammatory and the immune responses requires further investigation [37].

If there is no sign of bleeding or the platelet count is above 50×10^3/mm^3, then no therapy can be considered, but once again close monitoring is important.

Following delivery, the platelet count may continue to fall as maternal platelet antibodies continue to circulate, which can persist for up to 3 months after delivery, with significant variation as to the time of platelet nadir and subsequent time to recovery [6, 8, 24]. The majority of platelet counts will rise by the end of the first week; however, there are reported cases where the thrombocytopenia has persisted for several weeks and rarely months [3].

Screening

A good screening program for FNAIT testing would require an accurate, standardised and cost-effective test for common platelet antibodies or genotyping, an ability to predict the risk of bleeding to the fetus and then appropriate and agreed management of the disease when identified. FNAIT has a high rate of recurrence, and the phenotype of the illness appears to be more severe with each subsequent pregnancy. A number of research groups have published data on screening programs, including cost analysis, with the majority of groups concluding that a screening program consisting of HPA-1a typing and screening for antibodies in HPA-1a-negative women may reduce mortality and serious morbidity [13, 38, 39]. Recent research is also recommending HLA-DR genotyping to further identify mothers with fetuses at risk of FNAIT [17]. In addition some groups have suggested that screening of newborns may be more cost-effective than screening primiparous women; however, this strategy would miss fetuses that suffer from ICH in utero [14].

Further research into the correlation of maternal alloantibody titre as a predictor for FNAIT and bleeding risk, as well as maternal sensitization and standardisation of treatment, are required to assist in reducing the morbidity and mortality associated with FNAIT.

Maternal Thrombocytopenia

There are number of causes of maternal thrombocytopenia, which as a result of their pathophysiology have the ability to cause thrombocytopenia in a neonate. These include incidental thrombocytopenia of pregnancy, hypertensive diseases of pregnancy and immune thrombocytopenic disorders of pregnancy, such as idiopathic thrombocytopenia and systemic lupus erythematosus (SLE) [40]. The main distinction with maternal causes of thrombocytopenia is that they are unlikely to cause moderate or severe thrombocytopenia in the neonate and are therefore less likely to cause bleeding or associated complications in this children. A major point of difference from FMAIT is that in FMAIT, the mother always has a normal platelet count. Importantly, in maternal ITP, the maternal platelet count does not predict the neonatal platelet count, and screening of the neonatal platelet count and clinical observation for signs of bleeding is required.

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Bleeding in the Neonate

39

Sally Campbell and Paul Monagle

Introduction

The occurrence of bleeding in a neonate is stressful for physicians and parents alike. The approach to the bleeding neonate needs to take into account the implications of developmental hemostasis for interpretation of diagnostic tests. The most common abnormality found is thrombocytopenia; however, coagulation defects also occur, and the two can coexist together. Acquired coagulation defects are often present in sick neonates, and inherited coagulation defects can present in otherwise healthy neonates.

Hemostasis

Hemostasis involves complex interrelationships between platelets, vascular endothelium, and plasma proteins, as described in Fig. 39.1. Hemostasis is also described as primary and secondary and also fibrinolysis. Primary hemostasis refers to the adhesion, activation, and aggregation of platelets at the site of vessel wall injury. Secondary hemostasis is the activation of coagulation pathway, resulting in the formation of covalently cross-linked fibrin that stabilizes the platelet plug. Activation of the fibrinolytic pathway results in dissolution of clots to maintain or restore blood flow. These processes are intimately related to the activity and functions of the endothelial cells, particularly the dynamic expression of tissue factor and other key molecular activators and inhibitors.

The hemostatic system of the neonate and infant is evolving, dynamic, and very different from the adult. Normal neonatal coagulation factor levels would be interpreted as pathological in an adult [1, 2]. However the coagulation system of an infant is protective against both hemorrhage and thrombosis.

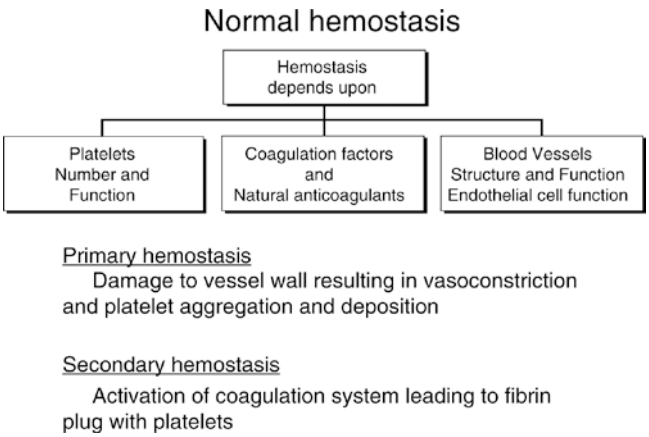

Fig. 39.1 Normal hemostasis

Platelets appear in the human fetus at 5 weeks postconception and increase during fetal life to reach a mean of 150,000/mm^3 at the end of the first trimester [3]. A recent large population study of neonates reported that the lower limit of normal platelet counts for neonates less than 32 weeks of gestation is 104,000/mm^3, compared with 123,000/mm^3 for neonates of more than 32 weeks [4]. The assessment of platelet function however is difficult, regardless of the age of the patient since it demands large volumes and specialized laboratory expertise and is also a poor surrogate for in vivo primary hemostasis [5, 6]. Studies examining neonatal platelet function have mostly been performed on cord blood rather than infant blood, and while sampling cord blood has the advantage of larger volumes, it is not equivalent in function to peripheral blood [7]. Overall these studies have demonstrated that the platelet function in neonates compared with adults is hyporeactive in some regards and hyperreactive in others [5, 6]. In vivo tests of platelet function such as bleeding time and platelet function analyzer (PFA-100™) do not show abnormalities. The apparent lack of reactivity seems to be balanced by an increase in large von Willebrand factor (VWF) multimers, enhanced VWF levels, and increased packed cell volume [7].

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Coagulation factor production can be detected from 10 weeks of gestation [8]. Concentrations of coagulation proteins increase with age and are consequently lower in preterm compared with term infants [6]. Reference ranges for coagulation assays in neonates and infants vary with laboratory analyzer and reagent system, and this needs to be taken into consideration when comparing abnormal results from different laboratories.

Neonates have lower levels of most coagulation factors compared with adults [9] (see Table 39.1). Levels of the vitamin K-dependent coagulation factors II, VII, IX, and X are half to a third of adult values, despite receiving vitamin K prophylaxis at birth. The contact factors are also reduced (factor XI, factor XII, prekallikrein, and high-molecular-weight kininogen). These and the vitamin K-dependent factors gradually increase to approach adult levels by 6 months of age. Factor V levels are decreased at birth compared with adults, and factor VIII levels are elevated at birth. The physiological causes for these developmental changes are not clear; however, one hypothesis is that the changes are driven by the function of coagulation proteins in other physiological systems such as angiogenesis, inflammation, and wound repair [10].

The levels of the major anticoagulant proteins, antithrombin, protein C, and protein S, are also reduced at birth compared with adult levels. The plasma concentration of antithrombin (AT) is physiologically low at birth (~0.50 U/mL) and does not increase to adult values until 3 months of age. Sick premature infants often have values of less than 0.30 U/mL. Whether the overall activity of the protein C/protein S system varies with age is unknown. However, at birth, the plasma concentration of protein C is very low and remains decreased during the first 6 months of life and remains lower than adult level until 8–10 years. Although the total amount of protein S is decreased at birth, the protein S that is present is completely free and active, because of the absence of C4b-binding protein [11, 12]. Plasminogen levels of the newborn are also lower than in adults, demonstrating reduced fibrinolytic activity [13].

This functional immaturity of neonatal pro- and anticoagulant proteins demonstrates that the hemostatic system is set differently to adults, and under normal circumstances, the infant is not at increased risk of either hemorrhage or thrombosis.

Table 39.1 Hemostatic components

	Neonates versus older children and adults
Primary hemostasis	
Platelet count	Decreased <32 weeks
Platelet function	Similar to adults >32 weeks
	Decreased
Coagulation factors	
FII, FVII, FIX, FX	Decreased
FV	Decreased
FVIII	Increased
FXI	Decreased
FXII	Decreased
Functional fibrinogen	Unknown
Regulation of coagulation	
Antithrombin	Decreased
Protein C	Decreased
Total protein S	Decreased
Free protein S	Increased
Alpha 2 macroglobulin	Increased

Approach to the Bleeding Neonate

The clinical setting in which a neonate presents with bleeding is extremely important giving clues to potential causes enabling investigations to be tailored to facilitate rapid diagnosis and treatment. Bleeding that occurs in an otherwise well neonate is highly suggestive of an inherited bleeding disorder, vitamin K deficiency, or an immune-mediated thrombocytopenia. The sick preterm infant however is much more likely to have an acquired coagulopathy, such as disseminated intravascular coagulation (DIC). Family history is also important. Family members may have a bleeding disorder without being formally diagnosed, and systematic questioning about a parental bleeding history is important. A medication history from the mother is also important, in regard to drugs that affect vitamin K metabolism.

Sites of bleeding which may suggest a coagulation disorder in neonates include:

- Puncture sites (heel prick, newborn screen, or immunizations).
- Upper and lower gastrointestinal tract.
- Bleeding from umbilical stump.
- Extracranial (subgaleal hemorrhage, cephalohematoma).
- Intraventricular hemorrhage (IVH).
- Pulmonary hemorrhage is most commonly related to lung factors rather than coagulopathy.
- Extensive purpura and/or bruising suggests a platelet disorder (of number and/or function).

Initial screening should include a complete blood count (CBC) with a blood smear examination (since examination of platelet size and morphology can lead to the diagnosis) and coagulation studies including fibrinogen. These results, in conjunction with clinical setting and family history, can then be used to tailor subsequent investigations.

Sampling problems are common in neonates. Poor venipuncture technique results in contamination and activation of the sample by tissue factor. The neonates' low procoagulant factor levels can result in prolongation of baseline coagulation, particularly the activated partial thromboplastin time

(aPTT). It is very important that laboratories experienced in handling neonatal coagulation studies examine the samples, and ideally each laboratory should have its own set of reference ranges for their analyzer and reagents. In practice this is difficult to achieve, and the use of published ranges may be required [9]. Neonates with polycythemia can also have spurious results due to the high packed cell volume (and therefore reduced plasma to citrate ratio in the tube) affecting the test. Before the diagnosis of a bleeding disorder in a neonate can be made, the abnormal tests must be reproducible, and the results should fit with the clinical phenotype and family history. Misdiagnosis in this group can lead to frequent and unnecessary treatments for the neonate.

Congenital Hemorrhagic Diseases

Congenital bleeding disorders are discussed in detail in Chapter 9. However, Fig. 39.2 shows the pathway to investigating specific factor deficiencies based on the initial coagulation screening tests.

The rare coagulation disorders show autosomal recessive inheritance. Individuals who are homozygous for the defect, or compound heterozygote, have a bleeding disorder. These disorders are more common in families with consanguinity. Pediatricians and hematologists should be aware of the risk in their local community and any relevant immigrant populations. The diagnosis may not be suspected; there may be language and cultural barriers. Two rare bleeding disorders are truly recessive with normal levels in both parents: combined deficiency of factors V and VIII (caused by genetic mutations in coding for chaperone proteins in the endoplasmic reticulum) and combined deficiency of the vitamin K-dependent factors (factors II, VII, IX, and X, due to mutations in genes controlling the vitamin K pathway).

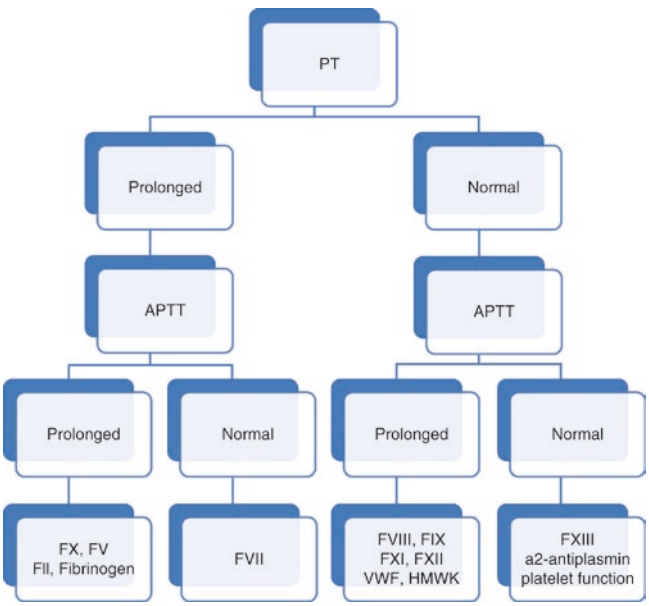

Fig. 39.2 Inherited causes of prolonged coagulation tests

A feature of many of the rare coagulation disorders is that the bleeding risk does not correlate well with the factor level.

Severe deficiencies of factor VII, factor X, factor XIII, or fibrinogen are the most likely of the rare disorders to present in the neonatal period. Infants with these disorders are particularly at risk of intracranial bleeding, as well as soft tissue bleeding. Factor XIII deficiency usually presents as delayed bleeding, often from umbilical stump, and will occur in the face of normal coagulation studies and CBC. The disorder has a high risk of intracerebral bleeding if not diagnosed and treated. Because of this, once the diagnosis is confirmed with factor assays, prophylaxis may be advisable [14]. Specific concentrates are available for fibrinogen, factor X, and factor XIII. When an infant presents with unexpected bleeding, it is helpful to test both parents as in these cases they will have partial deficiency of the missing coagulation factor, and this confirms the diagnosis.

Von Willebrand disease (VWD) is characterized by a qualitative or quantitative defect in VWF that rarely presents in the first months of life. Factor VIII is normal or raised at birth, and the levels of VWF rise and remain elevated for the first 6 months of life. Due to the nature of VWF levels in the first 6 months of life, diagnosis of the common mild VWD can be difficult in neonates. Testing for the milder forms of VWD in this age group should not normally be done. However if clinically apparent mucocutaneous and other bleeding is occurring, severe deficiency (Type 3) or function-antigen discrepancy (Type 2) may be the cause. Borderline results can occur due to VWF levels increasing with stress and should be repeated when the child is older [15].

Congenital Platelet Disorders

These are many and complex and have been reviewed [16, 17] and are discussed in more detail in Chapter 13. Some are associated with thrombocytopenia, and many have multisystem abnormalities. Severe platelet disorders present early in life with a bleeding phenotype that differs from the coagulation disorders. It is characterized by severe bruising and purpura at birth. The diagnosis may be difficult but is urgent since platelet transfusions may be life-saving. Glanzmann thrombasthenia (GT) is the most serious of these with recessive inheritance and a normal platelet count. The platelets do not function properly due to an absence or reduction in an essential surface glycoprotein (GPIIa/IIIb) and are unable to bind to fibrinogen, as well as other key hemostatic proteins.

Acquired Hemorrhagic Diseases

DIC is a complex disorder triggered by many conditions, including severe hypoxia, trauma, generalized infection, and surgical intervention. It involves the activation and consumption of coagulation proteins and platelets and the breakdown of fibrin. The true incidence of DIC remains ill-defined and is likely underdiagnosed in the neonatal age group. Risk factors for the development of neonatal DIC include hemodynamic instability, anemia, respiratory failure, acidosis, and sepsis particularly with endotoxemia as seen in gram-negative sepsis. Hypoxemia and acidosis can induce the release of tissue factor and tissue plasminogen activator by activated endothelial cells, thus activating both the extrinsic pathway and the fibrinolytic pathway simultaneously [18].

The developing hemostatic system of the neonate creates an extra diagnostic challenge, due to increased levels of fibrinogen after birth, which may initially mask DIC, and the high prevalence of thrombocytopenia that can be attributed to other causes. Added to this, there are no normal ranges for D-dimers in neonates.

When suspecting DIC, it is prudent to perform CBC and blood smear; coagulation screen including international normalized ratio (INR), aPTT, and fibrinogen; and D-dimer. Table 39.3 shows a common pattern of laboratory abnormalities in DIC, compared to liver disease. No single abnormality is diagnostic of DIC, and the global laboratory and clinical picture must be considered. DIC scoring systems that are well established in adults have not been tested or validated in neonates. The cornerstone of DIC treatment relies heavily on reversal of the underlying condition while providing tailored product support [19].

Vitamin K-dependent bleeding (VKDB), previously known as hemorrhagic disease of the newborn, refers to bleeding that occurs secondary to vitamin K deficiency in the first year of life. The diagnosis of VKDB is made on the coagulation studies (see Table 39.2) and confirmation (if necessary) by demonstration of low levels of factors II, VII, IX, and X which will correct rapidly after vitamin K administration.

VKDB is further divided into early (<24 h), classical (1–7 days), and late (>1 week, <9 months) depending on the timing of onset of bleeding and is discussed in detail in Chapter 18.

Acute neonatal liver failure is an uncommon condition where the sick infant has a coagulopathy, in addition to conjugated hyperbilirubinemia and hypoalbuminemia. The presentation of liver disease in neonates is that of acute liver failure and is usually accompanied by multi-organ failure. They can often be diagnosed as overwhelming sepsis, despite negative blood cultures. The most prominent features include marked coagulopathy, hypoalbuminemia, hypoglycemia, edema with or without ascites, and oliguria

Table 39.2 Interpretation of coagulation tests in the bleeding neonate with normal platelet count

		Differential diagnoses
PT prolonged	aPTT normal	Acquired conditions Vitamin K deficiency Inherited conditions FVII deficiency
PT prolonged	aPTT prolonged	Acquired conditions DIC[a] Liver disease Vitamin K deficiency Inherited conditions Deficiency of factor II, factor V, factor X, or fibrinogen Combined factor deficiency
PT normal	aPTT prolonged	Acquired conditions Heparin administration Lupus anticoagulant[b] Inherited conditions Deficiency of factor VIII, factor IX, factor XI, or factor XII
PT normal	aPTT normal	Inherited conditions Factor XIII deficiency

PT prothrombin time, *PTT* activated partial thromboplastin time
[a]DIC is characterized by hypofibrinogenemia, which will differentiate it from severe vitamin K deficiency
[b]"Lupus anticoagulant" which reflects the presence of antibodies which interfere with the laboratory tests in vitro. These are common and transient in young children after viral infections and are not usually associated with bleeding

Table 39.3 Comparison of DIC and liver disease

	DIC	Liver disease
INR	↑	↑
aPTT	↑	↑
Fibrinogen	↓/Normal	Normal
D-dimer	↑	Normal
Platelet count	↓	Normal or ↓[a]
Bilirubin	Normal	↑

[a]The reduced platelet count in liver disease is usually due to associated hypersplenism

[20]. The pattern of coagulopathy and laboratory tests is shown in Table 39.3; however this may vary according to the underlying cause of disease [21]. The differential diagnosis for this rare disorder includes five major entities: intrauterine insult, bacterial or viral sepsis, hematological disorders, inborn errors of metabolism, and primary liver disease [22]. One such example of primary liver disease is neonatal hemochromatosis (NH), a rare entity that causes liver disease by siderosis of extrahepatic tissues, which is most caused by transplacental transfer of maternal immunoglobulin (IgG) antibodies [23]. Primary liver diseases of the neonate can evolve with time; those who are born in fulminant liver failure often demonstrate evidence of fetal insult (often with intrauterine growth restriction and oligohydram-

nios) and premature birth [20]. An approach to the management of hemostatic disorders related to liver disease in children has recently been described [24].

A hematological condition that can present as neonatal liver failure is hemophagocytic lymphohistiocytosis (HLH), which is caused by excessive immune activation. Affected neonates have fever, hepatosplenomegaly, elevated serum ferritin, abnormal liver function tests, elevated triglyceride levels, hypofibrinogenemia, and cytopenias. This disease may be familial or idiopathic and is thought to be triggered by infections or other immune-activating events [25].

Thrombocytopenia in the Newborn

There are many causes and patterns of thrombocytopenia in the neonate, and diagnosis requires a systematic approach as recommended in a recent review [26]. In premature neonates, particularly those who are small for gestational age (SGA), thrombocytopenia in the first 72 hours is often attributed to maternal and birth factors (e.g., placental insufficiency, perinatal asphyxia, and antenatal/perinatal infection). After 72 hours, the most common cause is postnatally acquired infection or necrotizing enterocolitis (NEC). Importantly, thrombocytopenia in the presence of hematuria can herald renal vein thrombosis.

Severe thrombocytopenia of <50,000/mm^3 occurs in 1:7000 live births, and the major cause of this is neonatal alloimmune thrombocytopenia (NAIT). Maternally transferred platelet antibodies (from maternal ITP or lupus) can also result in neonatal thrombocytopenia. These conditions are discussed in more detail in Chapter 38.

Intraventricular Hemorrhage

The role of developmental hemostasis in the development of intraventricular hemorrhage (IVH) in the very low-birthweight (VLBW) infant and preterm infant is unclear. The diagnosis of IVH is most commonly made by cranial ultrasound, with MRI used once the infant approaches term age to help aid assessment of white matter injury [27]. MRI is more sensitive at detecting cerebellar hemorrhages and punctate and diffuse white matter injury than cranial ultrasound; however, cranial ultrasound can reliably detect large hemorrhages and cystic periventricular leukomalacia [28].

The immaturity of the cerebral circulation of preterm and VLBW infants, as well as the fragility of their germinal matrix, increases their risk of IVH, particularly in the first 10 days of life. Platelet counts less than 150,000/mm^3 affect up to 30% of all neonatal intensive care unit (NICU) patients and 70% of those born with a birthweight less than 1000 g [5]. Major morbidities, such as chronic lung disease, sepsis, NEC, and postnatal steroid therapy, are significantly more common in infants with IVH [29]. Anemia (hematocrit <28%) has been shown to prolong the bleeding time in neonates, and sepsis has been shown to reduce platelet adherence compared with healthy preterm platelets [3].

The exact role that thrombocytopenia and the theoretically hyporeactive neonatal platelets play in the development of IVH is unknown. Because of this, platelet transfusion in NICU is common practice, despite the lack of evidence. These practices vary widely across centers, from restrictive (active hemorrhage with a platelet count <50,000/mm^3) to liberal transfusion triggers (platelet count <100,000/mm^3). Platelet transfusions are not without risk, from bacterial contamination (fortunately rare due to bacterial testing), transfusion reactions, allergic reactions, alloimmunization, and transfusion-associated lung injury (TRALI). An added theoretical risk is that when adult platelets are used prophylactically in infants with mild-moderate thrombocytopenia, there may be an increased thrombotic risk [30]. A recent randomized control trial performed with 660 preterm infants demonstrated benefits of a restrictive platelet transfusion strategy, with infants randomized to the low-threshold group (<25,000 per cubic millimeter) having a better outcome than those randomized to the high threshold group (<50,000 per cubic millimeter) [31]. Term neonatal IVH is thought to be a different entity to that of preterm IVH. There may be an element of selection bias as routine surveillance for IVH is not performed in term infants, so the exact incidence of the disease is unknown [32]. Symptomatic intracranial bleeding in the term neonate is estimated at 4 per 10,000 live births [33]. Symptoms include poor feeding, hypotonia, seizures, and encephalopathy; however, these are not specific to intracranial bleeding alone. The most common risk factor for bleeding in the term neonate appears to be abnormal labor, as well as deliveries requiring instrumentation [34]. Other differential diagnoses in the term neonate with intracranial bleeding to consider include arteriovenous malformations, inherited and acquired coagulation disorders, and finally nonaccidental injury (NAI).

Differentiating Nonaccidental Injury from Inherited Bleeding Disorders

When an infant presents with bruising or bleeding, there is often concern that this is due to NAI. Typically the history from the parents/carers does not fit with the extent of bleeding, and the child may have additional injuries suggesting harm (torn frenulum, multiple fractures, evidence of head injury). Children with rare congenital bleeding disorders can be misdiagnosed as nonaccidental injury, so it is important

that appropriate laboratory testing be performed to exclude hemophilia, other severe factor deficiencies, and factor XIII deficiency. With extensive bruising the platelet count should be checked and consideration given to the possibility of GT. It is also possible for a child with hemophilia or other bleeding disorders to be subjected to NAI which complicates the process of appropriate care. Practical guidelines have previously been reported [35].

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Part VII

Evaluation of Bleeding Risk Prior to Invasive Procedures

Evaluation of Bleeding Risk Prior to Pediatric Invasive Procedures

40

Lisa Hensch

Introduction

Preoperative coagulation assessment for neonates, infants, and pediatric patients presents unique challenges. The majority of pediatric surgeries are elective procedures, and many of these patients present without prior hemostatic assessment or challenge. Some coagulation disorders, particularly mild deficiencies, may fail to present in the neonatal period and can manifest for the first time after routine pediatric procedures, such as tonsillectomy. Von Willebrand disease (VWD) is believed to have a prevalence of 1% [1] and represents an important risk for increased operative bleeding. Nonetheless, indiscriminant screening of pediatric patients for coagulation abnormalities is not recommended [2–5]. Pediatric patients with a concerning personal and/or family history of bleeding, or those undergoing high-risk procedures where increased bleeding is expected or can have catastrophic consequences (i.e., neurosurgery), should be considered for preoperative screening. In addition, there are a number of congenital syndromes and inherited factor deficiencies that are associated with increased bleeding. These patients should be discussed with a hematologist or coagulation specialist prior to surgery. A detailed plan for surgery should be formulated by a multidisciplinary team including the surgeon, anesthesiologist, coagulation specialist, and other treating teams as needed.

Preoperative Coagulation Assessment

Routine coagulation testing for healthy pediatric patients undergoing minor or intermediate surgeries is generally not recommended [2, 4, 5]. Coagulation screening in unselected patients can lead to increased costs, increased patient and family anxiety, and delayed procedures. Studies evaluating the routine use of coagulation assays in pediatric patients have shown that of patients with abnormal coagulation screening, only a small number have an underlying bleeding disorder [4, 6]. A study of pediatric patients screened for coagulation abnormalities using prothrombin time (PT) and activated partial thromboplastin time (aPTT) demonstrated that over 50% of abnormal values had normalized on repeat testing. They also demonstrated that in patients with repeatedly abnormal testing (most frequently a prolonged aPTT), nearly 80% had normal factor levels [3]. In patients referred for further evaluation of abnormal testing, patient and family history of bleeding only identified 45–60% of patients with clinically significant abnormalities [6, 7]. However, despite this low yield, it continues to be important to perform coagulation screening for pediatric patients for certain high-risk procedures, as bleeding history alone fails to identify all patients with a risk for bleeding. Nevertheless, history is essential as some bleeding disorders may not be detected by coagulation screening tests. Ideally, the decision to perform preoperative testing, and the selection of tests to be performed, should be guided by appropriate patient screening. This includes type of procedure, personal and family history of bleeding, and assessment of patient comorbidities.

Coagulation Screening Tests

If performed, coagulation screening for procedures usually consists of the PT, international normalized ratio (INR), and the aPTT. The details of these tests and interpretive guidance are discussed in Chapter 2. Interpretation of preoperative coagulation screening must be made with knowledge of the limitations of the tests being performed. Foremost, it is important to note that these are ex vivo tests that may not reflect the conditions in vivo [8]. These tests also fail to identify all types of coagulation deficiency/dysfunction associated with increased bleeding including platelet dysfunction

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and low fibrinogen/dysfibrinogenemia. Moreover, factor XIII deficiency, α2antiplasmin deficiency, and other causes of hyperfibrinolysis are not identified [9]. In addition, young infants undergoing preoperative screening may have prolonged PT/aPTT according to institutional reference ranges; however, the majority of these patients have values that are normal for age, and interpretation should be based on pediatric-specific reference ranges [10, 11]. Clinicians should be aware that coagulation reference ranges are frequently established for healthy adults rather than for healthy children. Finally, if the reference range is established to be within two standard deviations of the mean, it only captures 95% of "normal" individuals. Therefore, some patients with prolonged coagulation tests are actually normal variants [2].

With that understanding, patients with comorbidities such as renal or liver disease, patients taking medications that affect hemostatic function, patients with concerning personal and/or family bleeding histories, and those undergoing particular high-risk procedures should be considered for coagulation screening. It is also important to remember that each of these tests can be affected by pre-analytical and analytical factors. Providers should be aware of the causes of false-negative and false-positive results. False-negative results may be seen due to varying sensitivity of the reagent used, leading to a failure to identify patients with mild deficiencies [12]. In particular, patients with VWD may only be identified with this screening if they have concurrent low or low-normal factor VIII. Also, if the patient is under physiologic stress or had traumatic venipuncture, factor VIII levels may increase leading to a "falsely normal" aPTT. False-positive aPTT testing can also occur, and these causes are listed in Table 40.1. Notably, transient lupus anticoagulant is not uncommon in the pediatric setting [13]. A prolonged PT is less frequently encountered in preoperative screening. Important causes in the outpatient setting include vitamin K deficiency and liver disease; therefore screening should be considered if patient comorbidities (nutritional deficiency, known or suspected liver dysfunction) indicate. Factor VII deficiency and common pathway factor deficiencies are other causes for a prolonged PT. These deficiencies are rare and are discussed in more detail in Chapter 11. For patients that have been appropriately screened, abnormal coagulation assays are further investigated using factor-specific assays. Patients with abnormal factor levels associated with an increased risk for bleeding should have hematology consultation and an operative plan before invasive procedure. Furthermore, patients with a positive bleeding history and low to low-normal levels of factor VIII should additionally be considered for von Willebrand factor (VWF) assay if undergoing major procedure or if there is a history of bleeding. Additional screening, such as platelet function screening and fibrinogen levels, should be considered in patients with significant bleeding history.

Table 40.1 Causes of prolonged aPTT in pediatric preoperative coagulation screening [9, 12]

With increased bleeding risk	Without increased bleeding risk
Hemophilia A (factor VIII deficiency)	Normal variant
Hemophilia B (factor IX deficiency)	Factor XII deficiency
Hemophilia C (factor XI deficiency)	Lupus anticoagulant
Von Willebrand disease	Pre-analytical or analytical error
Anticoagulation	Increased C-reactive protein (CRP)
Critically low fibrinogen	Specimen contamination (frequently heparin)
	Prekallikrein deficiency
	High-molecular weight kininogen deficiency

A platelet function assay (PFA-100) may be performed depending on the individual patient and type of procedure being performed. Patients who present with mucocutaneous bleeding symptoms, abnormal bruising, petechiae, or family history of VWD should be considered for screening using the PFA-100, if available. Causes of abnormal PFA-100 screening and limitations are further discussed in Chapter 3. The PFA-100 has demonstrated variable sensitivity in VWD and qualitative platelet function defects, but, the collagen-epinephrine cartridge in particular appears to be more sensitive to these diagnoses than the bleeding time (no longer used in most institutions) [14, 15]. Like the PT/INR/aPTT, the PFA-100 is not recommended for general screening in pediatric patients [16]. Importantly, PFA-100 has not been shown to be able to predict post-procedural bleeding [17, 18]. However, for appropriately selected patients, an abnormal PFA-100 with no identified cause (lack of medication effect, thrombocytopenia, anemia, renal dysfunction, or known bleeding disorder), warrants additional testing and investigation, including VWF assay and/or platelet aggregation studies. These should be performed in consultation with a hematologist or coagulation specialist.

A complete blood count (CBC) or hemoglobin and hematocrit with platelet count are similarly not recommended for screening in healthy pediatric patients undergoing minor elective procedures. These tests are, however, recommended in cases where significant bleeding is expected [5]. In addition, those with a history of thrombocytopenia or syndromes that include thrombocytopenia (described below and in Chapter 13) should have an evaluation prior to invasive procedure. Platelet counts of >50,000/mm^3 are generally sufficient for invasive procedures, but ophthalmic surgery and neurosurgery should have targets closer to 100,000/mm^3. For major elective procedures (i.e., scoliosis repair), providers should consider evaluation and correction of anemia resulting from iron deficiency prior to procedure.

Patient History

An adequate assessment of patient history is imperative prior to any invasive procedure. This history should include history of current illness, past medical issues, review of allergies, surgical history including any complications, family history of anesthetic or bleeding complications, current medication list [19], and a bleeding history. Comorbid conditions, such as renal or liver dysfunction, should be noted and may warrant hemostatic function testing. Pediatric patients presenting for evaluation may have very little personal history, and a history of the events surrounding birth should be obtained, if possible. In particular, reported umbilical stump bleeding, prolonged bleeding after circumcision, and history of cephalohematoma are all potential indicators of hemostatic defect that should be further investigated [20]. History of excessive bleeding during or following previous surgeries should also prompt further inquiry and laboratory assessment. In addition, family history should be carefully evaluated for bleeding disorder(s) or symptoms. The symptoms of bleeding disorders can vary, and the use of bleeding assessment tools may be helpful to standardize this portion of evaluation.

Bleeding Assessment Tools

Clinicians often struggle with obtaining a pertinent bleeding history due to lack of standardization. In 1995, Srámek et al. described the use of a bleeding questionnaire in bleeding versus nonbleeding patients. They found that family history and bleeding in traumatic events were the most revealing [21]. Since that time, a number of bleeding assessment tools (BATs) have been developed by various institutions. A number of these are available for use from the World Federation of Hemophilia [22], and examples are given below in Table 40.2. The International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee Bleeding Assessment Tool (ISTH-BAT) was developed for use in pediatric and adult patients [20]. Importantly, it assesses symptoms, frequency, and severity. Rodeghiero and colleagues also describe symptoms of bleeding that should be deemed "clinically significant" versus trivial symptoms of bleeding [20]. Table 40.3 outlines the bleeding symptoms queried in the ISTH-BAT that are applicable to pediatric patients. In addition to the symptoms below, patients who have experienced menarche should be questioned about symptoms of menorrhagia. The ISTH-BAT was designed to reflect the severity of bleeding in Type 1 VWD, and the bleeding score on the ISTH-BAT has been demonstrated to correlate with VWF antigen level [23]. The ISTH-BAT may also be useful in screening for platelet function defects [24, 25]. Importantly, this bleeding assessment tool provides a method for standardized recording of lifelong bleeding histories [26]. The pediatric bleeding questionnaire (PBQ) was also developed to screen for VWD in pediatric populations and has a high negative predictive value [27]. The normal range of bleeding scores for children has been reported as 0–2 [28]. In children, both the ISTH-BAT and the PBQ bleeding scores are able to discriminate between unaffected patients and those with a bleeding disorder [29]. Bleeding assessment tools are often designed to be administered by experts; however, a self-administered pediatric bleeding questionnaire (self-PBQ) can also be used for screening in children [30, 31]. Unfortunately, there is little evidence to show that assessment by bleeding questionnaire can predict perioperative bleeding, and additional studies are needed to assess utility in this setting [32]. Nonetheless, they remain helpful tools to structure a standardized screening interview and can help the provider make the determination of whether laboratory assessment should be performed for patients undergoing low- and moderate-risk procedures.

Table 40.2 Bleeding assessment tools [22]

Bleeding assessment tools	Purpose
International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee Bleeding Assessment Tool (ISTH-BAT)	Intended for the detection of inherited bleeding disorders in pediatric and adult patients
Molecular and Clinical Markers for the Diagnosis and Management of Type 1 (MCMDM-1) VWD Bleeding Questionnaire	Distinguish between types of VWD and assess bleeding severity in VWD patients and family members (research)
Condensed MCMDM-1 VWD Bleeding Questionnaire	Used in clinical setting to assess bleeding severity in patients with VWD or possible bleeding disorder
Pediatric Bleeding Questionnaire (PBQ)	Used primarily as a screening tool for VWD in pediatric patients

Medication History

A variety of common and uncommon medications can affect hemostasis. Preoperative management of anticoagulants and antiplatelet medications is discussed in Chapter 30. For pediatric patients undergoing surgery, the medication list needs to be reviewed and evaluated for any that may be associated with an increased risk for bleeding. Careful attention should be paid to any over-the-counter medications that may contain non-steroidal anti-inflammatory drugs (NSAIDS) and to any herbal supplements. Though infrequent, as many as 3.5% of pediatric patients have used herbal or homeopathic medications [33], which can have effects on hemostatic function. For patients with seizure disorders, antiepileptic medications should be

Table 40.3 ISTH BAT bleeding symptoms applicable to pediatric patients

Symptom	Significant	Trivial
Epistaxis	Interferes with daily activities	<10 minute duration <5 episodes per year Seasonal occurrence Associated with upper respiratory tract infection
Cutaneous bleeding	Bruises: 5 or more >1 cm Petechiae Nontraumatic hematomas	
Minor wound bleeding	Requires frequent bandage change >1 occasion	<10 minute duration Bleeding from a wound that would require stitches in normal individuals
Oral bleeding	Gum bleeding: frankly bloody sputum Oral mucosa: causes swollen tongue or mouth	<10 minute duration
Gastrointestinal bleeding (hematochezia, hematemesis, melena)	All gastrointestinal bleeding is significant unless there is an underlying cause	
Hematuria	Macroscopic (pink or red urine)	Hematuria that occurs due to known condition
Tooth extraction	Requires return visit Delays of procedure or discharge	
Muscle hematoma hemarthrosis	Spontaneous	Related to traumatic injury
Central nervous system bleeding	Requires diagnostic or surgical intervention	
Other: Umbilical stump bleeding Cephalohematoma Cheek hematoma (from feeding) Conjunctival hemorrhage Excessive bleeding after circumcision or venipuncture	All these symptoms require laboratory investigation	

Adapted from the ISTH-BAT [20]

Table 40.4 Coagulation abnormalities associated with valproic acid

Acquired von Willebrand disease [36, 37]
Low fibrinogen [34, 37]
Low factor XIII [37, 38]
Thrombocytopenia [39]
Reduced factor VII from baseline [40]
Reduced factor VIII from baseline [40]
Abnormal coagulation screening tests

reviewed. A number of coagulation abnormalities have been associated with the use of valproic acid, particularly in children being treated for epilepsy. These are listed in Table 40.4.Valproic acid has been associated with intracranial bleeding and increased blood utilization during surgery [34, 35]. Preoperative management of pediatric patients on valproic acid undergoing major surgery should include discussions with their neurologist and possibly hematology. For any medications that affect hemostatic function, the decision to continue therapy should be made with the treating provider after careful assessment of the risks versus benefits of stopping medication in the perioperative period.

Congenital Syndromes Associated with Bleeding

In addition to congenital isolated bleeding disorders, pediatric providers should be aware of other congenital syndromes that may have an associated risk for bleeding. Selected syndromes are presented below and in Table 40.5. Please refer to Chapter 20, for additional information regarding bleeding in connective tissue diseases.

Table 40.5 Congenital syndromes associated with bleeding

Syndrome	Associated defect(s)
DiGeorge syndrome(22q11.2 deletion syndrome)	Thrombocytopenia [41–43] Platelet dysfunction [41–43]
Noonan syndrome	Platelet dysfunction [43, 45] Factor XI deficiency [45] Von Willebrand disease [45] Other or multiple factor deficiencies [45]
Jacobsen syndrome	Thrombocytopenia [43, 47, 48] Platelet dysfunction [43, 47, 48]
Hermansky-Pudlak syndrome	Platelet dysfunction [49]
Wiskott-Aldrich syndrome	Thrombocytopenia [50] Platelet dysfunction [50]
Connective tissue disease (primarily Ehlers-Danlos syndrome)	Defective interaction of platelets with collagen [43] Vascular fragility [43]
Glycogen storage disease type Ia	Platelet dysfunction [51] Von Willebrand disease [52]
Alagille syndrome	Vascular abnormalities [53, 54] Coagulopathy [53] Unknown causes [54]

DiGeorge Syndrome

DiGeorge syndrome, or 22q11.2 deletion syndrome, is a chromosomal microdeletion syndrome that is associated with congenital heart defects, and immunodeficiency. Immune thrombocytopenia and macrothrombocytopenia due to GP1BB (platelet receptor GPIb-V-IX) deletion may be seen [41–43]. Bernard-Soulier syndrome has been reported in patients as a result of GP1BB deletion with concurrent inheritance of a second dysfunctional allele [41, 42]. Relative to other patients undergoing surgery for congenital heart disease, increased bleeding and transfusion requirement in the postoperative period have been reported for patients with 22q11.2 deletion syndrome [44].

Noonan Syndrome

Noonan syndrome is an autosomal dominant congenital disorder with associated bleeding. In a systematic review, a majority of patients had coagulation testing abnormalities, over 40% reported bleeding symptoms, and nearly half were diagnosed with a bleeding disorder. Factor XI deficiency and platelet-related (thrombocytopenia, abnormal platelet aggregation) disorders were most commonly identified, but multiple factor deficiency and VWD are also seen [45]. Factor VII deficiency has also been reported [46].

Jacobsen Syndrome

Jacobsen syndrome is characterized by congenital heart disease, immunodeficiency, and intellectual disability. Patients with Jacobsen syndrome have thrombocytopenia in the neonatal period that normalizes during early adolescence. Importantly, however, patients with Jacobsen syndrome also have Paris-Trousseau syndrome with macrothrombocytes demonstrating abnormally large α granules, delayed megakaryocyte maturation, and dysmegakaryocytopoiesis attributed to heterozygous loss of the FLI-1 gene [47]. Platelet storage pool deficiency is also reported [48].

Procedural Considerations

Certain procedures, particularly those that are associated with heavy bleeding in "normal" populations, should have preoperative evaluation of coagulation status. In addition, surgical procedures in sensitive sites (spine, intracranial, ophthalmic) need a bleeding assessment including laboratory data prior to proceeding with a procedure. These children may require additional assessment or support as reflected in the screening algorithm in Fig.40.1. For example, in pediatrics, scoliosis surgery can have a high amount of blood loss. While this is sometimes dependent on surgical factors, such as the number of levels fused during posterior spinal instrumentation [55], there is evidence to suggest that these patients frequently have abnormal tests of coagulation [56, 57]. In addition, patients with neuromuscular scoliosis tend to have more bleeding than their idiopathic scoliosis counterparts [58]. Therefore, coagulation screening in these patients is important. Bleeding scores are also reported to correlate with hemorrhage in this population [59]. Another group of pediatric patients that should be considered for a more comprehensive evaluation of coagulation includes patients presenting with Wilms tumor (nephroblastoma). Acquired von Willebrand syndrome has been described in these patients, with a reported incidence of 4% [60–62], and bleeding in these patients can be unpredictable. Procedural factors should be carefully considered when deciding whether or not to assess coagulation status preoperatively.

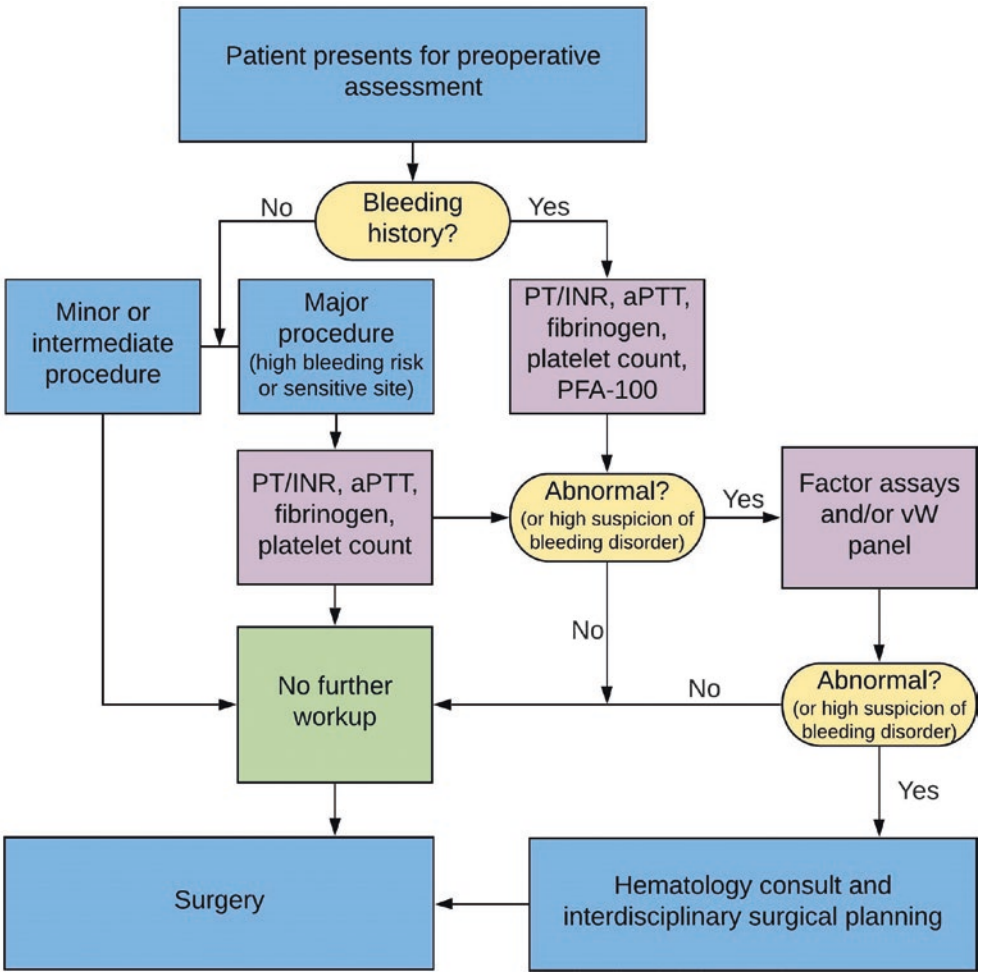

Fig. 40.1 Pediatric preoperative screening algorithm

Conclusion

Assessment of bleeding risk in pediatric patients represents a unique challenge. These patients often have little history or have never had a hemostatic challenge. Routine testing, however, can result in increased costs, anxiety, and delay, and is not recommended for most procedures. Particular conditions may increase the risk for bleeding and require coagulation screening. While prediction of bleeding remains difficult, a bleeding history is critical for evaluation [63]. The patient's history, family history, and type of procedure should also be used to guide the preoperative work-up. Abnormal test results may require further investigation or referral to a hematologist. When a bleeding disorder or risk is identified, a multidisciplinary approach to the hemostasis management plan is required.

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Evaluation of Bleeding Risk Prior to Invasive Procedures

41

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Overview/Introduction

Evaluation of bleeding risk prior to invasive procedures is a key component of management strategies to minimize bleeding throughout the periprocedural period. Advanced age, compromised end organ function, and other factors that impact hemostasis such as low platelet count or decreased red cell volume may put patients at an increased risk of bleeding. Medical conditions, including hereditary bleeding disorders and acquired medical conditions, medications affecting hemostasis, and type of procedure/surgery all contribute to the patient's risk of bleeding around the time of the procedure or surgery. Patients requiring antithrombotic therapy or complimentary medications that affect hemostasis need to be properly managed around the time of procedure as per multidisciplinary assessment and evidence-based and/or expert consensus guidelines. In general, a patient undergoing a procedure that is associated with a low-bleeding risk can safely continue antithrombotic therapy while a patient undergoing a procedure/surgery with a high bleeding risk will need to temporarily interrupt antithrombotic agents. The timing of when to stop and restart anticoagulants depends on the type of procedure, specific anticoagulant, and anticipated time for drug clearance based on patient specific factors. For urgent/emergent procedures that cannot be delayed, anticoagulation may require immediate reversal, and the patient may require additional hemostatic support throughout the periprocedural period. After the procedure is complete and hemostasis is achieved, it is important to assess whether ongoing anticoagulation is required and if so the appropriate time to reinitiate therapy and with what agent (short-acting agent or long-term oral agent).

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Guidelines/Consensus Pathways

There are multiple national and international organizations that have developed guidelines or census statements regarding the assessment of bleeding risk prior to an invasive procedure/surgery and periprocedural management of patients on antithrombotic therapy requiring invasive procedures or surgery. Examples of these include the British Committee for Standards in Haematology [1, 2], the European Society of Cardiology [3], the American College of Cardiology (ACC) [4], the American College of Chest Physicians (ACCP) [5], the American Society for Gastrointestinal Endoscopy [6], and the American Society of Regional Anesthesia and Pain Medicine [7]. When considering these guidelines, providers must incorporate newly published literature not included in the guideline when determining the applicability of the recommendations to their practice. The European Society of Anaesthesiology management of severe perioperative bleeding guidelines offers recommendations on the evaluation of coagulation status [8].

Evaluation of Bleeding Risk

Patient Assessment

A bleeding risk assessment must consider the patient's individual risk of bleeding, the pharmacokinetics and bleeding

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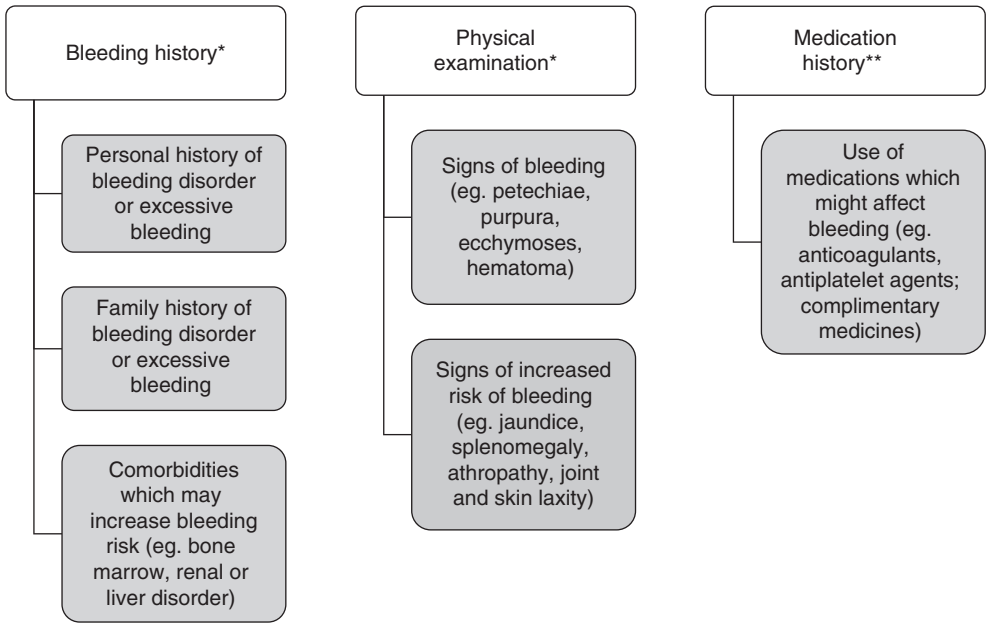

Fig. 41.1 Patient bleeding risk assessment. *If positive, consider use of bleeding assessment tool and/or referral to appropriate specialist. **If positive, manage by multidisciplinary assessment and as per evidence-based guidelines/ specialist guidelines

risk associated with the anticoagulant, the bleeding risk of the specific intervention with and without anticoagulation, and, if necessary, the risk of bleeding associated with a bridging agent (Fig. 41.1). The ability to manage a bleeding event throughout the periprocedural period should also be considered when developing a risk mitigation plan. This should include the availability of resources to address urgent or life-threatening bleeding such as topical hemostatic agents, supportive blood products, and specific reversal agents if available.

To assess the patient-specific risk factors for bleeding, a patient's medical and family history should be reviewed for any past bleeding episodes or history of similar risk procedures. In the event of past bleeding events, the history surrounding the bleed should be considered and include a review of contributing medications, provoking events (e.g., procedure/surgery, trauma, spontaneous), relevant labs (complete blood count, platelet count, coagulation labs, creatinine, AST/ALT, etc.), as well as management strategies and their outcomes. If there is no history of bleeding, it is important to also review if past procedures have been successfully completed while the patient was anticoagulated. Both patient and family medical history should also be reviewed for inherited or acquired bleeding disorders (see Part III of this textbook).

Providers should also complete a full review of current medications, pertinent labs, and comorbidities that may contribute to an increased risk of periprocedural bleeding. Medications that may increase the risk of bleeding include antiplatelet agents (e.g., aspirin, clopidogrel, ticagrelor, prasugrel), and nonsteroidal anti-inflammatory agents (e.g., ibuprofen, naproxen) should be evaluated [9]. Labs should be reviewed to determine baseline coagulation status prior to the procedure. For all anticoagulants this should include a complete blood count and platelet count to identify predisposing risks for bleeding as well as serum creatinine and liver function tests to evaluate for altered drug clearance. Drug-specific labs such as international normalized ratio (INR) for patients on warfarin, activated partial thromboplastin time (aPTT), anti-Xa for patients on heparin, etc. should be evaluated immediately prior to the procedure to ensure target levels of anticoagulation are appropriate.

Bleeding History

The use of a structured patient interview or questionnaire before surgery or invasive procedures to asses bleeding risk has been recommended in international guidelines [1, 8]. Personal and family bleeding history, history of excessive bleeding (e.g., posttraumatic or postsurgical), and history of comorbidities which may increase bleeding should be reviewed [1, 8]. Patients with congenital bleeding disorders, such as known or suspected von Willebrand disease, platelet defects, hemophilia A and B, or other rare bleeding disorders should be managed very carefully and in consultation with a hematologist [8]. Additionally, for patients with severe thrombocytopenia or coagulopathy, a hematologist should also be consulted.

Physical Examination

As part of a physical examination, signs of bleeding/anemia and increased risk of bleeding should be reviewed [8]. Signs of bleeding/anemia include petechiae, purpura, ecchymoses, and hematoma, while signs of increased risk of bleeding include jaundice or spider angiomata, splenomegaly, arthrop-

athy, joint and skin laxity, and telangiectasia [10]. Gender, body mass index, and comorbidities including arterial hypertension, diabetes mellitus, and renal dysfunction are independent risk factors for bleeding and transfusion [8].

Bleeding Assessment Tools

There are multiple bleeding assessment tools (BAT) that can assist providers in the identification of patients at high risk of bleeding. In the patient population in which the tool was validated, availability of the components of the score, complexity, and usability should all be considered when choosing a BAT. Scores have been developed to predict the risk of bleeding while on anticoagulation or procedure-related bleeding. Examples of scores to predict the risk of bleeding while on anticoagulation include HAS-BLED [11], HEMORR2HAGES, ORBIT, and ATRIA for patients with atrial fibrillation and the RIETE [12] registry risk score and the outpatient bleeding risk index for patients treated for venous thromboembolism (VTE) [13]. These scores have typically been validated in patients on oral vitamin K antagonists, and the reliability of these scores for patients anticoagulated with the direct oral anticoagulants (DOAC) is less well studied although few studies have applied these scores to DOAC populations [14]. DOAC-specific bleeding risk assessment tools are being proposed but have not yet been widely incorporated into clinical practice [15]. Bleeding risk scores to assess the bleeding risk associated with procedures include the CRUSADE score in patients with ACS and a tool used to evaluate risk in patients undergoing percutaneous coronary intervention [16, 17]. The complexity and accuracy of the scores must be weighed when determining if their use in clinical practice is feasible. A newer bleeding risk assessment tool, the ABC-bleeding score, incorporates biomarkers into the score to improve the prognostic value of the score, but these biomarkers may not be readily available to clinicians to make this a feasible score for frontline practitioners [18]. Regardless of the score that is used, it is important for clinicians to understand the intent of the score and evaluate individual patient's bleeding risk in a systematic matter.

Medication History

As part of the bleeding risk assessment, providers should complete a comprehensive review of the patient's medication list including all prescription, over-the-counter, and complimentary agents (such as herbals) and determine if they have an impact on bleeding. Clinicians should particularly assess if patients are taking antithrombotic medications such as anticoagulants or antiplatelet agents and review the indication for each medication. For full description of antithrombotic agents, see Chapter 30. Combination therapy with both anticoagulant and antiplatelet agents will further increase the risk of bleeding.

Considerations Specific for Patients on Medications Affecting Hemostasis

Patients on antithrombotic therapy and undergoing a procedure that is associated with a low-bleeding risk need no interruption of therapy. For patients undergoing a procedure/surgery with a high bleed risk, therapy will need to be temporarily interrupted. For patients with a low thrombotic risk, antithrombotic agents may be temporarily discontinued. For those with a moderate or high risk of thromboembolism, the situation can become challenging. Appropriate decision-making requires knowledge of thrombotic risk, procedure-related bleeding, concepts of bridging anticoagulation therapy, and timing of cessation and preinitiation of antithrombotic therapy.

If the procedure is considered to have a high enough bleeding risk to interrupt anticoagulation, it is important to understand the pharmacokinetics, pharmacodynamics, and reversibility of the specific anticoagulant when forming a periprocedural anticoagulation management plan. It is also important to decide what degree of anticoagulation, if any, is acceptable. For patients on warfarin, a reduced intensity of anticoagulation (i.e., INR <2) may be acceptable for some procedures, whereas full reversal (i.e., INR <1.4) may be required for high-risk procedures. The patient's end-organ function is also an important consideration when assessing estimated time to drug clearance. Holding a drug for three to four half-lives in patients with normal end-organ function is typically adequate to eliminate the effect of the drug [19].

Warfarin inhibits vitamin K epoxide reductase which is responsible for converting vitamin K to its active form, and downstream is required for development of functional clotting factors II, VII, IX, and X and the natural anticoagulants proteins C and S. The onset and duration of effect of warfarin is related to the half-lives of these clotting factors which range from 4 hours (factor VII) up to 72 hours (factor II) [19]. The rise of the INR with warfarin initiation is most correlated with the half-life of factor VII, whereas the pharmacodynamic half-life of warfarin is dependent on the half-life of factor II. Typically, it is recommended to hold warfarin for 5 days for a therapeutic INR to return to baseline [5, 7]. In certain cases, warfarin may need to be held longer such as patients who are elderly, have liver dysfunction, have baseline low warfarin dose requirements, have higher target INR ranges (e.g., 3.0–4.0), or whose INR is supratherapeutic at the time of holding. If the target pre-procedure INR is higher (i.e., <2), then holding for fewer days is possible. Alternative strategies to avoid a long re-initiation phase post-procedure involves holding fewer days and giving a small dose of oral vitamin K 1 mg prior to the procedure or holding for 2 days and then restarting at a lower dose [19].

As compared to warfarin, the DOACs have a more targeted anticoagulant effect on either factor IIa (dabigatran) or factor Xa (apixaban, edoxaban, rivaroxaban, and betrixaban)

and also have shorter half-lives making it easier to plan for known procedures. The half-life of the majority of the DOACs (dabigatran, apixaban, edoxaban, rivaroxaban) ranges from 5–15 hours with betrixaban as the main exception with a half-life of 19–37 hours [19, 20]. The DOACs are all renally cleared, although the extent varies quite significantly with betrixaban having the lowest degree of renal clearance (11%) and dabigatran being the most effected (80% renal clearance). For the DOACs with shorter half-lives, holding 1 day for low-bleeding risk procedures and 2 days for high-bleeding risk procedures is generally enough for patients with no end-organ dysfunction [2]. Holding longer is required for patients with compromised renal function or requiring neuraxial anesthesia [7]. For betrixaban, doses should be held for at least 72 hours prior to invasive procedures [20]. This strategy is currently being validated in a prospective study [21].

Anticoagulation with injectable agents also requires consideration when planning for invasive procedures. Patients in the outpatient setting may be receiving subcutaneous injections of a low-molecular-weight heparin (LMWH), fondaparinux, or unfractionated heparin (UFH) either as monotherapy (e.g., cancer or pregnancy) or as a bridging agent while holding warfarin. In the inpatient setting patients may require a very short-acting continuous infusion of UFH or an intravenous direct thrombin inhibitor (DTI) such as bivalirudin or argatroban again either as monotherapy or as a bridging agent. The same principles apply as above for holding based on the half-life of the specific anticoagulant and end-organ function of the patient to estimate the time to drug clearance. Fondaparinux has a longer half-life compared with LMWH at approximately 20 hours compared 5–7 hours for LMWH, although both undergo substantial renal clearance [19]. The half-life of UFH is dependent on the route of administration and is 1–3 hours via the intravenous (IV) route or 3–7 hours via the subcutaneous (SQ) route [22]. Heparin is cleared primarily through depolymerization [23]. LMWH and UFH are generally held for 12–24 hours prior to a procedure, whereas fondaparinux is held for 1–3 days depending on the procedural risk of bleeding. For the short-acting IV direct thrombin inhibitors (DTIs) and IV UFH, holding for a few hours is enough to return to baseline levels of coagulation.

Estimate of Procedural Bleeding Risk

Alongside of patient comorbidities (e.g., history of bleeding, renal dysfunction, age, active cancer, and chemotherapy) and medications affecting hemostasis (e.g., residual effects of antithrombotic agents, re-initiation of antithrombotic therapy within 24 hours after procedure), the predominant factor affecting procedural bleeding risk is the type of procedure or surgery.

Type of Procedure/Surgery

Procedures with a low-bleeding risk include non-major procedures (lasting <45 minutes), such as general surgical procedures, cutaneous procedures, and cholecystectomy. Procedures with a high risk include cardiovascular surgery, orthopedic surgery, head and neck cancer surgery, urologic surgery, and surgeries and procedures lasting ≥45 minutes (Table 41.1) [24].

Table 41.1 Classification of procedure/surgery according to bleeding risk

	Low-risk bleeding (≤1.5%)	High-risk bleeding (>1.5%, or in vulnerable areas)
Abdominal/ gastroenterology	Passage of endoscopic for diagnostic purposes (including balloon enteroscopy) with or without mucosal biopsy Endoscopic retrograde cholangiopancreatography without sphincterotomy Endoscopic ultrasound without fine-needle aspiration Nonthermal (cold) snare removal of small polyps Lumenal self-expanding metal stent placement (controversial)	Large polypectomy (>1 cm) Endoscopic mucosal and submucosal dissection Biliary or pancreatic sphincterotomy Percutaneous endoscopic gastrostomy Endoscopic ultrasound with fine-needle aspiration or needle biopsy Coagulation or ablation of tumors, vascular lesions Percutaneous liver biopsy Variceal band ligation (controversial)
Anesthesiology	Endotracheal intubation	Spinal and epidural anesthesia[a]
Cardiac surgery	None	All
Cardiovascular	Diagnostic coronary angiography (controversial)	Pacemaker or defibrillator placement[b] Coronary intervention Electrophysiology testing and/or ablation[b]
Dental	Tooth extraction Endodontic procedures (root canal)	Reconstructive procedures

Table 41.1 (continued)

	Low-risk bleeding (≤1.5%)	High-risk bleeding (>1.5%, or in vulnerable areas)
Dermatology	Minor skin procedures (excision of basal and squamous cell cancers, nevi, actinic keratoses, premalignant lesions)	Major procedures (wide excision of melanoma)
General surgery	Suture of superficial wounds	Major tissue injury Vascular organs (spleen, liver, kidney) Bowel resection Laparoscopy
Gynecologic surgery	Diagnostic colposcopy, hysteroscopy Dilation and curettage, endometrial biopsy Insertion of intrauterine device	Laparoscopic surgery Bilateral tubal ligation Hysterectomy
Interventional radiology	Simple catheter exchange in well-formed, nonvascular tracts (e.g., gastrostomy, nephrostomy, cholecystostomy tubes) Thoracentesis Paracentesis Aspiration of abdominal or pelvic abscesses, placement of small-caliber drains Peripheral catheter placement, nontunneled catheter (peripherally inserted central catheter) placement Inferior vena cava filter placement Temporary dialysis catheter placement	Percutaneous transhepatic cholangiography or nephrostomy Percutaneous drainage of liver abscess or gallbladder Chest tube placement Aggressive manipulation of drains or dilation tracts Biopsy of organs Hickman and tunneled dialysis catheter placement
Intravascular procedures	Venous access	Arterial puncture Transvenous ablation
Neurology	None	Lumbar puncture[a] Myelography Needle electromyography (controversial)
Neurosurgery	None	Intracranial, spinal surgery[a]
Ophthalmology	Cataract surgery Intraocular injections (Avoid retrobulbar anesthesia – controversial)	Periorbital surgery Vitreoretinal surgery
Orthopedic surgery	Arthrocentesis	Joint replacement Arthroscopy
Otolaryngologic surgery	Diagnostic fiber-optic laryngoscopy or nasopharyngoscopy, sinus endoscopy Fine-needle aspiration Vocal cord injection	Any sinus surgery Biopsy or removal or nasal polyps Thyroidectomy Parotidectomy Septoplasty Turbinate cautery
Plastic surgery	Injection therapy	Reconstruction
Pulmonary	Diagnostic bronchoscopy with or without bronchioalveolar lavage Endobronchial fine-needle aspirate (controversial) Airway stent placement (controversial)	Tumor ablation Transbronchial biopsy Stricture dilation
Rheumatology	Arthrocentesis	None
Urology	Circumcision Cystoscopy without biopsy	Extracorporeal shock-wave lithotripsy Transurethral prostatectomy Bladder resection Tumor ablation Kidney biopsy
Vascular surgery	None	Carotid endarterectomy Open or endovascular aneurysm repair Vascular bypass grafting

[a]Potential for profound neurologic consequences

[b]Better outcomes have been reported when antithrombotic therapy is not interrupted for pacemaker placement or catheter ablation for atrial fibrillation

The associated bleeding risks of procedure/surgery are classified into high-risk and low-risk categories by various surgical and subspecialty societies, although grades of bleeding severity are not standardized [25–27]. The American Society for Gastrointestinal Endoscopy designates low-risk procedures as those with clinical rates of bleeding of 1.5% or less [28]. Given this, high-risk procedures are those with clinical rates of bleeding greater than 1.5% among patients not receiving antithrombotic agents. High risk can also be defined as procedures that can result in intracranial, intraspinal, intraocular, retroperitoneal, intrathoracic, or pericardial bleeding [27]. Neuraxial anesthesia is also considered high-risk [29, 30].

Management Plan

Planned Procedures

For planned invasive procedures, development of the anticoagulation management plan generally starts by assessing the bleeding risk associated with the procedure to determine if interruption of anticoagulation is required. For procedures with a low risk of bleeding, interruption of anticoagulation is generally not necessary and may cause unwarranted harm. For example, the BRUISE Control study found that continuing warfarin without interruption for pacemaker or defibrillator implants led to a significantly lower incidence of pocket hematomas compared to interruption of warfarin and bridging with heparin [31]. For patients on DOACs, the BRUSIE Control 2 trial showed no difference in the rate of hematomas between those who continued DOACS uninterrupted compared with those who held their DOAC for 2 days prior to the procedure [32]. Other examples of procedures with low risk of bleeding include skin cancer excision, single tooth extraction, cataract eye surgery, and central line placement [9]. For procedures where anticoagulation is continued, it is important to ensure anticoagulation is appropriately dosed, and for warfarin it is important to maintain the INR below the upper threshold of the therapeutic target. For DOACs the timing of the last dose and procedure are generally coordinated to avoid peak concentrations (i.e., morning dose is delayed until after the procedure or omitted) [33, 34]. Routine laboratory assessment of coagulation status is generally not warranted in these scenarios [21].

For procedures associated with a high risk of bleeding, interruption of anticoagulation is generally required (Table 41.2). The patient's risk of thromboembolism determines the next steps in the management plan. For

Table 41.2 Classification of patient thromboembolic risk

Indication for anticoagulation	Risk factors	Low-risk criteria	Moderate-risk criteria	High-risk criteria
Bioprosthetic heart valve		3 months after placement		Within first 3 months of placement
Mechanical heart valve	Atrial fibrillation CHF HTN DM Age > 75 Prior CVA/TIA	Bileaflet aortic valve *AND* no risk factors Medtronic Hall tilting disc valve	Bileaflet aortic valve *AND* 1 or more risk factors	Prior thromboembolism during interruption of warfarin therapy Any mitral valve prosthesis Older caged-ball/tilting disc aortic valve prosthesis CVA/TIA (within 6 months)
Atrial fibrillation	*$CHADS_2$-VASc score* CHF (1 point) HTN (1 point) DM (1 point) Prior CVA/TIA/TE (2 points) Age ≥ 75 (2 point) Age 65–74 (1 point) Vascular disease (1 point) Female (1 point)	$CHADS_2$-VASc score 0–4 *AND* no prior CVA/TIA	$CHADS_2$-VASc score 5–6 Consider Bridge if CVA/TIA > 3 months	Prior thromboembolism during interruption of warfarin therapy $CHADS_2$-VASc score ≥ 7 CVA/TIA (within 3 months) Rheumatic valvular heart disease
Venous thromboembolism	*Non-severe thrombophilia:* Heterozygous factor V Leiden Prothrombin gene mutation *Severe thrombophilia:* Deficiency of antithrombin Protein C or S deficiency Homozygous factor V Leiden Antiphospholipid antibody syndrome Heterozygous factor V Leiden in addition to prothrombin gene mutation	Single VTE more than 12 months ago AND no other risk factors	VTE within past 3–12 months Non-severe thrombophilia Recurrent VTE	Prior thromboembolism during interruption of warfarin therapy Active cancer Less than 3 months since VTE Severe thrombophilia

patients at a low risk of thromboembolism such as atrial fibrillation with a $CHADS_2$ score ≤2, thromboembolic event that occurred more than 12 months previously, or mechanical valve in the aortic position, anticoagulation can generally be interrupted without a bridging agent prior to the procedure and restarted as soon as clinically appropriate [5]. For patients at high risk of thromboembolism such as the presence of a mechanical heart valve with a history of stroke within the last 6 months or a history of thromboembolism with previous interruption of anticoagulation, the duration time without anticoagulation should be minimized to mitigate risk. For patients on warfarin, this generally necessitates use of a bridging agent which most commonly include prophylactic dose LMWH, therapeutic dose LMWH, or IV UFH. In the presence of a mechanical heart valve, IV UFH is the preferred agent, but LMWH may be utilized in special circumstances (Fig. 41.2) [35]. The bridging agents should be started when the INR is less than 2.0; typically, warfarin is stopped 5 days prior to the procedure, and bridging is started 3 days prior to the procedure if the INR is not known (Table 41.3) [36]. The bridging agent is continued until 24 hours prior to the procedure for SQ LMWH or 4–6 hours prior to the procedure for IV UFH [5, 36]. An INR and PTT may be assessed prior to the procedure to ensure full resolution of anticoagulation.

For patients on a DOAC, bridging with a SQ or IV agent is not generally required due to their short half-lives which are similar to the SQ LMWHs. Standardized periprocedural protocols for DOAC management have been created and are being validated [21]. Appropriate strategies should include DOAC pharmacokinetic properties, procedure-related bleeding risk, and patient creatinine clearance. For patients with normal renal function, DOACs are typically held for at least 24 hours for low-risk procedures and at least 48 hours for intermediate- or high-risk procedures (Table 41.4) [4]. As renal function declines, the duration of interruption extends based on the extend of renal clearance for each drug [4]. Laboratory tests are not routinely used to assess degree of anticoagulation in patients receiving DOACs. In the setting of unknown clearance such as severe renal insufficiency, routine lab tests may be sufficient enough to rule out significant anticoagulant effects of the agent. The thrombin time (TT) is responsive to dabigatran and is the best routine clinical test available to distinguish between the presence and absence of drug effect. The aPTT and prothrombin time (PT) are also

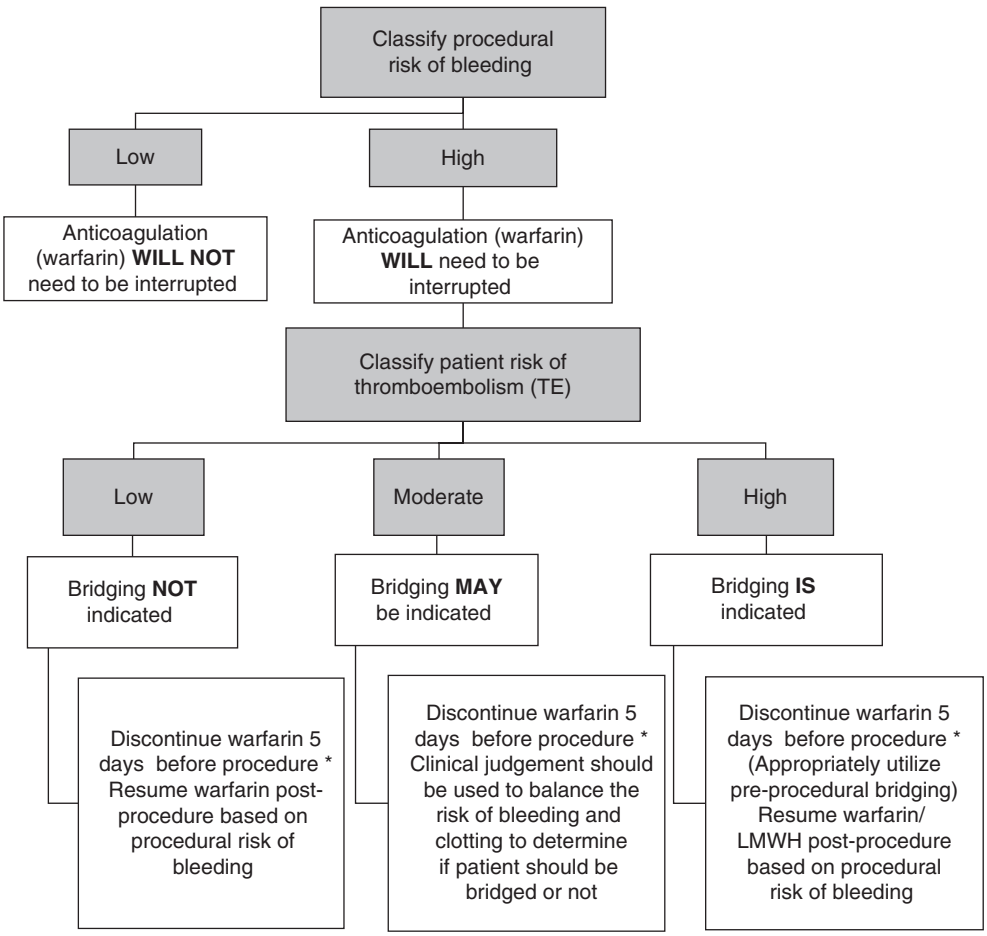

Fig. 41.2 Guideline for periprocedural anticoagulation and bridging for warfarin. *It may be necessary to hold warfarin longer than 5 days for select patient populations (e.g., elderly, liver dysfunction, low-dose requirements, target INR of 3.0–4.0, supratherapeutic INR)

Table 41.3 Pre-procedural bridging considerations

Agent	When to initiate	When to discontinue
Therapeutic LMWH (dalteparin & enoxaparin), dosed Q 12 hours	24–48 hours after last dose of warfarin (based on INR)	Give last dose 24 hours prior to procedure
Therapeutic LMWH (dalteparin & enoxaparin), dosed Q 24 hours		Give last dose 24 hours prior to procedure
Prophylactic LMWH (dalteparin & enoxaparin), dosed Q 24 hours		Give last dose 12–24 hours prior to procedure
Fondaparinux		Give last dose 36–48 hours prior to procedure
IV unfractionated heparin (UFH)		Discontinue 4–6 hours prior to procedure

Table 41.4 Guideline for periprocedural anticoagulation for DOACs

Calculated CrCl, mL/min	Half-life, hours	Timing of last dose before surgery‡	
		Low risk of bleeding (see Table 41.1)	High risk of bleeding (see Table 41.1)
Dabigatran		PI: Discontinue 1–2 days before if CrCl ≥50 mL/min, 3–5 days before if CrCl<50 mL/min	PI: Consider longer times if major surgery, spinal puncture, spinal or epidural catheter
>50	14–17	24 hours	2 days
30–50	16–18	2 days	4–5 days
<30	28	4 days	≥5 days
Rivaroxaban		PI: Discontinue ≥24 hours before	PI: Discontinue ≥24 hours before
>50	8–9	24 hours	2 days
30–50	9	24–48 hours	3–4 days
<30	9–10	2 days	4 days
Apixaban		PI: Discontinue ≥24 h before	PI: Discontinue ≥48 h before
>50	7–8	24 hours	2 days
30–50	17–18	24–48 hours	3–4 days
<30	≥ 17.5	2 days	4 days
Edoxaban		PI: Discontinue ≥24 hours before	
>50	6–11	24 hours	48 hours
30–50	11–17	24–48 hours	3–4 days
<30	17	2 days	4 days
Betrixaban		PI: Anticoagulant effect can persist for at least 72 hours after the last dose	
≥30	19–27	4 days	4 days
<30	Not reported	Do not use	Do not use

‡For minimal bleeding risk procedures: DOAC may be continued and interruption might not be necessary (anticipated effect would be similar to operating while on warfarin or LMWH)

affected by dabigatran but are not sensitive enough to distinguish between therapeutic and subtherapeutic levels and therefore are not reliable in this setting [37]. For the anti-Xa inhibitors, an anti-Xa level can be used to assess persistence of anticoagulant effect. Although agent-specific reagents are preferred to assess anti-Xa levels with the DOACs, they are not yet commercially available for routine use. Alternatively, anti-Xa levels calibrated for heparin/LMWH can be used qualitatively to assess presence of drug in the circulation, with a level less than assay signifying no clinically significant drug levels remaining [37].

Clinicians should also evaluate if antiplatelet agents should be temporarily interrupted. For most procedures low-dose aspirin can generally be continued. For high-bleeding risk surgery (such as cardiac surgery or major orthopedic surgery), antiplatelet agents should be interrupted based on their half-life and according to manufacturer and/or guideline recommendations. For lower-risk procedures the multidisciplinary team should discuss the risk and benefit of continuing vs interrupting antiplatelet medications.

Urgent/Emergent Procedures

See Chapters 42 and 43, for further discussion of this topic. For the majority of procedures, a preemptive anticoagulation management plan can be made, but in cases requiring an emergent or urgent surgery, providers need to assess bleeding risk of the procedure in the presence of anticoagulation, the time the last dose of the anticoagulation was ingested, and estimated drug clearance based on end-organ function to determine if immediate anticoagulation reversal is required. In cases where the last dose of anticoagulant is unknown (such as trauma cases) or drug clearance is unknown due to compromised end-organ function, laboratory testing may be useful to assess for presence of clinically significant drug levels (see section above). If anticoagulation is not reversed, proceduralists should be prepared in the case of a bleeding event. An understanding of the underlying indication for anticoagulation and thromboembolic risk is important when determining a reversal strategy.

For patients anticoagulated with warfarin, immediate reversal can be accomplished by repleating functional vitamin K-dependent clotting factors with concentrated clotting factors [e.g., prothrombin complex concentrates (PCC) and activated prothrombin complex concentrate (aPCC)] or fresh frozen plasma (FFP). Concentrated clotting factors are generally preferred over FFP for many reasons including a shorter time to administration, lower risk of bloodborne illness, transfusion-related acute lung injury, allosensitization, and smaller volume required for adequate factor replacement [38]. There are multiple concentrated clotting factor products available including three-factor PCC (e.g., Profilnine™), four-factor PCC (e.g., Kcentra™), and activated PCC (FEIBA™). Three-factor PCC contains inactivated factors II, IX, and X and small amounts of VII requiring co-administration with FFP for adequate factor VII replacement. Four-factor PCC contains mainly inactivated factors II, VII, IX, and X. FEIBA

also contains all four vitamin K-dependent clotting factors, but unlike PCC, factor VII is in the activated form. All of the concentrated clotting factors have relatively short pharmacodynamic half-lives and require concomitant vitamin K administration for sustained reversal of warfarin if required.

For patients requiring sustained reversal of warfarin in the setting of high post-procedural bleeding risk (e.g., neurosurgery or cardiac surgery), the dose (1–10 mg) and route of administration (IV vs by mouth [PO]) are important for onset of action and post-administration warfarin resistance. Vitamin K should be administered PO or IV. Administration via the IV and PO routes results in a similar decline in INR at 24 hours, but the effect of IV is more rapid and is the preferred route when urgent reversal is required such as an unplanned surgery/procedure [39]. For procedures requiring full reversal of anticoagulation, a 10 mg dose is generally required; however, high doses such as this may result in warfarin resistance for patients requiring re-initiation of warfarin post-procedure. In procedures where full reversal is not required, lower doses of vitamin K will lower the INR while allowing for an easier transition back to warfarin post-procedure [40].

For patients anticoagulated with dabigatran, there is a specific reversal agent, idarucizumab, that is approved for reversal in the setting of emergency surgery/urgent procedures. If this agent is available at the treating institution, it is the preferred strategy. Alternatively, 4PCC or aPCC can be administered at 50 units/kg per guideline recommendations [41]. For the direct oral Xa inhibitors there is a reversal agent available, andexanet alfa, but its approval is limited to reversal of rivaroxaban and apixaban in the setting of life-threatening or uncontrolled major bleeding and is not available for reversal in the setting of urgent/emergent surgery [42]. There are limited data available using andexanet alfa in this setting [43]. In the absence of data supporting the use of a specific reversal agent in this setting, guidelines recommend using 4PCC at 50 units/kg or alternatively aPCC at 50 units/kg if 4PCC is not available [41]. There are limited data available regarding the use of these agents to reverse betrixaban at this time.

For patients on a SQ anticoagulant at the time of surgery, the timing of the last dose will determine if urgent reversal is required. Heparin can be 100% neutralized using protamine. Approximately 60% of the anticoagulant effect of LMWH can be reversed with protamine. The dose is determined based on the agent and the time since the last dose [44]. Although data are available supporting the reversal of LMWH with andexanet, it has not yet been approved for reversal of LMWH for life-threatening bleeding or reversal in the perioperative setting [45]. There is no specific reversal agent to neutralize the anticoagulant effects of fondaparinux although guidelines recommend reversing with either 20 units/kg of aPCC or 90 μg/kg of recombinant activated factor VII [44].

Coagulation Assessment

There are multiple laboratory tests that can be used to assess the presence and extent of anticoagulation prior to invasive procedures. For warfarin the INR can be used to guide the bridging plan and determine the degree of anticoagulation prior to the procedure and ensure target levels are achieved. The INR is readily available and validated as both a venipuncture and point of care (POC) test.

For the DOACs, routine monitoring of coagulation assays is not used for determining therapeutic concentrations as agent-specific monitoring is not widely available. Routine coagulation assays may, however, be useful in determining if residual anticoagulant effect remains. In patients receiving factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) undergoing high-risk dental procedures or those with maxillofacial trauma, one may consider using an anti-factor Xa level that is calibrated to LMWH/UFH to exclude any relevant drug concentrations [2]. For those receiving direct thrombin inhibitors (e.g., dabigatran), the aPTT may be useful in determining residual anticoagulant effect. Though not specific, patients who are anticoagulated will have an elevated aPTT above baseline. Although the ecarin clotting time (ECT) is the most sensitive assay to determine therapeutic levels, it is unavailable for routine use in the United States [2].

Resumption of Anticoagulation

One of the most important considerations after the procedure is the appropriate time to restart anticoagulation to minimize post-procedure bleeding risk while mitigating the risk of thrombosis. Any time anticoagulation is interrupted, the patient's need for ongoing anticoagulation should be assessed. For those who require ongoing anticoagulation, an assessment of the risk of bleeding should be done. For patients at high risk of bleeding during the post-procedure period and also at high risk of a thromboembolism, prophylactic dose anticoagulation may be considered, or alternatively IV anticoagulants which are titratable and have a short half-life may be utilized until the patient is deemed stable to transition to oral agents with longer half-lives [41]. Thrombotic events associated with the newer drug-specific reversal agents have shed light on the need to restart anticoagulation as soon as clinically appropriate in patients at high risk of thromboembolism [45, 46]. After hemostasis is achieved, antiplatelet and anticoagulants (including DOACs) can generally be started within 24–48 after low-bleeding risk procedures and 48–72 after high-bleeding risk procedures. See Table 41.5 for details of resuming warfarin post-procedure.

Table 41.5 Post procedural: resuming anticoagulation

Agent	Procedural bleeding risk classification	When to resume anticoagulation[a]
Warfarin	Very low/low	Restart evening of procedure
	Moderate[b]	Restart evening of procedure
	High/very high	Restart evening of procedure Resumption may be deferred 1–2 days if concerned about bleeding risk
LMWH (dalteparin & enoxaparin), fondaparinux, UFH	Very low/low	Restart 12–24 hours after procedure
	Moderate	Patient risk for TE = moderate Restart 24–48 hours after procedure Patient risk for TE = high Restart 24 hours after procedure
	High/very high	Patient risk for TE = moderate Do not restart LMWH Patient risk for TE = high Restart 24–72 hours after procedure or longer based on hemostasis

Note: Even in the scenario that "bridging" is not indicated, post-procedure DVT prophylaxis should still be considered in procedures that require routine prophylaxis

TE thrombotic event

[a]Hemostasis should be established prior to resumption of any anticoagulation

[b]Warfarin resumption after procedures thought to have moderate bleeding risk may be deferred for 1–2 days at the discretion of MD if unexpected perioperative bleeding occurs

Summary

For patients undergoing an invasive procedure, a periprocedural bleeding risk assessment is required to minimize any avoidable bleeding associated with the procedure. A thorough bleeding assessment includes an evaluation of bleeding associated with the procedure in the presence and absence of anticoagulation, if applicable, and a patient assessment including personal and family history of bleeding events, medication history, physical evaluation, and past medical history including concomitant disease states. Multiple bleeding assessment tools are available for providers to assess using a validated method. For patients on antithrombotic agents for treatment or prevention of thromboembolism, a further risk assessment is required to determine if the procedure can be completed in the presence of anticoagulation or if interruption will be required. Creating a patient- and procedure-specific periprocedural anticoagulation management plan is an interdisciplinary task that should involve the proceduralist, anticoagulation management provider, and potentially the primary care provider, cardiologist, and oncologist depending on the indication for anticoagulation.

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Part VIII

Hemostatic Agents and Blood Components Used to Stop Bleeding

Hemostatic Agents and Blood Components Used to Stop Bleeding

42

Brady S. Moffett and Rachel S. Carroll

Tranexamic Acid

Brand Names (US) Lysteda™, Cyklokapron™

Description

Tranexamic acid is a synthetic amino acidantifibrinolytic. It competitively inhibits plasminogen activation but becomes a noncompetitive inhibitor at higher concentrations. Tranexamic acid results in the inhibition of fibrinolysis by displacing plasminogen from fibrin. Tranexamic acid is approximately ten times more potent than aminocaproic acid and its elimination half-life is 2–11 hours [1, 2]. Tranexamic acid is available in an intravenous solution and an oral tablet, which may be compounded into an oral solution which provides 500 mg per 10 mL [3].

Adult Use

Tranexamic acid can be used for menorrhagia [2], blood loss reduction during elective cesarean section [4], blood loss reduction during hip fracture surgery [5], blood loss reduction in orthognathic surgery [6], blood loss reduction in dental procedure patients on oral anticoagulant therapy [7], prevention of perioperative bleeding associated with cardiac and spinal surgery [8–11], blood loss reduction during total-hip and total knee replacement surgery [12–18], and trauma-associated hemorrhage [19] (Table 42.1).

Pediatric Use

In the pediatric setting, tranexamic acid can be used for the prevention of bleeding associated with extracorporeal membrane oxygenation (ECMO) during surgery for congenital diaphragmatic hernia (CDH) repair [20, 21], prevention of perioperative bleeding associated with cardiac surgery [22–24], menorrhagia [2, 25], blood loss reduction in hemophilic patients undergoing tooth extraction [26], treatment of hemoptysis patients [27–29], and prevention of perioperative bleeding associated with spinal surgery and craniosynostosis surgery [30–33].

Adverse Effects and Monitoring Parameters

Orally administered tranexamic acid can cause gastrointestinal upset, headache, abdominal pain, muscle pain, and thrombosis. Visual defects may occur; thus, patients should undergo routine ophthalmologist examinations. Intravenous tranexamic acid can also cause hypotension with rapid administration [34]. Seizures have been reported in pediatric trauma patients who have been administered tranexamic acid [35]. The dose and frequency of tranexamic acid should be adjusted in patients with renal dysfunction (see Table 42.2). Importantly, tranexamic acid should not be used when there is evidence of active intravascular thrombosis [1, 2]. Caution should be exercised if tranexamic acid is used concomitantly with prothrombin complex concentrates (PCC) or activated prothrombin complex concentrates(APCC) due to risk of thrombosis. If treatment with both agents is deemed necessary, it is recommended to wait 4–6 hours after the last dose of PCC or APCC before administering tranexamic acid [36].

Aminocaproic Acid

Brand Name (US) Amicar™

Description

Aminocaproic acid is an antifibrinolytic that reduces the conversion of plasminogen to plasmin by binding competitively to plasminogen which results in the inhibition of fibrin degradation. Aminocaproic acid is less potent than tranexamic

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Table 42.1 Tranexamic acid dosing

Indication	Dose and frequency	Duration
Menorrhagia	1300 mg PO TID	Up to 5 days/month during menstruation
Blood loss reduction during elective cesarean section	1000 mg IV at least 10 minutes prior to incision	
Blood loss reduction during hip fracture surgery	15 mg/kg IV at time of skin incision followed by 15 mg/kg IV 3 hours later	
Blood reduction during orthognathic surgery	20 mg/kg IV prior to incision	
Prevention of dental procedure bleeding in patients on oral anticoagulant therapy	Hold 10 mL of 4.8% solution in mouth and rinse for 2 minutes	Repeat four times daily for 2 days after procedure. *Patient shouldn't eat or drink for 1 hour after using oral rinse*
Prevention of perioperative bleeding associated with cardiac surgery	30 mg/kg IV prior to incision, followed by 16 mg/kg/hour IV until sternal closure 10 mg/kg IV prior to incision followed by 2 mg/kg/hour IV continued for 2 hours after surgery 10–15 mg/kg IV followed by 1–1.5 mg/kg/hour IV	
Prevention of perioperative bleeding associated with spinal surgery	2000 mg IV prior to incision followed by 100 mg/hour IV during surgery and for 5 hours postoperatively 10 mg/kg IV prior to incision followed by 1 mg/kg/hour IV for the remainder of the surgery; discontinue at time of wound closure	
Blood loss reduction during total hip replacement surgery	10–15 mg/kg (or 1000 mg) IV immediately before the operation or 15 minutes before skin incision The preoperative dose may be followed by 10 mg/kg IV administered 3–12 hours after the operation Postoperative doses ranged from a 10 mg/kg IV bolus (or 1000 mg) to a 1 mg/kg/hour IV infusion over 10 hours	
Blood loss reduction in total knee replacement surgery	10 mg/kg (or 1000 mg) IV approximately 10 minutes before deflation of the first tourniquet with a second dose (10 mg/kg) 3 hours after the first dose	
Trauma-associated hemorrhage	1000 mg IV followed by 1000 mg IV over the next 8 hours	
Prevention of bleeding associated with ECMO during surgery for CDH	4 mg/kg IV before repair, followed by 1 mg/kg/hour IV for 24 hours	
Prevention of perioperative bleeding associated with cardiac surgery in neonates	100 mg/kg IV Prime the bypass circuit with 100 mg/kg IV followed by 10 mg/kg/hour iv infusion	
Prevention of bleeding associated with cardiac surgery in children	6.4 mg/kg IV followed by 2–3 mg/kg/hour IV infusion	
Prevention of perioperative bleeding associated with spinal surgery in children	20 mg/kg IV and 10 mg/kg/hour IV infusion OR 10 mg/kg IV and 1 mg/kg/hour IV infusion	
Prevention of perioperative bleeding associated with craniosynostosis surgery in children	50 mg/kg IV prior to incision, followed by 5 mg/kg/hour IV infusion until skin closure OR 15 mg/kg IV prior to incision, followed by 10 mg/kg/hour IV infusion until skin closure	
Treatment of hemoptysis	Cystic fibrosis patients 60 mg/kg/day IV every 6 hours × 1 day, then switch to 500 mg PO QID (90 mg/kg/day), then 500 mg PO TID × 4 years with no toxicity 500 mg PO TID × 5 months 1000 mg PO TID chronic treatment Other patients 500 mg nebulized in 5 mL normal saline (adults) 250 mg nebulized in 2.5 mL normal saline (pediatric)	
Usual dosing: 15–25 mg/kg PO every 8 hours, or 10 mg/kg IV every 8 hours		

Adapted from Refs. [1–32]

acid as tranexamic binds noncompetitively to plasminogen. Aminocaproic acid has an elimination half-life of 2 hours and may accumulate in patients with renal dysfunction necessitating dose reduction. Aminocaproic acid is available as an intravenous solution, oral solution, and oral tablet [37, 38].

Adult Use

Aminocaproic acid can be used to enhance hemostasis when fibrinolysis contributes to bleeding [37], control of acute bleeding [37], control of bleeding with severe thrombocytopenia [39, 40], control of bleeding in congenital and acquired

Table 42.2 Tranexamic acid dosing in renal impairment

Indication	Serum creatinine	Dose and frequency
Menorrhagia	>1.4–2.8 mg/dL	1300 mg PO BID for up to 5 days
	2.9–5.7 mg/dL	1300 mg PO daily for up to 5 days
	>5.7 mg/dL	650 mg PO daily for up to 5 days
Blood loss reduction in adult cardiac surgery patients	>1.4–2.8 mg/dL	1300 mg twice daily (2600 mg daily) for up to 5 days
	2.9–5.7 mg/dL	1300 mg once daily for up to 5 days
	>5.7 mg/dL	650 mg once daily for up to 5 days
Blood loss reduction in pediatric and adult hemophilia patients undergoing tooth extraction	1.36–2.83 mg/dL	10 mg/kg/dose IV BID
	>2.83–5.66 mg/dL	10 mg/kg/dose IV once daily
	>5.66 mg/dL	10 mg/kg/dose IV every 48 hours 5 mg/kg/dose IV once daily

Adapted from Refs. [1, 24, 33]

coagulation disorder [41], blood loss reduction in patients on oral anticoagulant therapy undergoing dental procedures [2], and prevention of perioperative bleeding associated with cardiac surgery [37, 42].

Pediatric Use

Aminocaproic acid can be used in children for the prevention of perioperative bleeding associated with cardiac and spinal surgery [42–45], reducing blood loss in pediatric craniofacial surgery [46], prevention of bleeding associated with ECMO [47–49].

Adverse Effects and Monitoring Parameters

The most common adverse effect of enteral aminocaproic acid is gastrointestinal upset. Other adverse effects include thrombosis and an increase in blood urea nitrogen (BUN) and skeletal muscle weakness. Aminocaproic acid can also cause skeletal muscle weakness; therefore, creatinine phosphokinase (CPK) should be monitored in patients with symptoms and treatment should be discontinued with a significant rise in CPK. Other monitoring parameters include fibrinogen, BUN, and creatinine. Importantly, aminocaproic acid should not be used when there is evidence of active intravascular thrombosis [37] (Table 42.3).

Table 42.3 Aminocaproic acid dosing

Indication	Dose and frequency	Duration
Acute bleeding	4–5 g PO/IV during the first hour, followed by 1 g/hour for 8 hours (or 1.25 g/hour using oral solution) or until bleeding controlled (max daily dose: 30 g)	
Control of bleeding with severe thrombocytopenia	100 mg/kg (max dose: 5 g) IV over 30–60 minutes, followed by 1–4 g IV/PO every 4–8 hours or 1 g/hour (max daily dose: 24 g)	
Control of oral bleeding in congenital and acquired coagulation disorder	50–60 mg/kg PO every 4 hours	
Prevention of dental procedure bleeding in patients on oral anticoagulant therapy	Oral rinse: hold 4 g/10 mL in mouth for 2 minutes then spit out	Repeat every 6 hours for 2 days after procedure
Prevention of perioperative bleeding associated with cardiac surgery	10 g IV followed by 2 g/hour during surgery; no medication added to the bypass circuit 10 g IV prior to skin incision, followed by 10 g after heparin administration then 10 g at discontinuation of cardiopulmonary bypass	
Prevention of perioperative bleeding associated with cardiac surgery in pediatric patients	100 mg/kg IV after induction and prior to incision, 100 mg/kg during cardiopulmonary bypass, and 100 mg/kg after heparin reversal	
Prevention of bleeding associated with ECMO in pediatric patients	100 mg/kg IV prior to or immediately after cannulation, followed by 25–30 mg/kg/hour for up to 72 hours	
Prevention of perioperative bleeding associated with spinal surgery pediatric patients	100 mg/kg IV after induction, followed by 10 mg/kg/hour for the remainder of the surgery; discontinue at time of wound closure	
Usual dosing: 60–100 mg/kg PO every 6 hours (up to 24 g/day in adults)		

Adapted from Refs. [35–47]

Fibrinogen Concentrate (Human)

Brand Name (US) RiaSTAP™, Fibryga™

Description

Fibrinogen concentrate (coagulation factor I) is generated from pooled human plasma and is a physiological substrate of thrombin, factor XIIIa, and plasmin. Cross-linked fibrin, the end result of the coagulation cascade, is stabilized by factor XIIIa. Human fibrinogen concentration has a fairly long elimination half-life of 61–97 hours; however, this half-life

may be decreased in children and adolescents. Fibrinogen concentrate is available as intravenous powder, for reconstitution [43, 50].

Adult Use

Fibrinogen concentrate can be used in the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia) [43], supportive therapy in trauma patients who are bleeding [51–55], blood loss reduction in cardiovascular surgery [51, 56, 57], blood loss reduction in postpartum hemorrhage [58], and improvement in clot firmness after orthopedic surgery [59].

Pediatric Use

Fibrinogen concentrate can be used in children for the treatment of congenital fibrinogen deficiency [60, 61], pediatric cardiac surgery [62], reduction of blood loss after surgical craniosynostosis repair [63], pediatric blunt trauma [64], and leukemia [65].

Adverse Effects and Monitoring Parameters

Fibrinogen concentrate may cause hypersensitivity reactions, thrombosis, and headache. Similarly to all plasma-derived factor products, fibrinogen concentrate may also transmit disease, since the product is derived from human plasma. Monitoring parameters include fibrinogen levels and signs/symptoms of thrombosis and hypersensitivity. In general, a target fibrinogen level of 100 mg/dL is a goal concentration for hemostasis and wound healing. The reference range for normal fibrinogen is 200–450 mg/dL [43] (Table 42.4).

Table 42.4 Fibrinogen concentrate dosing

Indication	Dose, frequency, and duration
Congenital fibrinogen deficiency	[Target level (mg/dL) – measured level (mg/dL)] divided by 1.7 (mg/dL per mg/kg body weight) = mg/kg dose When baseline fibrinogen level is unknown: 70 mg/kg IV
Traumatic bleeding	25–50 mg/kg IV
Prevention of bleeding associated with cardiovascular surgery	2 g IV preoperative infusion
Reduction of postpartum hemorrhage	2 g IV post vaginal delivery or cesarean section
Improvement in clot firmness after orthopedic surgery	30 mg/kg IV
Reduction of blood loss after craniosynostosis repair surgery in children	30 mg/kg IV

Adapted from Refs. [48–60]

Factor VIIa (Recombinant)

Brand Name (US) NovoSeven™ RT

Description

Recombinant activated factor VII (rFVIIa) is a vitamin K-dependent glycoprotein that promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. Factor VII complexes with tissue factor and activates coagulation factors IX and X. When complexed with other factors, coagulation factor Xa with factor Va converts prothrombin to thrombin, a key step in the formation of a fibrin-platelet hemostatic plug. rFVIIa has a short terminal half-life of 2.6–3.1 hours, and patients may require frequent dosing if longer therapy is necessary. rFVIIa is available as an intravenous solution [44].

Adult Use

rFVIIa is indicated for use in patients with hemophilia A or B with inhibitors [44], congenital factor VII deficiency [44], acquired hemophilia [44], and Glanzmann thrombasthenia [44]. There have been numerous studies and reports on the unlabeled use of rFVIIa in bleeding patients. Overall, the data for recombinant rFVIIa has been reported to be used in patients with warfarin-related intracerebral hemorrhage (ICH) [66, 67], refractory bleeding after cardiac or liver surgery in nonhemophiliac patients [1, 34, 67–69], anticoagulation reversal [70–72], blood loss reduction after cardiac surgery [73], coagulopathy reversal in isolated traumatic brain injury (TBI) [74], diffuse alveolar hemorrhage in bone marrow transplant (BMT) patients [75], bridge to transplant in end-stage liver disease patients [75], trauma-related coagulopathy [75], refractory perioperative bleeding in noncardiac patients [75], life-threatening refractory hemorrhage of any cause in severely coagulopathic patients [67, 75], blood loss reduction in abdominal trauma patients [76], and esophageal varices [67].

Pediatric Use

rFVIIa can also be utilized in the pediatric population for reduction in blood loss and requirement for blood products after cardiac surgery [77, 78], coagulopathies [79], treatment of severe bleeding associated with dengue hemorrhagic fever [80], liver impairment [81, 82], and nonhemophilic hemorrhages [83].

Adverse Effects and Monitoring Parameters

rFVIIa may cause antibody formation, hypersensitivity reactions, thromboembolic events [84], and hyper or hypotension. Monitoring parameters include evidence of hemostasis. The prothrombin time, international normalized ration (INR),

Table 42.5 Recombinant activated factor VII dosing

Indication	Dose, frequency, and duration
Warfarin-related ICH	10–100 μg/kgIV administered concurrently with IV vitamin K *Lower doses (10–20 μg/kg) are generally preferred given the higher risk of thromboembolic complications with higher doses*
Treatment of refractory bleeding after cardiac surgery in nonhemophiliac patients	35–70 μg/kg IV 10–20 μg/kgin patients with a left ventricular assist device, to reduce thromboembolic events
Reduction in blood loss after cardiac surgery	40 μg/kg IV
Reverse coagulopathy in patients with isolated TBI	20 μg/kg IV (*in addition to other blood products*)
Diffused alveolar hemorrhage in BMT patients, bridge to transplant in end-stage liver disease, trauma-related coagulopathy, refractory perioperative bleeding in noncardiac patients, life-threatening refractory hemorrhage in coagulopathic patients	30 μg/kg IV repeated every 15 minutes to a maximum dose of 90 μg/kg
Blood loss reduction in abdominal trauma patients	24–72 μg/kg IV, repeat in 3 hours if no clinical improvement
Reduction in blood loss after cardiac surgery in pediatrics	90–180 μg/kg IV after cardiac surgery 40 μg/kg IV during surgery
Coagulopathies in pediatrics	5 μg/kg IV initial, followed by 10, 20,40, or 80 μg/kg IV
Treatment of severe bleeding associated with dengue hemorrhagic fever in pediatrics	100 μg/kg IV × 1 (or repeated doses every 4 hours as needed)
Chronic liver disease in children	38–118 μg/kg IV × 1
Nonhemophilic hemorrhage in pediatrics	90 μg/kg IV × 2
Usual dose range 40–90 μg/kg IV	

Adapted from Refs. [61–81]

activated partial thromboplastin time (aPTT), and factor VII may also be useful as adjunct tests to evaluate efficacy [44] (Table 42.5).

Desmopressin

Brand Names (US) DDAVP™, Stimate™

Description

Desmopressin is a synthetic analogue of vasopressin with the molecular structure modified to reduce its vasoactive actions; vasopressin activates both V1 and V2 receptors, whereas desmopressin only stimulates V2 receptors. Desmopressin increases plasma levels of VWF, factor VIII, and tissue plasminogen activator (t-PA) contributing to a shortened aPTT and bleeding time. These effects are likely due to stimulating the release of VWF from endothelial storage sites; however, this mechanism is not fully understood, and several hypotheses exist [85–89]. Prior to utilizing desmopressin for therapy, a therapeutic trial should be conducted to determine a patient's response. Most patients with type 1 von Willebrand disease (VWD) and factor VIII/VWF levels greater than 10 IU/mL (10%) will respond to desmopressin, but patients with type 2 VWD have a more variable response. To test responsiveness, blood samples are taken 30–60 minutes and 4 hours after an intravenous injection of desmopressin to obtain a reliable figure on recovery and clearance of factor VIII and VWF [90]. Desmopressin has an elimination half-life of 2–4 hours; however, the half-life is prolonged to 9 hours in patients with renal impairment [37].

Formulations

Desmopressin is available as a4 μg/mL injection and a 1.5 mg/mL nasal solution. The nasal formulation is ~2.75 times less potent than the injection formulation. Therefore, the nasal solution is often used for minor bleeding, while the intravenous injection is preferred for surgical bleeding prophylaxis and major bleeding. Desmopressin is also available as an oral tablet and a rhinal tube [86].

Adult Use

Desmopressin is utilized in the treatment and prevention of bleeding episodes in mild-to-moderate hemophilia A and mild-to-moderate VWD type 1 patients who respond to a desmopressin challenge [36, 59, 68]. Desmopressin can also be utilized in treatment of uremia associated with acute or chronic renal failure [91], prevention of surgical bleeding in patients with uremia [92] to stabilize platelet function in intracranial hemorrhage [93], prevention of blood loss reduction after cardiac surgery [94, 95], prevention of blood loss reduction in dental procedures [86], and prevention of blood loss reduction in patients with liver cirrhosis [96–99]. It is recommended to utilize VWF in addition to desmopressin if the postsurgical treatment is necessary for more than 3 days [86].

Pediatric Use

In the pediatric setting, desmopressin is utilized for heavy menstrual bleeding in adolescent females [100, 101], congenital VWD in patients who respond to a desmopressin challenge [85], congenital platelet defect disorders in patients who respond to a desmopressin challenge [85], circumcision in combined factor V and factor VIII deficiency [102], tonsillectomy and adenoidectomy [86], and otologic surgery [86]. Studies have shown that desmopressin administered as a one-time dose after cardiopulmonary bypass failed to reduce blood loss after cardiovascular surgery in pediatrics [103–105]. Of note, children under 2 years of age

tend to have a lower response to desmopressin in comparison to older children [86].

Adverse Effects and Monitoring Parameters

Desmopressin may cause flushing, hypo- or hypertension, headache, fatigue, hyponatremia, abdominal pain, abnormal lacrimation (intranasal formulation), conjunctivitis (intranasal formulation), and ocular edema (intranasal formulation). Monitoring parameters include fluid intake, urine volume, and signs/symptoms of hyponatremia [86]. Young children may be at an increased risk for hyponatremia-induced seizures when the intravenous formulation is utilized; fluid restriction and careful monitoring of serum sodium levels and urine output are warranted [106–110]. Due to the risk of hyponatremia, some institutions adopt sodium limits associated with desmopressin administration, i.e., avoidance of desmopressin if serum sodium is less than 130 mEq/L. Tachyphylaxis can occur with consecutive dosing of desmopressin, thus in situations where multiple doses of a medication is required for hemostasis [111] (Tables 42.6 and 42.7).

Table 42.6 Desmopressin dosing

Indication	Dose, frequency, and duration
Uremic bleeding associated with acute or chronic renal failure	0.4 μg/kg IV once
Prevention of surgical bleeding in patients with uremia and reduction in bleeding time in patients with liver cirrhosis	0.3 μg/kg IV once
Reduction of blood loss in intracranial hemorrhage	24 μg IV once Patients 20 kg = 8 μg Patients 50 kg = 20 μg Patients 100 kg = 40 μg or 0.3 μg/kg
Blood loss reduction after cardiac surgery	0.3 μg/kg IV once after coming off cardiopulmonary bypass
Dental procedure	0.3 μg/kg IV daily for 1–2 days
Heavy menstrual bleeding in adolescent females	Intranasal desmopressin: 1.5 mg/mL or 150 μg per spray 1 spray <50 kg; 2 sprays ≥50 kg Administered once daily started at onset of menses and continued for subsequent 2 days after menses
Hemophilia A and von Willebrand disease in infants ≥11 months, children, adolescents, and adults	Intranasal desmopressin: 1.5 mg/mL or 150 μg per spray Patients <50 kg: 150 μg (1 spray) Patients ≥50 kg: 300 μg (1 spray each nostril) If using preoperatively, administer 2 hours before surgery
Congenital VWD and congenital platelet defect disorders in pediatrics	0.3 μg/kg IV once, if used preoperatively administer 30 minutes before procedure; may repeat dose if needed
Tonsillectomy, adenoidectomy, and otologic surgery in pediatrics	0.3 μg/kg IV once or twice daily for 1–7 days
Generally, 0.3 μg/kg of desmopressin can increase the level of FVIII and von Willebrand Factor for two- to sixfold. Peak effect occurs 1 hour after injection. Recommended not use more than once daily due to development of tachyphylaxis [36]	

Adapted from Refs. [34, 83, 88, 101]

Table 42.7 Desmopressin dosing in renal impairment

Creatinine clearance	Dose
<50 mL/minute	Contraindicated (except 1.5 mg/mL nasal spray)
However, it has been used in acute and chronic renal failure patients experiencing uremic bleed or prevention of surgical bleeding	

Adapted from Refs. [34, 90, 91]

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Brand Name (US) Humate-P™

Description

Humate-P™ is derived from human plasma and contains factor VIII and VWF and small amounts of fibrinogen and albumin [55]. It is used primarily to replace endogenous factor VIII and VWF in patients with hemophilia A or VWD. Factor VIII in conjunction with activated factor IX activates factor X which converts prothrombin to thrombin and fibrinogen to fibrin. VWF promotes platelet aggregation and adhesion to damaged vasculature and acts as a carrier protein for factor VIII. Circulating levels of functional VWF are measured as ristocetin cofactor activity [VWF/RCo]). The average ratio of VWF/RCo to factor VIII in Humate-P™ is 2.4:1, which is more similar to the ratio in normal human plasma in comparison to other VWF/factor VIII products. The elimination half-life of VWF/RCo in Humate-P™ has a range of 3–34 hours in patients with VWD. Humate-P™ is available as an intravenous powder for reconstitution [112].

Adult Use

Humate-P™ is utilized in adult patients for the prevention and treatment of bleeding episodes in patients with hemophilia A [55]; treatment of spontaneous or trauma-induced bleeding and prevention of excessive bleeding during and after surgery in patients with severe VWD [55, 113, 114], including mild or moderate disease where use of desmopressin is known or suspected to be inadequate [55]; reduction of postpartum blood loss in VWD type 3 patients [115]; and in

the development of acquired von Willebrand syndrome after ventricular assist device implantation [112]. When used for surgical prophylaxis, target levels of VWF/RCo should be approximately 100 IU/mL(100%) and, at least for the first 3 days of treatment, a nadir of 50 IU/mL (50%) VWF/RCo, as well as similar targets for factor VIII [86]. Humate-P™ administered as a continuous infusion has also been reported to be successful for surgical prophylaxis [86].

Pediatric Use

Humate-P™ is utilized in pediatric patients with VWD undergoing surgery, bleeding events in VWD [116, 117], prophylaxis in VWD [116], and valproate-associated von Willebrand syndrome [117].

Adverse Effects and Monitoring Parameters

Adverse effects of Humate-P™ include antibody formation, hypersensitivity, thrombotic events, rash, dizziness, headache, and nausea/vomiting [118]. Monitoring parameters include heart rate, blood pressure, AHF levels prior to and during treatment, inhibitor development, hematocrit, signs/symptoms of intravascular hemolysis, bleeding, and VWF activity. In surgical patients, monitor VWF/RCo at baseline and after surgery and trough VWF/RCo and factor VIII/C daily. Humate-P™ is derived from human plasma and has the potential for infectious disease transmission [55] (Table 42.8).

Table 42.8 Antihemophilic factor/von Willebrand factor complex dosing (Humate-P™)

Indication	Dose, frequency, and duration
Treatment and prophylaxis of bleeding episodes	Dose, frequency, and duration are based on severity of bleed
Prophylaxis prior to surgical and/or invasive procedures	Dose, frequency, and duration are based on severity of surgery
Acquired VWD after ventricular assist device implantation	60 units/kg IV every 8 hours for 3 doses; then 60 units/kg IV every 12 hours; then 40 units/kg IV every day and unfractionated heparin started to maintain aPTT of 50 to prevent LVAD clotting
Reduction of postpartum blood loss in VWD type 3 patients	40–60 units VWF/RCo/kg IV TID or QID
Treatment of VWD in pediatrics and valproate-associated acquired von Willebrand syndrome	10–20 units VWF/RCo/kg IV for type 1 and 20–50 units VWF/RCo/kg IV for type 3 VWD either once or twice daily for 3 days
Dose and duration of treatment depend on the site and severity of bleeding. Subsequent dosing is generally based on the half-life of 8–12 hours [36]	

Adapted from Refs. [83, 111–117]

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Brand Name (US) Alphanate™

Description

Alphanate™ is derived from human plasma and contains factor VIII, VWF, and other plasma proteins. Alphanate™ is used to replace endogenous factor VIII and VWF. The average ratio of VWF/RCo to factor VIII in Alphanate™ is 0.5. Of note, Alphanate™ has less VWF per unit when compared with Humate-P™. The elimination half-life range for Alphanate™ is the same as Humate-P™(3–34 hours). Alphanate™ is available as an intravenous powder for reconstitution [86].

Adult Use

Alphanate™ is utilized for the prevention and treatment of hemorrhagic episodes in patients with hemophilia A [56] and prophylaxis with surgical and/or invasive procedures in patients with VWD when desmopressin is either ineffective or contraindicated [56, 119]. Alphanate™ is not indicated for surgical prophylaxis in patients with severe VWD, type 3 [56, 86].

Pediatric Use

Alphanate™ is used in pediatric patients with VWD for the treatment of bleeding episodes [120] and prophylaxis prior to surgery [56, 120].

Adverse Effects and Monitoring Parameters

Alphanate™ can cause antibody formation, hypersensitivity, thrombotic evens, rash, face edema, headache, dizziness, and nausea. Alphanate™ can also cause transmission of infections since it is derived from human plasma. Monitoring parameters are the same as those listed for Humate-P™ (Table 42.9).

Table 42.9 Antihemophilic factor/von Willebrand factor complex dosing (Alphanate™)

Indication	Dose, frequency, and duration
Treatment and prophylaxis of bleeding episodes	Dose, frequency, and duration are based on severity of bleed
Prophylaxis prior to surgical and/or invasive procedures	Dose, frequency, and duration are based on severity of surgery

Adapted from Refs. [83, 118–120]

Phytonadione (Vitamin K)

Brand Name (US) Mephyton™

Description

Phytonadione is a vitamin that is necessary for the liver to synthesize factor II, factor VII, factor IX, and factor X. However, the exact mechanism as to this stimulation is unknown. Phytonadione is available as in intravenous aqueous colloidal and an oral tablet [66].

Adult Use

Phytonadione is used in the prevention and treatment of hypoprothrombinemia caused by vitamin K antagonist (VKA)-induced or other drug-induced vitamin K deficiency [66], vitamin K deficiency secondary to VKA [121–123], and preprocedural/surgical INR normalization in patients receiving warfarin [121, 124].

Pediatric Use

Phytonadione is used in pediatric patients to treat vitamin K deficiency secondary to vitamin K antagonist administration [66] and bleeding in patients with chronic cholestasis [125].

Adverse Effects and Monitoring Parameters

Phytonadione can cause hypersensitivity reactions, flushing, dizziness, and abnormal taste. Prothrombin time, INR, and hypersensitivity reactions should be monitored following phytonadione administration [66] (Table 42.10).

Table 42.10 Phytonadione dosing

Indication	Dose, frequency, and duration
Hypoprothrombinemia due to drugs or Factors limiting absorption or synthesis	Oral, SubQ, IM, IV: initial, 2.5–25 mg (rarely up to 50 mg)
Vitamin K deficiency (supratherapeutic INR) secondary to VKAs	INR 4.5–10 (no bleeding): 2012 ACCP guidelines recommend against routine phytonadione administration. Others recommend consideration of phytonadione 1 mg PO or 0.5 mg IV INR >10 (no bleeding): 2012 ACCP guidelines recommend against administration of phytonadione. Others recommend consideration of phytonadione 2–2.5 mg PO or 0.5–1 mg IV If minor bleeding at any INR elevation: hold warfarin, may administer phytonadione 2.5–5 mg PO, monitor INR more frequently, may repeat dose after 24 hours if INR correction incomplete; resume warfarin at an appropriately adjusted dose when INR is in desired range If major bleeding at any INR elevation: the 2012 ACCP guidelines recommend administration of four-factor prothrombin complex concentrate and phytonadione 5–10 mg IV
Preprocedural/surgical INR normalization in patients receiving warfarin	1–2.5 mg PO once administered on the day before surgery; recheck INR on day of procedure/surgery
Bleeding in pediatric patients with chronic cholestasis	5 mg IV once

Adapted from Refs. [121–126]

Four-Factor Prothrombin Complex Concentrate (Human)

Brand Name (US) Kcentra™

Description

Kcentra™ is derived from human plasma and contains factor II, factor VII, factor IX, factor X, protein C, and protein S. Factors facilitate the activation of prothrombin into thrombin which converts fibrinogen into fibrin resulting in clot formation. Proteins C and S are vitamin K-dependent inhibiting zymogens involved in regulating the coagulation process. Protein S serves as a cofactor for protein C which is converted to activated protein C (APC). APC is a serine protease which inactivates factor Va and factor VIIIa, limiting thrombotic formation. The elimination half-life of this product is dependent on the half-life of its individual components; factor II, 48–60 hours; factor VII, 1.5–6 hours; factor IX, 20–24 hours; factor X, 24–48 hours; protein C, 1.5–6 hours; and protein S, 24–48 hours. Kcentra™ is available as in intravenous powder for reconstitution [67]. Three factor prothrombin complex concentrates (Profilnine™) differ from Kcentra in that they do not contain factor VII but only contain factor II, factor IX, and factor X [126–128].

Adult Use

Kcentra™ is indicated for VKA reversal in patients with acute major bleeding or need of an urgent surgical/invasive procedure [67]. Reports have also shown Kcentra™ to be effective in the reversal of direct factor Xa anticoagulants [129, 130], an alternative agent to fresh frozen plasma (FFP) in patients with serious/life-threatening bleeding related to vitamin K antagonist therapy [131], and in acquired, non-warfarin-related coagulopathy in major trauma and surgery [132–135].

Pediatric Use

Data supporting four-factor prothrombin complex concentrate use in pediatric patients is limited to case reports or

case series [136, 137]. These data show prothrombin complex concentrate can be used for prophylaxis in patients with severe congenital factor X deficiency [126, 127], dilutional coagulopathy [138], and after cardiopulmonary bypass [139]. Prothrombin complex concentrate may also be useful in pediatric patients with limited total blood volume and high risk of volume overload; however, there have been no formal studies validating this.

Adverse Effects and Monitoring Parameters

Kcentra™ can cause hypersensitivity reactions, hypercoagulopathy, hypo- or hypertension, tachycardia, headache, and nausea/vomiting. Infection can also be transmitted since Kcentra™ is derived from human plasma. The INR should be monitored at baseline and at 30 minutes post-dose, and a patient's clinical response should be monitored during and after treatment [67] (Tables 42.11, 42.12, 42.13).

Table 42.11 Four-factor prothrombin complex concentrate dosing

Indication	Dose and frequency	Duration
Vitamin K antagonist (VKA) reversal in patients with acute major bleeding or need for an urgent surgery/invasive procedure	Pretreatment INR: 2 to <4 25 units/kg IV (max: 2500 units) Pretreatment INR: 4–6 35 units/kg IV (max: 3500 units) Pretreatment INR: >6 50 units/kg IV (max: 5000 units)	Repeat dosing is not recommended (has not been studied)
Reversal of direct factor Xa anticoagulants	50 units/kg IV	Once
Serious/ life-threatening bleeding related to vitamin K antagonist therapy	25–50 units/kg IV	Once
Acquired, non-warfarin-related coagulopathy in major trauma and surgery	20–40 units/kg IV	Once
Prophylaxis in patients with severe congenital factor X deficiency in pediatrics	15 units/kg IV every 8–12 hours in perioperative period, 20 units/kg IV every 72 hours for prophylaxis 25 units/kg IV every 72 hours 30 units/kg IV every 72 hours 30 units/kg IV twice per week	
Dilutional coagulopathy in pediatrics	30 units/kg IV	Once

Adapted from Refs. [127, 131–140]

Table 42.12 Four-factor prothrombin complex concentrate components

Ingredient	Amount per 500 unit vial
Total protein	120–280 mg
Factor II	380–800 units
Factor VII	200–500 units
Factor IX	400–620 units
Factor X	500–1020 units
Protein C	420–820 units
Protein S	240–680 units
Heparin	8–40 units
Antithrombin	4–30 units
Human albumin	40–80 mg
Sodium chloride	60–120 mg
Sodium citrate	40–80 mg

Adapted from Ref. [127]

Table 42.13 Comparison of three- and four-factor prothrombin concentrations

	Kcentra™ 500 unit vial	Profilnine™[a] 500 unit vial
Factor II	380–800 units	NMT 150 units/100 units factor IX
Factor VII	200–500 units	NMT 35 units/100 units factor IX
Factor IX	400–620 units	100 units
Factor X	500–1020 units	NMT 100 units/100 units factor IX
Heparin	8–40 units	
Protein C	420–820 units	
Protein S	240–680 units	
Antithrombin III	4–30 units	

Abbreviations: *NMT* not more than
[a]Also contains polysorbate 80
Adapted from Refs. [127–130]

Thrombin Powder

Brand Name (US) Recothrom™

Description

Recombinant thrombin powder is a topical product that activates platelets and catalyzes the conversion of fibrinogen to fibrin to promote hemostasis. Thrombin is available as a topical powder for reconstruction, topical pad, topical solution, and topical sponge [140].

Adult Use

Thrombin is utilized for hemostasis [140], control of localized, accessible bleeding from lacerated tissues [36], control

Table 42.14 Thrombin powder dosing

Indication	Dose, frequency, and duration
Hemostasis	Apply powder directly to the site of bleeding or on oozing surfaces

Adapted from Refs. [34, 141–142]

of bleeding after dental extractions or at surgical sites [36], and blood loss reduction in total knee arthroplasty [141].

Pediatric Use

Thrombin powder has been studied in pediatric patients and is approved to aid in hemostasis, specifically in burn patients [140].

Adverse Effects and Monitoring Parameters

Patients who receive thrombin powder should be monitored for abnormal hemostasis. Thrombin powder may also cause pruritus. Of note, this product is for topical use only [140] (Table 42.14).

Protamine Sulfate

Brand Name (US) Not Applicable

Description

Protamine is a strongly alkaline substance derived from the sperm of salmon and other fish species. When protamine is administered alone, it has anticoagulant effects. However, when protamine is administered in the presence of heparin, a strong acidic medication, a stable salt is formed, and the anticoagulant activity of both medications is inhibited. Protamine has a very rapid onset of action (5 minutes), and the elimination half-life is approximately 7 minutes. Protamine neutralizes heparin as it is administered; therefore, subsequent doses are not usually required. Protamine is available as an intravenous solution [142].

Adult Use

Protamine is utilized in adults for the reversal of heparin and low-molecular-weight heparins [142, 143]. When heparin is given as a continuous IV infusion, only heparin given in the preceding several hours should be considered when administering protamine [144]. Protamine can also be utilized for low-molecular-weight heparin (LMWH) overdose, but the anti-Xa activity is never completely neutralized [145–147]. Protamine is also used to neutralize heparin in patients previously on cardiopulmonary bypass, the most effective dosing being individualized management [148], and to reduce bleeding complications after carotid endarterectomy [149].

Pediatric Use

Protamine is utilized in the pediatric patient to reverse heparin and low-molecular-weight heparin, to neutralize heparin from combined estimated blood volume of the patient and cardiopulmonary bypass circuit [145, 146], and for the treatment of severe post-reperfusion coagulopathy in liver transplant patients [147].

Adverse Effects and Monitoring Parameters

Severe hypotension can occur with rapid administration of protamine; thus, protamine should be administered over at least a 10-minute period. Transient hypotension can still be expected within 3–4 minutes after administration [150]. There is also a risk for anaphylaxis with protamine administration, which mainly occurs during cardiac surgeries [151]. Since protamine has weak anticoagulant activity, due to an interaction with platelets and proteins including fibrinogen, protamine overdose can cause bleeding. This effect should be distinguished from the rebound anticoagulation that may occur 30 minutes to 18 hours following the reversal of heparin with protamine [142] (Table 42.15).

Anti-Inhibitor Coagulant Complex

Brand Name (US) Feiba NF™

Description

Anti-inhibitor coagulant complex is a human plasma-derived factor product and contains nonactivated factors II, IX, and X and activated factor VII. Anti-inhibitor coagulant complex also contains factor VIII bypassing activity at approximately equal units to the other factors and 1–6 units of factor VIII coagulant antigen per milliliter. Anti-inhibitor coagulant complex shortens the activated partial thromboplastin time of plasma containing factor VIII inhibitor. Strengths are expressed in terms of factor VIII inhibitor bypassing activity, and one unit of activity is defined as the amount of anti-inhibitor coagulant complex that shortens the aPTT of a high titer factor VIII inhibitor reference plasma to 50% of the blank value. The elimination half-life of anti-inhibitor coagulant complex is approximately 4–7 hours. Anti-inhibitor coagulant complex is available as an intravenous powder for reconstitution [152].

Adult Use

Anti-inhibitor coagulant complex is utilized in adults for control and prevention of bleeding episodes in hemophilia patients with inhibitors [152], moderate to severe bleeding

Table 42.15 Protamine dosing

Indication	Time since last heparin dose (min)	Dose of protamine (mg) IV to neutralize 100 units of heparin
Intravenous heparin overdose in adults and pediatrics	<30	1
	30–60	0.5–0.75
	60–120	0.375–0.5
	>120	0.25–0.375
Subcutaneous heparin overdose	*Not reported*	1–1.5 mg given
Severe post-reperfusion coagulopathy in liver transplant patients	*Not reported*	0.5 mg
Enoxaparin overdose in adults	≤8 hours	The dose of protamine should equal the dose of enoxaparin
	>8 hours or if a second protamine dose is needed	0.5 mg protamine for every 1 mg enoxaparin
Dalteparin or tinzaparin in adults	*Not reported*	1 mg protamine for every 100 anti-Xa units of dalteparin or tinzaparin. If aPTT is prolonged 2–4 hours after the first dose or if bleeding continues, consider additional doses of 0.5 mg for each 100 anti-Xa unit
Low-molecular-weight heparin	≤4 hours	The dose of protamine should equal the dose of LMWH. If the aPTT is still prolonged 2–4 hours after the initial dose, may administer a second dose of 0.5 mg protamine per 1 mg LMWH

Each milligram of protamine sulfate neutralizes not less than 100 units of heparin. Doses should not exceed 50 mg. Since heparin is rapidly cleared from the circulation, the dose of protamine required decreased with the time elapsed following heparin administration

Adapted from Refs. [143–153]

in patients with acquired hemophilia [153, 154], perioperative management in hemophilia patients with inhibitors, life-threatening bleeding associated with dabigatran use [155–161], life-threatening bleeding associated with rivaroxaban use [162], reversal of warfarin-related bleeding [163], and refractory bleeding management in cardiac surgery [164].

Pediatric

Anti-inhibitor coagulant complex is utilized in pediatrics for control and prevention of bleeding episodes in hemophilia patients with inhibitors [152], prevention of bleeding episodes in factor X deficiency [165], and hemothorax in children with congenital coagulopathy [166].

Adverse Effects and Monitoring Parameters

Thrombotic and thromboembolic events can occur following anti-inhibitor coagulant complex use, especially with doses ≥100 units/kg. Therefore, caution is advised in patients with atherosclerotic disease, crush injury, septicemia, or concomitant treatment with rFVIIa or antifibrinolytics due to increased risk of developing thrombotic events from circulating tissue factor or predisposing coagulopathy. Monitoring parameters include signs of symptoms of DIC, hemoglobin, and hematocrit. Of note, aPTT and thromboelastography (TEG) should not be utilized to monitor response; DIC can occur when practitioners attempt normalize these values with anti-inhibitor coagulant complex [152] (Table 42.16).

Recombinant von Willebrand Factor (Vonvendi™)

Recombinant VWF(rVWF) is used in patients with VWD or bleeding associated with VWD [167]. The recombinant product does not have factor VIII included in the product and can be used in patients when VWF needs to be replaced, but factor VIII does not need to be replaced. VWF promotes platelet adhesion to damaged vascular tissues and acts a stabilizing protein for factor VIII.

Adult and Pediatric Use

rVWF has been used in adults for treatment of VWD, control of bleeding episodes, and perioperative management for bleeding [167, 168]. In general, dosing of rVWF is calculated based upon baseline VWF activity and response to a dose of rVWF. Doses of rVWF range from 20–30 units/kg/dose for minor bleeding to 40–60 units/kg/dose for major bleeding in the perioperative setting to higher doses of 50–80 units/kg/dose for major bleeding [167]. Calculation of dose for perioperative bleeding is based on the formula: [target peak plasma VWF/ristocetin cofactor (RCo) activity – baseline plasma VWF/RCo activity] x (kilograms body weight)/(incremental recovery). The incremental recovery of VWF is determined by VWF/RCo at 30 minutes post-dose – VWF/RCo at baseline (units/dL)/Dose (units/kg).There are no pediatric data for the use of rVWF (Table 42.17).

Table 42.16 Anti-inhibitor coagulant complex dosing

Indication	Dose, frequency, and duration
Joint hemorrhage in adult and pediatric hemophilia patients with inhibitors	50–100 units/kg IV every 12 hours until pain improves (max 200 units/kg/day)
Mucous membrane bleeding in adult and pediatric hemophilia patients inhibitors	50–100 units/kg IV every 6 hours for at least 1 day or until bleeding resolves (max 200 units/kg/day)
Soft tissue bleeding and other severe bleeding in adult and pediatric hemophilia patients with inhibitors	100 units/kg IV every 12 hours until bleeding resolves (max 200 units/kg/day)
Moderate to severe bleeding in adults due to acquired hemophilia	50–100 units/kg IV every 8–12 hours until bleeding resolves
Perioperative management in adult and pediatric hemophilia patients with inhibitors	50–100 units/kg IV administered immediately preoperative then 50–100 units/kg IV every 6–12 hours until bleeding resolved and healing achieved (max 200 units/kg/day)
Routine prophylaxis in adults and pediatric hemophilia patients with inhibitors	85 units/kg IV every other day
Life-threatening bleeding associated with dabigatran use in adults	25–100 units/kg IV
Life-threatening bleeding associated with rivaroxaban use in adults	30 units/kg IV
Prevention of bleeding episodes in pediatric patients with factor X deficiency	74 units/kg IV once weekly *This therapy should be individually tailored to each patient*
Reversal of warfarin-related bleeding in adults	INR <5: 500 units IV INR ≥5: 1000 units IV Intravenous vitamin K also administered concomitantly
Refractory bleeding management in adult patients undergoing cardiac surgery	1225 units IV.
Hemothorax in children with coagulopathy	100 units/kg IV every12 hours for 3 days, then 100 units/kg IV every 24 hours for 4 days

Adapted from Refs. [156–170]

Adverse Effects and Monitoring Parameters

Goal VWF plasma activity for control of bleeding after minor surgery is 50–60 units/dL for peak and maintained at >30 units/dL as a trough. For control of bleeding after major surgery, peak plasma concentrations should be maintained at 100 units/dL and trough concentrations >50 units/dL [167]. Adverse events are infrequent and include thrombosis, pruritus, nausea and vomiting, and anaphylaxis [167].

Table 42.17 Vonvendi dosing

Indication	Dose, frequency, and duration
Minor hemorrhage	Initial, 40–50 units/kg; maintenance dose, 40–50 units/kg every 8–24 hours based on location and extent of bleeding
Major hemorrhage	Initial, 50–80 units/kg; maintenance dose, 40–60 units/kg every 8–24 hours for 48–72 hours based on location and extent of bleeding
Perioperative management: Elective surgery:	Assess VWF activity 12–24 hours before surgery and administer rVWF at that time to allow endogenous FVIII/C activity to increase to ≥30 units/dL for minor surgery or ≥60 units/dL for major surgery. Dosing of rVWF ranges 20–60 units/kg/dose
Perioperative management: Emergency surgery:	Baseline VWF/RCo and FVIII/C activity should be assessed within 3 hours prior to initiating the surgical procedure if feasible. The loading dose (1 hour preoperative dose) can be calculated as the difference in the target peak and baseline plasma VWF/RCo activity divided by the incremental recovery. If the incremental recovery is not available, assume 2 units/dL per units/kg. Dosing of rVWF ranges 20–60 units/kg/dose

Antidotes to Anticoagulant Medications

A cause of bleeding can be adverse events or over dosages of anticoagulant medications. In addition to or in lieu of blood product administration, the use of medications mentioned previously in this chapter can be used to treat bleeding secondary to anticoagulant medications. There are also medications that are specifically used to treat bleeding based upon the anticoagulant used.

Warfarin inhibits vitamin K epoxide reductase which results in the reductions of circulating vitamin K-dependent clotting factors, factor II, factor VII, factor IX, and factor X. Bleeding related to warfarin can be treated with vitamin K, either enterally or intravenously, depending on the severity and risk of bleeding. Intravenous vitamin K should be administered slowly and cautiously due to the risk of anaphylaxis [121, 124]. Warfarin-related bleeding can also be treated with prothrombin complex concentrate (Kcentra™) or anti-inhibitor coagulant complexes (Feiba NF™) [163, 167]. rFVIIa (NovoSeven™) can also be used to treat warfarin-related intracranial hemorrhage (ICH) [71].

Unfractionated heparin (UFH) effect can be reversed using protamine. The amount of protamine administered is based upon the amount of UFH administered and the time from discontinuation of UFH [143]. Overdose of protamine can result in anticoagulation; therefore, accurate dosing is important [144]. Recombinant factor VIIa (NovoSeven™) has also been used to reverse UFH effect in patients who

have undergone surgical procedures [34, 78, 81]. Enoxaparin effect can also be reversed using protamine [144].

Fondaparinux is a factor Xa inhibitor that has no specific antidote. Reports have suggested efficacy of prothrombin complex concentrate (Kcentra™) or anti-inhibitor coagulant complexes (Feiba NF™) [170]. rFVIIa (NovoSeven™) is an option for treatment of life-threatening bleeding.

Bivalirudin and argatroban and direct thrombin inhibitors that have short half-lives. The primary method for treating bleeding is discontinuation of the infusion, and the effects of the medication will cease rapidly. Anti-inhibitor coagulant complex (Feiba NF™) can be used to treat bleeding caused by these medications, though data are limited, and hemodialysis will remove 20–25% of the medication.

Rivaroxaban and apixaban are oral factor Xa inhibitors that can be reversed with intravenous andexanet alfa (Andexxa™) [171]. Prior to approval of andexanet alfa (Andexxa™), prothrombin complex concentrate (Kcentra™), anti-inhibitor coagulant complex (Feiba NF™), and recombinant factor VIIa (NovoSeven™) have been used to treat life-threatening bleeding from oral factor Xa inhibitors [172, 173].

Dabigatran is an oral direct thrombin inhibitor that can be reversed with idarucizumab (Praxbind™) [174]. Prior to use of and approval of idarucizumab (Praxbind™), Anti-inhibitor coagulant complex (Feiba NF™) has been used to treat life-threatening bleeding from dabigatran [155] (Table 42.18).

Table 42.18 Medications used in the treatment of anticoagulant overdose

Medication	Pharmacokinetics of overdose medication	Treatment of overdose	Notes
Warfarin	Inhibition of vitamin K epoxide reductase, resulting in decreased generation of factors II, VII, IX, and X Half-life: 2–5 days Elimination: primarily urine (92% as metabolites)	Vitamin K (oral or injectable), prothrombin complex concentrate (Kcentra™)	Slow intravenous infusion rates with vitamin K to prevent anaphylaxis
Unfractionated Heparin	Accelerates action of antithrombin to inactivate thrombin (factor IIa) and factor Xa Half-life: 1–2 hours Elimination: nonrenal mechanisms	Protamine	Excess Protamine can result in anticoagulation
Enoxaparin	Factor Xa inhibitor Half-life: 4.5–7 hours Elimination: 40% excreted in the urine unchanged	Protamine	Excess Protamine can result in anticoagulation
Fondaparinux	Factor Xa inhibitor Half-life: 17–21 hours Elimination: 77% excreted in the urine unchanged	Prothrombin complex concentrate (Kcentra™), anti-inhibitor coagulant complex (Feiba NF™), recombinant activated factor VII (NovoSeven™)	
Bivalirudin	Direct thrombin inhibitor Half-life: 25 minutes for adults, 20 minutes for infant, and 15 minutes for newborns Elimination: primarily urine (~20% unchanged drug)	Anti-inhibitor coagulant complex (Feiba NF™)	Discontinuation of infusion should reverse anticoagulant effects rapidly due to short half-life. Hemodialysis has been used to treat overdose (~25% removed over 4 hours)
Argatroban	Direct thrombin inhibitor Half-life: 39–51 minutes Elimination: primarily feces (~16% unchanged drug in urine)	Anti-inhibitor coagulant complex (Feiba NF™)	Discontinuation of infusion should reverse anticoagulant effects rapidly due to short half-life. Hemodialysis has been used to treat overdose (20% removed over 4 hours)
Rivaroxaban	Factor Xa inhibitor, oral Half-life: 5–9 hours Elimination: primarily urine (~36% unchanged drug)	Andexanet alfa (Andexxa™), prothrombin complex concentrate (Kcentra™), anti-inhibitor coagulant complex (Feiba NF™), Recombinant activated factor VII (NovoSeven™)	No laboratory monitoring available to assess efficacy of reversal

(continued)

Table 42.18 (continued)

Medication	Pharmacokinetics of overdose medication	Treatment of overdose	Notes
Dabigatran	Direct thrombin inhibitor, oral Half-life: ~2 hours Elimination: primarily urine (40–50% unchanged drug)	Idarucizumab (Praxbind™), anti-inhibitor coagulant complex (Feiba NF™)	Hemodialysis has been used to treat overdose (50–60% removed over 4 hours). No laboratory monitoring available to assess efficacy of reversal
Apixaban	Factor Xa inhibitor, oral Half-life: ~12 hours Elimination: primarily urine (~27% unchanged)	Andexanet alfa (Andexxa™), prothrombin complex concentrate (Kcentra™, Feiba NF™), recombinant activated factor VII	No laboratory monitoring available to assess efficacy of reversal

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Blood Components

43

Lisa Hensch

Red Blood Cells

Etiology of Anemia

Red blood cells (RBCs) are indicated primarily to treat symptomatic anemia. The three primary causes of anemia are decreased or absent bone marrow synthesis, increased destruction (hemolysis), and blood loss. Decreased or absent production of erythrocytes may result from iron deficiency, bone marrow infiltration by malignancy or fibrosis, chemotherapy, decreased erythropoietin production in renal failure, or infection. Hemolysis may be either immune or nonimmune in nature. Causes of intravascular and extravascular hemolysis are listed in Table 43.1. When hemolysis is suspected clinically, a series of laboratory tests may be necessary for confirmation [1]. Laboratory tests used for the identification of hemolysis are listed in Table 43.2. Common causes of acute blood loss include trauma, surgery, obstetrical complications, gastrointestinal hemorrhage, or coagulopathic states, such as disseminated intravascular coagulation and liver disease. Occasionally, patients may present with ongoing anemia, manifested by falling hemoglobin/hematocrit without observation of external bleeding. These patients may require an extensive workup to determine the exact cause of their anemia in order to initiate appropriate treatment.

Table 43.1 Causes of hemolysis

Intravascular hemolysis	Extravascular hemolysis
Incompatible transfusion, especially associated with anti-A, anti-B, anti-Jk[a], or anti-Jk[b]	Membranopathies (hereditary spherocytosis, hereditary elliptocytosis)
Mechanical hemolysis (prosthetic valves, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), march hemoglobinuria)	Hemoglobinopathies (sickle cell disease, thalassemia, hemoglobin C disease)
Complement mediated (paroxysmal cold hemoglobinuria, cold agglutinin syndrome, paroxysmal nocturnal hemoglobinuria)	Metabolic defects (glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency)
Microangiopathic hemolytic anemia (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and others)	Drug induced (penicillin)
Severe autoimmune hemolytic anemia (IgM)	Autoimmune hemolytic anemia (AIHA)
Snake and spider bites	Hypersplenism
Infection (severe malaria, *Clostridium perfringens*, *Babesia*)	Infection (malaria, *Babesia*, *Anaplasma*)
Activated T antigen	Intravenous immunoglobulin
Osmotic hemolysis	
Thermal hemolysis	

Indications

Transfusion of RBCs is indicated in the setting of symptomatic anemia to increase oxygen-carrying capacity. While the use of "transfusion triggers" may help to guide clinical decision-making, the decision to transfuse should be pri-

Table 43.2 Laboratory testing for hemolysis

Lab tests	Hemolysis
Reticulocyte count[a]	Increased
Unconjugated bilirubin	Increased
Haptoglobin	Decreased
Plasma-free hemoglobin	Increased
LDH	Increased. LDH isoenzyme 2
Urinalysis	Hemoglobin positive, RBCs not increased

[a]In the setting of hemolysis, ~15% of adults and children do not show increased reticulocyte counts [2, 3]

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marily based on the clinical status of the patient. Patients with a hemoglobin less than 6 g/dL generally require transfusion, while patients with a hemoglobin greater than 10 g/dL rarely require transfusion [4]. Between these thresholds, transfusion should be considered on a case-by-case basis, with attention paid to symptoms of anemia. Hypotension, tachycardia, tachypnea, angina, and ST segment depression are clinical indicators of symptomatic anemia. In addition, acute blood loss of greater than 20% of circulating volume is an indication for immediate red cell transfusion. RBCs are not indicated solely for volume expansion. RBCs are also required as replacement therapy during red cell exchange for patients with severe symptoms of sickle cell anemia (acute chest syndrome, stroke, or multiple organ failure) or hemolytic disease of the fetus and newborn. Chronic asymptomatic anemia can often be treated with alternative therapies such as iron or erythropoietin, rather than transfusion of RBCs [4]. Transfusion strategies should be aimed at optimizing clinical outcomes while minimizing potential harm [5].

General Features

The volume of a single unit of RBCs is 250–350 mL, depending on the storage media used. This includes 200–250 mL of RBCs, 20–100 mL of plasma [6], and 63–70 mL of anticoagulant [7]. The hematocrit of each unit is between 55 and 65% when AS-1, AS-3, and AS-5 additive solutions are used and is 75–80% in CPDA-1 [8]. Each unit also contains approximately 250 mg of iron [6] (Fig. 43.1).

The storage lesion RBCs age during storage. The changes associated with aging include increased acidity, decreased adenosine 5′-triphosphate, increased extracellular potassium, decreased 2,3-diphosphoglycerate (DPG), and changes to the RBC morphology [9]. The initial pH of a red cell unit is around 7.0; however, glycolysis continues to occur during storage leading to a drop in pH to 6.5 [10]. Decreases in pH facilitate the loss of 2,3-DPG during prolonged storage [11]. This results in a shift of the oxygen dissociation curve in stored blood to the left. 2,3-DPG is restored in transfused red cells 24–72 h after transfusion [12]. Of particular concern in patients who are massively transfused and in the neonatal population, extracellular potassium in RBC units increases from 1 mmol/L to nearly 30 mmol/L after 42 days of storage [13]. This increases the risk for transfusion-associated hyperkalemia. Storage-associated changes in the membrane of the RBCs also make them less deformable, making it more difficult for these RBCs to reach the microvasculature [10]. These changes have led to a number of studies aimed at examining the efficacy and safety of aged RBCs in transfusion.

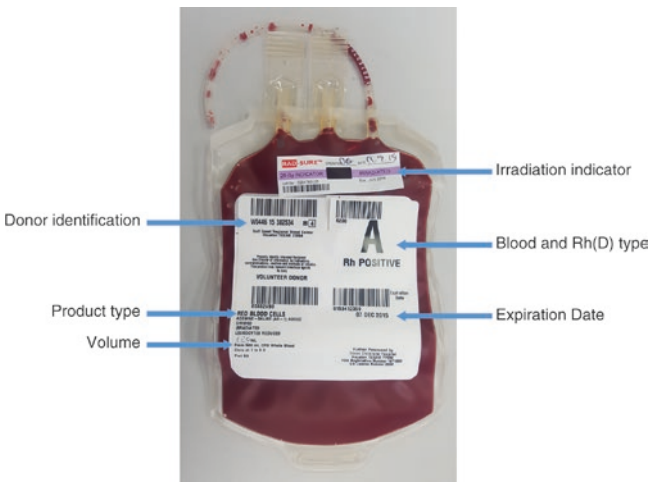

Fig. 43.1 Red blood cell unit

Preparation, Dosage, and Administration

Pretransfusion testing A pretransfusion sample is used for type and screen or type and crossmatch. Appropriate patient identification and collection is vital. Wrong blood in tube events in the blood bank (sample labeled for the wrong patient) have been estimated to be as high as 1:14,606 for all specimens and 1:28 for mislabeled or rejected specimens [14]. Clerical errors remain the primary cause of ABO incompatible transfusions which can cause fatal transfusion reactions. For most patients, a type and screen is valid for 3 days and may be ordered to facilitate faster crossmatching should transfusion become necessary. A type and crossmatch is ordered for blood that will be transfused in the immediate future. The blood bank uses these samples to determine the ABO and Rh type of the patient and to issue ABO-specific or ABO-compatible and Rh-compatible units. Depending on the transfusion history of the patient, an electronic crossmatch, immediate-spin crossmatch, or antihuman globulin crossmatch will be performed. For patients with a negative antibody screen, a type and crossmatch takes approximately 45 min. Should the patient have a positive antibody screen on initial testing, an extended panel of cells will need to be tested. Clinicians should be aware that acquiring and releasing units for patients with antibodies may require several hours to several days depending on the number of antibodies and frequency of the corresponding antigen(s) in the donor population.

Dosage In patients who do not have ongoing bleeding, RBCs should be transfused one unit at a time followed by an assessment of clinical response [15]. In adults who are not actively bleeding, one unit of RBCs is expected to increase the hematocrit by 3% or 1 g/dL increase in hemoglobin [6].

In the pediatric and neonatal populations, dosing is 10–15 mL/kg. This dose is expected to increase the hemoglobin by 2–3 g/dL [16].

Administration In non-emergent situations, blood should only be transfused with a clinical transfusion order from a licensed care provider and with the patient's informed consent [17]. RBCs are transfused through a 170–260 μm filter to remove clots and macroaggregates [17]. The use of a blood warmer is encouraged, especially in those patients receiving rapid transfusions. Once the unit has been spiked, the transfusion must be completed within 4 h due to the increasing risk of bacterial contamination. If a transfusion reaction is suspected, the current transfusion should be immediately suspended, and all transfusions should be discontinued until the blood bank has confirmed the reaction is not a hemolytic transfusion reaction. In the setting of a mild allergic reaction such as hives or itching that resolves immediately with the administration of diphenhydramine, the transfusion may continue. Adverse reactions associated with transfusion will be discussed later in this chapter. Finally, RBCs should only be transfused in the same IV line with 0.9% normal saline, ABO-compatible plasma, 5% albumin, or other FDA-approved product [17]. Transfusion with solutions containing dextrose can be associated with hemolysis, while the calcium in Ringer's lactate may lead to clotting [18]. Some studies have reported that infusion with Ringer's lactate is safe in rapid transfusion settings [19, 20]; however, this is not a universally accepted practice [18].

Alternatives to Allogeneic Red Cell Transfusion

Whole blood Until the development of component therapy, whole blood was the mainstay of transfusion medicine. Today, the use of whole blood occurs primarily in military operations [21, 22]. The switch to component therapy had the unintended consequence of allowing patients, particularly those with massive hemorrhage, to be transfused in component ratios that are not equivalent to that of whole blood which contributes to dilutional coagulopathy and ongoing hemorrhage. Many adult trauma services have now adopted practices based on damage control resuscitation. An important part of damage control resuscitation is transfusing patients with component ratios that approximate whole blood [23]. As a result, attention has shifted towards the use of whole blood in trauma. A perceived limitation of whole blood in this setting is that whole blood should ideally be an exact match to the recipient's blood type. Unfortunately, in the setting of acute trauma, this information is not always available. This has led to the utilization of cold-stored "low titer" group O whole blood or units where the anti-A and anti-B titers are below the institutional cutoff (acceptable titer varies among institutions, i.e., <100 [24] or <50 [25]). A study in the civilian trauma setting reported no clinical or laboratory evidence of hemolysis in patients receiving up to four units of uncrossmatched low-titer (anti-A and anti-B) type O Rh-positive whole blood [25]. A second study reported similar clinical outcomes to patients treated with conventional therapy [26]. Transfusion of up to 20 mL/kg in pediatric patients without adverse events has also been described [27]. Patients receiving cold-stored whole blood may also benefit from the increased hemostatic effects of cold-stored platelets discussed below. Fresh whole blood (<2 days from collection) has also been used in the setting of pediatric craniofacial surgery [28] and pediatric cardiac surgery [29, 30].

Autologous whole blood Preoperative autologous donation is an option for patients undergoing elective surgical procedures. The collection of autologous units is most advantageous for patients with rare blood types, multiple alloantibodies, or IgA deficiency. Units may additionally be frozen to extend the storage time in these select populations. In other patients, autologous donation offers little benefit and, if not appropriately managed, increases the risk for preoperative anemia [31]. Requirements for autologous donation are not as stringent as those governing volunteer donation, and as such, these units cannot be transitioned into the general inventory of components if left unused.

Acute normovolemic hemodilution (ANH) ANH is achieved by removal of whole blood and dilution with crystalloid or colloid solutions. ANH is optimally reserved for patients with expected blood loss of greater than 1500 mL [32]. These units are stored in citrate solution and, at room temperature, can be held for up to 8 h [32]. Units are transfused back to the patient in the reverse order of collection, thus using the more dilute units first, while continued surgical bleeding is expected, and saving the units with the highest hematocrit for last. Since blood lost during the surgical procedure has a lower hematocrit from hemodilution, the net RBC mass loss is reduced [32]. ANH is associated with fewer allogeneic red cell, platelet, and plasma transfusions as well as improved outcomes [33]. This therapy may be combined with preoperative iron therapy to achieve a higher starting hematocrit. Of note, concerns over increased bleeding tendency due to lower hematocrit caused by ANH have yet to be resolved.

Cell salvage During cell salvage, blood from the operating field is collected in a reservoir, washed, and ultimately transfused back to the patient [32]. It is important to remember that this blood may be contaminated with inflammatory mediators, debris from the surgical field, and lysed red cells. There are general contraindications for use in oncologic procedures and procedures with contaminated

fields. Cell salvage has proven efficacious to reduce the requirement for allogeneic transfusion in orthopedic and cardiovascular procedures where greater than 1 L of blood loss is expected [34].

Special Situations

Emergency release In emergent situations, blood may need to be released before typing and crossmatching can occur. Often, group O Rh-negative RBCs are transfused to female patients of childbearing age, and either group O Rh-negative or Rh-positive RBCs are transfused to male patients. If the age of the female patient is not known, clinical judgment is required. In addition, for female patients requiring large numbers of RBC units, the decision may also be made to switch to Rh-positive RBCs. These decisions are often based on blood bank inventory of group O Rh-negative RBCs and the transfusion requirements for the patient. Each hospital blood bank should have a policy regarding when to consider switching to Rh-positive RBCs in Rh-negative patients. Before transfusion of any unit, a sample should be obtained for type and crossmatch. Once ABO and Rh are confirmed, RBCs and other blood components can be switched to ABO- and Rh-compatible blood components. Some studies show that the sensitization of Rh is not high in acutely bleeding patients with hemorrhagic shock when Rh-positive RBCs are transfused to Rh-negative patients [15].

Sickle cell disease Patients with sickle cell disease require frequent RBC transfusions and are at high risk of forming alloantibodies. The development of alloantibodies makes it more difficult to find crossmatch-compatible blood and puts these patients at risk of having hemolytic transfusion reactions, especially in emergent situations. In one center, the practice of phenotype matching sickle cell patients for Rh (DCE), K, Kidd, and Duffy A has been shown to reduce the likelihood of alloimmunization [35]. In 2010, 83% of institutions surveyed provided some degree of phenotype-matched red cells, yet alloimmunization rates remain high [36]. Whenever possible, transfusion services should provide Rh (DCE)- and K-compatible units for patients with sickle cell disease [37]. In patients who have already developed RBC antibodies, extended phenotype matching for antigens such as Kidd, Duffy, and S should be strongly considered. Units for patients with sickle cell disease should also be hemoglobin S negative. In emergent settings with massive bleeding, it may become necessary to transfuse patients with units that are not phenotype matched.

Platelets

Thrombocytopenia and Platelet Dysfunction

Platelets are responsible for primary hemostasis. Inadequate number or function of platelets can have significant consequences for the patient. Mucocutaneous bleeding, such as petechiae, purpura, ecchymosis, epistaxis, or gum bleeding are the common manifestations of platelet dysfunction/deficiency. Common causes of thrombocytopenia are listed in Table 43.3. Platelet dysfunction may be seen in the setting of renal disease (uremic thrombocytopathy), various medications (aspirin, clopidogrel, ticlopidine, dipyridamole, etc.), mechanical intervention (cardiac bypass, extracorporeal membrane oxygenation (ECMO), ventricular assist devices), and congenital diseases (Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc.).

Indications

Platelet transfusion is indicated when the patient has thrombocytopenia or platelet function defect. Platelet transfusions in the consumptive disorders heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura (TTP) are generally contraindicated due to the risk of arterial thrombosis and increased mortality rates [38]. Platelets are also not indicated in stable patients with idiopathic thrombocytopenic purpura (ITP), as they are rapidly cleared by the immune system and therefore offer little benefit [4]. Generally accepted thresholds for platelet transfusion are listed in Table 43.4.

Table 43.3 Causes of thrombocytopenia

Causes of thrombocytopenia
Splenomegaly
Disseminated intravascular coagulation (DIC)
Dilutional thrombocytopenia
Heparin-induced thrombocytopenia (HIT)
Hematologic malignancy
Chemotherapy
Hemolysis, elevated liver enzymes, low platelets (HELLP)
Idiopathic thrombocytopenic purpura (ITP)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Infection

Table 43.4 Thresholds for platelet transfusion

Indication	Platelet count (per mm^3)
Bleeding prophylaxis	>10,000
Bleeding prophylaxis in sepsis/DIC	>20,000
Active bleeding or planned invasive procedure	>50,000
Pulmonary hemorrhage, central nervous system bleeding, ophthalmic hemorrhage, neurosurgical procedure	>100,000

General Features

There are two general types of platelet products: whole blood-derived and apheresis platelets. Whole blood-derived platelets are obtained by separating platelet-rich plasma from RBCs by a soft spin. Platelets are then separated from plasma using a second centrifugation step, resulting in platelets suspended in approximately 40–70 mL of plasma [7]. AABB standards state that these units must have greater than 5.5×10^{10} platelets remaining at the end of the 5-day shelf life [8]. Platelets may also be collected from a single donor by apheresis. At the end of storage, these units must contain greater than 3.0×10^{11} platelets [8]. Platelets are stored at room temperature with constant gentle agitation. Studies have shown that platelets can maintain function after interruption in agitation of up to 24–30 h [39, 40]. Previously, platelets expired after 5 days as a result of the risks for bacterial contamination, but the Food and Drug Administration (FDA) has approved an expiration of 7 days with additional bacterial testing or pathogen inactivation strategies which is now used by some blood banks. When whole blood-derived platelets are pooled for transfusion, the new expiration time becomes 4 h from the time of pooling (Fig. 43.2).

Fig. 43.2 Apheresis platelets

Pathogen inactivated platelets Pathogen inactivated platelets have been available in Europe for a number of years. This process mitigates some of the risks associated with transfusion by targeting gram-positive and gram-negative bacteria, viruses, and parasites [41]. In the United States, only one reduction method is currently FDA approved. In the INTERCEPT™ system, a photosensitive psoralen (amotosalen) is added to platelet components and then illuminated with long-wavelength ultraviolet light (UVA) leading to intercalation of the psoralen in RNA and DNA. This causes crosslinking of RNA and DNA, blocking repair and replication [41, 42]. Leukocytes are also inactivated by the same process, leading to reduced risk of developing transfusion associated graft vs. host disease and reduced transmission of intracellular pathogens such as cytomegalovirus and Epstein-Barr virus [43]. Analyses have shown that pathogen inactivated platelets are associated with decreased 24-hour corrected count increments (CCI) and increased platelet refractoriness [44]. However, compared to conventional platelets, pathogen-inactivated platelets have similar hemostatic efficacy without an increase in serious adverse events [44, 45]. Pathogen-inactivated platelets are likely to see increasing use in the United States given the substantial benefits of inactivation of pathogens and leukocytes in blood components.

Cold-stored platelets Cold storage of platelets was largely abandoned years ago in light of the finding that cold-stored platelets had shortened in vivo lifespans compared to those stored at room temperature (22 °C) [46]. However, storage at room temperature increases the risk of bacterial contamination. The room temperature platelets also develop a "storage lesion" leading to increased lactic acid, loss of discoid shape, degranulation, and impaired aggregation [47]. This has led to renewed interest in cold-storage of platelets. Research suggests that cold-stored platelets are more "activated" and may have superior hemostatic effects when compared to room temperature platelets [48]. Enhanced clot strength is at least partially attributed to factor XIII binding to platelet surfaces during cold-storage leading to an increase in fibrin-crosslinking [49]. Researchers suggest that the enhanced hemostatic properties of cold-stored platelets make them ideal for hemorrhaging patients [47]. Currently this product is not routinely available but may see increased utilization in the future.

Pretransfusion Testing

Prior to platelet transfusion, the recipient's ABO and Rh type should be determined. However, platelets have very few contaminating RBCs. ABO-identical or Rh-identical units are preferred, but not required. Platelets are suspended in plasma and can contain significant titers of anti-A and anti-B. Therefore, it is of greater importance that transfused plasma is compatible with the recipient's RBCs to minimize the potential for hemolysis. Each institution should have a policy regarding the maximum volume of ABO-incompatible platelet transfusions per day, such as one apheresis platelet unit per day in adults and/or 5 mL/kg per day in pediatric patients.

Dosage

In most institutions, one dose of platelets in an adult consists of one apheresis unit of platelets or 4–6 pooled whole blood-derived platelet units. This dose is expected to increase the platelet count by 30,000–60,000/mm^3. In the pediatric setting, one dose is considered to be 5–10 mL/kg in infants and neonates and 1 unit per 10 kg in older children [16]. It is important to assess for adequate platelet increment. A sample for testing should be obtained 10–60 min after transfusion. The CCI can be used to determine if the patient has had an adequate response to transfusion. A CCI of less than 5000 on two occasions [50] or a percent platelet recovery of <30% [51] may indicate platelet refractoriness. These calculations are given in Table 43.5.

Table 43.5 Determination of platelet refractoriness

Calculations to determine platelet refractoriness
Platelet increment
Posttransfusion platelet count – pretransfusion platelet count
Corrected count increment
$\frac{\text{Platelet increment} \times \text{body surface area}}{\text{Number of platelets transfused} \times 10^{11}}$
Percent platelet recovery
$\frac{\text{Platelet increment} \times \text{weight}(\text{kg}) \times 75\,\text{mL/kg} \times 100\%}{\text{Number of platelets transfused} \times 10^{11}}$

Platelet Refractoriness

When a patient has a poor response to platelet transfusion, the underlying cause needs to be determined. Platelet refractoriness occurs in up to 15% of patients receiving chronic platelet transfusions [52]. The etiology may be nonimmune or immune in nature. Nonimmune causes include splenomegaly, infection, DIC, medications (amphotericin), hematopoietic stem cell transplants, and ongoing bleeding. Human leukocyte antigens (HLAs), human platelet antigens (HPAs), drugs, and ABO antibodies comprise the immune causes of platelet refractoriness. Various strategies can be employed to identify the cause of immune-related platelet refractoriness. First, any patient with suspected platelet refractoriness should be transfused with ABO-identical platelets. If further workup is warranted, tests for HLA and HPA causes of platelet refractoriness include the lymphocytotoxicity assay, platelet and lymphocyte immunofluorescence tests, ELISA, solid-phase red cell agglutination assays, and multiplex flow cytometric bead-based assays. There is currently no gold standard, and ELISA is generally employed as a screening method [53]. When an HLA or HPA antibody is identified, patients can be managed with HLA- or HPA-matched platelets to help achieve adequate platelet recovery [54]. However, obtaining matched platelets can be time-consuming and costly. Platelet crossmatching can also be used to find compatible platelets for transfusion and has been shown to significantly improve the CCI [55] and subsequently reduce the need for transfusion. Additionally, the use of intravenous immune globulin has been shown to improve response to random donor platelet transfusions in refractory patients [56].

Administration

Platelets should be administered through a 170–260 μm filter. They can be infused at 2–5 mL per minute for the first 5 min and then up to 300 mL/h, as tolerated, thereafter [17]. Transfusion through a blood warmer has traditionally been

discouraged; however, newer studies indicate that warming platelets may improve recovery and have no deleterious effects on function [57].

Plasma

The utility of plasma was largely discovered during the resuscitation of injured soldiers during World War II. Though plasma contains mostly water, it is an essential component of hemotherapy as a source of all clotting factors. Acquired factor deficiency may result from massive hemorrhage, DIC, dilutional coagulopathy, liver disease, vitamin K deficiency, and warfarin therapy. In addition, the use of plasma is vital in the setting of thrombotic thrombocytopenic purpura for plasma exchange therapy and for other indications for plasma exchange.

Indications

Massive Transfusion and Dilutional Coagulopathy

Plasma should be used early in trauma resuscitation to prevent the onset on dilutional coagulopathy. Features and consequences of massive transfusion are discussed later in this chapter.

Liver Disease

Liver disease results in a complex derangement of the clotting system. The synthetic function of the liver is compromised, resulting in a decrease in all coagulation factors synthesized by the liver, as well as decreased synthesis of procoagulants [58]. In fact, some studies show that the reductions in natural anticoagulants such as protein C and antithrombin are more significant than the reduction in clotting factors [59]. This makes the international normalized ratio (INR) a poor predictor of bleeding risk. Despite this, patients with liver disease still have a significant risk for bleeding due to portal hypertension and, in severe cases, hyperfibrinolysis. Deficiency of clotting factors can complicate gastrointestinal bleeding and therapeutic procedures in this population. For these reasons, transfusion of plasma is sometimes indicated, particularly when the patient is already bleeding. However, while a dose of plasma may significantly reduce a highly elevated INR, the same effect is not seen when the INR is only minimally elevated [60, 61]. Plasma transfusion simply to correct a minimally elevated INR is not indicated. (See Chapter 14, for additional information regarding liver disease.)

Disseminated Intravascular Coagulation (DIC)

DIC results in deficiency of clotting factors by consumption due to continuous thrombin formation. Low levels of both platelets and clotting factors increase the risk for bleeding in these patients. In patients who have active bleeding or require a procedure, plasma transfusion is recommended by the International Society on Thrombosis and Hemostasis if the INR is >1.5 or fibrinogen is less than 150 mg/dL [62]. High doses of plasma, up to 30 mL/kg, are sometimes used to treat bleeding patients with DIC, though some studies indicate that this practice does not significantly increase in vivo clotting factors over standard dosing [63].

Vitamin K Deficiency

Vitamin K deficiency results in decreased production of the vitamin K-dependent proteins including factors II, VII, IX, and X, as well as proteins C and S. Vitamin K deficiency may result from poor nutrition, prolonged antibiotic therapy, or warfarin use. Nonbleeding patients with supratherapeutic INRs may be treated with vitamin K. IV vitamin K will result in faster correction of a supratherapeutic INR than oral vitamin K. For patients requiring warfarin reversal who present with life-threatening bleeding, Kcentra™, an FDA-approved prothrombin complex concentrate, should be administered [64]. If Kcentra™ is not available for reversal, plasma may be used. (See Chapter 18, for additional information regarding vitamin K deficiency and Chapter 42, for additional information about Kcentra™.)

Plasma Exchange

TTP is a category I indication for plasma exchange [65]. Even if a patient with TTP is actively bleeding, platelets should not be given due to the potential risk for exacerbating TTP [38]. These patients require both replacement of ADAMTS13 (found in plasma) and removal of its inhibitor. Furthermore, plasma may be used to replace clotting factors, specifically fibrinogen, in patients who require daily plasma exchange using albumin as a replacement fluid. Additional information regarding the indications for therapeutic apheresis can be found in the American Society for Apheresis Guidelines [65].

General Features

Plasma may be separated from whole blood by centrifugation or collected by plasmapheresis. Plasma components that are separated from whole blood have a volume of approximately 200 mL. Plasma units obtained by apheresis are commonly referred to as "jumbo" units and are generally 400–600 mL [6] but may have volumes up to 500–800 mL [7]. FFP is expected to contain 1 IU/mL of each clotting factor (Fig. 43.3).

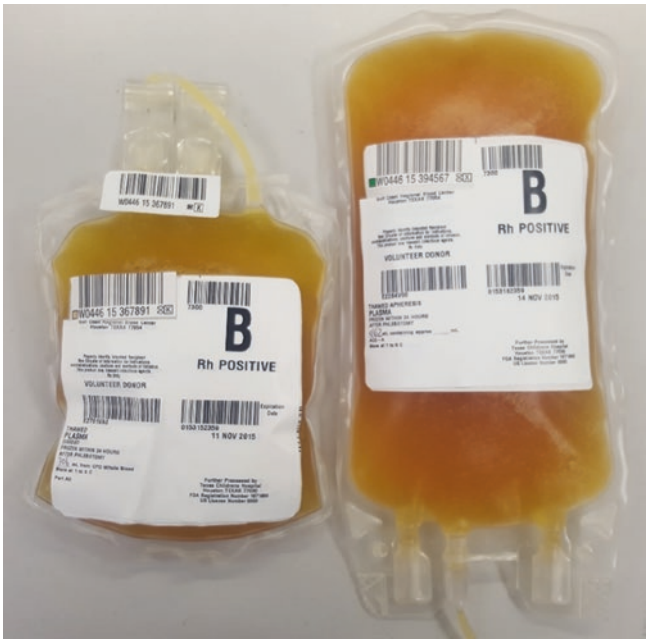

Fig. 43.3 Thawed plasma, whole blood derived (left) vs. apheresis (right)

Types of Plasma

Fresh frozen plasma, thawed plasma, and PF24 (plasma frozen within 24 h after phlebotomy) Fresh frozen plasma is derived from plasma separated from whole blood and frozen within 8 h of collection. After thawing, it remains fresh frozen plasma for 24 h. From 24 h after thawing until 5 days, it is called thawed plasma. PF24 is derived from plasma separated from whole blood and frozen after 8 h and within 24 h of collection. Due to the availability, many blood banks give FFP, thawed plasma, and PF24 the same name. Therefore, clinicians may not notice the difference. Thawed plasma has decreased, though still therapeutic, amounts of factors V and VIII [66].

Liquid plasma After liquid plasma is separated from the cellular components (red cells and platelets), it is stored at 1–6 °C rather than frozen. The shelf life of liquid plasma is 5 days after expiration of whole blood. If the whole blood is collected in CPD, the shelf life is 26 days, and if the whole blood is collected in CPDA-1, it is 40 days. Data show that 50% of all factor levels are present until 15 days after collection. There are significant decreases in factor V, factor VII, factor VIII, von Willebrand factor, and protein S levels [67]. However, a separate study showed liquid plasma had better hemostatic ability than thawed plasma when evaluated by thromboelastography and thrombin generation assay [68].

Pretransfusion Testing

Plasma may contain significant amounts of anti-A and/or anti-B antibodies unless collected from a group AB donor. Therefore, plasma should be compatible with the recipient's red cells.

Dosage

The usual dose of plasma in adult patients is 10–20 mL/kg and should result in a 20% increase in coagulation factors [4]. If plasma is being transfused in preparation for a procedure, it is important to be cognizant of the half-lives of the clotting factors in vivo. Table 43.6 gives the approximate half-life of each factor. Factor VII has the shortest half-life (3–6 hours). It is, therefore, recommended that plasma not be transfused until within ≤4 hours of any planned procedure.

Administration

While many institutions keep thawed or liquid plasma on hand, oftentimes plasma must be thawed prior to transfusion, a process which can take up to 30 min. Plasma should be administered at 2–5 mL/min for the first 5 min and can be given at 300 mL/h thereafter, or as rapidly as tolerated [17]. Plasma is transfused through a 170–260 μm filter.

Cryoprecipitate

General Features

Cryoprecipitate is produced from human plasma. When frozen plasma is thawed to 1–6 °C, the precipitate that forms is composed of fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin. The precipitate is then refrozen

Table 43.6 Factor half-lives

Clotting factor	Half-life in hours
Fibrinogen	72–120
Prothrombin	72
Factor V	36
Factor VII	3–6
Factor VIII	12
Factor IX	24
Factor X	40
Factor XI	80
Factor XII	60
Factor XIII	120–200

Adapted from Bolliger et al. [69]

Fig. 43.4 Cryoprecipitate, single-unit (left) vs. five-unit pool (right)

and must be thawed at 30–37 °C prior to use. Each unit of cryoprecipitate contains approximately 250 mg of fibrinogen and 150 units of factor VIII [70], though the FDA mandates each unit have 150 mg of fibrinogen and 80 IU of factor VIII. The volumes of cryoprecipitate units vary, as there is no regulation regarding volume [7], but in general, one unit is approximately 15 mL [17]. In the pediatric setting, it may be appropriate to use single units of cryoprecipitate; however, for adults, cryoprecipitate is frequently made into five-unit pools (Fig. 43.4).

Indications

Hypofibrinogenemia Currently, the primary use of cryoprecipitate is to treat congenital or acquired hypofibrinogenemia or dysfibrinogenemia. Acquired hypofibrinogenemia most frequently results from situations associated with massive bleeding including trauma, cardiac surgery, liver disease, and obstetrics. Acquired hypofibrinogenemia also results from consumptive coagulopathies, such as DIC. Transfusion thresholds for cryoprecipitate are dependent on the patient's underlying condition. For example, trauma patients should have >150–200 mg/dL [71], and obstetric patients should have >300 mg/dL of fibrinogen at the time of delivery [72].

Factor XIII deficiency Congenital factor XIII deficiency is a rare disease that is associated with a lifelong bleeding tendency and abnormal wound healing [73]. It is not frequently detected on routine tests of coagulation, such as the prothrombin time (PT) or partial thromboplastin time (PTT). Although clot solubility testing has traditionally been used as a screening test for factor XIII deficiency, it is not a sensitive test. ELISA methods for testing the A subunit are now available [74] and are preferred. In the United States, factor XIII deficiency can be treated with Tretten™, an FDA-approved recombinant factor XIII, or Fibrogammin™, a factor XIII concentrate. Cryoprecipitate or plasma may be considered in emergency situations when this recombinant factor or factor concentrate is not available.

Hemophilia A and von Willebrand disease (VWD) Historically, cryoprecipitate was used to treat both hemophilia A and VWD. Cryoprecipitate is no longer used to treat hemophilia A because recombinant factor VIII is readily available. Likewise, it is not used to treat von Willebrand disease as von Willebrand factor (Vonvendi™) and von Willebrand factor/factor VIII concentrates (Humate-P™, Alphanate™, Wilate™, etc.) are available. These products offer the benefits of having a consistent factor concentration and lack the inherent risks of transfusion, such as transfusion-transmitted infection, associated with cryoprecipitate. Cryoprecipitate may be considered in emergency situations in which no virus-inactivated factor concentrate is available.

Uremia Cryoprecipitate has been shown to decrease bleeding associated with uremia [75], though it appears that the response is variable [76] (see Chapter 19).

Pretransfusion Testing

ABO compatibility and crossmatching are not required for cryoprecipitate units.

Dosage

In most settings, a single "dose" of cryoprecipitate for an adult is composed of a five- to ten-unit pool of cryoprecipitate. A more exact calculation of the appropriate dose is shown below in Table 43.7.

Administration

Cryoprecipitate is administered through a 170–260 μm filter as rapidly as tolerated [17].

Table 43.7 Calculation for cryoprecipitate dosing

Dose of cryoprecipitate
Plasma Volume (PV)
(70 ml/kg × weight (kg)) × (1-hematocrit/100)
Cryoprecipitate units
$\frac{\left(\text{target fibrinogen}\ (\text{mg/dL}) - \text{initial fibrinogen}\ (\text{mg/dL})\right) \div 100\ \text{mL/dL} \times \text{PV}}{250\ \text{mg/dL}}$

Massive Transfusion

Massive transfusion is traditionally defined as >10 units of RBCs transfused within 24 h [77]. Other definitions include transfusion of >4 units of RBCs in 1 h with continued need for blood components or replacement of >50% of the total blood volume by blood products within 3 h [78]. While massive transfusion protocols were developed for trauma in military settings, they are now commonly used in the setting of civilian trauma, obstetrics, gastrointestinal hemorrhage, cardiac surgery, spinal surgery, and liver transplantation [78]. Transfusion strategies have been developed to diminish the effects of dilutional coagulopathy associated with massive transfusion of RBCs and crystalloids. In acute trauma, patients may present with coagulopathy prior to transfusion, and those who present with an INR >1.5 have increased mortality [79]. Early support with FFP improves survival in these patients [80]. A large, randomized controlled trial found that a transfusion ratio of 1:1:1 for plasma, platelets, and red cells was superior to a 1:1:2 ratio for achieving hemostasis in trauma settings, but found no difference in patient mortality [81]. In the setting of massive bleeding, it is imperative to remember to transfuse FFP and platelets and to not fall behind. Additionally, while not immediate, laboratory data may be used to help guide therapy in the setting of massive bleeding. All operating rooms at our institution receive a "stat pack" that expedites labs for PT, PTT, fibrinogen, D-dimer, hemoglobin, hematocrit, platelet count, electrolytes (Na, K, iCa), and blood gasses during massive transfusions. ROTEM™ or TEG™ may provide additional useful information that can be used to guide therapy in the setting of trauma [82]. (See Chapters 6 and 7 for information about ROTEM™)

Complications of Massive Transfusion

Dilutional coagulopathy/thrombocytopenia In the setting of massive transfusion, hemorrhaging patients frequently receive large volumes of fluid, including crystalloids and RBCs which contribute to the cycle of ongoing coagulopathy [83]. Infusion of greater than 3 L of crystalloids, or only 500 mL of colloids, can lead to increased postoperative bleeding [84]. In acute blood loss, bleeding results in the loss of both RBC mass and coagulation factors. While hypotension and oxygen-carrying capacity can be improved with the infusion of fluids and red cells, this does not replace clotting factors necessary for adequate coagulation. Transfusion support with plasma and platelets is essential in this setting.

Acidosis In the setting of massive transfusion, acidosis may result from lactic acid accumulation in underperfused tissue as well as secondary to the decreased pH (<7.2) and elevated lactate in stored red cell units. Along with hypothermia and coagulopathy, acidosis is part of the lethal triad of damage resuscitation and must be addressed [85]. Conversely, metabolic alkalosis may develop the day after massive transfusion due to the metabolism of citrate to bicarbonate, which can be difficult to correct.

Hyperkalemia Massive and rapid transfusion of RBCs can lead to the development of hyperkalemia. Hyperkalemia may lead to cardiac arrhythmias resulting in death. One study demonstrated a fivefold increase in risk for the development of hyperkalemia in trauma patients receiving massive transfusion versus those who were not transfused [86]. The development of hyperkalemia is even more prevalent in the pediatric population, specifically neonates and infants, and, in this population, appears to correlate with the rate of transfusion rather than the transfused volume [87]. Pretransfusion modifications to prevent hyperkalemia include the use of fresher units or washed units; however, these are not usually viable options in emergent situations. There are a number of treatment options available for hyperkalemia listed in Table 43.8 aimed at reducing cardiac toxicity, removing potassium from the extracellular compartment, as well as increasing elimination [88].

Hypothermia Hypothermia in trauma may occur as a result of massive hemorrhage and resuscitation with cold fluids. Coagulation defects associated with hypothermia are seen when patient temperatures reach <34 °C [89]. At this temperature, platelet activity and enzyme activity are impaired [90]. Prevention of hypothermia involves warming the room, warming the patient with blankets or heat lamps, and using blood warmers for all fluids [91]. In addition, hypothermia decreases the metabolism of citrate, thereby increasing the likelihood of hypocalcemia.

Hypocalcemia Calcium is a critical component of both the coagulation cascade and normal platelet function. Citrate, which chelates calcium, is commonly used in the laboratory setting and in the storage of blood components, to prevent activation of the coagulation cascade. In massive transfusion,

Table 43.8 Treatment of hyperkalemia

Medication	Dose
Calcium gluconate Calcium chloride	1 g IV 500 mg to 1 g IV
Insulin with glucose	10 units of insulin in 500 mL D10W IV 10 units insulin bolus followed by 50 mL D50W
0.5% Albuterol	10–20 mg nebulized
Sodium bicarbonate	50–100 mEq IV
Sodium polystyrene sulfonate (Kayexalate)	15–60 g oral or rectal
Furosemide	20–80 mg IV

rapid transfusion of citrated blood components can lead to hypocalcemia. Severe hypocalcemia is associated with depressed circulatory function [92] and alterations in the coagulation cascade. Ionized calcium should be carefully monitored during massive transfusion. It is also important to monitor the patient for signs of citrate toxicity/hypocalcemia, including numbness and paresthesias, after resuscitation. Hypocalcemia can be treated with intravenous infusion of calcium gluconate or calcium chloride.

Component Modifications

A summary of general features of each of the components used to maintain hemostasis is provided in Table 43.9. Additionally, there are several modifications to components that can be performed by the blood bank to increase the safety of transfusion in particular patient populations.

Leukocyte reduced Leukocyte reduction is indicated to decrease febrile, nonhemolytic transfusion reactions (FNHTRs), human leukocyte antigen (HLA) alloimmunization, and cytomegalovirus transmission. In order to be labeled as leukocyte reduced, RBC units and apheresis platelets must have less than 5×10^6 residual white blood cells in more than 95% of tested units [8] in the United States. The rate of FNHTRs has been shown to be significantly decreased by the practice of universal leukocyte reduction in some centers [93, 94]. Latent cytomegalovirus (CMV) in leukocytes may reactivate following transfusion and cause infection in CMV-negative hosts. Components that are leukocyte reduced are considered to be CMV-safe. Studies have found similar rates of CMV transmission between CMV-seronegative and leukocyte-reduced blood components in "at-risk" populations such as bone marrow transplant patients and very low birth weight neonates [95, 96]. Leukocyte reduction may occur either prestorage or at the bedside. It is important to note that bedside leukocyte reduction in patients taking angiotensin-converting enzyme inhibitors has been associated with anaphylactic reactions following activation of the bradykinin cascade [97]. Prestorage leukocyte reduction prevents cytokine buildup during storage [9].

CMV seronegative Though in most clinical situations leukocyte reduction (CMV safe) is considered to be equivalent to CMV-seronegative components, there is still debate. CMV-seronegative components may be considered in the following patient populations: CMV-seronegative recipients of CMV-seronegative hematopoietic stem cell (HSC) or solid organ transplants, CMV-negative HSC candidates, congenital immunodeficiencies (severe combined, DiGeorge), CMV-seronegative pregnant women, and fetuses requiring intrauterine red cell exchange. Each institution should develop their own policy to guide decision-making regarding CMV-safe versus CMV-seronegative components in these

Table 43.9 General features of blood components

	RBC	Plasma	Platelets	Cryoprecipitate
Shelf life after collection	42 days in AS-1, AS-3, AS-5; 35 days in CPDA-1; 28 days in CPD	1 year	5 or 7 days	1 year
Shelf life after thawing		24 h as fresh frozen plasma, after that until 5 days after thawing as thawed plasma		6 h, 4 h if pooled in open system
Storage temperature	1–6 °C, 1–10 °C during transport	< −18 °C, 1–6 °C after thawing	20–24 °C	< −18 °C, 20–24 °C after thawing
Volume	250–350 mL	200–250 mL	50 mL whole blood-derived, 300 mL apheresis platelets	15 mL, however volume varies
	RBCs. Hematocrit 55–65% in AS-1, AS-3, and AS-5; 75–80% in CPDA-1 and CPD	All plasma proteins including coagulation factors, natural coagulation inhibitors	Platelets, most coagulation factors. Labile factors (factor V and factor VIII) are decreased	Fibrinogen, von Willebrand factor, factor XIII, factor VIII, fibronectin
Indication	Increase hemoglobin/hematocrit and thus increase oxygen-carrying capacity	Improve coagulopathy, replenish ADAMTS13 for TTP	Increase platelet count, improve platelet function	Increase fibrinogen level
Dose	10–15 mL/kg	10–15 mL/kg will result in 15–20% rise in coagulation factor levels assuming ideal recovery. It may not be true for labile factors (factor V and factor VIII) and factor VII due to the short half-life	1 unit per 10 kg, 1 apheresis unit for adult as one dose	1 unit per 10 kg

More detailed information on blood components is found in *Standards for Blood Banks and Transfusion Services*, 29th edition [8]

populations. Consideration should also be given to the prevalence of CMV. Prevalence in the United States is approximately 50% and is nearly 90% in certain populations [98].

Irradiation Irradiation of cellular components (RBCs, platelets, granulocytes, and liquid plasma) is used to prevent transfusion-associated graft-versus-host disease (TA-GVHD). Absolute and probable indications are listed in Table 43.10. Irradiated components may also be appropriate in patients with solid tumors and absolute neutropenia secondary to chemotherapy. While healthy term neonates are not at high risk of developing TA-GVHD, many institutions provide irradiated components to all neonates less than 4 months, as they may have an immunocompromised state (very low birth weight, extremely low birth weight) or a yet-to-be-detected immunodeficiency [99]. Irradiation increases the release of potassium from RBCs into the extracellular fluid [100]. If the red cell unit has been irradiated, washing may be considered to remove excess potassium to prevent hyperkalemia in neonates and infants [101].

Washing RBC and platelet units may be washed with saline to remove most plasma components including proteins and antibodies. Indications for washing are listed in Table 43.11. Unfortunately, washing also results in loss of RBCs and platelets as well as decreased red cell survival after transfusion.

Table 43.10 Indications for irradiation

Indications for irradiation
Hematopoietic stem cell transplant patients
Directed donation from relative
Granulocyte transfusions
Hodgkin lymphoma
Intrauterine transfusions
Chemotherapy with purine analogs such as fludarabine
Alemtuzumab therapy
Congenital cell-mediated immunodeficiencies
HLA-matched products
Premature neonates <1200 g
Other malignancies treated with cytotoxic agents (if severely immunocompromised)
Antithymocyte globulin

Table 43.11 Indications for washing

Indications for washing RBC units or platelets
High potassium (RBC units)
Recurrent and severe allergic reaction
IgA deficiency with or without antibody
Intrauterine transfusion of maternal red cells with antibody
Posttransfusion purpura
Activated T antigen [106, 107]
Maternal platelet transfusion in neonatal alloimmune thrombocytopenia

Washing is indicated to prevent repeated severe allergic reactions including anaphylaxis [6]. In the presence of anti-IgA in the recipient, washing should be more thorough. Literature suggests that two washing with 2 L of saline may be needed to completely remove trace amounts of IgA [102]. Washing may also be considered for non-ABO-specific platelet transfusions to remove anti-A and/or anti-B antibodies contained in plasma. Maternal platelets, used in the treatment of neonatal alloimmune thrombocytopenia, also require washing to remove antiplatelet antibodies. As previously mentioned, washing can remove potassium in irradiated RBC units intended for neonates and can also be used to remove potassium from units intended for rapid or high-volume transfusion to neonates. However, the additional time needed to wash components for transfusion frequently limits their use in this area. Formerly, paroxysmal nocturnal hemoglobinuria was an indication for washed RBCs; however, a large retrospective study indicates that washing is not necessary as long as ABO-identical components are used [103]. Lastly, patients with red cell T activation, seen in the pediatric population associated with *Streptococcus pneumonia*-associated hemolytic uremic syndrome, clostridial infections, and necrotizing enterocolitis, may have hemolysis when transfused with the anti-T normally present in adult blood [104]. However, a clear association has not been established, and emergent transfusion should not be delayed for washing of the red cell unit [105].

Volume reduced Volume reduction may be performed on platelet or RBC units. This process removes excess volume, reducing the risk of transfusion-associated circulatory overload [9]. In RBCs volume reduction may also be used to remove excess potassium prior to neonatal transfusion or transfusion to a patient at risk for the development of hyperkalemia from large-volume transfusions [108]. Volume reduction is not a substitute for washing, but it may be used to reduce recipient exposure to donor plasma proteins [9]. Of note, plasma still remains in the volume-reduced product, and sensitized patients may have anaphylactic reactions to remaining plasma proteins. Finally, volume reduction may be used to help achieve a particular hematocrit [9].

Frozen RBCs Frozen RBCs are primarily used to store and stockpile units from rare donors. Glycerol, a cryoprotectant, is added to these units prior to freezing for up to 10 years [7]. These units must be deglycerolized prior to transfusion, and incomplete deglycerolization may result in hemolysis. Of note, deglycerolization removes plasma proteins, making these units appropriate for patients with anaphylactic/severe allergic reactions [6]. Recent studies have indicated that frozen storage may mitigate some of the effects of prolonged liquid storage of red cells and that these units may be superior to older, liquid units [109, 110], though larger clinical trials are necessary.

Adverse Reactions

Transfusion is one of the most commonly performed hospital procedures, and associated adverse reactions are commonly underreported. In 2010 the Centers for Disease Control began to monitor adverse reactions related to transfusion as part of the hemovigilance module of the National Healthcare Safety Network [111]. The overall adverse reaction rate reported between 2010 and 2012 via the hemovigilance program was 0.24%, with 8% of those being severe or fatal [111]. Common adverse reactions are listed below.

Transfusion-related acute lung injury (TRALI) TRALI is defined as acute lung injury occurring during or within 6 h of transfusion. Clinically, patients develop hypoxemia with oxygen saturation <90% on room air, $PaO_2/FiO_2 < 300$, and bilateral infiltrates on chest X-ray [112]. While TRALI has been reported in association with all products, it occurs most frequently in association with plasma and platelets. TRALI is postulated to occur via both immunologic and non-immunologic mechanisms. Immunologic mechanisms are related to antibodies against human leukocyte antigens or human neutrophil antigens. These antibodies are derived from donor plasma. Reporting of suspected TRALI reactions is imperative to identify the donor to determine ongoing eligibility for donation. Mitigation strategies, primarily directed at using male or never pregnant female donors for plasma products, have been shown to decrease the incidence of TRALI [113]. TRALI is the second most common cause of fatal transfusion reactions, accounting for 19% of fatal reactions reported to the FDA in 2016 [114].

Transfusion-associated circulatory overload (TACO) TACO is now the most common cause of fatal transfusion reactions, accounting for 44% of fatal reactions reported to the FDA in 2016 [114]. Despite this, TACO is commonly underrecognized. A recent multi-institutional study found that TACO occurred in nearly 1% of transfusions, of which only 59% were recognized as a possible transfusion reaction, and just 5.1% were reported to the transfusion service [115]. Clinical features of TACO include orthopnea, dyspnea, pulmonary edema on chest X-ray, elevated brain natriuretic peptide (BNP), elevated central venous pressure (CVP), evidence of a positive fluid balance, and evidence of left heart failure [112]. Evidence of TACO excludes a diagnosis of TRALI. Risk factors for the development of TACO include larger volumes of transfusion and faster rate of transfusion [116]. For this reason, patients with underlying cardiac insufficiency or preexisting evidence of volume overload should be transfused more slowly. Management is supportive, including the use of diuretics.

Table 43.12 Signs and laboratory data associated with acute hemolytic transfusion reaction

Clinical signs	Laboratory tests
Back or flank pain	Elevated lactate dehydrogenase
Chills/rigors	Decreased haptoglobin
Fever	Increased bilirubin
Red urine	Hemoglobin present in urine
Decreased urine output	Peripheral smear with spherocytes
Disseminated intravascular coagulation	Positive direct antiglobulin test
Hypotension	Positive elution test
Pain at IV site	Plasma discoloration (hemolysis)
Renal failure	

Adapted from the CDC hemovigilance protocol [112]

Acute hemolytic transfusion reaction (AHTR) AHTRs occur within 24 h of cessation of the transfusion and may present with any of the clinical signs and laboratory abnormalities listed in Table 43.12 [112]. AHTRs occur most frequently as a result of clerical error leading to the transfusion of ABO-incompatible blood. Most of these occur at the bedside [117]. New information technology such as bar coding and radiofrequency identification can be used for collection of the pretransfusion sample, at the time of issue and at the bedside to reduce the frequency of human error [118]. AHTRs from ABO-incompatible transfusions lead to intravascular hemolysis. It is critical that AHTRs be identified as quickly as possible. The severity of clinical manifestations is related to the volume transfused [117]. The transfusion must be stopped immediately and supportive therapies initiated. These include intravenous fluids, diuretics, and transfusion of other blood components should DIC develop. Additional causes of AHTR include improper temperature of storage or transfusion, drugs administered with transfusion, bacterial toxins, mechanical lysis resulting from rapid transfusion through small-bore needles, and transfusion with incompatible fluids [6].

Febrile nonhemolytic transfusion reaction (FNHTR) FNHTRs are defined as fever greater than or equal to 38 °C (100.4 °F) and a change of at least 1 °C (1.8 °F) from the pretransfusion value or chills/rigors occurring within 4 h of transfusion [112]. It is a diagnosis of exclusion. FNHTRs are mediated primarily through cytokines, produced either by donor leukocytes during storage or by the recipient following transfusion. FNHTRs occur in 0.3–6% of red cell transfusions [119]. Pretransfusion treatment with acetaminophen may reduce febrile transfusion reactions [119]; however, this may also mask symptoms of an acute hemolytic transfusion reaction. The prac-

tice of universal leukocyte reduction has been found to decrease the incidence of febrile transfusion reactions in some centers [93, 120].

Delayed hemolytic transfusion reactions (DHTRs) Delayed hemolytic transfusion reactions typically occur 3–14 days following transfusion and are associated with extravascular hemolysis [121]. The hemovigilance protocol defines DHTR as a newly identified alloantibody occurring between 24 h and 28 days after transfusion associated with hemolysis or spherocytes [112]. DHTRs are most commonly caused by Rh (DCE), K, Kidd, and Duffy antibodies. Of these, Jk^a is the most commonly implicated [122]. Once a clinically significant antibody is identified, the patient will require antigen-negative units, which may result in delays in issuing compatible RBC products. Rarely in patients with sickle cell disease or thalassemia, hyperhemolytic transfusion reactions may occur. Hyperhemolysis is characterized by a drop in hemoglobin to below the pretransfusion value with destruction of both donor and recipient RBCs [123] and a drop in reticulocytes below the patient's baseline. The risk of hyperhemolysis in this setting has been reported to be 4% [124]. Additional transfusion may exacerbate the degree of hemolysis. Successful treatment with plasma-to-RBC replacement, corticosteroids, intravenous immunoglobulin (IVIG), and rituximab has been reported [125].

Allergic transfusion reaction (ATR) ATRs are common and are associated with a wide range of manifestations. They are primarily mediated by IgE with subsequent histamine release [121]. Symptoms of an allergic transfusion reaction develop within 4 h of transfusion and include flushing, localized angioedema, maculopapular rash, hives, pruritus, hypotension, edema of the tongue and/or lips, and bronchospasm [112]. In many instances, the reaction is mild and can be treated with temporary cessation of the transfusion and diphenhydramine. Transfusion may continue if symptoms resolve. Severe reactions, such as anaphylaxis, may occur. These require treatment with epinephrine and possible intubation in the setting of respiratory failure. Transfusion should not be restarted in these patients, and they should be monitored carefully. Causes of allergic transfusion reactions are listed in Table 43.13.

Table 43.13 Allergic transfusion reactions

Causes of allergic transfusion reactions
Peanut allergens [126]
Shellfish [127]
IgA deficiency [128]
C4 deficiency [129, 130]
Haptoglobin deficiency [131]
Methylene blue [132]

Septic transfusion reaction Septic reactions are characterized by the rapid onset of fever and hypotension and are most commonly associated with platelet transfusions. Platelets may be easily contaminated by skin flora, and their storage at room temperature allows for bacterial growth. *Propionibacterium acnes* and *Staphylococcus epidermidis* are the most frequently identified bacteria in cultures of platelet concentrates at a rate of 1:1169 apheresis platelets tested [133]. However, actual recipient infection is more commonly seen with *Staphylococcus aureus*, the number one cause of fatal platelet-transmitted infections, and *Serratia marcescens* [114]. *Babesia microti* infections are transmitted by RBC transfusion and were the most commonly reported cause of RBC transfusion-transmitted fatal infections between 2012 and 2016 [114]. New testing strategies aimed at detecting *Babesia* in the blood supply are being investigated [134]. *Yersinia enterocolitica* infection is also associated with RBC transfusion [135]. Transfusion-transmitted bacteremia is reported to occur as a result of 1:100,000 platelet transfusions and 1:5,000,000 red cell transfusions [135].

Transfusion-transmitted diseases Currently, blood products are tested for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human T-cell lymphotropic virus, West Nile virus, and syphilis. Additionally, there is one-time donor screening for *Trypanosoma cruzi*. As of 2018, the US blood supply is also screened for Zika virus. The approximate risk for transfusion-transmitted viral infections in the United States is listed in Table 43.14. Additional infectious disease risks include malaria and prion disease.

Summary

Transfusion of blood components is one of the most frequently performed procedures in the United States. While the safety of our blood supply is constantly improving, it is important to be aware that risks associated with transfusion remain. As we seek to better understand and mitigate these risks, we should ensure that each transfusion occurs only in the setting of an appropriate indication and at a dose that is

Table 43.14 Estimated risks for transfusion-transmitted viral infection in the United States

Infection	Risk per unit
Hepatitis B	1:765,000–1:1,006,000 [136]
Hepatitis C	1:1,149,000 [137]
HIV	1:1,467,000 [137]
HTLV I/II	1:2,679,000 [137]

suitable for the patient. Each patient should be evaluated for the need for various product modifications to verify that they will receive the safest product available. Patients should also be evaluated for therapies that would decrease or eliminate the need for transfusion. In non-emergent settings, patients should be assessed for initial response to one unit or dose prior to transfusing multiple doses of a particular product. Both laboratory data and clinical criteria are required for this evaluation. The decision to transfuse should only be made after careful consideration of the associated risks and benefits.

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Index

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