Jun Teruya
Editor

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Preface

When I was a resident, my mentor told me that we should never let patients die as a result of bleeding. Years later, I still always remember his words and try to follow his advice.

This textbook is intended to offer clinicians who treat patients with active or massive bleeding with a comprehensive and state-of-the-art overview of the major issues specific to managing bleeding patients. Clinicians who may encounter such patients include, but are not limited to: intensivists, surgeons, obstetricians, internists, pediatricians, hematologists, pulmonologists, otorhinolaryngologists, clinical pathologists, transfusion medicine physicians, physician assistants, and nurse practitioners.

Care of such patients and clinical conditions can be quite complex and acutely progressive. For example, it is not uncommon to see patients with bleeding and thrombosis at the same time. Furthermore, there are number of new oral anticoagulants on the market, and switching from one to another can be challenging. In addition, the best time to discontinue an anticoagulant before surgery and when to restart after surgery is a major concern. Each section of this book has been meticulously structured to review the overall scope of issues involved in the management of various bleeding conditions, including clearing patients for invasive procedures or surgery and hemotherapy recommendations for ongoing massive bleeding.

Managing active bleeding requires an urgent response, so we have done our best to create a useful and easy reference for patient care. With that in mind, we tried to be as concise and specific as possible so that clinicians can easily find guidance when faced with a bleeding patient.

In order to diagnose and manage these patients, working with quality hematology and coagulation laboratories is necessary. Without the pertinent laboratory data, management of bleeding patients may be neither effective nor efficient. For instance, if a new male patient comes to the emergency room with bleeding and is found to have a prolonged activated partial thromboplastin time, the clinician may want to know the factor VIII and factor IX levels for management. If the results are not available quickly, a decision has to be made to give either factor VIII or factor IX without supporting data. Having a high-quality coagulation lab on site is a significant factor in the successful management of bleeding patients. At least some key coagulation tests should be available around the clock.

Multidisciplinary care is an integral part of managing bleeding patients. This book is unique in the inclusion of collaborating authors from a variety of integrated disciplines including transfusion medicine, hematology, pediatric hematology, critical care medicine, pediatric critical care medicine, obstetrics, and anesthesia. All invited authors are recognized experts in their field. I hope this book will be a valuable resource to manage patients with bleeding successfully without losing any one of them due to bleeding.

I am very grateful for the contributions of all expert authors to these chapters. All authors understood the scope of this project and were willing to take precious time from their very busy schedules to contribute to the completion of this textbook.

I would also like to acknowledge Dr. Vadim Kostousov who helped me identify the content experts for each chapter from around the world.

Lastly, I would like to thank my wife and twin daughters for their love and continued support of me in many ways.

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About the Editor

Jun Teruya received an M.D. degree and Doctor of Science degree 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 Bank there when he was a second year resident and Assistant Director the next year while he was a Blood Bank fellow. He received an award of Best Clinical Teacher of Clinical Pathology at MGH. Since he moved to the current institution, Texas Children's Hospital, Baylor College of Medicine in 2001, he has been getting numerous consults for bleeding patients.

He has received a several teaching awards at the current institution including Pediatric award for excellence in teaching by a non-pediatric faculty, best educator in clinical pathology, and funniest professor award voted by Baylor medical students. He was also selected as a top doctor in Transfusion Medicine and Coagulation by Houstonia Magazine 2013 and Best Doctor in America 2015–2016.

Part I

Diagnosis of Bleeding by Lab Testing

Screening Coagulation Assays, Factor XIII and D-Dimer

1

Dorothy M. Adcock and Brian F. Poirier

Introduction

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 serve 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, being composed of proenzymes, procoagulant proteins, and anticoagulant proteins (see Fig. 1.1). 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 Chap. 2.

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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 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 and factor XIII. Factor VIII is believed to be synthesized by hepatic sinusoidal endothelial cells [4]. Although B subunit of factor XIII is synthesized in the liver, the A subunit is synthesized in the bone marrows; hematopoietic cells, megakaryocytes, and monocytes. Due to hepatic immaturity at birth, the normal reference intervals 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

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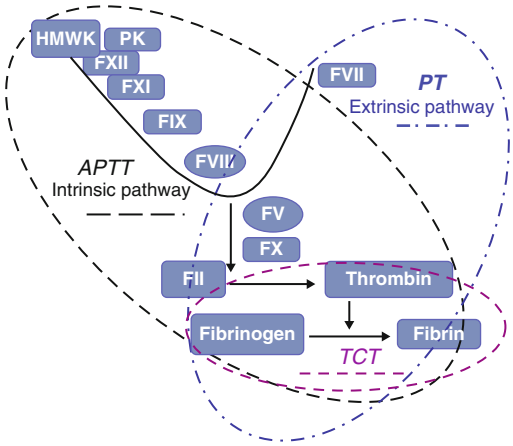

Fig. 1.1 In vivo model of coagulation

the fibrin clot is evaluated using a distinct set of assays. Global screening assays that evaluate both the hemostatic and fibrinolytic systems that require whole blood testing are discussed in Chap. 5. In addition to performing screening laboratory assays, the evaluation of a bleeding patient should include a complete medical 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; PT, activated partial thromboplastin time (aPTT), and functional fibrinogen level or a thrombin time (a surrogate fibrinogen assay). In vitro fibrin clot formation can be initiated through the intrinsic system by adding a contact activator (e.g., ellagic acid, silica, kaolin) or 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 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. Important limitations of the PT and aPTT include; (1) both assays can be prolonged factitiously due to a number of 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. The limitation of the thrombin time is that it is affected by even a small amount of heparin or direct thrombin inhibitor anticoagulant. Therefore, it does not accurately reflect the functional fibrinogen value when the patient is receiving heparin or direct thrombin inhibitor therapy or if the specimen is contaminated by heparin [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 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 to avoid contamination from a port or intravenous infusion. Samples should be adequately mixed immediately following collection and processed in a rapid fashion. In vitro hemolysis should be avoided as this may interfere with clot-based results.

The PT evaluates factors of the extrinsic pathway (factor VII), common pathway (factors X, V, II), and fibrinogen (Fig. 1.2) [2, 3, 10]. In the PT assay, coagulation is initiated by adding tissue factor and phospholipid (this combination is called thromboplastin) to recalcified plasma and the time to form a fibrin clot is measured in seconds. PT reagents contain a heparin neutralizer and can neutralize up to 1 unit/mL. Therefore, the PT does not typically prolong in the presence of heparin unless the heparin is much higher than the therapeutic level. The aPTT evaluates factors of the contact pathway (high molecular weight kininogen [HMWK], prekallikrein [PK], factor XII), intrinsic pathway (factors VIII, IX, XI), and common pathway (factors X, V, 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

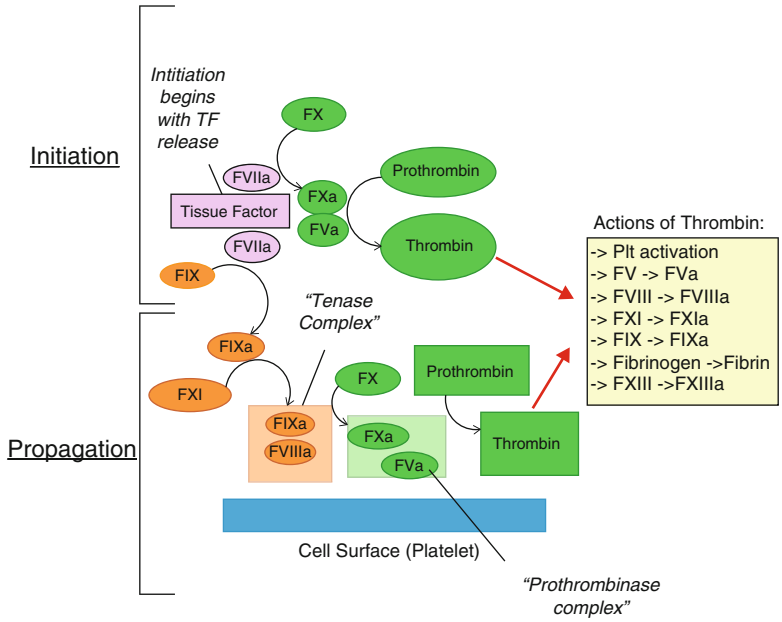

Fig. 1.2 In vitro model of secondary hemostasis

factor deficiency is variable between reagent manufacturers and therefore between laboratories. The aPTT may also elevate when multiple factors fall in the lower end of the normal range, especially in a pediatric patient [11]. Neither 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 and/or functional fibrinogen should be measured [13]. Functional fibrinogen is measured using a citrated plasma sample exposed to a thrombin in the presence of phospholipid and calcium. 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 thrombin time are prolonged, 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 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. Some factor inhibitors, such as specific FVIII and V inhibitors, require incubation at 37 °C for 1–2 h 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 a specific coagulation factor inhibitor assay commonly referred to as a Bethesda assay [14]. Non-specific inhibitors interfere with multiple factors or a component of multiple reactions in a factor assay, 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 typically lead to incomplete correction in normal plasma mixing studies [14, 15]. In order to determine the basis of aPTT, PT, and/or thrombin time 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 h of the trauma or until the patient stabilizes [17]. In hypothermic patients, the values of the PT and aPTT may underestimate the coagulopathy [17].

A number of hemorrhagic diatheses may occur despite a normal aPTT, PT and functional fibrinogen level (see Table 1.1). A normal aPTT does not rule out mild deficiencies of factor VIII, IX, and/or XI as these factor activities must fall to 20–40 % factor activity or less, depending on the reagent used in the assay, 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 1.1 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 20–40 % before the aPTT is prolonged
Hereditary or Acquired FXIII deficiency	Can lead to significant bleeding potential with spontaneous bleeding
Alpha 2 Antiplasmin deficiency	Can be hereditary or acquired (liver disease, DIC, nephrotic syndrome, fibrinolytic therapy), can lead to significant bleeding potential with spontaneous bleeding
Abnormal platelet number or function	Can be hereditary or acquired
Vascular or collagen abnormality	Such as Ehlers Danlos syndrome, vasculitis
Anatomical cause	

Table 1.2 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 with liver disease. Inhibitor development 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 and reagent sensitivity. Will not affect the TT

Prolonged PT, Normal aPTT, and Normal Thrombin Time or Functional Fibrinogen

When the PT is prolonged but the aPTT and thrombin time (or functional fibrinogen) are normal, a deficiency of factor VII should be considered (see Table 1.2) [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 depending on the drug concentration and duration of 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 with liver disease; and on these instances, the PT mixing study tends to demonstrate near correction into the normal reference interval, but not complete correction within the normal reference interval. For example, if the normal interval of the PT is 11–14.1 s and a patient has a PT result of 35 s, a mixing study that demonstrates complete correction would have a 1:1 mix result that falls into reference interval (11–14.1 s) and one that demonstrates near correction may correct to a PT of about 14.2–15 s. A PT mix that demonstrates incomplete correction would have a 1:1 mix result usually above about 18 s (with a normal reference interval of 11–14.1 s) 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, function as clearing rather than neutralizing antibodies [23, 24]. These antibodies cause prolongation of the PT due to 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 antagonism. Hereditary deficiency of factor VII is uncommon, 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 would 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 Thrombin Time or Functional Fibrinogen

Prolongation of the aPTT with a normal PT and thrombin time (or functional fibrinogen) 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 1.3) [1–3, 27]. Heparin therapy or contamination as well as direct thrombin inhibitor (DTI) anticoagulants elevate 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 televancin may elevate the aPTT, and in some circumstances the PT, without increasing bleeding risk [29, 30]. The degree of prolongation of the aPTT and PT 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 due to its inhibition of phosphatidyl choline [3]. Severe deficiency of any of the contact factors typically greatly prolongs the aPTT, yet clinically is not associated with an increased bleeding potential. Mild deficiencies of a contact factor pathway generally will not affect the aPTT.

In a previously healthy male or female patient who presents with acute, possibly catastrophic, spontaneous hemorrhage into soft tissues and muscle, and has a prolonged aPTT, normal PT, and thrombin time or fibrinogen, acquired hemophilia (an acquired factor VIII inhibitor) or acquired von Willebrand syndrome (AVWS) should be considered [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 should be considered early in the evaluation of abnormal bleeding in the postpartum setting [35]. FVIII inhibitors may develop 1–4 months and rarely as late as 1 year postpartum. Acquired factor VIII inhibitors are quite rare in children, but have been reported [36]. In the presence of a FVIII inhibitor, the aPTT is elevated while the PT is normal. 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 measured (see next paragraph). Acquired inhibitors to factor VIII are the most frequent acquired factor inhibitor reported. Acquired inhibitors to factor IX or XI are rare [37, 38].

Acquired factor VIII deficiency can also occur as a feature of AVWS (see Table 1.4) [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

Table 1.3 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	FVIII inhibitors are by far the most common and may lead to severe spontaneous bleeding; can occur as an alloantibody (in hemophilia A) or autoantibody; inhibitors against other clotting factors are rare
Lupus anticoagulant (LA)	Increases risk for thrombosis and obstetric complications. Leads to bleeding only when LA is associated with thrombocytopenia or a 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 1.4 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)

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 lymphoproliferative disorders, certain cardiac valve disorders, ventricular septal defects, essential thrombocytosis, Wilm's 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 and type 2 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 situations of skewed lyonization), 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 activity) to mild (6–40 % factor activity) 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 (in the range of 20–40 %) of postpartum hemorrhage 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 activity less than 15 %. The bleeding tendency is variable and does not always correlate to factor XI activity, 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, and 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 [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. Therefore, VWF serves an important role in both primary and secondary hemostasis. When VWF is decreased, factor VIII levels are decreased concordantly. The aPTT is not an adequate screen for VWD as the aPTT will not prolong until factor VIII levels fall below 20–40 %, 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," these non-specific inhibitors are more commonly associated with an increased thrombotic risk and obstetric morbidity, rather than increased bleeding risk [27, 50]. As LA are non-specific inhibitors, aPTT mixing studies generally demonstrate incomplete correction. 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 phospholipid concentration is characteristic of LA [27, 50]. As PT reagents contain a greater concentration of phospholipid compared to aPTT reagents, most PT assays are not prolonged in the presence of LA. LA may interfere with the phospholipid required in aPTT-based 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 measured, 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 VIII and XI activities are normal.

Prolonged Thrombin Time, normal PT, and normal aPTT

In practice, this pattern of results most commonly occurs due to the presence of heparin (either from therapy or contamination) or direct thrombin inhibitor (DTI) therapy (see Table 1.5) [20]. As drug concentration increases, the aPTT will elevate with heparin, while 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 prolong when fibrinogen levels fall below about 80 to 100 mg/dL, but this depends on the reagent used in the laboratory.

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

Prolonged PT and Prolonged aPTT, normal Thromibn Time, or Functional Fibrinogen

Prolongation of the PT and aPTT with a normal thrombin time or functional fibrinogen 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 poisoning (rat poison), or an anti-Xa inhibitor anticoagulant (see Table 1.6) [1–3, 15, 20, 56]. Some lipoglycopeptide antibiotics, such as daptomycin or telavancin, may elevate the aPTT and PT, due to interference with the phospholipid 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 occurs in the presence of a factor V inhibitor, factor X inhibitor, or in the presence of 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].

In a previously healthy male or female patient who presents with acute, spontaneous hemorrhage and has a prolonged aPTT and PT and normal thrombin time or functional fibrinogen, 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

Table 1.5 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
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
Anticoagulant therapy: UFH[a], LMWH[b], Fondaparinux	Tend to prolong the aPTT as well but not the PT as PT reagents contain heparin neutralizers
Fibrin split products at high concentration	Interferes with fibrin polymerization and may lead to prolongation of the PT and/or aPTT, although the TT is most sensitive. Does not increase bleeding risk by itself
Monoclonal antibodies, as seen in multiple myeloma	Interferes with fibrin polymerization and may lead to prolongation of the PT and/or aPTT, although the TT is most sensitive. Does not increase bleeding risk by itself

[a]Unfractionated heparin
[b]Low molecular weight heparin

Table 1.6 Prolonged aPTT and prolonged PT (normal fibrinogen/TT)

Cause	Comment
Vitamin K deficiency or Vitamin K antagonism (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	Suggests 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
Lupus anticoagulant with hypoprothrombinemia	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 Bethesda 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

received vitamin K may suffer life-threatening intracranial and retroperitoneal hemorrhage occurring between days 1 and 7 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, 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 antagonism, the aPTT and PT are elevated and both may be so greatly prolonged they yield "no clot detected". The thrombin time is normal as is functional fibrinogen. Normal plasma mixing studies demonstrate correction of the aPTT into the normal range and 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 (often including functional fibrinogen) are decreased, except for factor VIII. In severe liver disease, the thrombin time tends to be elevated due to decreased and/or dysfunctional fibrinogen. 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/antagonism 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/antagonism, factor IX is decreased but factor V normal. In liver disease, both factors IX and V activities are decreased.

Anticoagulant rodenticides (rat poisons) are long-acting anticoagulants similar to warfarin [56, 60–62]. While they act as vitamin K antagonists, they 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 when significant, may result in fatal hemorrhage. Simple ingestion, however, 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 and these agents can be measured using high-pressure liquid chromatography or mass spectrometry [63]. A serum warfarin level shows no cross-reactivity with any of the superwarfarins and 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 with time as the rodenticide is released from the adipose tissue. In cases of superwarfarin poisoning,

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 Prolonged Thrombin Time

This pattern may occur with a significantly decreased or abnormal fibrinogen (where the functional fibrinogen value is less than 80–100 mg/dL), severe liver disease or multiple factor deficiencies as may occur with DIC (see Table 1.7). This pattern of results may also occur with DTI therapy, depending on the plasma concentration of DTI and reagent sensitivity to drug.

In 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, with vitamin K deficiency often further contributing to impaired synthesis of functional factors, 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 [68]. To effectively distinguish liver disease from vitamin K deficiency or antagonism, factor V, VIII, and VII (or one of the other vitamin K-dependent factors) should be measured. With vitamin K deficiency, factor V and VIII will be normal and factor VII decreased, while with liver disease factors V and VII are decreased but 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 markedly prolonged due to consumption of all factors, and the platelet count is decreased to a greater degree. Furthermore, signs of microangiopathic anemia may be seen on blood smear (e.g., schistocytes) with DIC. 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 protein, may lead to prolongation 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

Table 1.7 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

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 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 also present at a later age. The major cause of death is intracranial hemorrhage. Another characteristic feature of afibrinogenemia is spontaneous splenic rupture [43]. Afibringenemia 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. With hereditary hypofibrinogenemia, patients tend to bleed with provocation rather than suffer spontaneous bleeding. Fibrinogen levels are generally in the range of 100 mg/dL.

Normal PT, Prolonged aPTT, and Prolonged Thrombin Time with Normal or Low Fibrinogen

This pattern of results suggests the presence of an anticoagulant drug, specifically heparin or a DTI (see Table 1.8). Depending on the plasma concentration of DTI and reagent responsiveness, the PT may also be prolonged. As most PT reagents contain a heparin neutralizer, the PT tends not to prolong 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 (such as using Hepzyme™ Siemens Healthcare Diagnostics) will correct the aPTT and thrombin time to normal range (in an otherwise normal specimen); however, larger concentrations of heparin (such as >2 units/mL) 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 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. 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.

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 % activity), moderate (5–30 % activity), and mild (30–60 % activity). Severe factor FXIII deficiency has an estimated incidence of 1 in 4 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.

Table 1.8 Prolonged aPTT, normal PT, and prolonged TT with normal or low fibrinogen

Cause	Comment
Anticoagulant therapy: direct thrombin inhibitor anticoagulant (dabigatran)	Thrombin time is exquisitely sensitive such that a normal TT can rule out significant dabigatran effect. May cause prolongation of the aPTT depending on drug concentration and reagent sensitivity
Anticoagulant therapy: heparin or heparin contamination	Typically does not prolong the PT as PT reagents contain heparin neutralizers
Acquired heparin-like inhibitor	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

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 FXIII-deficient patients following replacement therapy, but is more likely to develop de novo in association with another disease such as systemic lupus erythematosus, 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 detect only 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 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 pathologic states including venous thrombosis, DIC, consumptive coagulopathy associated with certain snake bites, 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 Chap. XX.

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). Since molecular weight of FEU is 340,000 Da and DU is approximately 195,000 Da, FEU concentration is approximately two times greater than DU concentration. Thus, for practical purposes, in order to get FEU from DU, it is common practice to multiply DU by 2 [83].

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.

Table 1.9 Impact of common coagulopathies on the PT, aPTT, 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	↑	↑	↑	

Summary

In the work up of a bleeding patient, initial evaluation of basic laboratory screening tests is a critical step in establishing possible causes of, and treatment for, clinically significant bleeding. The data from screening assays must be evaluated in the context of the physical assessment, clinical history, and other laboratory assays, particularly the complete blood count. Initial assessment of the three critical tests discussed in this chapter (the PT, aPTT, and clot-based fibrinogen assay or thrombin time) provide initial data that can help guide further work up and, ultimately, appropriate therapy (see Table 1.9). Crucially, because coagulation testing is quite variable depending on reagent and testing platforms used, consultation with coagulation laboratory personnel can often provide invaluable input when analyzing assay results. In our experience, good dialogue between the clinician and the laboratory can be critical in making a proper diagnosis, and we encourage clinicians to consult with their laboratory when working up difficult cases.

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Platelets

2

Kandice Kottke-Marchant

In the diagnostic approach to a patient for possible platelet disorders, 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.

Clinical History for Patients with a Bleeding Diathesis

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]. 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 are 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 food 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 associated with 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].

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 the leukemias, myeloproliferative disorders, myelodysplastic disorders, or consumptive coagulopathies, such as DIC [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 peripherally collected specimen 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 h after collection, although mean platelet volume decreases after 3 h. An air-dried Wright-stained smear can be made from the EDTA specimen for platelet morphologic analysis.

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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, the 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 [10]. The mean platelet volume (MPV) is an indication of platelet size, with normal MPV ranges 7–11 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]. Alternate techniques based on messenger ribonucleic acid (mRNA) detection in platelets (reticulated platelets) correlate with thrombopoiesis, 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 diameter, with abundant purple-staining granules (Fig. 2.1) [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 disorder, or a congenital macrothrombocytopenia. Some platelet disorders are associated with unique platelet and/or leukocyte morphology. Giant platelets are seen in Bernard–Soulier disease; 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.

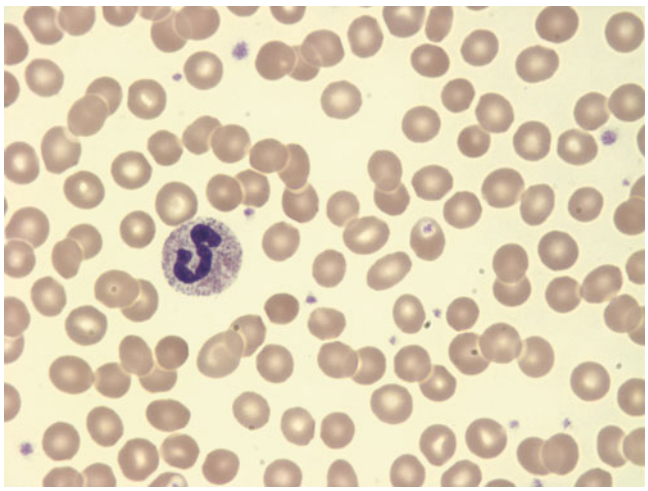


Fig. 2.1 Platelet morphology. A Wright-stained peripheral smear shows platelets as small (2–3 μm) diameter non-nucleated cells with a purple granular cytoplasm, reflective of the many alpha granules (original magnification ×100)

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, 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 [10].

Platelet function test types can be categorized as (1) screening, (2) aggregation, and (3) specialized testing. Within each category, the various platelet functions measured include

adhesion, aggregation, activation, and granule release. Screening platelet tests measure global platelet function and are widely available in clinical laboratories. Platelet aggregation is the most commonly used platelet function test and is available in dedicated hemostasis laboratories. Specialized platelet testing includes more targeted assays for detailed diagnosis and typically is available only 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 which utilize small stand-alone devices and can be used in laboratories that otherwise could not perform platelet function studies; some can be utilized in the near-patient setting [16, 21]. However, 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 (formerly Ultegra, Accumetrics, San Diego, CA), the Plateletworks™ (Helena Laboratories, Beaumont, Texas), and the Impact-R (Matis Medical, Israel). Thromboelastometry measures a combination of coagulation, platelet function, and fibrinolysis and is not covered further in this chapter.

PFA-100

The PFA-100 System (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) is a device that measures both platelet adhesion and aggregation in whole blood, using a high-shear testing system (Fig. 2.2) [22].

Specimen Considerations

Specimens for PFA-100 testing should be collected using a peripheral venipuncture when possible [23]. The PFA-100 utilizes a whole blood specimen collected into a light blue top vacutainer tube containing 3.2 % buffered trisodium citrate. It is recommended that each laboratory should establish its own reference range using blood specimens from normal individuals. Specimens should be kept at room temperature and transported to the laboratory, with testing completed within 4 h 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 coated with aggregation agonists (collagen/epinephrine [EPI] or collagen/adenosine diphosphate [ADP]) with a 147-μm diamter central aperture. 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 (5000–6000 s^{-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 prolonged closure time indicates platelet dysfunction; 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 <150,000 platelets/μL or hematocrit <35 %; 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 s. Beyond that, the closure time is reported as >300 s. Duplicate testing is only recommended when the initial result shows a prolonged closure time.

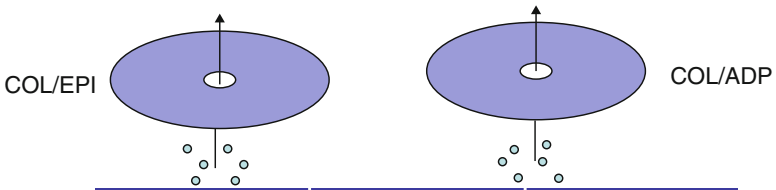
Good quality control must be maintained on the instrument, including daily electronic checks and vacuum checks, as well as validation of each new cartridge lot with a fresh normal sample. External proficiency testing for the PFA-100 has recently become available; this challenge utilizes normal donor 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. 2.2 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.

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.

Platelet aggregation testing can be performed either in whole blood or using a suspension of platelets in plasma,



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. 2.2 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

termed platelet-rich plasma (PRP). Blood for platelet aggregation studies should be drawn into an anticoagulant solution of 3.2 % sodium citrate. Ideally, blood should be obtained from a peripheral venipuncture. Guidelines for performing platelet aggregation testing have been developed by CLSI (H58A) [24].

Light Transmission Aggregation

Platelet aggregation studies are most commonly performed using platelet-rich plasma with optical detection of aggregation (turbidimetry).

Specimen Considerations

For optical platelet aggregation assays, the whole blood specimen should be kept at room temperature and transported to the laboratory expeditiously, with testing completed within 4 h of phlebotomy [24]. The first step in sample processing requires the production of PRP by differential centrifugation of erythrocytes and leukocytes, resulting in a top suspension of platelets and plasma.

Prior to testing, the platelet count in the PRP is often normalized to 200,000–250,000/μL by mixing appropriate ratios of PRP and PPP, although some recent studies have suggested that this practice may affect platelet aggregation results, and not adjusting or adjusting the platelet count with saline may be more appropriate [29]. With optical aggregation methodologies, PRP platelet counts <100,000/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]. Agonists typically include ADP, collagen, arachidonic acid, epinephrine, and occasionally thrombin receptor-activating peptide (TRAP) (Fig. 2.3). For optical aggregation, the adequacy of the aggregation response is followed by quantifying the maximal percentage of aggregation or the slope of the aggregation curve.

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

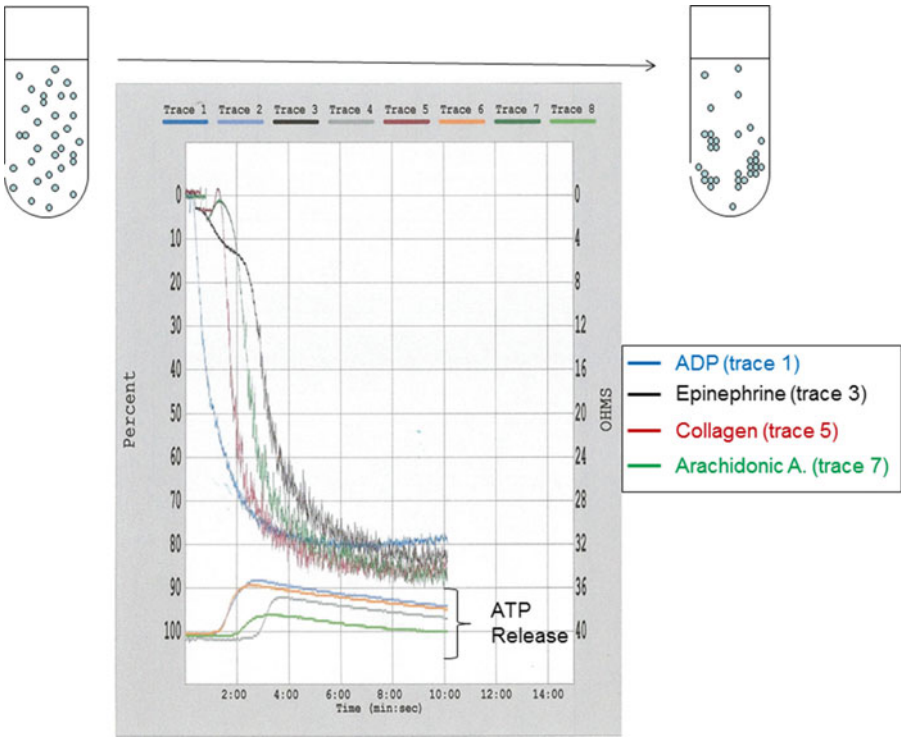


Fig. 2.3 Normal platelet aggregation. The diagram at the top of the figure shows platelet aggregation cuvettes before (turbid) and after aggregation (clear with platelet clumps). Platelet aggregation with 5 μM ADP (*blue*), 100 μM epinephrine (*black*), 2 mg/mL collagen (*red*), and 0.5 mg/mL arachidonic 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)

than 70 or 80 % aggregation, but all laboratories should establish their own reference ranges for each agonist.

Another important reagent used in the evaluation of platelet function by aggregation is the antibiotic ristocetin, which facilitates the binding of vWF to the glycoprotein Ib/IX/V complex. 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. 2.4).

Many factors can affect platelet aggregation results, such as thrombocytopenia, thrombocytosis, processing technique, processing temperature, stirring rate, and processing time [24]. In addition, clinicians ordering the tests should advise patients to discontinue, if possible, any medication, such as aspirin or nonsteroidal anti-inflammatory agents, which may interfere with the assessment of the test results [4, 5].

A survey of platelet function testing techniques among North American Specialized Coagulation Laboratory Association (NASCOLA) member laboratories revealed that there is a wide variety in practice in the performance of platelet aggregation testing [31]. The NASCOLA study revealed that the majority of laboratories reported results containing quantitative values (% aggregation and/or slope) and a qualitative interpretation. The majority of laboratories utilized the agonists collagen, arachidonic acid, epinephrine, and ristocetin; however, the final test concentrations of these agonists varied widely, sometimes by several orders of magnitude.

There is little data in the literature to define the sensitivity and specificity of agonist concentration for the diagnosis of platelet disorders. However, the median concentrations of the agonists from this survey give some guidance for typical concentrations used in practice. These findings were incorporated into the CLSI guideline for platelet aggregation testing in an attempt to standardize laboratory practice [24, 32]. The standard agonists used include: ADP, 0.5–10 μM, typically 5 μM; collagen, 1.0–5.0 μg/mL, typically 2 μg/mL; epinephrine, 0.5–10 μM, typically 5 μM; ristocetin low dose, ≤0.6 mg/mL; and ristocetin high dose, 0.8–1.5 mg/mL. Arachidonic acid, 0.5–1.6 mM can be added to the panel to interrogate prostaglandin pathways/aspirin effect.

Whole Blood Aggregometry

Platelet aggregometry studies can also be performed in whole blood by an impedance technique. [33] Agonists tested include those used in light transmission aggregation (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.

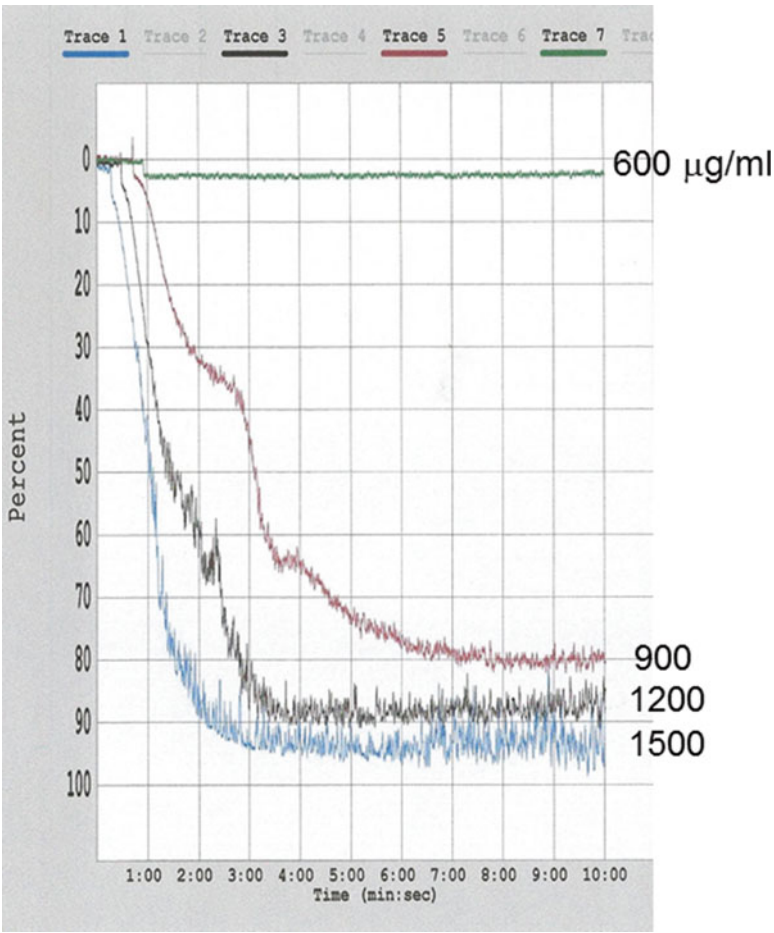


Fig. 2.4 Platelet aggregation with ristocetin. Ristocetin stimulates a conformational change in von Willebrand factor, leading to aggregation through the glycoprotein Ib/IX/V complex. Note that aggregation is virtually absent at low ristocetin concentration (600 µg/mL), becoming progressively stronger until complete aggregation is reached somewhere between 900 and 1500 µg/mL (optical platelet aggregation using a Chronolog aggregometer)

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 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. 2.3) [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, but this technique is only employed 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. 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. It 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, is done before and after addition of a platelet agonist, such as TRAP or ADP [38].

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 anticipated that implementation of reticulated platelet counts may help to avoid bone marrow examination in some individuals with thrombocytopenia [39]. The immature platelet fraction (IPF) on the Sysmex XE and XN-series analyzers (Sysmex Corp, Kobe, Japan), where a nucleic acid-specific fluorescent dye is detected in platelets, 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, whole mount EM shows a decrease or absence of the organelles (cytoplasmic dense bodies) storing adenine nucleotides, serotonin, and calcium.

Platelet Genetic Testing

Genetic testing for diagnosis of platelet disorders is not widely available. However, targeted mutation analysis and sequencing of some genes associated with inherited platelet disorders, such as *MYH9* (May-Hegglin Anomaly, Sebastian, Fechtner and Epstein syndromes, etc.), HPS1 and HPS3 (Hermansky-Pudlack), *MPL* (congenital amegakaryocytic thrombocytopenia), and *WAS* (Wiskott–Aldrich syndrome, X-linked thrombocytopenia), is available at some clinical reference laboratories [42, 43]. Panels are also offered to detect mutations in the genes in the GPIb/V/IX complex to assay for Bernard-Soulier syndrome or the GP IIb/IIIa complex in Glanzmann thrombasthenia. In patients with *MYH9* disorders, immunofluorescence analysis of myosin IIA can highlight abnormal protein localization within the neutrophils; the pattern of localization correlates to the site of *MYH9* mutation.

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 mainly been limited to large medical centers, but there has been significant technological development of newer platelet function assays that have brought some platelet function testing capabilities to smaller laboratories and point-of-care settings.

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Von Willebrand Disease Laboratory Workup

3

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]. 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 quick and useful 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 VWF antigen (VWF:Ag) as in Type 1 and Type 3 VWD or 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 includes all three tests as any missing test can result in 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 can be indicative of a quantitative VWD.

VWF Activity

VWF activity (VWF:Act) is the assessment of VWF ability to bind to platelet VWF receptor, glycoproteinIb-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

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by addition of ristocetin [11]. Ristocetin induces VWF conformation change that facilitates the binding of VWF to GPIb [12]. Since VWF:Act measurement is dependent on ristocetin, it is also referred to commonly as ristocetin cofactor activity (VWF:RCo). Although there are ristocetin-independent method to determine VWF:Act [13], VWF:RCo remains the gold standard for VWD diagnosis at this time [14]. 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 [15, 16].

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 [17] and a normal ratio of >0.5–0.7 is expected for Type 1 VWD and Type 2N VWD.

VWF Multimer Analysis

VWF multimer analysis (VWF:MA) is the gold standard in determination of VWF multimer distribution [18]. 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 [19, 20]. As shown in Fig. 3.1, absence of high or intermediate molecular weight multimer is indicative of Type 2A, Type 2B, platelet type, or acquired VWD. 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 assay (VWF:CBA) is used to determine the ability of VWF to bind to collagen. VWF:CBA varies greatly depending on the type of collagen used in the specific assay [21–23]. Therefore, unlike VWF:RCo, VWF:CBA is not a standardized assay and should not be used in place of VWF:RCo for VWD diagnosis [24]. However, VWF:CBA can be used as a supplemental test for multimer abnormalities as high molecular multimers demonstrate a higher collagen-binding affinity and increase VWF:CBA [25]. Therefore, VWF:CBA is sometimes used as a screening test for VWF:MA. Importantly, VWF:CBA cannot detect all

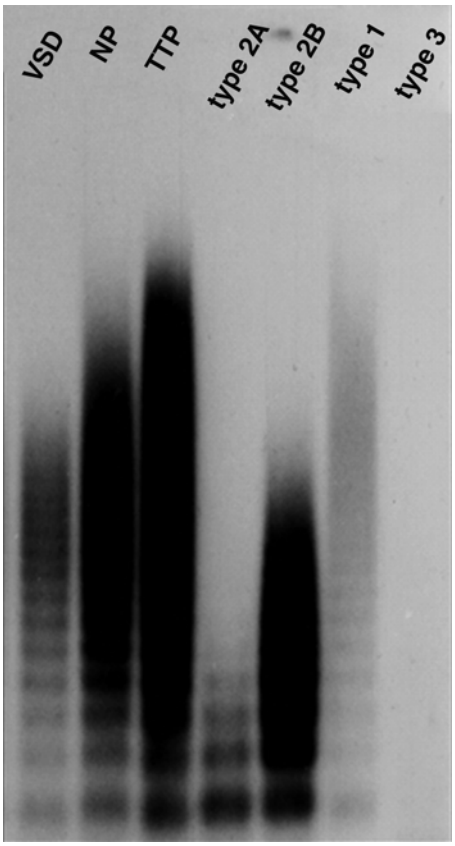

Fig. 3.1 Shows the various expected multimer analysis results of different VWD subtypes. *VSD* valvular stenotic disease, *TTP* thrombotic thromcytopenic purpura

VWF collagen-binding abnormalities as the collagen type used for the assay is different from those in the subendothelial collagen [26].

Factor VIII Binding Assay

FVIII binding assay (VWF:FVIIIB) is an ELISA test to determine patient's VWF ability to bind to extraneous FVIII [27]. VWF:FVIIIB 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 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.

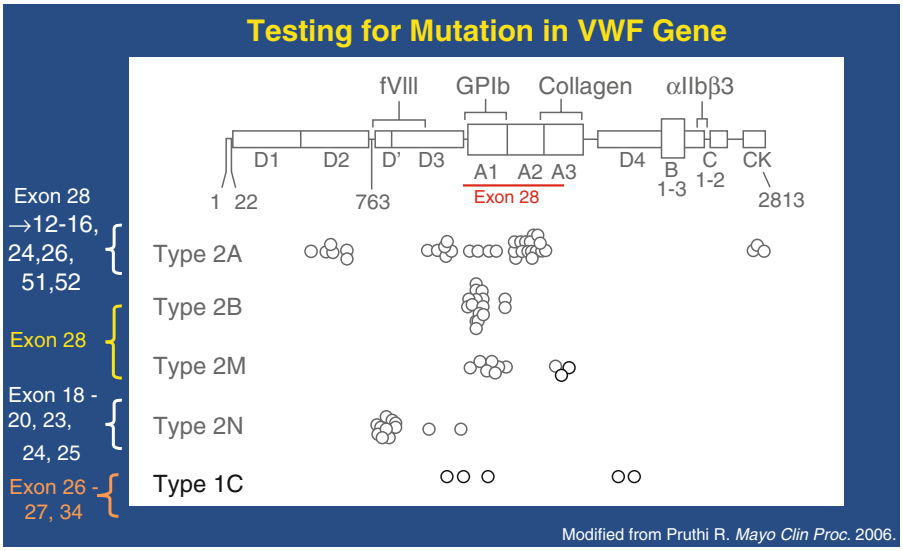

Fig. 3.2 Shows the known mutations in the VWF gene that have been associated with various VWD subtypes. Modified with permission from Annual Review of Medicine. From Sadler J. New Concepts in Von Willebrand Disease. Annu Rev Med. 2005 Feb 1;56(1)

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 [28]. However, RIPA cannot distinguish between the two disorders, as both platelets and VWF are native from patient [29].

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 [30]. 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 [31].

VWF Propeptide to Antigen Ratio

VWF propeptide to antigen ratio (VWF:pp/Ag) is to determine the clearance rate of VWF [32]. As discussed in Chap. 7, VWF propeptide dimer (VWF:pp) are 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 acquired VWD. 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) [33]. In these variants, the increased clearance makes desmopressin an ineffective treatment [34].

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 [35] (Fig. 3.2). Currently, the cost of a complete VWF gene analysis is 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 [36]. However, exon 28 analysis alone cannot detect all diseases causing mutations as Type 2N and some Type 2A mutations extend beyond the exon 28 [37]. In its current state, molecular analysis should be used 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

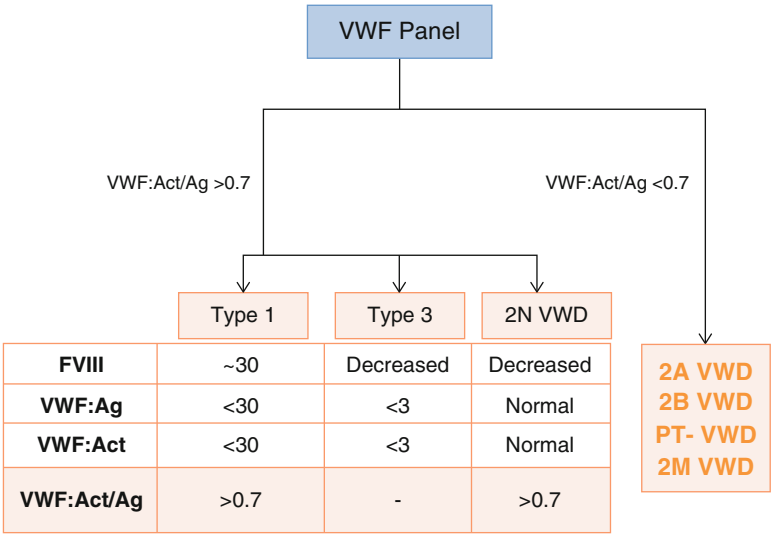

Fig. 3.3 Shows the laboratory features that distinguish Type 1, 3, and 2N VWD from other Type 2 VWD. Of note, although Type 2N is a VWF functional defect as a F8 carrier protein, the coagulation function of VWF remains normal

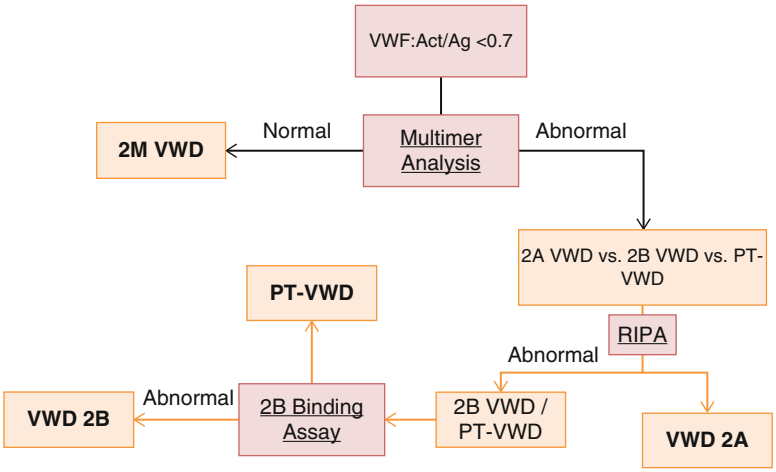

Fig. 3.4 Shows an overall algorithmic approach to subclassify the various Type 2 VWD. Of note, Type 2N is not included in this flowchart as it does not present with decreased VWF:Act/Ag ratio

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. 3.3). 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:FVIIIB can differentiate the two diseases.

If there is a decreased VWF:Act/Ag of <0.5–0.7, a qualitative defect in VWF coagulation function is present (Fig. 3.4). 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 all subtypes of Type 2 VWD, targeted VWF genetic analysis can be performed.

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Hyperfibrinolysis

4

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. 4.1) plays an important role in regulating the size of the clot [1, 2]. The activation 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. Fibrin increases the activity of tPA 500-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 only thought to be clinically significant 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 68 kDa 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 an active form by vascular endothelial cells. tPA is a specific activator of plasminogen, but it is slow at activating plasminogen in the absence of fibrin, which increases the activity of tPA about 500-fold. Two forms of tPA circulate in blood, active tPA and inactive 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 [3].

uPA is a 54 kDa 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 92 kDa 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. tPA and uPA activate plasminogen to plasmin through proteolytic cleavage releasing a plasminogen activation peptide. Active plasmin then lyses fibrin-releasing fibrin degradation fragments.

Fibrinolytic activity is regulated by three proteins, PAI-1, antiplasmin, and TAFI. PAI-1 is a 52 kDa 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 is secreted by the liver, adipose tissue, and megakaryocytes [6]. 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 5–50-fold during inflammation or infection. Antiplasmin (also known as α_2-antiplasmin and plasmin inhibitor) is

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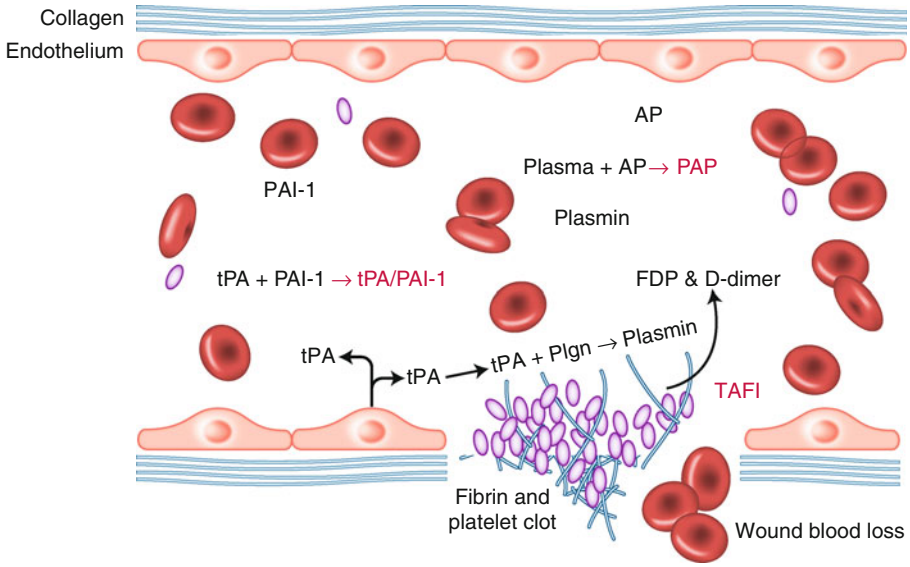

Fig. 4.1 Fibrinolytic System. Fibrinolysis begins with the secretion of tissue plasminogen activator (tPA) from endothelium. tPA along with plasminogen (Plgn) binds to fibrin where tPA converts plasminogen into plasmin, which lyses fibrin releasing fibrin degradation fragments (FDP) including D-dimer. 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

70 kDa SERPIN that rapidly inhibits 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 and slowing the rate of plasminogen activation and fibrinolysis [8]. There is no known inhibitor of TAFIa, but it has a short half-life of about 10 min at 37 °C, converting into an inactive form TAFIai. Changes in TAFI levels 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 hyperfibrinolysis.

Fibrinolysis Regulation

How fast a clot is lysed is related to the level of tPA activity in blood, which is affected by four processes (Fig. 4.2): (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. Increased tPA secretion can be triggered by bradykinin, histamine, beta-adrenergic agonists, and 1-deamino-8-D-arginine vasopressin (DDAVP). The highest concentrations of tPA are found in venous blood downstream from capillary beds where most of the endothelium are located. 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 min for active tPA and 5–6 min 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.

Procedures or disorders that increase soluble or vascular surface fibrin like cardiopulmonary bypass, severe trauma, prolonged surgery, and disseminated intravascular coagulation

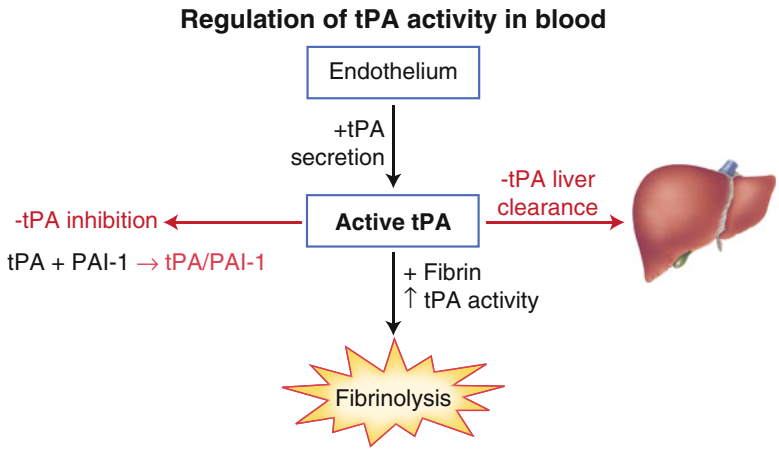

Fig. 4.2 Regulation of tPA activity. The rate of clot lysis is controlled primarily by the concentrations of active tissue plasminogen activator (tPA) in blood and intravascular fibrin. Active tPA levels are regulated by three processes: (1) the rate of tPA secretion from endothelium, (2) the rate of 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

Table 4.1 Fibrinolytic assays for evaluation of hyperfibrinolysis

Clinical assays
Tissue plasminogen activator (tPA)
tPA antigen
tPA activity
Plasminogen activator inhibitor 1 (PAI-1)
PAI-1 antigen
PAI-1 activity
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 antigen
uPA activity
Thrombin activatable fibrinolysis inhibitor (TAFI)
TAFI antigen
TAFI activity

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.

Clinical Evaluation of Fibrinolysis

The Actively Bleeding Patient

A variety of assays are available for evaluation of the fibrinolytic system (Table 4.1). 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 [9]. Figure 4.3 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 [10]. Because the sample is whole blood containing platelet and plasma PAI-1, only patients with severe hyperfibrinolysis will be detected using viscoelastometry [11]. 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.

A general screening test for increased fibrinolytic activity is the euglobulin clot lysis time [12]. An acid precipitate of plasma is prepared that is rich in plasminogen activators,

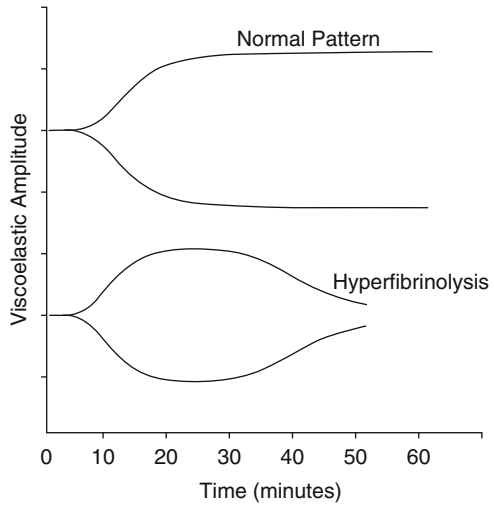

Fig. 4.3 Detection of hyperfibrinolysis using viscoelastometry. The *upper curve* shows a normal tracing with a stable maximum viscoelasticity. The *lower curve* shows a progressive loss of viscoelasticity associated with accelerated fibrinolysis and an increased risk of bleeding

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 lyis 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.

Hyperfibrinolytic Syndromes

For patients who 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) [13, 14]. 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 [15]. 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 follow 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 min, while tPA/PAI-1 complex has a longer half-life of 5–6 min [16]. 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 [17].

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

5

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Thromboelastometry Basics

The ROTEM™ Devices

Rotational thromboelastometry (ROTEM™, Tem International GmbH, Munich, Germany and TEM Systems, Inc., Durham, NC, USA) is a whole blood viscoelastic hemostasis analyzer, which evolved from the original 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 5.1).

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The ROTEM™ *delta* device (Fig. 5.1a, 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, 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), 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. 5.1a, c–e), CE marked in Europe since November 2013 (FDA validation studies are running), which provides platelet function analysis based on the well-established whole blood "impedance aggregometry" or "multiple electrode aggregometry" technology (more than 400 hits in PubMed) [34–38]. 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. 5.1f, 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 pin-and-cup technology. This allows for using the same algorithms as already established for the ROTEM™ *delta* device. With the ROTEM™ *sigma* device, pipetting is no longer required, which significantly increases user-friendliness and reproducibility of the results.

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Table 5.1 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 limit 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 results 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]	Two channels per device (if TEG™ platelet mapping is performed, channels are blocked for other viscoelastic testing)	Four channels per device (the ROTEM™ *platelet* module provides two additional channels for impedance aggregometry)
Viscoelastic assays [9–15]	Five 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)	Seven different assays (NATEM, 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, 16–23]	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 and prothrombin complex antagonists (PCC)
Turnaround time [6, 11, 13, 24–28]	Reference rang for r-time in kaolin-TEG 4–8 min; no early variables of clot firmness available; turnaround time 20–30 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	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, 29–33]	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 ("theragnostic approach")
Platelet function analysis [34–39]	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	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 have to be investigated	ROTEM™ *sigma*; cartridge-based system using the proven pin-and-cup technology but lyophilized bead reagents instead of liquid reagents; ROTEM™ *sigma* beads contain a heparin inhibitor as the liquid reagents do; the same algorithms can be used as with the ROTEM™ *delta* device

ER emergency room, *ICU* intensive care unit, *OR* operating room. Courtesy of Klaus Görlinger, Tem International

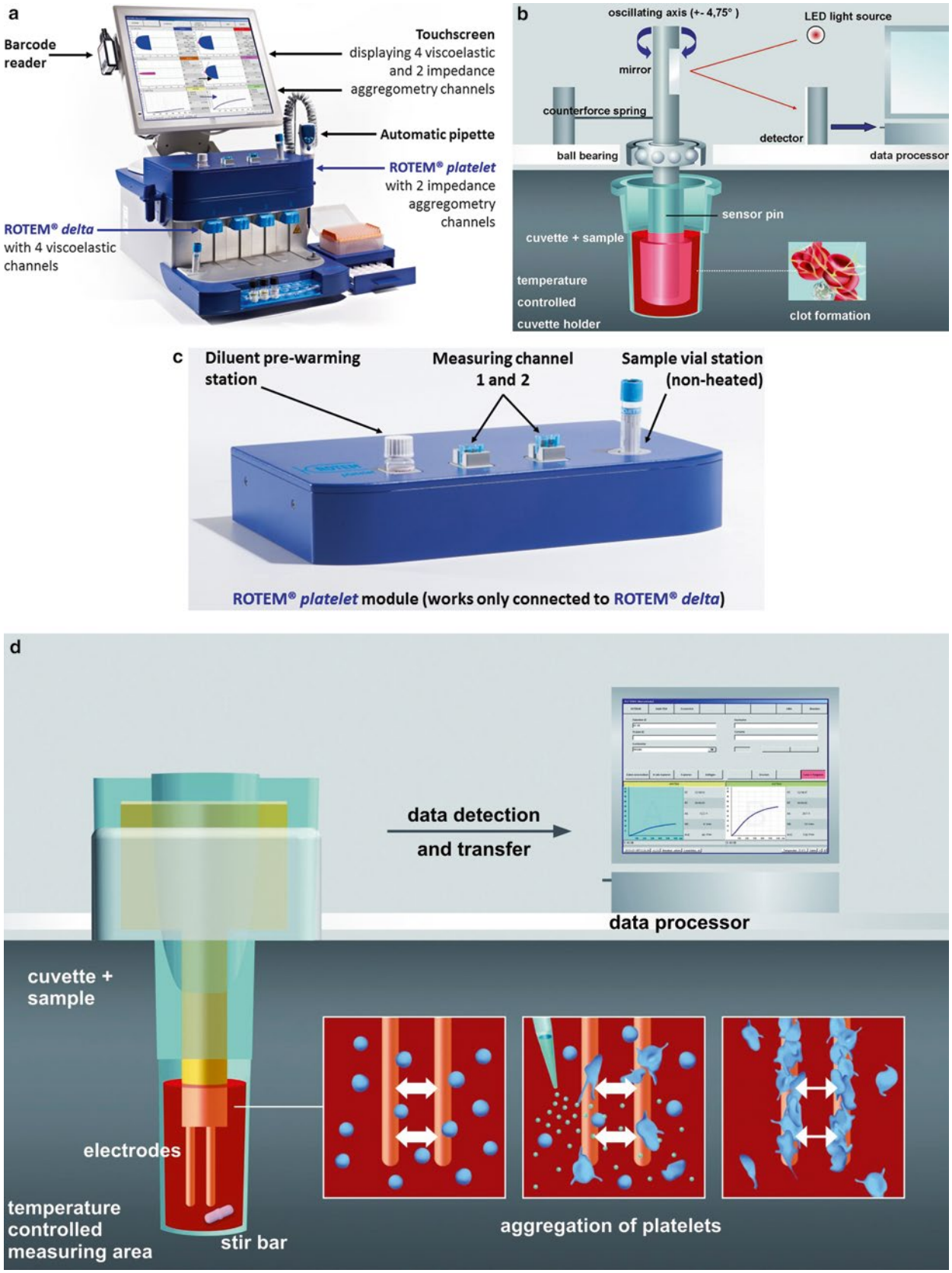


Fig. 5.1 (**a**–**g**) ROTEM™ devices. (**a**) ROTEM™ *delta* device (thromboelastometry) plus ROTEM™ *platelet* module (whole blood impedance aggregometry), (**b**) ROTEM™ *delta* measuring principle, (**c**) ROTEM™ *platelet* module, (**d**) ROTEM™ *platelet* measuring principle, (**e**) ROTEM™ *platelet* 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 1 (C = cartridge ROTEM™ assay). Courtesy of Klaus Görlinger, Tem International

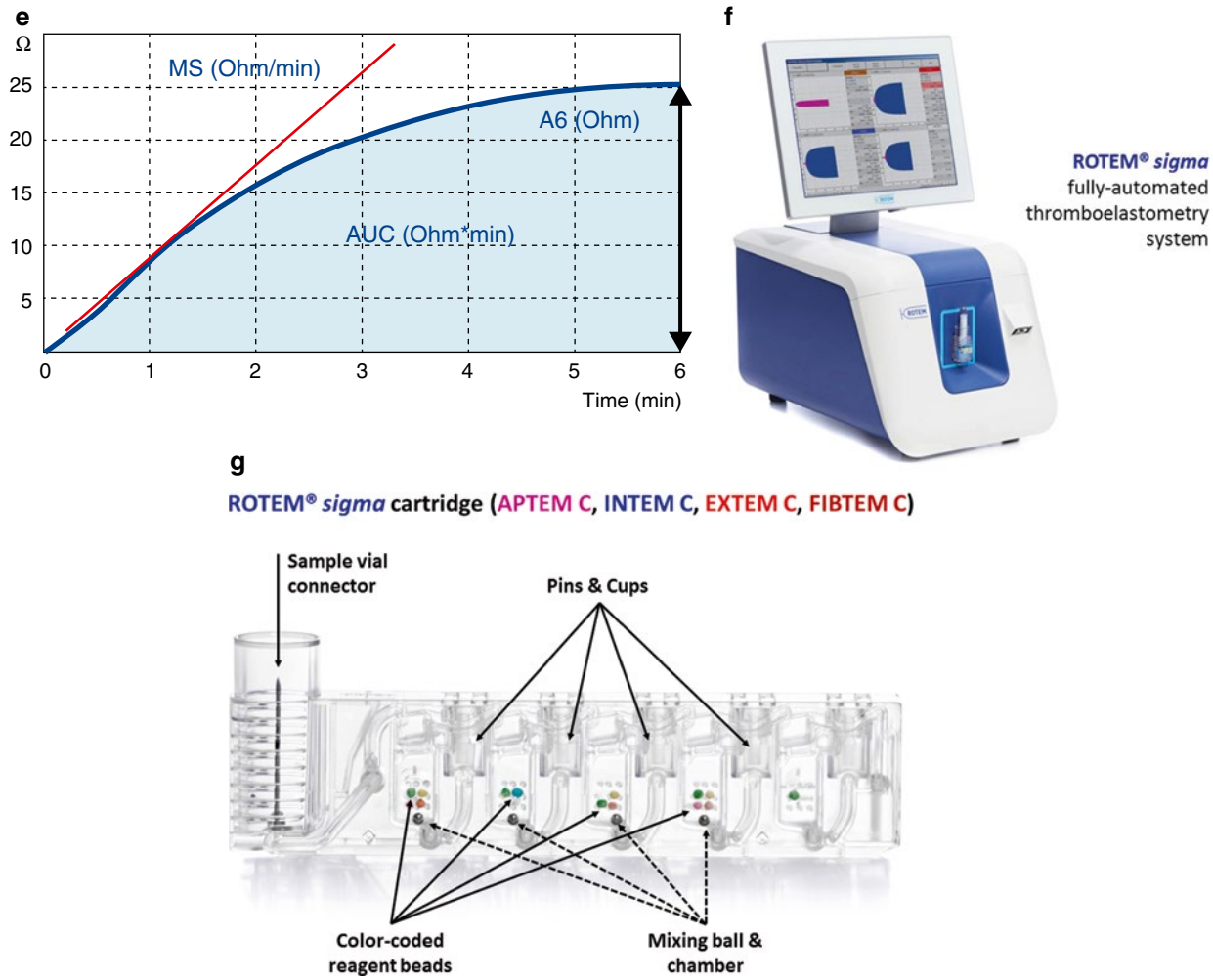


Fig. 5.1 (continued)

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, 29–33]. Accordingly, the ROTEM™ *delta* device is not only suitable to detect a coagulopathy in real time but also to differentiate between different causes of coagulopathies, e.g., between hypofibrinogenemia and thrombocytopenia, and is designed to guide hemostatic therapy in bleeding patients. 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/minute. After starting the test by recalcifying the citrated whole blood in the cup and adding an activator (tissue factor, ellagic acid, kaolin, 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. 5.1b). In addition, 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 5.1). 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. 5.1g), providing four channels each (cartridge 1, FIBTEM C, EXTEM C, INTEM C, APTEM C; cartridge 2, FIBTEM C, EXTEM C, INTEM C, HEPTEM C; here C stands for cartridge). A cartridge for platelet function analysis based on whole blood impedance aggregometry—analog to the ROTEM™ *platelet* module—is under development.

ROTEM™ Assays

Thromboelastometric assays use citrated whole blood (300 µL/assay), which is recalcified and activated by tissue factor (extrinsic pathway), ellagic acid (intrinsic pathway), or ecarin (direct prothrombin activation). Some assays contain further additives (Table 5.2). 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 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 [29–31]. Up to four viscoelastic tests can be performed and displayed on the touch screen, simultaneously (Fig. 5.1a). Here, extrinsically activated assays (EXTEM, FIBTEM, and APTEM), intrinsically activated assays (INTEM, HEPTEM, and KAOTEM), an ecarin-activated assay (ECATEM), and a nonactivated assay (NATEM) are available. Note that the KAOTEM and ECATEM are only available in Europe.

Similar to the prothrombin time, the **EXTEM** assay is activated by recalcification (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 depend on the activity of the coagulation factors VII, X, V, II, and fibrinogen in EXTEM test. EXTEM CT can be used to guide FFP and

Table 5.2 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 (coumadin/ warfarin); indication for PCC administration
FIBTEM	$CaCl_2$ + recombinant tissue factor + polybrene + cytochalasin D	Fibrin polymerization; dose calculation for fibrinogen concentrate or cryoprecipitate
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)
KAOTEM	$CaCl_2$ + kaolin	High sensitivity to low molecular weight heparin (LMWH) effects; actually only available in Europe
ECATEM	$CaCl_2$ + ecarin	Direct thrombin inhibitors (e.g., hirudin, argatroban, bivalirudin, dabigatran); not sensitive to heparin; actually only available in Europe
NATEM	$CaCl_2$	Tissue factor expression on monocytes; other anticoagulants (e.g., LMWH)
ROTEM™ *platelet* assays		
ARATEM	Arachidonic acid (AA)	COX-1 (e.g., aspirin) and GPIIb/IIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis
ADPTEM	Adenosine diphosphate (ADP)	ADP (P2Y12) (e.g., clopidogrel and prasugrel) and GPIIb/IIIa inhibitor effects; effects of CPB, trauma, and sepsis
TRAPTEM	Thrombin-receptor-activating peptide-6 (TRAP-6)	Thrombin (PAR-1) (e.g., vorapaxar) and GPIIb/IIIa inhibitor effects; effects of CPB, trauma, and sepsis

Courtesy of Klaus Görlinger, Tem International

PCC administration in patients suffering from bleeding due to vitamin K-dependent factor deficiency, e.g., due to warfarin therapy [17–23]. Furthermore, early variables of clot firmness (A5 and A10) in EXTEM can be used for early detection of fibrinolysis [41].

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 [41]. Thereby, platelet contribution to clot formation and clot strength is eliminated in this assay [30]. 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 and hypofibrinogenemia. 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].

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 [42–45]. 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. Furthermore, FIBTEM seems to be more sensitive to fibrinolysis compared to EXTEM [46, 47].

All extrinsically activated liquid assays contain polybrene, a heparin inhibitor which allows for immediate elimination of heparin effects (up to 5 units heparin/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 recalcification 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 depend on coagulation factors XII, XI, IX, VIII, X, V, and II and fibrinogen. 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**) can be used in combination with INTEM in order to reveal (residual) heparinization or protamine overdose [48, 49].

The **KAOTEM** assay is activated by recalcification and addition of kaolin. This assay is also sensitive to low molecular weight heparin (LMWH).

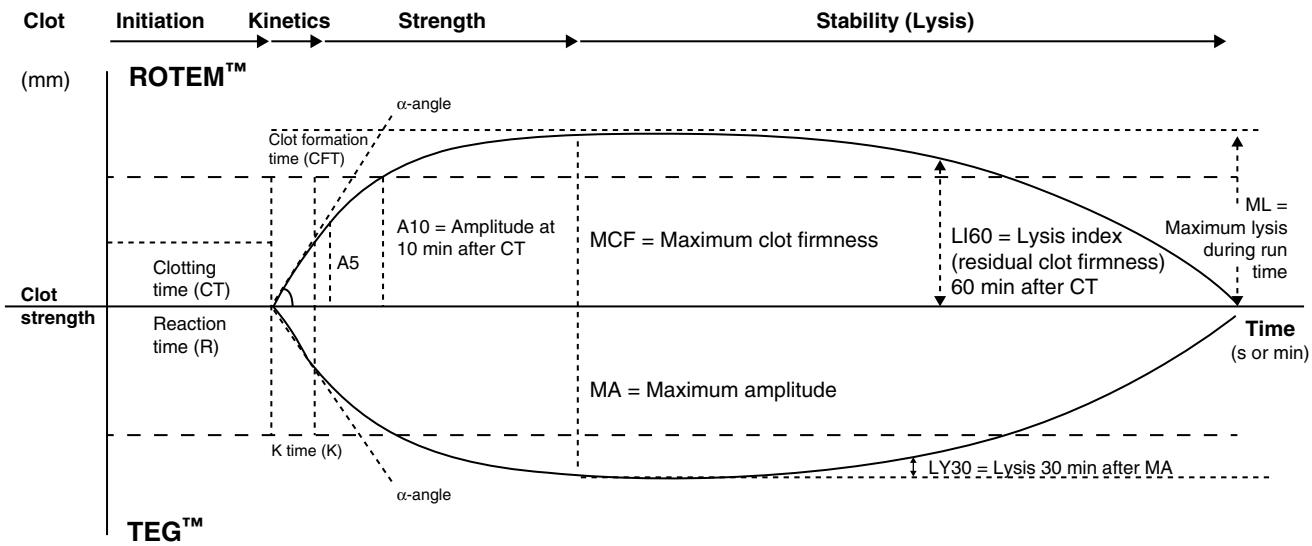
The **ECATEM** assay uses the viper venom ecarin as an activator. Ecarin directly converts prothrombin to meizothrombin which has already a low level of thrombin activity. Crucially, meizothrombin is inhibited by hirudin and other direct thrombin inhibitors (such as hirudin, argatroban, bivalirudin, and dabigatran), but not by heparin [50, 51]. 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.

Finally, the **NATEM** assay is activated by recalcification (star-tem™ reagent) only. The test is very sensitive to any endogenous activator such as tissue factor expression on circulating monocytes in infection, sepsis, cirrhosis, and patients treated with extracorporeal assist devices [44, 52–54]. Therefore, this assay may be helpful to detect a pathophysiological change from trauma-induced coagulopathy (TIC) to disseminated intravascular coagulopathy (DIC).

Besides the standard liquid reagents, lyophilized single-potion or single-use reagents (SUR) are available in Europe and several other countries [40]. 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). Notably, extrinsically activated SURs do not contain a heparin inhibitor and, therefore, must not be used in patients with therapeutic anticoagulation with unfractionated heparin, e.g., in cardiovascular surgery. This may have to be considered in patients with endogenous heparinization due to endothelial glycocalyx degradation, too.

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. 5.2, Table 5.3, and ROTEM™ *delta* manual) [55–58]. 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



	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. 5.2 ROTEM™ ("temogram") and TEG™ trace displaying the clinically most important parameters and their informative value. FDPs = fibrin(ogen) split products. Courtesy of Klaus Görlinger, Tem International

the results. Notably, specific age-related reference ranges for **infants/children** and trimester-related reference ranges for **pregnant woman** have been published, too [59–62].

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) [44, 52–54]. EXTEM CT is a reliable indicator of sepsis-induced DIC diagnosed by the Japanese Association for Acute Medicine (JAAM) DIC core and is strongly associated with severity of DIC [63]. 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]. In several settings, EXTEM CT is superior in predicting bleeding complications compared to INR. Thereby, a lot of inappropriate prophylactic interventions with FFP or PCC can be avoided without increased incidence of bleeding complications [24, 64–69].

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.

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

Table 5.3 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
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 5 min after CT
A20	Amplitude at 20 min	mm	Amplitude of clot firmness 5 min after CT
MCF	Maximum clot firmness	mm	Maximum amplitude of clot firmness reached during the run time
Clot lysis parameters			
ML	Maximum lysis	%	Maximum lysis detected during the run time, 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
Research parameters			
MCE	Maximum clot elasticity	–	MCE = 100 × MCF/(100 – MCF)
G	Shear elastic modulus strength	–	G = 5000 × 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
Research parameters for the first derivative curve (Sørensen 2003 [55]**)**			
max*V*	Maximum velocity	mm/min	Maximum of the first derivative of the curve
max*V*–*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 International

deficits [31]. The combination of EXTEM and FIBTEM clot firmness parameters (A5, A10, or MCF) is needed for accurate discrimination [13, 14, 23, 27–30, 33].

Clot Propagation Parameters (Clot Firmness)

One of the most important ROTEM™ parameter 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 amplitude reflects the mechanically 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. However, A5 is not yet available in the USA as of early 2016. 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 10–15 min after starting the test [6, 13, 26–28, 33]. EXTEM and INTEM A10 and A5 correlate with platelet count and fibrinogen concentration, FIBTEM A10 and A5 correlate well with plasma fibrinogen concentration, and PLTEM A10 (A5) = EXTEM A10 (A5) – FIBTEM A10 (A5) correlates well with platelet count [13, 27, 33, 70]. Notably, clot firmness parameters are superior in predicting bleeding compared to platelet count [71–74]. Furthermore, low clot firmness values have been demonstrated to be associated with an increased incidence of hyperfibrinolysis. An EXTEM A5 ≤ 35 mm can identify more than 90 % of patients developing hyperfibrinolysis, finally [28]. 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 [75].

Clot Lysis Parameters

The clot lysis parameter 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. 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 [76]. Notably, the correlation between severity of fibrinolysis and patient outcomes seems to be setting specific. Whereas in severe trauma 3–5 % fibrinolysis within 1 h runtime is associated with increased mortality, even 50 % fibrinolysis during liver transplantation is not [77, 78]. On the other hand, a shutdown of fibrinolysis (0 % fibrinolysis at 1 h runtime) can be associated with increased mortality even in trauma [77, 78]. Notably, hypofibrinolysis seems to play a major role in the pathophysiology of myocardial infarction, thrombosis, sepsis, and DIC [52, 79–81].

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) [56]. 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, viscoelastic testing is not sensitive to von Willebrand disease since the system does not include a collagen surface and does not induce high sheer stress.

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. However, ROTEM data in patients with antiphospholipid syndrome are sparse.

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. It provides two channels for whole blood impedance aggregometry in addition to the four viscoelastic channels of ROTEM™ *delta* (Fig. 5.1a, 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 Ω × min), the amplitude at 6 min (A6 in Ω), and the maximum slope (MS in Ω/min). AUC is the clinically most important parameter and reflects the overall platelet aggregation (Fig. 5.1e).

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 [82–85]. Therefore, these pre-analytic factors have to be standardized and validated, and hospital-specific reference ranges and cutoff 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, as well as mortality in severe trauma and sepsis [35–39, 56, 86–98]. Furthermore, the effects of drugs, such as desmopressin and tranexamic acid, on platelet function can be monitored by whole blood impedance aggregometry [99, 100]. However, the optimal role of platelet transfusion in patients with early platelet dysfunction in severe trauma and sepsis remains unclear.

Predictive Value of Thromboelastometry and Impedance Aggregometry

The positive predictive value of thromboelastometry and impedance aggregometry to predict bleeding in elective surgery is low, but the negative predictive value is very high (up to 100 %) [91, 92, 101, 102]. 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 significant bleeding requiring a hemostatic intervention. In contrast to patients scheduled for elective surgery, in patients with preexisting hemostatic disorders, such as cirrhosis, trauma, sepsis, or specific drug effects, thromboelastometry and impedance aggregometry provide a positive predictive value, too [33, 39, 93–95, 103–105].

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. If both thromboelastometry and impedance aggregometry show normal results, the probability of coagulopathic bleeding is very low and the patient should be rechecked for surgical bleeding (Fig. 5.3.).

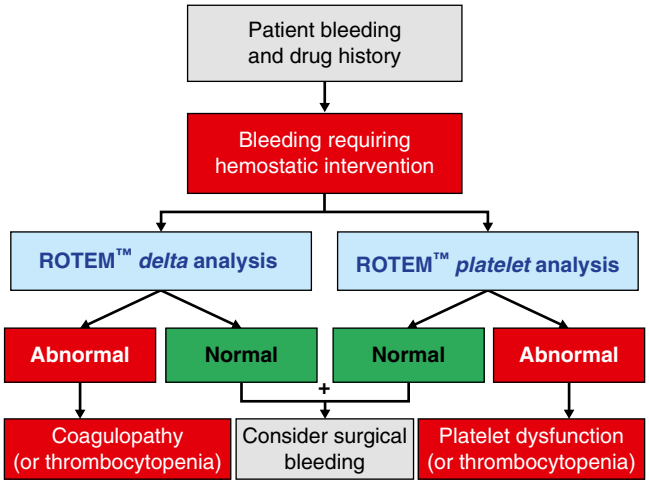


Fig. 5.3 ROTEM™ diagnostics flowchart (improved diagnostic performance by combining thromboelastometry (ROTEM™ *delta*) with whole blood impedance aggregometry (ROTEM™ *platelet*). Courtesy of Klaus Görlinger, Tem International

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. Thus, early prediction of massive transfusion is crucial for decision-making to start plasma transfusion in severe trauma [106–108]. 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 [33, 39, 75, 104, 109, 110]. In these trauma studies, the optimum cutoff value to predict massive transfusion has been identified as EXTEM A5 ≤ 35 mm, INTEM A10 < 44 mm, and FIBTEM A10 (MCF) ≤ 7 (9) mm [75, 104, 110]. None of the patients with a FIBTEM A10 ≥ 12 mm on admission received a massive transfusion finally [104]. EXTEM A5 (≤35 mm) was more accurate in predicting massive transfusion than INR (>1.2) [75]. 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 [33]. Accordingly, the panel of the "2014 consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation" recommends thresholds for EXTEM

A10 (MCF) <40 (50) mm and for FIBTEM A10 (MCF) < 10 (12) mm to consider platelet or fibrinogen administration in bleeding trauma patients, respectively [23]. Chapman et al. could identify an optimum threshold for TRAPtem < 53 Ω × min (ROC AUC, 0.97) and for ADPtem of < 43 Ω × min (ROC AUC, 0.95) at hospital admission for prediction of massive transfusion by impedance aggregometry using ROTEM™ platelet [39].

Similar cutoff values have been published to predict bleeding and transfusion in other perioperative settings. 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) [111]. In patients preoperatively treated with thienopyridines (ADP-receptor antagonists), the best cutoff 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 %) [91]. If TRAPtest was ≥75 U, even ADPtest < 22 U was not associated with severe bleeding (negative predictive value, 100 %) [92]. A comparative study between the two impedance aggregometry devices Multiplate™ and the ROTEM™ *platelet* device identified the best cutoff value to predict bleeding at 5–10 min after heparin reversal with protamine as ASPItest ≤ 26 U, ARAtem ≤ 15 Ω × min, ADPtest ≤ 33 U, ADPtem ≤ 36 Ω × min, TRAPtest ≤ 78 U, and TRAPtem ≤ 78 Ω × min. Transfusion requirements correlated significantly with the number of platelet activation pathways inhibited [112]. This is in line with the results of other authors [92, 97].

In liver transplantation, the cutoff values that best predict bleeding and transfusion have been determined as EXTEM A10 (MCF) ≤ 35 (44) mm and FIBTEM A10 (MCF) ≤ 8 (9) mm [103, 113].

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 [114]. 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 Claus fibrinogen about 65 min after venipuncture in this study. The higher fibrinogen requirements in PPH fit well with the increased reference ranges for FIBTEM and Clauss fibrinogen at the end of pregnancy [60–62]. A randomized controlled trial (RCT) assessing the effect of FIBTEM-guided fibrinogen concentrate administration versus placebo for treatment of postpartum hemorrhage is just running [115].

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 and INTEM; tissue factor (TF)-expression on circulating monocytes, characterized by a shortening of CT in NATEM despite prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT); and shutdown of fibrinolysis, characterized by less than 3 % lysis within 1 h [44, 52–54, 63, 105, 116]. 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 study when given later than 3 h after injury [117], and why a shutdown of fibrinolysis (here defined as LY30 of 0 % in TEG™) detected in trauma patients at admission at hospital was associated with increased mortality, too [77, 78].

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, 118–120].

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, PTT, fibrinogen, and platelet count) and ROTEM™ tests to identify patients with hypercoagulability and thrombotic complications [121]. 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 an MCF cutoff value of >68 mm with a sensitivity and specificity of 94 %. FIBTEM MCF, with a cutoff 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 cutoff 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 [122]. Twenty-nine percent of the included patient population has been recruited from the orthopedic and spine department. Again, none of the routine coagulation tests have 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 cutoff 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 vs. 11 mm in healthy controls) may play a role in non-cirrhotic patients with portal vein thrombosis [123] and in patients with increased flaploss rate (EXTEM MCF>72 mm and FIBTEM MCF>25 mm) in patients undergoing reconstructive microsurgery [124].

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 BMI and inflammatory markers [125].

Tissue Factor Expression on Monocytes 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, extracorporeal membrane oxygenation (ECMO), and ventricular assist device (VAD), dialysis), as well as ischemia/reperfusion lead to TF-expression on circulating monocytes [44, 52–54, 63]. 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 [126–128]. TF-expression on circulating cells can be detected very sensitively (in picomolar concentrations) but not specifically by a reduction in CT in NATEM [52, 53]. Since heparinoids (e.g., by glycocalyx degradation or therapeutic administration) can mask this effect, heparinase should be added to the blood sample or test system to eliminate a potential heparin effect [52].

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.

Hypofibrinolysis (Fibrinolytic 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 [54, 129, 130]. 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 [131, 132].

However, Chapman et al. could demonstrate that not only increased fibrinolysis (>3 %) but also a fibrinolytic shutdown (0 % lysis within 30 min after maximum amplitude in kaolin-TEG) at hospital admission is associated with increased mortality in trauma patients [77, 78]. Accordingly, Adamzik et al. showed that the ROTEM™ LI60 in NATEM can discriminate between intensive care patients suffering from severe sepsis (NATEM LI60>96.5 % corresponding to a ML<3.5 % within 1 h after CT) and postoperative patients with systemic inflammatory response syndrome (SIRS) or healthy volunteers [52]. Furthermore, the LI60 (ROC AUC, 0.901; $P<0.001$) proved to be more accurate in detection of 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 septic 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) [105].

In conclusion, both hyper- and hypofibrinolysis 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 [32]. Levrat et al. included 87 trauma patients in a prospective observational trial. Patients with hyperfibrinolysis were more severely injured, had greater coagulation abnormalities, and a higher mortality rate (100 % vs. 11 %) [133]. Schöchl et al. identified in his 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 [134]. 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 [135]. In contrast, even 50 % fibrinolysis during liver transplantation is not associated with increased mortality.

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 [70]. Similar results were shown in a prospective cohort study in 334 blunt trauma patients performed by Tauber et al. They identified cutoff 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 [110].

Furthermore, early platelet dysfunction after trauma and in sepsis is associated with increased mortality [93–95].

Pathophysiology of Perioperative Hemostasis

In contrast to hereditary bleeding disorders, pathophysiology of posttraumatic or perioperatively acquired bleeding is most often multifactorial. For example, TIC, DIC, and coagulopathy in cirrhosis are different pathophysiological entities requiring different treatment strategies [19, 23, 33, 63, 66, 116, 136]. Notably, patients can be at risk of bleeding and thrombosis at the same time [137, 138].

One common issue in perioperative bleeding is that bleeding, coagulopathy, and transfusion are independent risk factors for poor outcomes and can built up each other in a vicious circle [139]. 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 [140]. Finally, this can result in single or multiple organ failure.

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 [141]. 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, and **prevent** secondary bleeding and coagulopathy. However, overtreatment should be avoided to prevent thrombotic or thromboembolic events in the postoperative phase [9, 118]. Here, a "therapeutic window" concept may address this issue most appropriate [34, 98, 142].

Despite or just because of the multifactorial pathophysiology of perioperative bleeding, a systematic diagnostic approach is required to identify the underlying hemostatic disorder and to guide hemostatic therapy in a specific and timely manner ("theragnostic approach") [19, 23, 136, 143].

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 [23, 144, 145]. In order to guide hemostatic therapy in bleeding patients, algorithms have been developed as a link between ROTEM™ diagnostics and hemostatic therapy ("theragnostic approach") [19–21, 34, 56, 108, 143, 146–149]. Due to the increasing number of publications and data available—the number of ROTEM™ publications doubled since 2012—these algorithms changed 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 hospital costs, in particular in cardiovascular surgery [9, 118, 150–155]. Several cohort studies reported similar results in liver transplantation, trauma, and PPH, but only three RCTs are published in the setting of trauma, burns, and pediatric orthopedic surgery [20, 70, 110, 155–165]. However, further RCTs are just running [NCT01826123, NCT02200419, NCT01545635, NCT02416817, NCT02239991, NCT 02352181, NCT02461251, ISRCTN46295339, 115].

An evidence-based ROTEM™-guided algorithm for severe bleeding management is presented in Fig. 5.4 and characteristic thromboelastometric traces in Fig. 5.5a–j.

Since the ROTEM™ parameter A5 is not yet FDA approved, 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

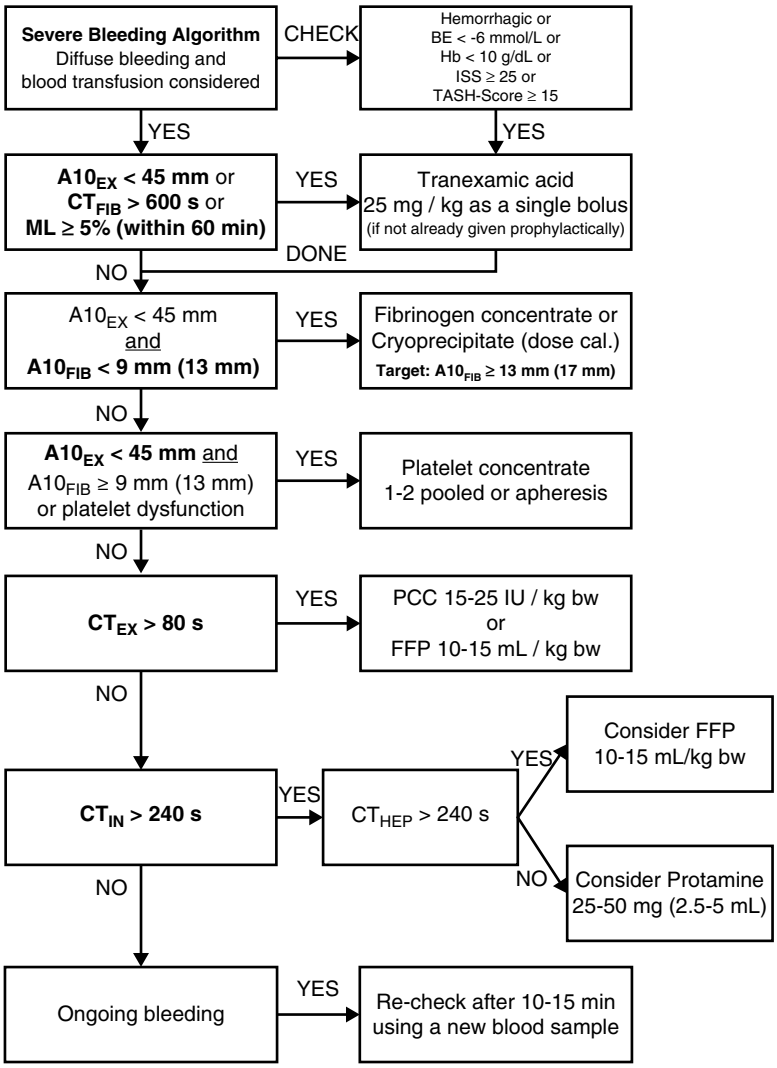


Fig. 5.4 Evidence-based ROTEM™ A10 severe bleeding algorithm. $A10_{EX}$ = amplitude of clot firmness 10 min after CT in EXTEM; $A10_{FIB}$ = amplitude of clot firmness 10 min after CT in FIBTEM; BE = base excess; bw = body weight in kg; CT_{EX} = coagulation time in EXTEM; CT_{FIB} = coagulation time 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 h run time); PCC = prothrombin complex concentrate; TASH score = trauma-associated severe hemorrhage score. Courtesy of Klaus Görlinger, Tem International

and A5 for FIBTEM is usually 1 mm and for EXTEM, APTEM, INTEM, and HEPTEM 9–11 mm [11, 13, 26, 27]. The bias between early clot values (A5 and A10) and MCF is displayed on Table 5.4.

Clinical Assessment

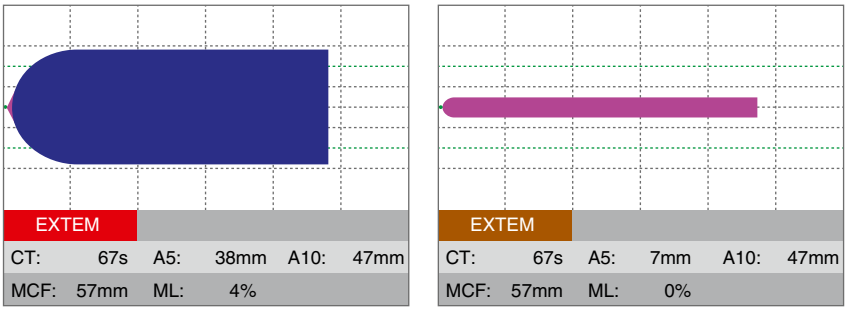
Hemostatic interventions should be performed only in patients with diffuse bleeding and if blood transfusion is considered. Severity of trauma (ISS ≥ 25), clinical bleeding scores (e.g., TASH score ≥15), hemodynamic instability (e.g., hemorrhagic shock), hypothermia (core temperature <35 °C), and results of blood gas analysis (e.g., pH < 7.2, BE < −6 mmol/L, Hb < 10 g/dL, Ca^{++} < 1 mmol/L) should be considered, too, since they may be associated with an increased risk of hyperfibrinolysis and hypofibrinogenemia [74, 119–121]. Accordingly, decision-making for hemostatic interventions should not be based on ROTEM™ results solely, in the absence of clinically relevant bleeding.

Management of Fibrinolysis

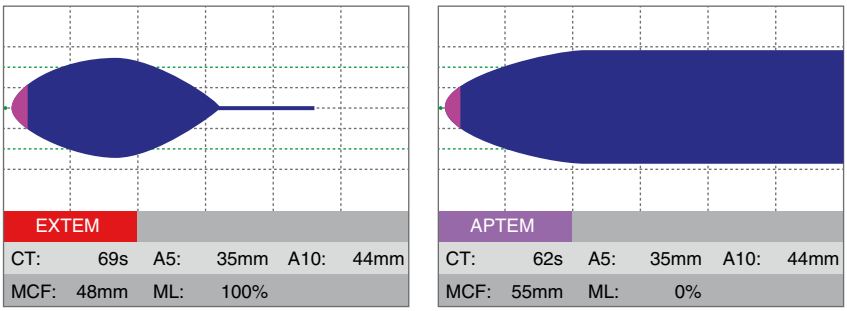
Hyperfibrinolysis (>3 % within 30 min after MA) as well as fibrinolytic shutdown (0 % within 30 min after MA) is associated with increased mortality in severe trauma [77, 78]. Therefore, exogenous inhibition of the fibrinolysis system in severely injured patients requires careful selection, as it may have an adverse effect on survival, in particular if tranexamic acid is given later than 3 h after injury [77, 78, 117]. In contrast to trauma, even 50 % fibrinolysis during liver transplantation is not associated with increased mortality but with an increased incidence of thrombotic events. Therefore, it is still under discussion, whether antifibrinolytic drugs should be given prophylactically in 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.

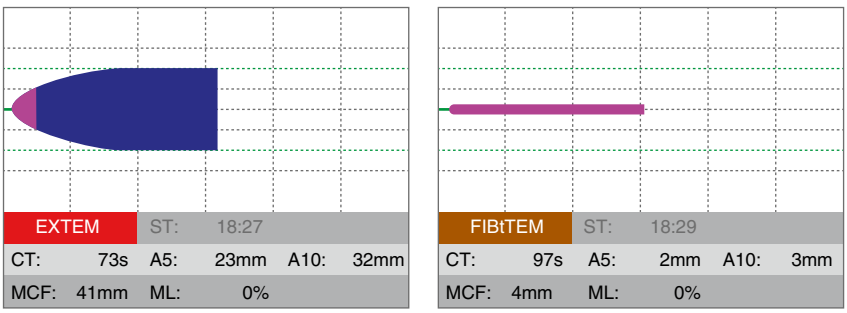
Normal clot:
EXTEM CT 43-82 s
EXTEM A10 40-60 mm
EXTEM MCF 52-70 mm
EXTEM ML < 15%
EXTEM LI60 > 85%
FIBTEM A10 6-21 mm
FIBTEM MCF 7-24 mm



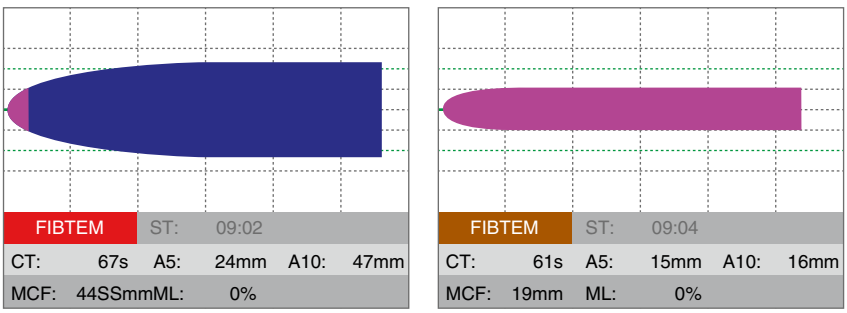
Hyperfibrinolysis:
EXTEM ML ≥ 15% within 60 min (LI60 ≤ 85%);
ML ≥ 5% may already be associated with increased mortality in severe trauma;
APTEM confirms TXA effect



Fibrinogen deficiency:
EXTEM A10 < 40 mm
and
FIBTEM A10 < 10 mm



Thrombocytopenia:
EXTEM A10 < 40 mm
and
FIBTEM A10 ≥ 10 mm



Hypercoagulability (high thrombotic risk):
EXTEM CT < 40 s
EXTEM CFT < 50 s
EXTEM CFT > 68 mm
FIBTEM MCF > 24 mm
LI60 ≤ 3%

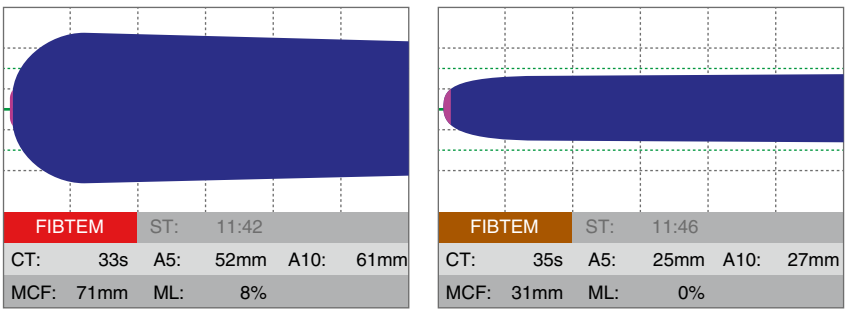
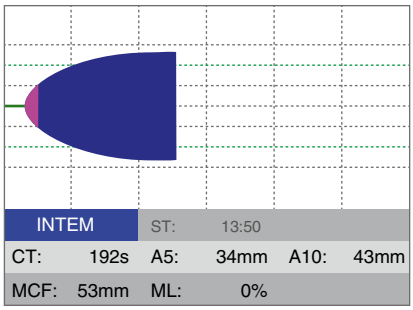
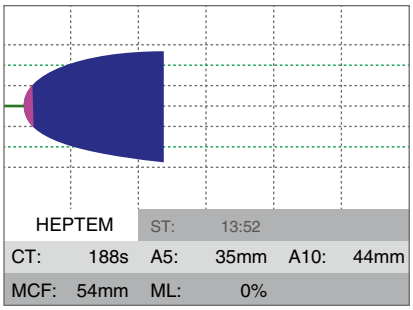


Fig. 5.5 (**a**–**j**) Characteristic thromboelastometry traces. The diagnostic performance is increased by test combinations, e.g., EXTEM and FIBTEM, EXTEM and APTEM, or INTEM and HEPTEM. *4 F-PCC* four-factor prothrombin complex concentrate, *A10* amplitude of clot firmness 10 min after CT, *CFT* clot 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, Tem International

Normal clot (adequate heparin- reversal with protamine after CPB):

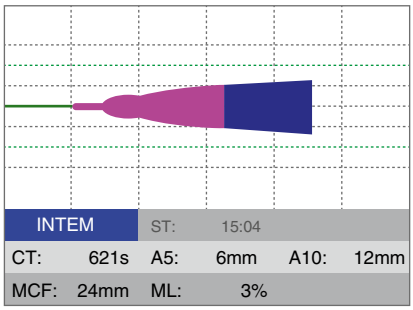
INTEM CT 122-208 s
INTEM A10 40-60 mm
INTEM MCF 51-72 mm
HEPTEM CT ≈ INTEM CT

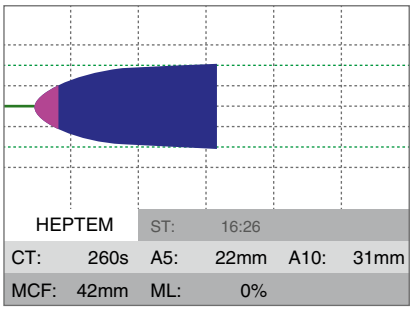




Heparin, low dose (endogenous anti-coagulation during OLT or severe trauma):

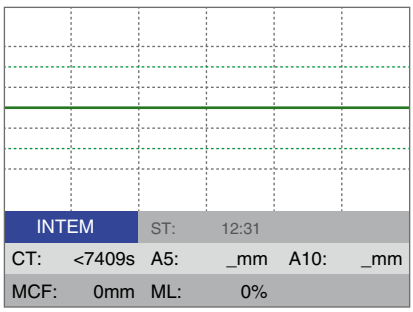
INTEM CT >> HEPTEM CT
(ΔCT > 20% HEPTEM CT)

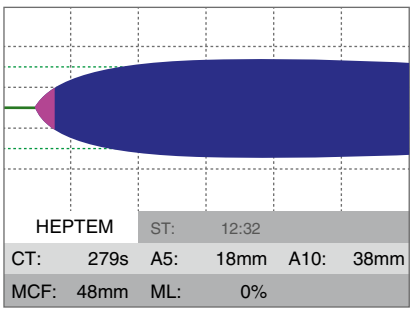




Heparin, high dose (during CPB):

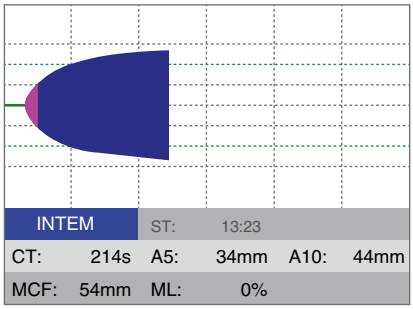
INTEM flat-line (CT > 1200s)
and
HEPTEM CT < 280 s

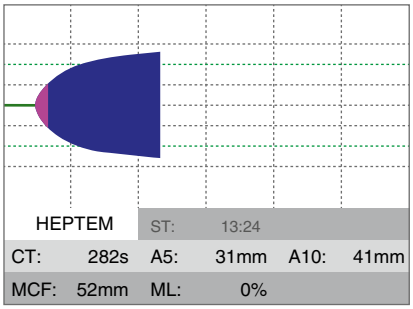




Protamine overdose (after heparin-reversal):

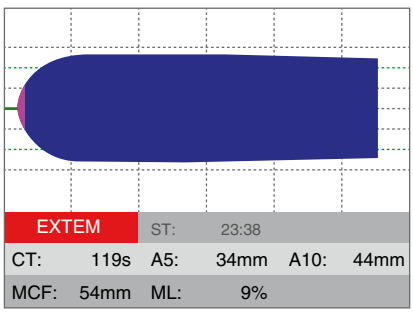
HEPTEM >> INTEM CT
(ΔCT > 20% HEPTEM CT)





Deficiency of vitamin K-dependent factors (warfarin therapy):

EXTEM CT > 80 s
(here, EXTEM CT decresed to 70 s after 4F-PCC administration; right graph)



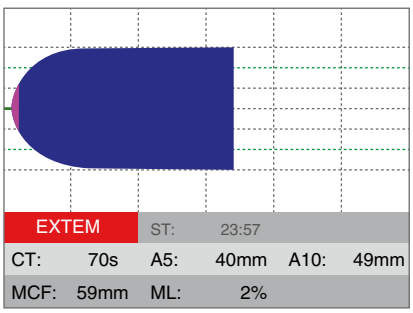


Fig. 5.5 (continued)

Table 5.4 Bias between early clot firmness values (A5 and A10) and maximum clot firmness (MCF) for all assays as obtained from Bland–Altman analyses

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

Courtesy of Klaus Görlinger, Tem International
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 [11, 13, 26, 27]

Table 5.5 FIBTEM-guided fibrinogen substitution

Targeted increase in FIBTEM A10 (A5) (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]

Courtesy of Klaus Görlinger, Tem International
Here, fibrinogen dose calculation is based on the targeted increase in FIBTEM A10 (A5) in mm [20, 147, 168]. In case of severe bleeding, the achieved increase in FIBTEM A10 (A5) may be lower than the calculated increase

An EXTEM A5 threshold of ≤35 mm (EXTEM A10 ≤ 45 mm) detects more than 90 % of patients which will develop hyperfibrinolysis, finally [28]. Notably, FIBTEM seems to be more sensitive to fibrinolysis compared to EXTEM [46, 47]. A flat line in FIBTEM characterized 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 [166]. In contrast, high factor XIII levels attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood [45].

Management of Clot Firmness

TIC is functional characterized by a reduced clot firmness in EXTEM with an A5 < 35 mm (A10 < 45 mm) and predicts the need for massive transfusion [23, 33, 75]. Reduced clot firmness can be based on hypofibrinogenemia, fibrin polymerization disorders (e.g., due to colloids), thrombocytopenia, and severe thrombocytopathy (reduced platelet aggregation due to activation of platelets' thrombin receptors) [29, 93].

FIBTEM A10 (A5) can be used for rapid and correct discrimination between hypofibrinogenemia and thrombocytopenia [13, 27, 70, 104]. A FIBTEM A10 < 9 mm (A5 < 8 mm) is associated with an increased risk of massive bleeding and can be used as a trigger value for fibrinogen substitution [23, 104, 110, 111, 113]. Here, the targeted FIBTEM A10 value is usually ≥13 mm (A5 ≥ 12 mm). However, some patients may even need a higher trigger value of 13 mm (with a targeted value of 17 mm)—in particular in patients with severe bleeding due to PPH, unstable pelvic fractures, traumatic brain injury (TBI), or major aortic surgery [114, 150, 167]. The required fibrinogen dose can be calculated based on the targeted increase in FIBTEM A10 (A5):

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

Here, the correction factor (140–160 $\text{mm} \times \text{kg} \times \text{g}^{-1}$) depends on the actual plasma volume [20, 147, 150, 168]. In case of severe bleeding, the achieved increase in FIBTEM A10 (A5) 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 contains about 2 g fibrinogen. Table 5.5 provides a quick overview about the fibrinogen concentrate or cryoprecipitate dose needed to achieve the targeted increase in FIBTEM A10 (A5) [20, 21, 147, 168].

If clot firmness in EXTEM is reduced (A10 < 45 mm or A5 < 35 mm) but FIBTEM clot firmness is above the trigger value (A10 ≥ 9 mm or A5 ≥ 8 mm), platelet transfusion has to be considered in severe bleeding. Notably, ROTEM™ analysis has been shown to be superior to platelet count in prediction of bleeding in patients with severe thrombocytopenia [72, 73]. The expected increase in EXTEM A10 (A5) per transfused pooled or apheresis platelet concentrate is 5–10 mm in adult patients [71, 74, 169]. Therefore, the number of transfused platelet concentrates can be calculated based on the targeted increase in EXTEM A10 (A5). At least one pooled or apheresis platelet concentrate is needed per targeted increase of 10 mm. In case of very low EXTEM A10 (<25 mm or A5 < 15 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. 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 (Fig. 5.1a, c–e). Characteristic ROTEM platelet traces are displayed in Fig. 5.6a–f. Besides detection of the effects of antiplatelet drugs and other drugs with antiplatelet effects (e.g., analgetics, antidepressants, antibiotics, cardiovascular drugs), 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 [39, 56, 91–95, 170, 171]. However, actually it is not yet clear whether early trauma- or sepsis-induced platelet dysfunction should be treated with platelet transfusion or not. In liver transplantation, platelet transfusion is associated with increased mortality, independent from the platelet count prior to transfusion [73, 172]. Therefore, decision-making for platelet transfusion should be done carefully and alternatives (e.g., desmopressin, tranexamic acid or fibrinogen) may be considered [99, 100, 150, 167, 173–175].

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., warfarin, heparin, direct thrombin inhibitors (e.g., hirudin, argatroban, or bivalirudin), or direct oral anticoagulants (DOACs, such as dabigatran, rivaroxaban, apixaban, or edoxaban). Notably, a protamine overdose can prolong CT, too [48, 49].

Usually a CT prolongation in EXTEM indicates a deficiency of coagulation factor from the extrinsic or common pathway (factor 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), cirrhosis, or hemodilution/consumption during severe bleeding. Since the vitamin K-dependent inhibitors proteins C and S in these situations are low, too, the coagulation system can be rebalanced at a low unstable level—associated with a high risk of bleeding and thrombosis [138, 139]. EXTEM CT correlates well with INR in patients treated with warfarin [17]. However, the activity of the vitamin K-dependent coagulation factors usually is decreased below 30 % of their normal activity if CT in EXTEM exceeds 80 s [20, 24]. Notably, a severe fibrinogen deficiency can prolong CT in EXTEM, too. Therefore, EXTEM CT can be used for guiding therapy with PCC or FFP only in case of a normal A10 (A5) in FIBTEM [9, 19, 20, 23, 148]. Accordingly, management of clot firmness precedes management of coagulation time in the ROTEM™ algorithm. Usually, a dose of 15–25 units/kg of PCC is sufficient to normalize EXTEM CT, to reduce INR below 1.5, and to stop coagulopathic bleeding [10–22, 176].

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 [176–180]. In patients with warfarin-induced bleeding complications, four-factor PCCs have been proven to be superior to FFP transfusion regarding efficacy and safety [181–184]. 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) [9, 19–23, 156, 157, 160, 182]. 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 TRALI, TACO, and TRIM [106, 176–186]. Administered in a targeted way, the risk of thrombotic events by using four-factor PCCs seems to be low [187–189]. However, further studies are needed for final risk assessment.

Notably, direct thrombin inhibitors such as dabigatran can result in a marked increase in both EXTEM and INTEM CT as well as in ECATEM CT. The ecarin-based ROTEM™ assay ECATEM is specific for direct thrombin inhibitors such as hirudin, argatroban, bivalirudin, and dabigatran [50, 51, 190–192].

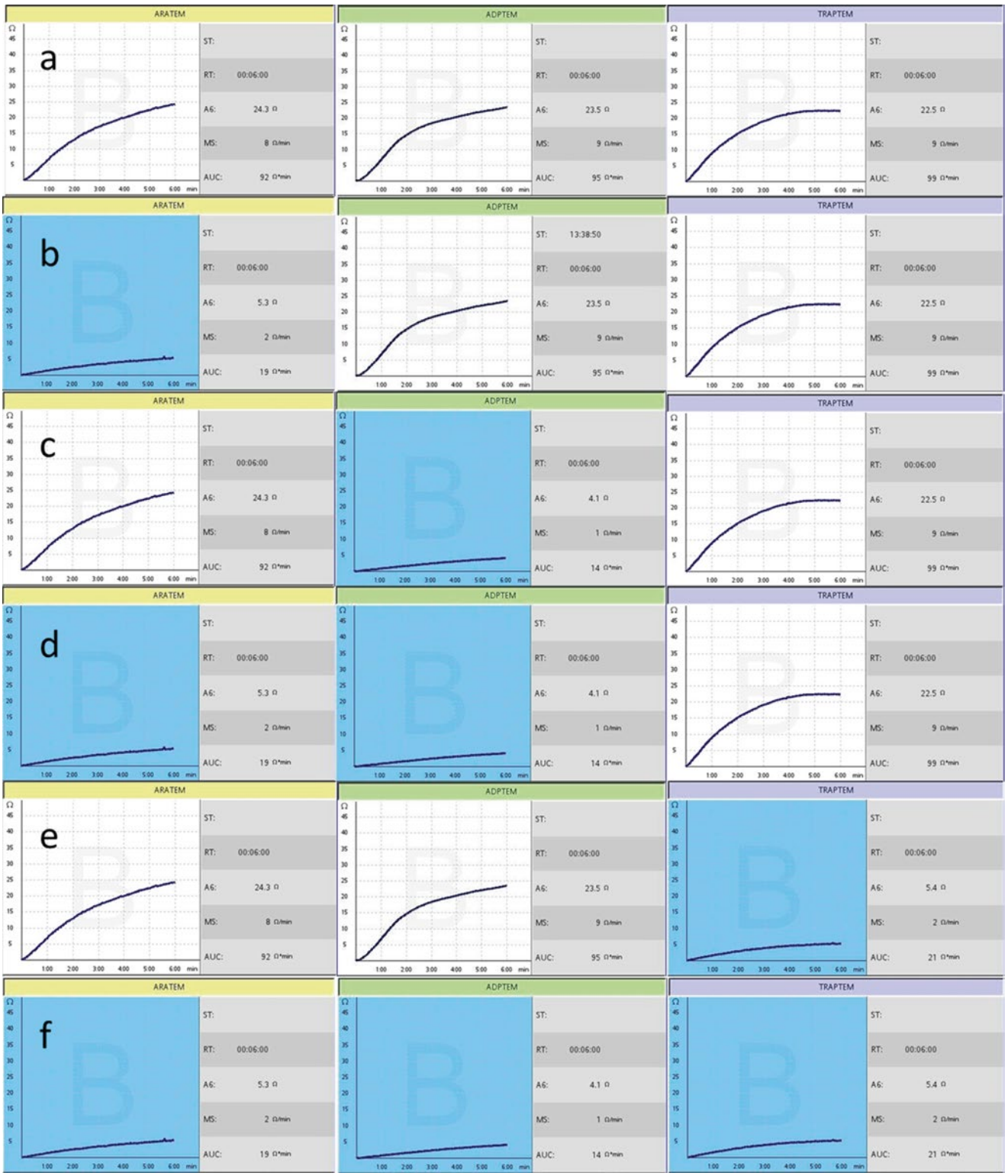


Fig. 5.6 (**a–f**) Characteristic whole blood impedance aggregometry traces (ROTEM™ *platelet*) achieved by activation with arachidonic acid (ARATEM; *left* column), ADP (ADPTEM; *middle* column), and TRAP-6 (TRAPTEM; *right* column). (**a**) Normal platelet function, (**b**) selective inhibition of 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, GPIIb/IIIa-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, Tem International

Activated PCCs (Factor Eight Inhibitor Bypassing Agent = FEIBA) are only indicated in acquired hemophilia with inhibitors [193]. Due to the high risk of arterial thromboembolic events, the off-label administration of recombinant activated factor VII (rFVIIa) should be restricted to bleeding not responding to comprehensive coagulation therapy [194, 195]. The implementation of thromboelastometry-guided bleeding management algorithms usually eliminates the need for rFVIIa administration as a rescue therapy [9, 118, 152, 153].

A prolongation of INTEM CT can be based on a heparin 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 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 [14, 148]. Protamine administration can be considered. Notably, a protamine overdose can prolong the CT in the INTEM, HEPTEM, as well as EXTEM. In case of CT prolongation in INTEM and HEPTEM—not due to a protamine overdose—FFP transfusion can be considered in bleeding patients.

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 min after the hemostatic intervention with a new blood sample, and the algorithm has to be started, again.

In case of normal results in both, thromboelastometry and impedance aggregometry, surgical bleeding should be considered and the patient should be reexamined surgically (Fig. 5.3.).

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 pediatric surgery [32, 34, 151, 155, 160–162, 165, 196]. Görlinger, Fries, and Schöchl reported in their retrospective analysis that implementation of a ROTEM™-guided algorithm in their institutions reduced transfusion requirements for FFP, 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 %; $p < 0.001$) [20]. These results could be confirmed by several other cohort studies and RCTs [9, 70, 110, 118, 149, 151–159, 163, 196, 197].

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™) [53].

Besides reduction of transfusion requirements and the need for large volume (≥4 units of RBC) or massive transfusion (≥10 units of RBC), for surgical reexploration for bleeding, or for postoperative hysterectomy [9, 118, 152, 153, 161, 162], several studies could show improved patient outcomes, such as reduced incidence of pulmonary complications/postoperative ventilation time [161, 162, 181], acute kidney injury/need for renal replacement therapy [118, 152], thrombotic/thromboembolic events [9, 118], nosocomial infections/sepsis [118, 153], multiple organ failure (MOF) [159, 197], stay at ICU [151, 153, 161, 162], and mortality [70, 118, 156, 159]. Furthermore, hospital 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 [9, 20, 118, 148, 153, 162, 163, 198–204].

Therapeutic Window Concept

The algorithm presented in Fig. 5.4 is 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 minimize the risk of ischemia (stent thrombosis) and bleeding [34, 98, 103, 120–122]. Accordingly, bleeding management algorithms guided by thromboelastometry and whole blood impedance aggregometry are designed to minimize the risk of both, bleeding and thrombosis, by an individualized therapy. Here, the right therapeutic intervention, in the right dose and the right sequence, is defining the framework of the therapeutic window, e.g.:

- EXTEM A10: 45–60 mm
- FIBTEM A10: 9–20 mm
- EXTEM CT: 40–80 s
- ADPtem: 35–45 Ω×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 [9, 118–122].

Guidelines, Health Technology Assessments, Knowledge Translation, and Implementation

Based on the actually available evidence, the implementation of ROTEM™-guided algorithms is highly recommended (Grade 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) [140, 180, 193]. Viscoelastic testing is an essential part of multimodal protocols/algorithms that typically consist of a predeterminated bundle of diagnostics and interventions intended to reduce blood loss and transfusion requirements [180]. In particular, therapeutic interventions with highly effective coagulation factor concentrates, such as fibrinogen concentrate and PCC, should be guided by thromboelastometry (Grade 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 B) 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) [193].

The cost-effectiveness of ROTEM™-guided bleeding management has also been proven by several health technology assessments and pharmaco-economic analyses [199, 203, 205–207]. However, guidelines and health technology assessments can only change practice and improve patients' outcomes in combination with knowledge translation and implementation. Therefore, the "STOP Bleeding Campaign" was initiated in 2013 [141].

Thromboelastometry as an Integral Part of a Patient Blood Management Program

Patient blood management (PBM) is the timely application of a multidisciplinary, evidence-based medical concept, which helps to optimize the patient's own blood volume and minimize blood loss and thereby significantly reduces or even avoids allogeneic blood transfusion. 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 [4, 6, 69, 93, 119, 163, 181, 196, 208–211]. Accordingly, all hospitals in the UK have been asked by NHS Blood and Transplant, the UK Department of Health, and the UK National Blood Transfusion Committee to establish a patient blood management program, including POC testing and implementation of bleeding management protocols. Recently, a German PBM network has been founded, and a prospective multicenter trial enrolling about 100,000 patients is running to assess safety, efficiency, and cost-effectiveness of implementing a PBM program in surgical patients [212].

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Part II

Bleeding Associated with Disease Condition

Known Bleeding Disorders for Surgery

6

Miguel A. Escobar and Trinh Nguyen

Introduction

Management of bleeding disorders in the perioperative setting involves achieving and maintaining a desired (missing) factor level for hemostasis. Where factor concentrates or recombinant factors are available, they are treatment of choice. In some congenital factor deficiencies, however, plasma-derived concentrates and recombinant factor products are not available. Under these circumstances, fresh frozen plasma (FFP) which contains all coagulation factors may be used. Transfusion of 10–15 mL/kg of FFP will usually raise factor levels by 15–20 % [1]. The drawback for FFP, however, is the large volume required to achieve a desired factor level. In individuals such as cardiac failure patients who are sensitive to even slight volume shifts, circulatory overload is a concern. Cryoprecipitate is a human blood-derived product that is rich in factors I (fibrinogen), VIII, XIII, and von Willebrand factor (VWF). In areas where plasma-derived concentrates or recombinant factor (fibrinogen, FVIII, FXIII, or VWF) products are not available, cryoprecipitate may be an option to prevent bleeding complications during and after surgery.

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Adjunctive measures toward hemostasis include antifibrinolytics such as ε-aminocaproic acid or trans-*p*-aminomethylcyclohexane carboxylic acid (tranexamic acid), especially in surgeries involving the gastrointestinal tract (nasal, oral, intestinal), where fibrinolytic activity is high. In general the ε-aminocaproic acid dose is 100 mg/kg (max 3 g) every 6 h orally, and tranexamic acid dose is 10 mg/kg (adults 1300 mg/dose) orally every 8 h [2]. 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 FVIII from the Weibel–Palade bodies. 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:RCo and 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 <50 kg (150 μg/day) or one spray per nostril per day in persons >50 kg (300 μg/day). Intravenous or SQ dosing is 0.3 μg/kg body weight. The IV route is the preferred route in surgical prophylaxis [3, 4]; however, intranasal dosing has been used with success. Adverse effects including tachyphylaxis, fluid retention, hyponatremia, and seizures limit its use to 3 days.

The surgery itself should be undertaken in a facility that has experience in caring for individuals with bleeding disorders. 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 packed red blood cells [4]. Nowadays these procedures, especially major surgeries, are done by comprehensive teams in hemophilia centers.

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Von Willebrand disease

There are many plasma-derived concentrates of von Willebrand factor commercially available. The VWF:RCo to FVIII:C ratio ranges from 1:1 to 2:1, depending on the VWF product used. Each unit/kg body weight VWF increases the VWF:RCo by 1 %.

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, 5]. 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 h after the first dose to keep VWF:RCo and FVIII:C above 50 % [3, 5] (see Table 6.1). Daily monitoring of VWF:RCo and FVIII:C to maintain troughs >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].

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 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 pre-op period and continued every 6 h. Tranexamic acid 1300 mg every 8 hours for 5 days is another option for this individual. Topical sealants should also be considered during surgery to achieve hemostasis.

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 reveals a post-DDAVP VWF:RCo and FVIII:C levels of >90 %, she could have received DDAVP every 24 h starting in the pre-op period then continued for another 48 h.

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 h to maintain goal trough VWF:RCo and FVIII:C >50 % for 7–14 days until wound healing has completed [3, 5] (see Table 6.1). Desmopressin monotherapy is not adequate for major surgeries; however, DDAVP and antifibrinolytics may be utilized as adjunctive therapy.

Table 6.1 Goal VWF:RCo in the perioperative period

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

Sample Case

A 45-year-old woman with type II VWD is scheduled for hysterectomy. She weighs 60 kg. Her VWF:RCo measured is 32 IU/dL and FVIII activity is 40 IU/dL. Prior challenge showed a poor response to DDAVP. In this case, a loading dose of 60 IU/kg would increase both VVWF: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 of 1:1. Subsequent daily dosing will be based on follow-up VWF:RCo and FVIII:C in 12–24 h. Antifibrinolytics can be used to provide additional hemostasis.

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 [6]. 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 postoperative rather than during the surgical procedure. There are many recombinant and plasma-derived concentrates of FVIII commercially available. For individuals that undergo major surgical procedures, an in vivo recovery and half-life study should be done in the non-bleeding state with a 3–5-day washout period. Each IU/kg body weight of FVIII increases the FVIII:C by 0.2 IU/dL. The following formula can be used to calculate FVIII dosing: weight (kg) × desired FVIII:C (IU/dL) × 0.5.

In 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 specialized team of specialists 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 persons with hemophilia A, a pre-op FVIII:C of 50–80 % is recommended. In the postoperative period, goal FVIII:C of 30–80 % for 1–5 days may be necessary depending on the surgery [4, 6]. A daily dose of 30–40 IU/kg should achieve these goals [7], and daily monitoring of FVII:C levels are recommended if treatment extends beyond 3 days (Table 6.2).

Table 6.2 Goal FVIII:C in the perioperative period

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

Sample Case
A 65-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. 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, goal FVIII:C of 60–80 % is desirable for the first 72 h followed by FVIII:C of 40–60 % on days 4–6 and 30–50 % until day 14 [4, 8]. 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 30 % FVIII:C 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 %. Daily monitoring of levels and adjusting dose and frequency is advisable (Table 6.2).

Continuous Infusion

Some hemophilia centers use continuous infusions to maintain hemostasis during surgeries. 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 % [6]. Batorova et al. report using continuous infusions for surgical prophylaxis with an initial factor bolus dose of 50 IU/kg to goal 100 % [9]. 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 FVII: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 [9, 10].

Hemophilia A and B with Inhibitors

Patients with high-titer inhibitors undergoing surgery are more challenging due to the fact that bypassing agents are not 100 % effective and there are variable responses to these products among individuals. Surgical experience with this group of individuals has grown in the last 15 years providing less morbidity and improving quality of life. Although these procedures should be undertaken in hemophilia treatment centers with experience, patients with inhibitors should not be denied indicated procedures. It is important to develop a pre-, intra-, and postoperative detailed plan involving all the different specialties before the surgery [11]. Two products have been approved by the FDA to treat patients with hemophilia and inhibitors: recombinant activated factor VII (recombinant factor VIIa) (NovoSeven™; Novo Nordisk, Bagsvaerd, Denmark) and factor VIII inhibitor bypassing activity, FEIBA™ (Baxalta, Vienna, Austria). The latter is a plasma-derived activated prothrombin complex concentrate (aPCC) rich in activated FVII and mainly nonactivated factors II, IX, and X. Both products are used for the treatment of bleeding episodes as well as perioperative management. There are no studies suggesting one product is superior to the other. As such, personal physician preference guidance by experience and availability of product may dictate which bypassing agent is utilized for surgical prophylaxis. Thromboembolic events have been reported with both bypassing agents.

Minor Surgery

The recommended dose for rFVIIa in persons with hemophilia with an inhibitor is 90 μg/kg body weight immediately prior to surgery followed by repeat dosing every 2 h given its short half-life. As hemostasis is maintained, the interval between doses may be slowly increased (see Tables 6.2 and 6.3).

Sample Case
A 2-year-old boy 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 40 kg. Pre-op dose rFVIIa: 90 μg/kg × 40 kg = 3600 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 h as necessary.
If FEIBA™ was used, then the dose calculated: 50 IU/kg × 40 kg = 2000 IU given once prior to the procedure followed by additional doses every 12 h.

Table 6.3 Goal FIX:C in the perioperative period

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

Major Surgery

For major surgeries, a loading dose of rFVIIa 90 μg/kg body weight, repeated dosing is necessary every 2 h during surgery and continued post-op with an even slower taper in the post-op period until the wound is healed [12, 13] (see Tables 6.2 and 6.3). Giangrande et al. [14] proposed a protocol for elective orthopedic surgery (major surgery) in hemophilia patients with inhibitors. Here, a higher pre-op rFVIIa dose of 120–180 μg/kg body weight is proposed. In the post-op period, rFVIIa 90 μg/kg body weight remains scheduled every two 2 h for 48 h. If hemostasis is maintained, the frequency may be decreased to 90 μg/kg every 3 h for the next 48 h. On days 5–8, the frequency may be decreased to every 4 h, and if adequate hemostasis persists, dosing may be decreased to 6 h for another 48–96 h with possibility of discharge at day 12 [14]. The protocol that is used in our hemophilia treatment center is depicted in Table 6.4. We prefer to start surgery with rFVIIa due to the flexibility in dosing and frequency, but 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 g. The post-op dose: 90 μg/kg × 80 = 7200 μg every 2 h × 48 h. On days 3–5, administer rFVIIa 7200 mg every 3 h × 48 h, followed by 7200 mg q4 h × 72 h, and then 7200 μg q6h. If hemostasis is maintained, he may be discharged home by day 12. Doses may need to be adjusted if bleeding complications arise (see algorithm Table 6.4).

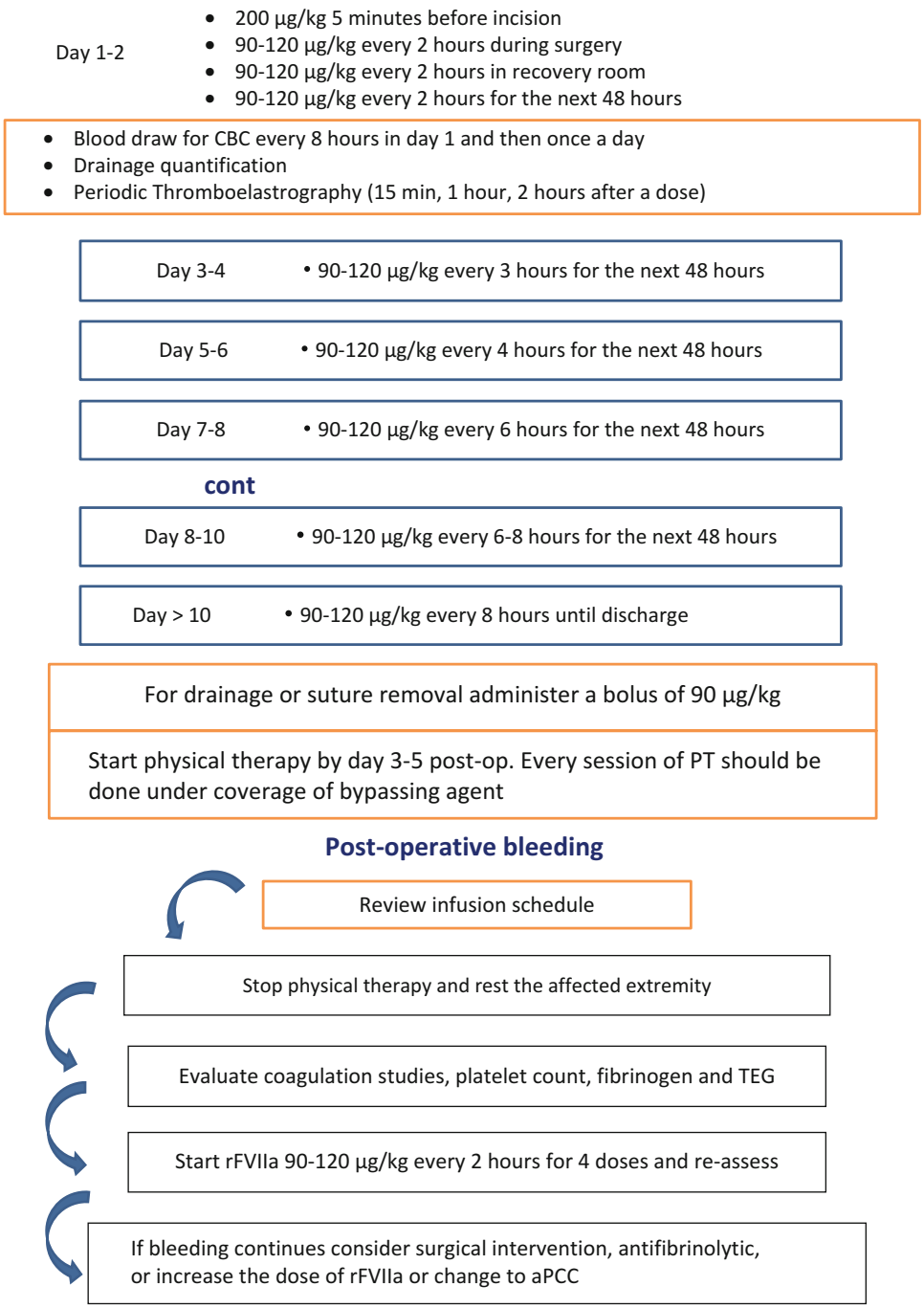
Continuous Infusion

Continuous infusion of bypassing agents for surgical prophylaxis has been studied, but would defer this practice until more data is available [13].

Hemophilia B

The overall management for surgery is similar to individuals with hemophilia A. There are plasma-derived and recombinant FIX (rFIX) products commercially available. One IU/kg of plasma-derived FIX product increases the activity by 0.1U/dL. For plasma-derived FIX dose, the formula is weight (kg) × desired FIX activity (FIX:C) (in IU/dL). Recombinant FIX product has lower recovery than plasma-derived FIX

Table 6.4 Surgical protocol for patients with inhibitors using rFVIIa



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: weight (kg) × desired FIX:C ÷ 0.8 (or 0.7, child).

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 = 8750 IU.

If this was a 35 kg child scheduled for surgery, rFIX dose would be: 35 × 100 IU/dL ÷ 0.7 = 5000 U.

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, pre-op FIX:C of 50–80 %. Post-op, goal FIX:C of 30–80 IU/dL should be maintained for 1–5 days, depending on the surgery [4, 8] (see Table 6.3).

Major Surgery

Pre-op FIX activity of 80–100 % is recommended for major surgery in individuals with hemophilia B [15]. In the post-op period, goal FIX:C of 60–80 % are 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 6.3).

Hemophilia B with Inhibitors

Persons with hemophilia B with inhibitors are treated with rFVIIa or FEIBA™ at similar dosing as in individuals with hemophilia A with inhibitors for both bleeding and surgical prophylaxis.

Rare Bleeding Disorders

For the rare bleeding disorders, there are limited data from which general recommendations are proposed. Generally levels between 15 and 40 % are recommended pre-op for adequate hemostasis. In persons with factors 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. Where there are recombinant products or plasma-derived factor concentrates available, these are first line over FFP or cryoprecipitate for factor replacement. In deficiencies where there is a specific replacement, it is advisable to have a recovery study prior to surgery to help aid in dosing and frequency of factor replacement. For surgeries involving the nose, mouth, GI, 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 [16]. In the USA, a plasma-derived concentrate of fibrinogen (RiaSTAP™; CSL Behring, Marburg, Germany) has been approved for use in individuals with afibrinogenemia or hypofibrinogenemia. It is not FDA approved for use in surgery; however, there are data suggesting the use of plasma-derived fibrinogen concentrate in the perioperative setting with successful hemostasis during and after surgery [17] Median single dose used for surgery in this study was 63.5 mg/kg. Goal fibrinogen pre-op is 100–150 mg/dL with levels at least above 50 mg/dL maintained until wound healing is complete. Mannucci et al. [18] suggest doses of at least 20–30 mg/kg body weight for major surgeries with target fibrinogen >50 mg/dL.

Where fibrinogen concentrates are not available, cryoprecipitate a source rich in fibrinogen can be used to increase fibrinogen levels. Each bag of cryoprecipitate, which contains approximately 300 mg of fibrinogen, will raise fibrinogen level by about 10 mg/dL. In the pediatric population, 1–2 units/10 kg child increases fibrinogen by 60–100 mg/dL [1]. An adult dose of approximately ten single bags of cryoprecipitate increases fibrinogen by 60–100 mg/dL [19].

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

Factor II

There are no plasma-derived or recombinant FII concentrates available. PCCs may be used; however, they contain significant quantities of other vitamin K-dependent factors. Thromboembolic complications have been reported with the use of PCCs. There are three PCCs that are commercially available in the US market—Kcentra (CSL Behring, Marburg, Germany), Bebulin VH (Baxalta, Westlake Village, California), and Profilnine SD (Grifols Biologicals, Los Angeles, CA). None of these products have been approved for congenital prothrombin deficiency. Prothrombin levels 20–40 % are usually adequate to maintain hemostasis [20]. General dosing ranges 20–30 IU/kg of prothrombin followed by 5 IU/kg every 24 h [18, 21]. FFP can also be used at a loading dose of 15–20 mL/kg of body weight, followed by 3 mL/kg every 12–24 h. In patients that need extensive surgery, the use of plasma exchange with FFP can be done before the operation avoiding the use of PCCs [22]. Laboratory monitoring for disseminated intravascular coagulation during and after PCC use is recommended.

Factor V

There are currently no commercially available factor V (FV) concentrate for replacement therapy. FFP is the only factor replacement option. 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 h to attain levels of approximately 25 % of normal [23]. Levels should be monitored during and after surgery to prevent bleeding complications [23, 24]. Minor surgeries (i.e., dental extractions) can be treated with local measures and 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 h), DDAVP or even FVIII products may be used to help maintain FVIII levels [18]. Bolton-Maggs et al. [21] suggest administering FVIII products along with FFP every 12 h each to maintain FVIII above 50 % and FV >25 %. Levels of both factors V and VIII should be monitored during and in the post-op period.

Factor VII

Bleeding manifestations vary widely among individuals with congenital factor VII (FVII) deficiency. Severe bleeding is typically seen in individuals with levels <1–2 %, although individuals with higher levels may also bleed significantly or none at all. Recombinant FVIIa 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 FVII activity >15–20 % is recommended [18, 23, 25]. Dosing should be repeated every 4–6 h 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 [25]. 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 >15–20 % [26].

Plasma-derived FVII concentrates are available in Europe [16]. 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. In 2015, Coagadex™ (Bio Products Laboratory, Hertfordshire, UK), a plasma-derived factor X concentrate, was approved in the USA for the treatment of bleeding episodes and for perioperative management of patients with congenital factor X deficiency. For surgery plasma factor X level should be approximately 70–90 IU/dL followed by 50 IU/dL in the postoperative period. Dosing can be done every 24 h using the following formula: required dose (IU) = body weight (kg) × desired factor X rise (IU/dL or % of normal) × 0.5 [27, 28]. When factor X concentrate is not available, FFP can be used with a loading dose of 10–20 mL/kg followed by 3–6 mL/kg every 12 h to achieve FX levels >10–20 % [29]. PCCs containing FX with 1:1 ratio of factors X to IX will increase factor X activity by 1.5 % per IU/mL. Dosing of PCCs is recommended at 20–30 U/kg every 24 h [18]. Due to concomitant increases in other factors (II, VII, IX) 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 [20].

Factor XI

There are no commercially available factor XI (FXI) concentrates for use in the USA. FFP can be used at a loading dose of 15–20 mL/kg body weight, followed by 3–6 mL/kg every 12 h. For minor and major surgery, a minimum level of 30 % and 45 % of normal, respectively, is recommended [20]. Mannucci [18] recommends maintaining FXI >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 factor XI levels is warranted [23]. 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 reported [30].

Circumcision should be held at birth if cord blood reveals FXI activity <10 %. A repeat FXI level should be measured at six 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 [21, 31]. In the case of a tonsillectomy/adenoidectomy with FXI level below 30 %, replacement with factor XI or 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 % [32].

Corifact is a plasma-derived FXIII concentrate (CSL Behring, Marburg, Germany) available in the USA. In individuals with known FXIII A-subunit deficiency, there is also a recombinant FXIII A-subunit that is now available (Tretten™; Novo Nordisk, Bagsvaerd, Denmark), although data for surgical use has not been reported.

For surgical prophylaxis, Manucci [18] suggests replacement with FXIII to maintain FXIII levels >5 % for both minor and major surgeries, while Nugent [32] suggests maintaining higher levels FXIII > 10–20 %.

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

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

7

Shiu-Ki Rocky Hui

Hemophilia A

Hemophilia A is a X-linked disorder due to congenital deficiency of factor VIII (FVIII). The frequency of Hemophilia is estimated to be approximately 1/5000 male births across ethnic group. 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 [3]. Although Hemophilia A affects mostly male, in rare occasion the disease can manifest in female via chromosome lionization [4–6]. In addition, approximately 30 % of Kemophilia A can present as de-novo mutation. Therefore, diagnosis of Hemophilia A should be considered even in the absence of a strong family history [7–9].

Factor VIII Protein

Unlike most other plasma coagulation proteins, which are produced by hepatocytes, FVIII is mainly produced by liver endothelial cells [10, 11]. This is likely the reason for elevated FVIII even under liver failure.

Factor VIII protein is produced as a six-domain protein, A1-A2-B-A3-C1-C2 [12–14]. 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 [15]. Once FVIII is released into circulation, it binds to von Willebrand factor (VWF) which serves to increase FVIII survival and regulate FVIII activity. Upon activation by thrombin, FVIIIa serves as a co-factor for Factor IXa in the activation of factor X to factor Xa and ultimately generation of thrombin [15–18]. Hemophilia A has been linked to a variety of well-known molecular mutations including inversions, large deletion, frameshift, nonsense, and missense defects [19, 20]. The severity of the disease can often be predicted by the site and type of mutation in the FVIII gene [21–24].

Diagnosis of Hemophilia A

The diagnosis of Hemophilia A begins in recognizing the X-linked inheritance pattern of an unexplained and isolated prolongation of PTT that is corrected in mixing study [25]. Subsequent laboratory workup should then identify a FVIII deficiency. However, it is important to note that an initial finding of an isolated prolonged PTT with mixing study correction does not immediately imply Hemophilia A [26]. Other PTT pathway factor deficiencies such as Factor IX (FIX) and Factor XI (FXI) deficiencies or even non-clinically significant Factor XII deficiencies will present with the same initial laboratory finding [27]. Therefore, it is important to order FIX and FXI along with FVIII to rule out other potential congenital bleeding disorders. Specifically important is to consider the von Willebrand disease (VWD), when considering the diagnosis of Hemophilia A, as carrier defect (Type 2N) or deficiency (Type 1 and 3) of VWF will result in decrease of FVIII. The diagnosis of these specific VWD will be discussed later in this chapter.

Severity of Hemophilia A is directly related to the degree of deficiency of FVIII activity as measured by one-stage assay, Mild Hemophilia is defined by FVIII activity between 5 snd 40 %, moderate disease is activity 1–5 %, while severe Hemophilia is below 1 %. Although FVIII activity via one-stage assay in general can predict bleeding phenotype, in very rare situation, there can be discrepant clinical bleeding symptoms with FVIII activity via one-stage assay. In such scenario, a two-stage FVIII assay may be used to better define patient's disease [28, 29].

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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, factor IX (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 mutation [30]. 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 hepatocyte. FIX is a vitamin K-dependent protein, requiring gamma-carboxyglutamation to be fully functional. FIX can be activated into FIXa via the intrinsic pathway by FXIa or the extrinsic pathway by tissue factor and FVIIa [31]. FIXa in the presence of calcium, FVIIIa, and phospholipids in turn activates FX into FXa and ultimately 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 [30].

Diagnosis

A deficiency in FIX may indicate vitamin K deficiency instead of Hemophilia B, especially in neonates [32]. Since FVII is also a vitamin K-dependent factor, an isolated prolonged PTT without prolongation of PT makes Hemophilia B likely as half-life of FVII is shorter than FIX. Like FVIII in Hemophilia A, 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 %, moderate disease is activity 1–5 %, while severe Hemophilia B is below 1 %.

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 [33, 34]. Due to the variation of clinical presentation, a complete and accurate laboratory workup is important for the subtyping of VWD [35]. The laboratory workup for VWD will be discussed in detail in Chapter XX.

von Willebrand Factor

Unlike most other coagulation proteins, VWF is not produced by the liver which also helps to explain elevated FVIII and increased thrombotic risk in the setting of liver dysfunction. VWF is produced by both megakarocytes and endothelial cells (Fig. 7.1) as a 2813 amino acid long prepropeptide (Fig. 7.2) in the endoplasmic reticulum, which is then dimerized into 800kD dimers. These dimers are then polymerized into mature VWF multimers up to 20,000kD in length and VWF propeptide dimmers (VWF:pp) 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 body of endothelial cells or alpha granules of platelets. Upon activation, mature VWF and VWD:pp are released from storage into circulation; once released, VWF multimers are cleaved at specific site in the A2 domain into multimers of variable sizes by a metalloprotease, ADAMTS13 [36–38]. 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 is ultra large multimers [39] or bleeding when there is absence or decrease in large multimers [40].

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 glycoprotein Ib-V-X complex (GPIb) on platelet surface. This interaction is important in recruiting and activating platelets at site of vascular injury [41]. 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 [42, 43].

von Willebrand Disease

As discussed previously, VWD can present with widely different bleeding phenotypes depending on the underlying pathophysiology. In general, VWD (Table 7.1) can be broadly divided into two types of VWF defects, quantitative (type 1 and type 3) and qualitative (type 2). It is important to

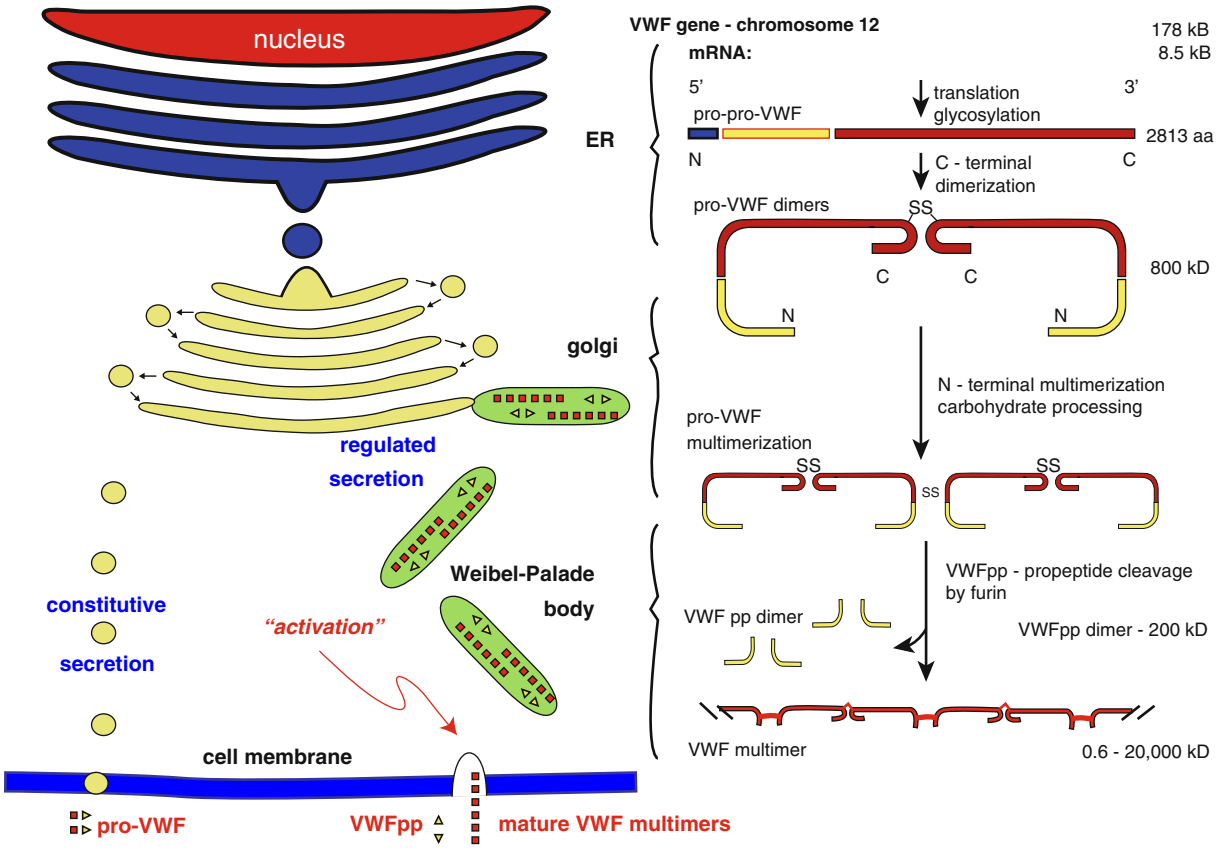

Fig. 7.1 demonstrates the production of VWF multimers in endothelial cells. Matured VWF and propeptide are stored within Weibel-Palade bodies ready for release upon activations. From Haberichter SL, Regulated release of VWF and FVII and the biologic implications, Pediatr Blood Cancer, 2006 May 1: 46(5):547–53

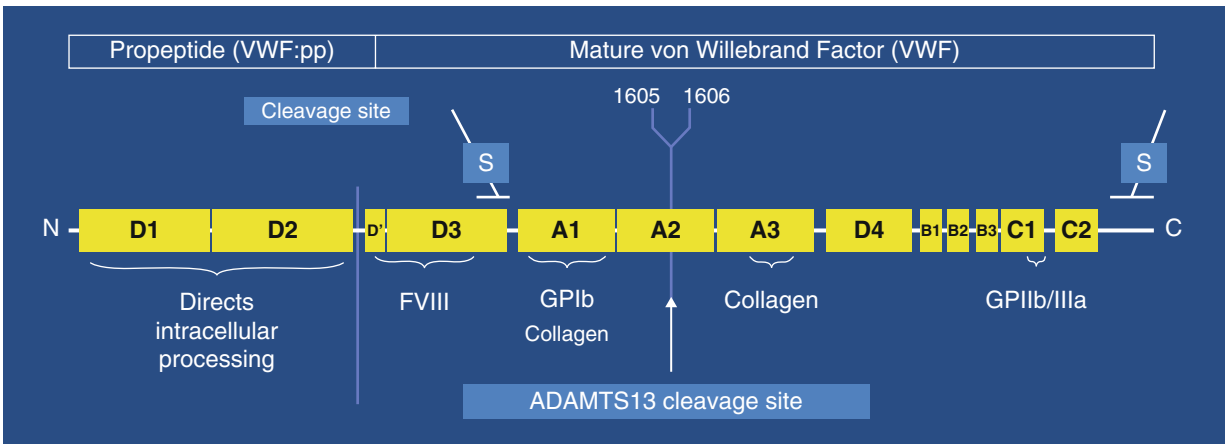

Fig. 7.2 showed the various known VWF domains and their respective contributions to the VWF function

Table 7.1 Various VWD subtypes and their expected laboratory findings

Condition	VWF:Act	VWF:Ag	FVIII	VWF:Act/Ag	VWF:MA
Type 1	<30	<30	L to N	>0.7	Normal but light
Type 2A	<30	<30–200	L to N	<0.7	Missing large multimer
Type 2B/PT-VWD	<30	<30–200	L to N	<0.7	
Type 2M	<30	<30–200	L to N	<0.7	Normal
Type 2N	30–200	30–200	Significantly lower	>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

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 algorithm is found in details in Chapter **.

Type 1 VWD

Type 1 VWD account 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 30 % without any observable VWF function defects that VWF activity to antigen ratio (VWF:Act/Ag) should be >0.5–0.7 [44]. In addition, VWF multimer analysis (VWF:MA) should show a normal size distribution with decreased intensity. Mechanism for type 1 VWD is due to decreased synthesis of VWF; however, type 1 variants (type 1C and type 1 Vicenza) have been shown to have increased clearance and decreased VWF half-life. It is important to rule out such type 1 variants as desmopressin treatment will not be an effective treatment as the therapy yield only short-lasting effect [45]. In both type 1C VWD and type 1 Vicenza, desmopressin challenge is expected to show good 1 h post-administration response with a decreased 4 h post-administration response [46]. Compared to other type 1 VWD, VWF propeptide to antigen ratio (VWF:pp/Ag) is increased, which is the defining characteristic of these type 1 variants [47]. 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 is proven challenging as VWF is an acute phase protein. Since the level can be increased several folds from baseline, a one-time normal VWF:Ag and VWF:Act cannot definitively rule out type 1 VWD [48]. 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 of them has been universally validated. Until a better marker can be established, the most effective method to distinguish acute phase from baseline study remains to be repeat testing.

Low 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 30-50 % can be difficult to define [44]. 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 % [49]. 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 [50], which may be related to post-translational modification [51]. Individuals with "low VWF" should be made aware of increased risk for bleeding, but should not be considered as having true VWD.

Type 3 VWD

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 [44]. As FVIII level can fall within moderate Hemophilia A range, it is important to rule out type 3 VWD.

Type 2A VWD

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 [44]. Therefore, laboratory workup demonstrates a qualitative defect of decreased VWF:Act but relatively normal VWF:Ag, which results in decreased VWF:Act/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 VWD

Type 2B VWD accounts for approximately 3-5 % of all VWD. Although its laboratory finding is similar to type 2A VWD with decreased VWF:Act/Ag ratio and loss of high molecular weight multimer, the mechanism for disease is entirely different [44]. Type 2B VWD is due to 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 [52]. 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-VWD/Platelet-type VWD

As in type 2B VWD, the pathogenesis of platelet-type VWD (PT-VWD) is due to abnormal spontaneous interaction between platelet GPIb and VWF [44]. However, in contrast to type 2B VWD, the gain of function mutation is in the platelet GPIb receptor [53]. Overall, initial laboratory workup is indistinguishable from type 2B VWD, including decreased VWF:Act/Ag, loss of high molecular VWF, thrombocytopenia, and even abnormal RIPA. Specialized laboratory test, 2B binding assay can be used to differentiate PT-VWD from type 2B VWD. As in type 2B VWD, desmopressin is contraindicated for treatment of PT-VWD.

Type 2M VWD

Type 2M VWD accounts for only 1–2 % of VWD. The initial laboratory workup, similar to type 2A, 2B or PT-VWD, showed decreased VWF:Act/Ag [44]. 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 [54]. Therefore, multimer analysis for type 2M VWD is normal and does not demonstrate loss of high or intermediate molecular weight VWF. It is the presence of normal multimer distribution with decreased VWF:Act/Ag that makes up the defining laboratory characteristic of type 2M VWD.

Type 2N VWD

Type 2N VWD is qualitative VWF disorder that accounts for 1–2 % of all VWD [44]. 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 [55]. As the coagulation function of VWF is unaffected, the VWF laboratory workup is unremarkable at first glance; normal VWF:Ag, VWF:Act, VWF:Act/Ag, and even normal multimer analysis. However, FVIII activity can be decreased to as low as 5–15 %, making 2N VWD sometimes difficult to differentiate from Hemophilia A. The inheritance pattern of 2N VWD is autosomal in contrast to X-linked in Hemophilia A. FVIII binding assay (Discuss in Chapter **) can be used to distinguish type 2N VWD from Hemophilia A. It is important to note that like other VWD subtypes, 2N VWD can coexist in patients with Hemophilia A. Therefore, concurrent 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 7.2), secondary of loss of VWF quantitative or qualitative functions [56]. Dozens of diseases have been associated with aVWS; nonetheless, laboratory findings often mimic subtype of congenital VWD, especially type 2A VWD with decreased VWF:Act/Ag and loss of high to intermediate molecular weight VWF. The loss of high molecular weight VWF can be secondary to either pathological high shear stress as in aortic stenosis [57], presence of autoantibodies against VWF [58], or even direct absorption by tumor cells [59]. Less commonly, aVWS may result from decreased overall VWF production as opposed to selective loss of high molecular weight VWF as in the case of hypothyroidism [60]. Bleeding diathesis of aVWS may vary, but bleeding symptoms and VWF laboratory abnormalities usually resolve upon resolution of underlying disorders.

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 7.3) that can provide some important standard of care guidance in managing these patients

Table 7.2 Shows the 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 %*

Table 7.3 Published recommendations for peri-operative management of Hemophilia A, B, and VWD patients

	Hemophilia A [61, 62]	Hemophilia B [61, 62]	von Willebrand disease [62]
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 [64] × 3–4 days [63]	>50 % prior [64] × 3–4 days [63]	80–100 % prior + >30–50 % × 3–4 days, up to 2 weeks [63]

around time of procedures, surgeries, or deliveries. It is important to note that factor concentrates should be used in place of plasma products as 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 surgerical settings. Antifibrinolytic may be used in conjunction with standard factor replacement [61]; 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.

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Bleeding Associated with Coagulation Factor Inhibitors

8

Charles S. Eby

Abbreviations

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

Presentation

Patients with clinically important 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 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 location of the factor in the coagulation cascade. Figure 8.1 shows the coagulation cascade and the factors included in PT and aPTT screening tests. Figure 8.2 provides an algorithmic approach to evaluating 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 [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. When the 50:50 mix results show incomplete correction, the next step is to perform additional coagulation testing based on an algorithm (Fig. 8.2).

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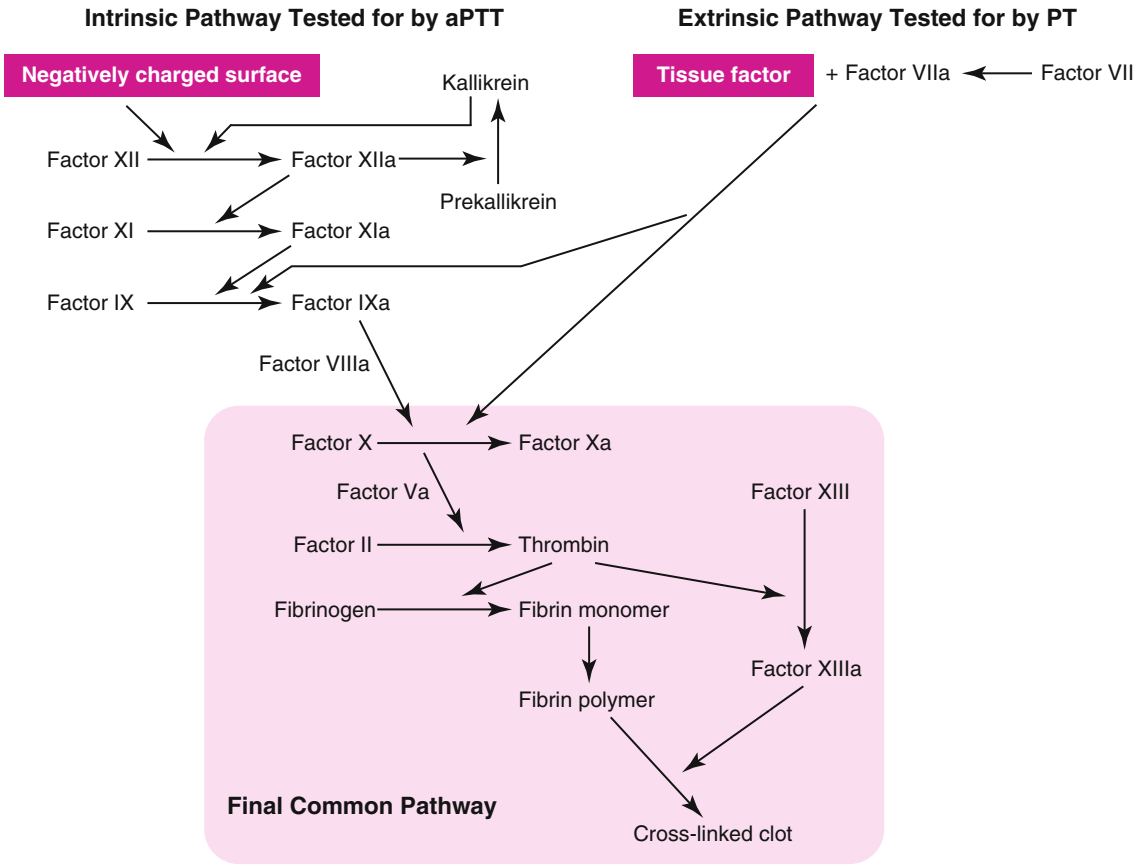

Fig. 8.1 Model of the classic coagulation cascade and screening coagulation tests. aPTT reagent activates FXII to initiate the intrinsic pathway. PT reagent activates FVII to initiate the extrinsic pathway. Factor deficiencies or inhibitors of the intrinsic pathway prolong the aPTT and of the extrinsic 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. In: Kottke-Marchant K, ed. An Algorithmic Approach to Hemostasis Testing. Northfield, IL: College of American Pathologists; 2008. Reproduced with permission

A specific neutralizing antibody will result in a moderate-to-severe in-vitro deficiency of its target factor. However, neighboring factor assays may show a mild inhibition due to partial interference of the specific inhibitor in these assays (Table 8.1). 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 [2]. The results of several large prospective registries or population-based cohorts have been published recently with similar findings for clinical presentations [2–5] (Table 8.2). 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 (post-partum, medication [6], 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 3 % of all

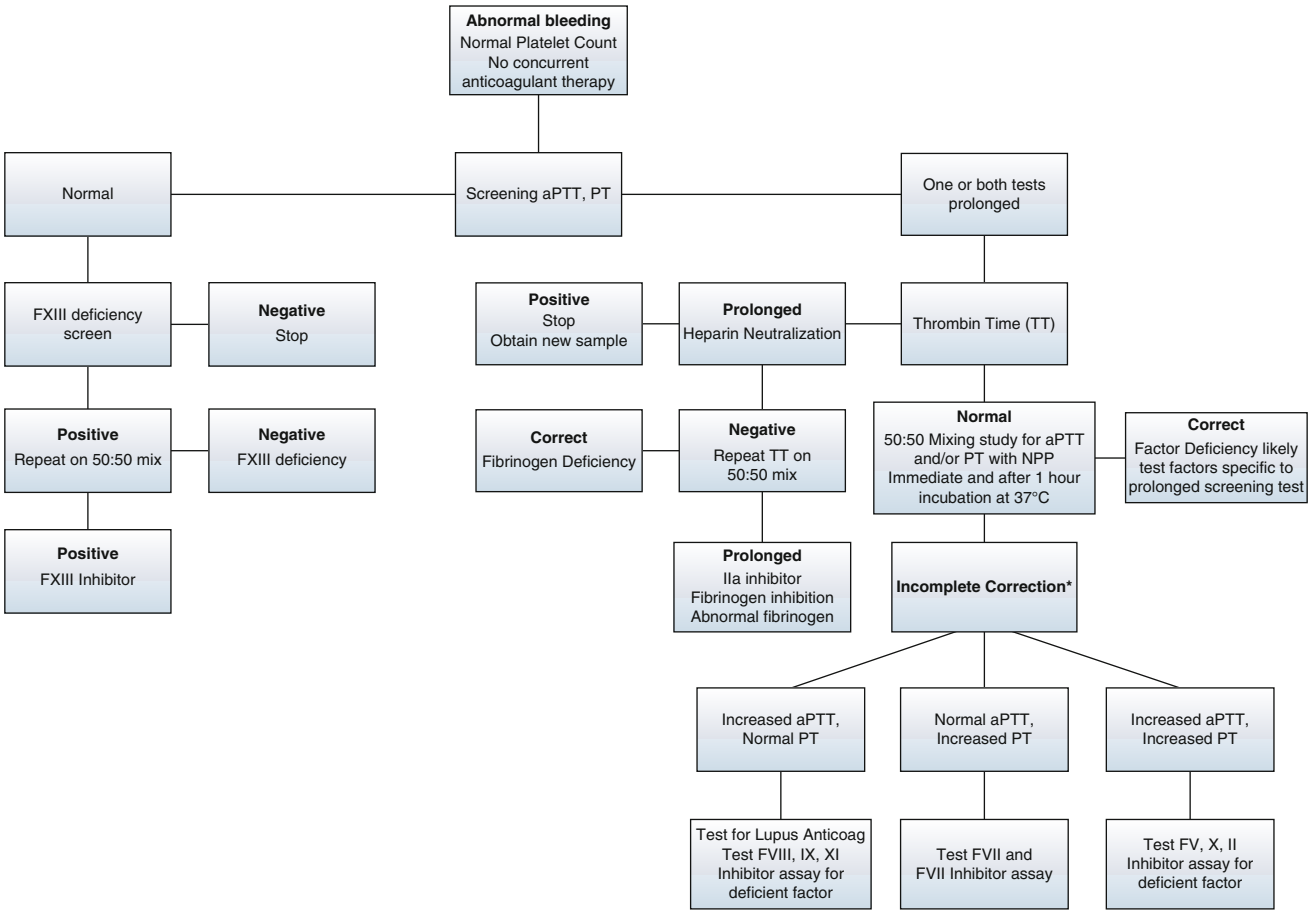

Fig. 8.2 A diagnostic algorithm for laboratory evaluation of a suspected acquired bleeding disorder

Table 8.1 Apparent activity of intrinsic factor pathway coagulation factors in plasma containing a FVIII inhibitor. Recovered factor activities corrected for dilution

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

cases [2]. The median onset of bleeding is 2.5 months postpartum. Patients have excellent responses to hemostatic and immunosuppression treatment with >85 % complete remissions and much lower mortality rates compared to older patients [7].

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 [3]. Bleeding can be spontaneous, post-trauma, 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 [2, 3].

Laboratory Findings

The aPTT is prolonged, while the PT is within the reference range. An aPTT 50:50-mix will show incomplete correction which is more prolonged after incubation for 1–2 h.

FVIII activities range from <1 to ~50 % and most inhibitor results are >10 Units (Table 8.2). 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 a two-stage aPTT-based Factor XII, XI, or IX (Table 8.1). The inhibitor behavior is diminished when the factor assay is performed on serial dilutions of the patients' plasma. Patients with Factor VIII inhibitors may also have positive lupus anticoagulant (LA) results using an aPTT-based method [8]. However, this usually is due to interference from the Factor VIII neutralizing

Table 8.2 Presentation and clinical outcome of 154 patients with acquired hemophilia A in United Kingdom 2001–2003 [2]

Median age (years)	78
FVIII activity on presentation	
<1 %	30 %
1–5 %	36 %
>5–50 %	34 %
Initial inhibitor titer	
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 %

antibody rather than a manifestation of an additional autoantibody since the DRVVT-based LA test, which activates Factors X and V of the common pathway (Fig. 8.4), is negative in most patients with FVIII inhibitors [8].

Immediate Management-Stop Severe Bleeding

Neither the severity of FVIII deficiency or the strength of the inhibitor titer predicts bleeding severity [2]. Most symptomatic acquired FVIII inhibitor patients require infusions of hemostatic biological products to stop acute hemorrhaging (Table 8.3). Rarely, weak inhibitors (inhibitor titer <5) 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 by-pass the inhibited function of FVIII by infusing recombinant Factor VIIa (rFVIIa) or a pooled plasma concentrate containing partially activated Factors X, IX, VII, and II: VIII inhibitor bypass activity (FEIBA) [9]. 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 [4, 9]. For both by-pass therapies, effectiveness is based on clinical monitoring

Table 8.3 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 +/− prednisone
Plasma exchange	

of bleeding and not based on 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 [10]. However, concern for transmission of porcine parvovirus lead to its discontinuation around 2000. In 2015, The FDA approved recombinant porcine FVIII (rPFVIII) for treatment of life-threatening bleeding in patients with acquired FVIII inhibitors based on satisfactory hemostasis outcomes in 28 inhibitor patients [11]. 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 antifibrinolyic treatment with tranexamic acid or epsilon aminocaproic acid. In the setting of life-threatening bleeding not responding to hemostatic therapies, extracorporeal immunoabsorption, which in not available in the United States, and plasmapheresis may be effective interventions to reduce inhibitor titers.

Concurrent Management: Immunosuppressant Therapy to Eliminate FVIII 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 1.0 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 [3, 4, 12].

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 [12], and may have a higher CR rate, but does not affect long-term outcomes of CR and survival [2, 12]. (2) Intravenous immunoglobulin (IVIG) is not effective as a monotherapy or in combination with prednisone and cyclophosphomide [2, 12]. (3) Rituximab is not an effective first-line monotherapy [12]. (4) Patients with initial severe FVIII deficiency and high inhibitor titers have lower CR rates and poorer survival [4, 12, 13]. (5) Relapses do occur, ranging from 15 to 24 % during the first year of follow-up [2, 12]. 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 [13].

For the minority of patients who do not respond to prednisone or prednisone + cyclosporine, there are alternative immunosuppression therapies to consider including cyclosporine and azathioprine. Rituximab has grown in popularity as a second-line treatment [14].

Acquired Inhibitors of Other Coagulation Factors

FVIII is by far the most immunogenic coagulation factor and yet the incidence of FVIII inhibitors is < 2/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 make it difficult to provide definitive descriptions of their presentations and prognoses, or recommendations for management [15, 16]. 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. 8.1).

Acquired Inhibitors Other than VIII Which Prolong the aPTT: FIX, XI, XII

Formation of inhibitory autoantibodies to FIX (acquired hemophilia B) consists of less than probably ten 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 [17]. 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 [15]. In a series of 14 cases, 8 presented with spontaneous or trauma-induced bleeding, 4 with thrombotic events, and one was asymptomatic. Immunosuppression therapy resolved all inhibitors [18].

Reports of acquired inhibitors to FXII usually are in the context of antiphospholipid syndrome or liver disease [15]. 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: FVII

While inherited FVII deficiency is estimated to have a prevalence of 1 per 500,000, acquired, isolated FVII deficiencies are extremely rare, are associated with underlying malignancies, infections, and hematopoietic stem cell transplants, and inhibitory antibodies are identified in a minority of cases [19, 20]. Bleeding complications range from mild to severe [21]. One patient's plasma demonstrated a time-dependent in-vitro inhibition of FVII in NPP, similar to acquired FVIII inhibitors [22]. Given the rarity of acquired FVII inhibitors, management of bleeding and immune suppression strategy would be empiric, borrowing from the experience with acquired FVIII inhibitors.

Recombinant Factor VIIa appears to be non-immunogenic when administered as a replacement in congenitally deficient FVII patients or as a bypass hemostasis agent based on the paucity of acquired antibody reports since NovoSeven™ (rFVIIa) was approved in 1999 in USA [23].

Acquired Inhibitors Which Prolong both aPTT and PT: FX, FV, Fibrinogen

Historically, Factor V (FV) was a relatively frequent target of acquired inhibitory autoantibodies, due to exposure to bovine FV. An effective surgical hemostasis technique is 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 [24]. Nevertheless, 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 [25]. 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 positive inhibitor titer based on a modified Bethesda or Nijmegen methods [26]. 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 [24]. Frequently, FV inhibitors spontaneously remit, especially when a suspected antibiotic is discontinued, and not all patients required immunosuppression [25].

Prothrombin (Factor II) 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, which correct with 50:50 mixing, and very low Factor II activity (see Chap. 18).

Acquired inhibitors of thrombin are very rare, and when described, were usually associated with exposure to bovine thrombin glue, and less often with underlying autoimmune disorders or monoclonal gammopathies [15]. 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.

Acquired Factor X (FX) deficiency is most commonly due to absorption of the coagulation protein to amyloid deposits in patients with amyloidosis [27]. Neutralizing FX autoantibodies are extremely rare [28]. A recent literature review identified 34 case reports, but only 26 % provided convincing laboratory evidence of a FX inhibitor [29]. Cases were associated with malignancies, 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.

Acquired inhibitors of fibrinogen are uncommon and 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, TT, which do not correct with 50:50 mixing. A Reptilase time would distinguish a fibrinogen inhibitor or dysfibrinogen 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 [30].

Acquired Inhibitors Which Do not Prolong aPTT or PT: FXIII

Both inherited and acquired severe deficiencies of FXIII are extremely rare. Presenting symptoms include spontaneous hemorrhage, including central nervous system, 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. 8.1). 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. Confirmatory studies would include a urea solubility test on a 50:50 mixture of patient and NPP to demonstrate inhibitor activity and performance of

FXIII quantitative antigen and activity tests, which are provided by a few reference laboratories. Notable findings from a systematic literature review of 28 cases of FXIII inhibitors included: median age 65.5; 70 % associated with a medication, specifically isoniazid in 30 %; and 30 % were idiopathic [31]. There were five fatal intracranial bleeds and overall mortality rate was 29 %. Various strategies were employed to stop bleeding (FXIII concentrate, plasma exchange, FFP, cryoprecipitate) 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 investigation similar to the algorithm outlined in Fig. 8.2. Once an inhibitor is identified, interventions to restore hemostasis and initiate immunosuppression are indicated for most patients (Table 8.3). 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, most patients are elderly and deaths from bleeding, treatment-related sepsis, and other comorbidities are fairly common.

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Pregnancy-Associated Bleeding

9

Karin A. Fox

Introduction and Background

Bleeding is a leading cause of maternal mortality worldwide, second only to preexisting medical conditions [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], it remains a leading *preventable* cause of death. Lack of adequate postpartum monitoring or 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 major morbidity [1], underscoring the risks inherent in pregnancy and the need for appropriate planning and multidisciplinary care for women with pregnancy-associated bleeding.

Physiologic Changes in Pregnancy

With the exception of fetal and neonatal growth and development, there is no other time in which physiologic changes occur throughout the body as rapidly as during and after pregnancy. Virtually every major organ system adapts to allow the female body to host a semi-allogenic fetus (or fetuses in the case of twins or higher order multiples) and successfully meet the physiologic demands of providing necessary nutrients and oxygen to the growing fetus, providing additional respiration and removal of waste, and 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

In the first trimester, significant remodeling of the cardiovascular system and alteration of physiologic function begins. 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 gestation, and returns to pre-pregnancy levels by 12 weeks postpartum [5]. This occurs with up to a 21 % decrease in systemic vascular resistance (SVR) [5, 6], primarily through a progressive increase in heart rate (HR) and stroke volume (SV). Recall that:

$$\mathrm{CO} = \mathrm{SV} \times \mathrm{HR}. \tag{9.1}$$

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

Blood Volume: Circulating white and red blood cell volume gradually increases, 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 physiologic anemia and mild decrease in platelet count at term, but also results in decreased blood viscosity, which may permit improved perfusion. The increased total blood volume from 3250 to 4820 mL [9] provides sufficient reserve to allow a woman to lose a physiologic amount of blood at delivery without cardiovascular compromise. A larger blood loss at delivery is required before signs of advanced hemorrhagic shock are seen, compared to the nonpregnant state, but should deterioration occur, it may occur more precipitously. While sudden, rapid bleeding may alert the clinician and care team to the

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risk of shock, slow, steady, or intermittent bleeding can be equally hazardous by leading to large cumulative losses that may go unnoticed until vital signs show 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 mL/min of blood flowing thro ugh the uterine arteries in singleton pregnancies [10]. Rich collateral supply from cervical branches of the uterine arteries and ovarian vessels ensure adequate perfusion, but are also a source of profound bleeding. This can occur whenever the uterus fails to adequately contract after delivery, leaving venous sinuses open to ooze; with significant lacerations of the uterus, cervix, or vagina; or should vessels become injured at the time of surgery. During normal vaginal delivery, blood loss is approximately 500 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 displacement of the diaphragm by the growing fetus. 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 nonpregnant state. The kidney compensates partially by increasing excretion of bicarbonate ions, which results in a serum bicarbonate concentration closer to 18–22 mEq/L during pregnancy [13]. These respiratory changes facilitate gas exchange between mother and fetus, but are important to the clinician attending to hemorrhagic shock, as acidosis in its early stages may be present when arterial blood gases would otherwise appear relatively normal in the nonpregnant state. In other words, if maternal arterial blood gas values are consistent with acidosis using nonpregnant standards, the pregnant or newly delivered patient is surely acidotic.

Coagulation Factors

Bleeding at delivery is universal; 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, XII and von Willibrand factor [14]. Fibrinogen levels also 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 (such as von Willibrand disease or factor XIII deficiency) predisposes a pregnant patient to increased risk of peripartum hemorrhage. Conversely, obstetrical hemorrhage can quickly lead to disseminated intravascular coagulopathy (DIC), particularly if massive hemorrhage occurs, or if blood loss is sufficient to cause hyperfibrinogenemia. 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 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 <300 mg/dL conferred the highest relative risk (59.0) [15]. Conversely, low fibrinogen levels are one of the earliest laboratory changes seen 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 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, 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 9.1, 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 risk of death from ruptured ectopic pregnancy appears 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 nonspecific 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.

Table 9.1 Pregnancy-specific conditions associated with postpartum hemorrhage

	Special considerations
First trimester	
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

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 L 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 is 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 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], and hemorrhage may ensue treatment often consisting of dilatation and curettage in early pregnancy. At the time of uterine evacuation, heavy bleeding can 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 comprising 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, 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 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 retroplacental bleeding occurs, but does not cause separation of the placental edges from which blood can be allowed to escape vaginally, and should be suspected 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 (RBC) 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 tenfold 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 one 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 1.74–2.09),

blood transfusion (OR 4.39, 95 % CI 3.76–5.12), and hysterectomy (OR 39.7, 95 % CI 22.42–70.3) [32]. Additionally, placenta is one of the major risk factors for morbidly adherent placenta, including placenta accreta, increta, and percreta, especially in women with prior cesarean deliveries (see Sect. 9.4.3) [33].

Postpartum Hemorrhage

Postpartum hemorrhage is classified as *primary*, when occurring in the first 24 h after delivery, and is most commonly due to uterine atony, reproductive tract injury including lacerations, hematoma formation, or uterine inversion or coagulopathy. *Secondary* postpartum hemorrhage occurs between 24 h to 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. 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 is essential for recognizing 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.

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 [35]. 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 of postpartum hemorrhage by approximately 10 % compared to expectant management [36, 37].

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 9.2). 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 [38–40]. Second-line agents such as methylergovine (Methergine™) or 15-methyl PGF2-α 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™ (Cook, Spencer, IN) or Ebb™ Glenveigh, Chattanooga, TN) 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

Table 9.2 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
Methlergonovine (Methergine)	200 μg	IM, IV	Avoid in patients with hypertension
		May repeat every 2–4 h	
	200 μg	Oral, 3–4× daily up to 7 days	
Carbroprost (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

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 [41–43]. Reported success rates with balloon tamponade range between 65 and 100 % [44, 45].

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 described by B-Lynch et al. [46], Hayman et al. [47], and Cho et al. [48] physically brace a uterus that has been manually compressed, by holding the anterior and posterior uterine surfaces together, there by reducing the open spaces within the cavity. Success rates with the use of compression sutures range between 76 and 100 %, with decreased rates of success when placement of the sutures is delayed by 2–6 h after delivery [49].

Morbidly Adherent Placenta: Placenta Accreta/Increta/Percreta

Morbidly adherent placenta includes the spectrum of placental invasion into or through the myometrium including placenta accreta, increta, and percreta and affects between 1 in 533 [33] to 1 in 731 [50] based on data from large, multicenter studies in the U.S., 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 [51]. The Nordic Obstetrical Surveillance System identified 4.6/10,000 deliveries [52], and in Canada, the most recent incidence is 14.4/10,000 deliveries [53].

The risk of morbidly adherent placenta 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 196–400]) [52]. Other risk factors include advanced maternal age, smoking, and other uterine surgery, such as myomectomy or septum revision, and in vitro fertilization [51].

Cesarean hysterectomy is the definitive surgical treatment of placenta accreta; however, increasingly conservative interventions, with an attempt to leave all or a majority of the uterus intact, have been employed, including use of intrauterine balloon tamponade, partial myometrium resection along areas of invasion, intra-arterial balloon occlusion, and sequential revascularization [54]. In a review of case series in which patients with placenta accreta were managed conservatively, 58 % required delayed hysterectomy due to infection, hemorrhage, or DIC, up until 9 months after delivery [55].

Hemorrhage at the time of delivery is common, with mean estimated blood loss ranging between 4 and 7.5 L, but may far exceed this in extreme cases [33, 52, 56, 57]. In one study of 66 patients with accreta, 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 [58]. The invasive placenta often bulges out into the confined spaces of the pelvis, obstructing visualization and easy access to the uterine arteries, and placental invasion promotes abundant, irregular neovascularization — vessels that are a potential source of bleeding. (Fig. 9.1). Any disruption of the placental surface can lead to torrential bleeding. Antenatal diagnosis and proper preparation, with multidisciplinary

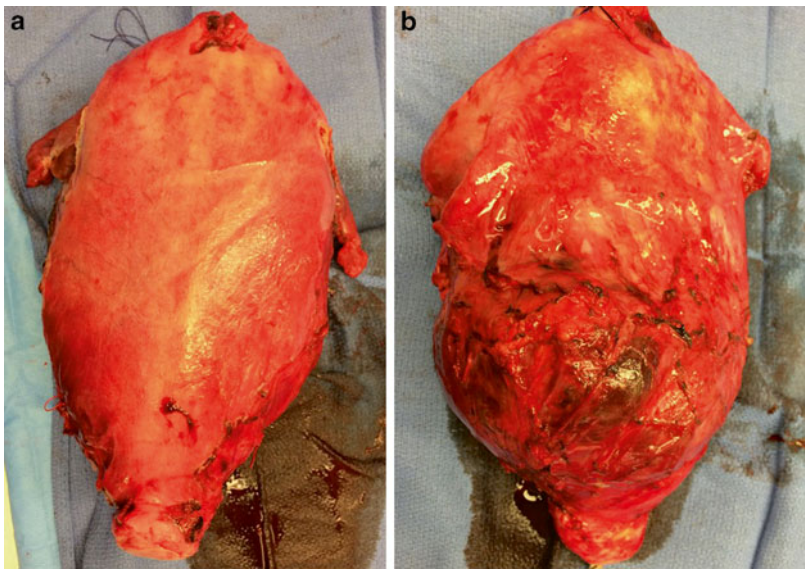

Fig. 9.1 *Panel A*: Normal, posterior uterine surface. *Panel B*: Anterior uterine with placenta accreta. Note the bulging placental tissue, covered by tortuous, irregular neovascularization

team support, and avoidance of removal of the placenta have been shown to reduce mean estimated blood loss [57, 59]. Still, the rate of massive transfusion 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 good 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 [60]. 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 and acute systemic hypotension and cardiac arrest, hypoxia, and fulminant consumptive DIC, often with profound hypofibrinogenemia. The maternal death rate is approximately 40–60 % [60], and of survivors, only approximately 15 % survive neurologically intact [61]. Amniotic fluid embolism occurs classically during delivery or within 30 min postpartum. The onset of symptoms is usually rapid and unpredictable. Emergent release of O-negative or type-specific RBCs and appropriate plasma and cryoprecipitate is essential to resuscitation efforts.

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 unit, 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 [62–64]; however, obstetrical hemorrhage and trauma are similar in volume and likely in pathophysiologic mechanisms [65].

The American College of Obstetricians and Gynecologists has developed an Obstetrical Hemorrhage Safety Bundle, which 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" [66].

The availability of cryoprecipitate as well as 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 one 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 [67]. 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 [68]. In the setting of hypofibrinogenemia, to maintain an adequate fibrinogen level of >300 mg/dL, transfusion of 5–10 units of cryoprecipitate is useful.

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 TEG, ROTEM, and FIBTEM, may allow rapid results [69, 70] and targeted resuscitation while minimizing use of blood products.

Use of adjunctive or alternative hemostatic agents such as activated factor VII, fibrinogen concentrates, or tranexamic acid for obstetrical hemorrhage is not standard, but has been reported. In one multi-center randomized controlled trial, factor VIIa 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 nonfatal thrombotic events [71]. 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 (RiaSTAP™) in the setting of postpartum hemorrhage appears promising in the setting of hypofibrinogenemia [72]. Fibrinogen concentrate does not change the need for transfusion, total blood loss, or total amount transfused if given preemptively in patients with normofibrinogenemia [73]. It can be given to patients regardless of ABO blood group. Although there is a formula to calculate the required dose of RiaSTAP™ (see Chap. 7), there is little prospective data regarding its use in the setting of pregnancy and delivery. More data is needed before strong recommendations can be made for its use in the setting of obstetrical hemorrhage.

Conclusion

Early recognition of obstetrical hemorrhage, starting with risk assessment of every patient, prior planning including use of hemorrhage and massive transfusion protocols, and prompt attention to and treatment of the patient should hemorrhage ensue are key to optimal patient outcomes and to reduce preventable obstetrical morbidity and mortality.

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Bleeding Associated with Thrombocytopenia

10

Sarah E. Sartain and Jenny M. Despotovic

Introduction

Platelets are a critical component of coagulation, most importantly in 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 and $450 \times 10^9/mm^3$ regardless of age [6], and a decrease in circulating platelet count can increase tendency for bleeding. Low platelets, 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. 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/thrombosis (HIT), 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]. 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 [8]. See Table 10.1 for a list of diagnoses that should be considered in the differential diagnosis of ITP. The management of bleeding in ITP is very 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 [9] but much less frequent in adults; or secondary to another disorder, including autoimmune diseases such as systemic lupus erythematosis (SLE), inflammatory bowel diseases (IBD), immunodeficiencies such as common variable immune deficiency (CVID) or DiGeorge syndrome, thyroid disease, infection (human immunodeficiency virus (HIV), hepatitis C, hepatitis B, *Helicobacter pylori*), chronic lymphocytic leukemia (CLL), or pregnancy [9, 10]. Secondary ITP is most successfully treated by optimal management of the underlying condition [11, 12].

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Table 10.1 Differential diagnosis of immune thrombocytopenia

Category	Diseases
Macrothrombocytopenia	MYH9 group, familial thrombocytopenias, GATA 1 Group, Bernard Soullier syndrome, grey platelet syndrome, montreal platelet syndrome
Congenital thrombocytopenia	TAR, X-linked thrombocytopenias, Wiskott-Aldrich Syndrome, Fanconi anemia, Bernard Soullier 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 [15, 18, 21], 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 noctural hemoglobinuria, common variable immunodeficiency syndrome, von Willebrand disease type 2B, Evan's syndrome, pseudothrombocytopenia

Categorization

The International Working Group on ITP Consensus Report recommends the following categories to stratify ITP cases according to duration of disease [10]:

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, are the most common manifestations. Moderate bleeding that may warrant treatment can include wet purpura, epistaxis, menorrhagia, and oral bleeding. Life-threatening bleeding occurs very rarely [13–17]; 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 $20 \times 10^9/mm^3$), but platelet count correlates poorly with bleeding risk [14].

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 [9]. Adult ITP is generally chronic, with about 80 % of adults having a course that persists indefinitely [18, 19].

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 cornerstone of the laboratory evaluation of suspected ITP is 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 [20, 21]. Hepatitis C and HIV testing is recommended for all adults, and *Helicobacter pylori* testing is recommended for high risk or symptomatic patients [21]. ANA (anti-nuclear antibody) testing can be obtained for patients with high suspicion of autoimmunity [20, 22, 23]. The role of bone marrow examination is controversial and recommended only in circumstances where the diagnosis is not clear due to the presence of atypical features. New recommendations 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 [9]. 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 especially given the multifactorial etiology of ITP, antibodies are not always present and identifiable in cases of ITP. 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 [24–27]. Glycoprotein-specific antibody testing (direct antibody testing) has a high specificity (~75–95 %), but the sensitivity is low [28, 29]. For these reasons, the American Society of Hematology recommends against routine platelet antibody testing for the diagnosis of childhood or adult ITP [30].

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 [9]. 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 [9].

Management of ITP in Adults

The minority of patients can be managed with observation. 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. It is estimated that less than 30 % of adults can be successfully managed with observation [9].

Management of ITP in Pregnancy

ITP in pregnancy is generally mild in women with no history of ITP prior to the pregnancy. It can typically be followed with close observation if the platelet count is $>30{,}000/mm^3$ and there are no symptoms [30]. Affected patients may require treatment for severe thrombocytopenia, bleeding, or prior to 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 [9, 30]. A platelet count $>50{,}000/mm^3$ is generally recommended for vaginal delivery, but ideally should be higher for cesarean delivery or for epidural/spinal anesthesia [30]; the ITP diagnosis itself is not an accepted indication for cesarean delivery. The fetus/newborn should be monitored for passively acquired antiplatelet antibody leading to thrombocytopenia [31]. 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, intravenous immune globulin (IVIG) and steroids can be considered. The affected neonate should have spontaneous resolution as the passively acquired antibodies clear the body, at least by 12 weeks of age [30].

Front-Line Therapies

There are several treatment options for the temporary improvement in bleeding symptoms and platelet count in ITP, which function by interfering with immune destruction of antibody-coated platelets. Front-line treatment options include intravenous immune globulin (IVIG) 1 g IV × 1–2 doses, anti-D immune globulin 50–75 mm^3/kg IV × 1 dose, or corticosteroids. Steroid dosing and duration recommendations are varied, but most commonly a course of 1–4 mm^3/kg/day of oral prednisone for 2–4 weeks (including a taper) is recommended [8–10, 21]. High-dose IV methylprednisolone 30 mm^3/kg/day (maximum of 1 g/day) or oral prednisone 4–8 mm^3/kg/day for 3–7 days, followed by a prolonged taper to day 21, is also an acceptable treatment regimen [30]. IVIG and anti-D immune globulin 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 [10]. 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. Antifibrinolytic agents (aminocaproic

acid and tranexamic acid) can be helpful adjuncts to therapy for mucosal bleeding symptoms [21, 30]. Medications that affect platelet number or function should be avoided (aspirin, NSAIDs). Activity restrictions may be required depending on the platelet count and bleeding symptoms. IVIG and corticosteroids are both considered acceptable front-line treatment options in pregnancy [9].

Management of Life-Threatening Bleeding

If a patient is experiencing life-threatening bleeding, an aggressive approach with a combination of therapies is needed. IVIG and high-dose IV steroids should be given, with consideration of platelet transfusion/drip to facilitate hemostasis acutely [8, 21]. 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 [9].

Second-Line Therapies

For patients who fail front-line therapy or have persistent/severe disease, a second-line therapy may be considered to achieve a more durable platelet response. Examples of second-line treatments include splenectomy, rituximab, thrombopoietin receptor agonists, and alternative immunosuppressive agents [8, 9, 21]. The choice of agent/treatment is dependent on a variety of factors and should be made on a case-by-case basis.

Heparin-Induced Thrombocytopenia/Thrombosis

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening clinical syndrome caused by immune reaction and antibody formation upon exposure to heparin. HIT most commonly occurs after exposure to unfractionated heparin, and very rarely, to low molecular weight heparin products [32, 33]. 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 [34–36]. The incidence is much lower in children, those receiving prophylactic dosing or with heparin used as line flush, and in those receiving low molecular weight heparin products [34]. The highest risk appears to be in the cardiac surgery setting [37]. Thrombocytopenia, typically not severe, is the most common clinical manifestation of HIT [34]. Platelet counts rarely fall below 20,000/mm^3 [40], with median counts ranging from 40,000 to 60,000/mm^3 [41]. While HIT is not typically associated with bleeding symptoms, the most common complication is thrombosis [34]. Venous thrombi are more common (occurring in ~30–60 % of diagnosed patients) [34, 37, 42, 43] than arterial thrombi, which occur in ~3–10 % of patients [34, 43, 44]. Patients with heparin-induced thrombocytopenia and thrombosis (HITT) have high morbidity and mortality rates [42, 43]

Pathophysiology

In susceptible individuals, treatment with heparin 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 [33, 34, 45–48]. 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 [49, 50].

As in other immune disorders, the incidence of antibody development with heparin exposure is significantly higher than the incidence of clinical HIT [34, 37]. It is not clear why some patients are susceptible to developing HIT, or why some only develop thrombocytopenia while others have life-threatening thrombosis.

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 [34, 51, 52]. 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 [41]. Laboratory testing, often with long turnaround times, should only be pursued for patients with a high clinical suspicion. The 4 T scoring system is a clinical prediction tool developed to assist clinicians in determining appropriate candidates for laboratory testing [34]. The 4Ts are: *T*hrombocytopenia, *T*iming of platelet count fall, *T*hrombosis, and other causes for *T*hrombocytopenia. See Table 10.2 for calculation of the 4T score. Patients with a low 4T score have a low probability of HIT and likely do not require testing for PF4 antibodies. This tool, however, has limitations, as patients with a high 4T score don't necessarily have a diagnosis of HIT [38, 39, 53]. If the decision is made to send laboratory testing, the platelet [^{14}C] serotonin release

Table 10.2 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 5–10 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

assay should be sent, as it is the gold standard test for the diagnosis of HIT [54]. However, this test is technically challenging and not widely available, limiting usefulness when making treatment decisions [34, 55]. ELISA to detect the heparin/PF4 complexes is more readily available, but is associated with higher false positive rate [55, 56].

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 [35, 57]. Given the ongoing risk of thrombosis (as high as 25–50 %) despite discontinuation of heparin, these patients require alternative anticoagulation [35, 58].

Generally, low molecular weight heparin should not be used due to cross-reacting antibodies [40, 59]. Warfarin is not a good substitution for heparin secondary to the risk of venous limb gangrene or skin necrosis on initiation [60–62]. Acceptable non-heparin anticoagulant alternatives include the direct thrombin inhibitors Lepirudin, Argatroban, and Bivalirudin, as well as the factor Xa inhibitors Danaparoid and Fondaparinux [35]. 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 [34]. In patients with renal insufficiency, Argatroban should be considered for treatment of HIT, as it is not renally cleared [63].

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a very rare but potentially life-threatening condition with an incidence of approximately 1–4 per million person years [64, 65]. The disorder is secondary to a deficiency of ADAMTS13 (A Disintegrin and Metalloproteinase with a Thrombospondin type 1 Motif, member 13) [66], responsible for cleaving high molecular weight von Willebrand factor multimers [67, 68]. 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 [65]. 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 [69]. TTP is a life-threatening condition with high morbidity and mortality. The mortality rate in untreated TTP approaches 90 %[70], but with treatment is approximately 10–20 %[71]. 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 cleaving protease, ADAMTS13, released by endothelial cells and megakaryocytes [67, 68, 72].

Physiologically, periods of shear stress result in a partial unfolding of ultra-large von Willebrand factor multimers, allowing ADAMTS13 cleavage at the Tyr-Met bond in the second A-domain of von Willebrand factor [67, 68, 73]. Without the metalloprotease, the high molecular weight von Willebrand factor 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 [74].

In acquired TTP, the ADAMTS13 protease is inhibited by IgG type antibodies generated by a dysfunctional immune system [66, 75, 76]. Drugs, infection, underlying autoimmunity, pregnancy, and pancreatitis can all lead to the development of acquired TTP [77–84]. There are many drugs implicated in drug-induced TTP, the most common of which include clopidogrel, tacrolimus, sirolimus, mitomycin, alpha interferon, gemcitabine, quinine, and cyclosporine [77, 84, 85]. 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 [84, 86–88]. Classically, the presentation of TTP has been described by a "pentad" of symptoms: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever [89]; however, the pentad is variably present with some features found more commonly than others [87]. Laboratory findings in TTP include anemia, thrombocytopenia (often $<20 \times 10^9/mm^3$), and reticulocytosis on the 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 [74, 84, 90]. Disseminated intravascular coagulation (DIC) can develop secondary to overwhelming hemolysis and tissue ischemia/necrosis [86, 87].

Diagnosis

The combination of thrombocytopenia, schistocytosis, and LDH is often sufficient to suggest a diagnosis of TTP [74, 87]. 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 can be measured [70, 88]. 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 [84, 91–93]. Additionally, presence of detectable antibodies at initial diagnosis has been associated with higher mortality risk and worse clinical outcome [94–96]. 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 [95].

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 diarrheal-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" [70]. 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: pre-eclampsia or HELLP syndrome (hypertension, elevated liver enzymes, and low platelets during pregnancy); autoimmune disorders, including ITP, lupus, antiphospholipid antibody syndrome, and scleroderma; sepsis; malignancy; and malignant hypertension [84, 97]

Screening for Other Disorders

A high percentage of those with acquired TTP eventually develop other underlying autoimmune diseases, including systemic lupus erythematosus and anti-phospholipid antibody syndrome [80, 97]. Testing for autoimmunity, at least by a thorough screening for signs and symptoms specific to autoimmune disorders, should be performed and monitored over time [97]. Additionally, these patients are at risk for thromboses [82] and should avoid high 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 von Willebrand factor multimers, by plasma exchange [74, 98]. 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 upon clinical suspicion. If plasma exchange is not readily available, plasma infusion can be initiated until exchange is available [99]. The mortality rate of TTP was over 90 % prior to the institution of plasma exchange for treatment, but has now improved to 10–20 % [71, 100]. 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 [74, 87]. Although the standard in exchange is FFP, an alternative is cryoprecipitate-poor plasma, which is deficient in von Willebrand factor. [101]. 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 [86, 93, 102]. More recent studies have demonstrated that ADAMTS13 levels should be >10 % prior to discontinuing TPE [95]. LDH levels can also be followed as a marker for disease exacerbation [90]. Patients with high titer ADAMTS13 antibody, or patients with exacerbations after the cessation of plasma exchange, may benefit from the addition of corticosteroids to plasma exchange therapy [74, 87]. Steroids add the benefit of inhibiting antibody production for a more long-term, sustained, response.

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 von Willebrand factor multimers [70, 102]. 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 [97, 102]. Renal damage usually requires a lengthier recovery—as long as several months—and full recovery is often uncertain [97]. Platelet count has proven an important predictor of response to TPE; failure of response requires an increase in the number or volume of plasma exchange or addition of other treatment modalities [102]. Similarly, a decrease in platelet count after initial recovery should alert the clinician that control of the disease has not been achieved [102]. The duration of plasma exchange varies greatly, with most studies reporting a duration ranging from 7 to 20 days [71, 98, 103, 104].

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 [92]. Rituximab, an anti-CD20 monoclonal antibody, is an immunosuppressant agent now considered a standard second-line therapy for those with acquired, and especially antibody-mediated, TTP [105, 106]. There have been recent studies evaluating the use of rituximab as a front-line agent in combination with plasma exchange in high-risk patients, as well as using rituximab as prophylaxis against relapse, with promising results [105, 107, 108]. The drug is especially efficacious in patients with evidence of TTP and underlying systemic autoimmunity [109]. Rituximab depletes CD20-positive B-lymphocytes, preventing antibody formation that can last up to 6–9 months [107, 110]. The drug should be administered in 4 weekly doses at 375 mm^3/m^2 [91, 109, 111–113]. 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 [110], studies have demonstrated improved outcomes and fewer relapses in patients receiving the combination therapy [106, 108]. Rituximab should be given immediately after plasma exchange to maximize the time in circulation prior to the next exchange. Therefore, it is recommended to proceed with rituximab concurrent with plasma exchange, if medically indicated. 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 [113]. While rituximab is becoming standard of care for treatment of adult TTP, there is little evidence to date for the use of Rituximab in pediatric TTP [88].

A variety of other immunosuppresants 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 [70, 87, 97, 105]. Splenectomy has been performed in TTP patients in an effort to prevent additional relapse, with some success [99, 104, 114]; however, this treatment modality is not routinely recommended because of the complications and risks associated with splenectomy [99, 115].

Recurrence

Relapses occur in 20–65 % of TTP patients [91, 93, 100, 116, 117]. Relapse rates are high in patients presenting with severe ADAMTS13 deficiency (<10 %) and can be common in patients with an underlying autoimmune disorder [91–93, 97]. Relapses are most common in the year following the TTP episode [91]. 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 immunosuppressant agents may be trialed [99].

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 [118]. Approximately 75 % of children have their first TTP episode in the neonatal period, and 25 % present between 2 months and 4 years of age [88]. Patients with more mild mutations may present in adulthood [119]. Neonates present with icterus, hyperbilirubinemia, severe hemolytic anemia that often leads to hemoglobinuria and acute renal insufficiency, and severe thrombocytopenia ($<20 \times 10^9/mm^3$) [88]. Older children and adults often present after a triggering event, such as infection, stress, or hormonal changes, with thrombocytopenia and hemolytic anemia [88]. Exacerbations of the disease typically occur at regular intervals of about 3 weeks [74]. The disorder is inherited in an autosomal recessive pattern, leading to compound heterozygous or homozygous mutations of the ADAMTS13 gene [120]. ADAMTS13 gene sequencing should be obtained (performed only by specialty laboratories) in patients without detectable ADAMTS13 antibodies to rule out congenital TTP [88].

The approach to treatment of congenital ADAMTS13 deficiency is replacement of the ADAMTS13 protein, typically through infusion of fresh frozen plasma (FFP) [74]. This may be done periodically at the time of TTP exacerbation, but after several exacerbations, a scheduled regular infusion of FFP is typically prescribed to prevent potentially life-threatening complications, usually at 2–3 week intervals [88, 121]. The schedule of infusion should be based on the individual patient presentation, but increasing the interval between infusions beyond 4 weeks can increase the risk of relapse [88]. FFP and the infusion complications, as well as donor exposure, cannot be taken lightly. Importantly, treatment of neonates with congenital TTP often requires plasma exchange, rather than FFP infusion alone, secondary to the accompanying severe hyperbilirubinemia [88]. An emerging therapy for congenital TTP is a recombinant ADAMTS13 replacement product [115]. Administration of recombinant ADAMTS13 in vitro has been shown to replenish von Willebrand factor cleaving activity in the plasma from TTP patients [122]. Therefore, recombinant ADAMTS13 may be a viable therapeutic option in the near future.

Platelet Refractoriness

Platelet transfusions are required for a variety of causes of thrombocytopenia. In some cases, transfusion of platelets is a life-saving intervention. Approximately 20 % of hematology and oncology patients, however, do not achieve the expected response to platelet transfusions and are considered platelet refractory [123]. Platelet refractoriness is associated with an increased risk of morbidity and mortality and is related to significant bleeding events [124]. The definition of "optimal response" to platelet transfusion historically has been defined as an increase in platelet count of at least $5{,}000–10{,}000/mm^3$ 1 h after transfusion [125]. More accurately, one can measure the 1-h corrected count increment (CCI), an objective measure of whether a patient is refractory to platelet transfusion [126, 127]. The formula requires the post-transfusion 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 $\times 10^{11}$. An acceptable CCI value is considered <5,000 on 2 separate occasions [128].

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, disseminated intravascular coagulation, febrile illnesses, sepsis, graft vs. host disease, bleeding, and medications, among others [123, 127, 129–131]. A high 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 human platelet antigens (HPA) after prior exposure (i.e., maternal-fetal incompatibility during pregnancy, prior transfusions, transplantation) [127, 132]. HLA alloimmunization is secondary to leukocyte contamination of the platelet transfusion product [133]. Much less commonly, antibodies to platelet-specific antigens are a cause of platelet refractoriness [132, 134–136].

Diagnosis

A patient is confirmed to have platelet refractoriness if the 1-h post-transfusion CCI value is less than 5,000 on at least two occasions [128]. 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 [126, 131]. 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

[132]. 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 [127]. Patients with alloimmunization require HLA-compatible platelet transfusions to raise platelet count increments [137]. This can be achieved by transfusing HLA-antigen-negative platelets (corresponding to specificity of anti-HLA antibodies), HLA-matched platelets, or crossmatch compatible platelets. 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 [138]. By this method, donor units are chosen that lack HLA antigens that react with the patient's antibodies. 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 [127]. Importantly, these platelet units should be irradiated prior to transfusion to decrease the risk of transfusion-associated GVHD [139]. Crossmatching involves identifying compatible platelet units by crossmatching with the platient's plasma. This method is quick (a few hours) and allows for a larger donor pool than HLA-matching [127, 140]. Platelets should be leuko-reduced (removal of white blood cells from platelet products by filtration) or irradiated prior to transfusion in frequently transfused patients (i.e., hematology/oncology, parous patients) to prevent alloimmunization [141]. Several studies in patients with acute myelogenous leukemia have shown that leukoreduction reduces the incidence of platelet refractoriness secondary to HLA antibody formation from ~50 to ~20 % [141–143]. However, it is important to realize that leukoreduction does not reduce the incidence of platelet refractoriness if the patient develops HPA antibodies [132, 141, 144].

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 [145]. 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 [125, 146]. Here we will primarily focus on hereditary platelet function defects.

Platelet Disorders with Giant Platelets

Giant platelet disorders include Bernard–Soulier syndrome (BSS), the MYH-9 group of platelet disorders, Gray Platelet syndrome, and Platelet-Like von Willebrand disease (vWD). BSS is an autosomal recessive disorder characterized by thrombocytopenia, large platelets, and prolonged bleeding time [147]. The syndrome is secondary to a deficiency of the platelet GP Ib-V-IX complex [148, 149], which normally functions in platelet adhesion to the endothelium by binding von Willebrand factor [150]. The disorder can be diagnosed with an abnormal platelet function analyzer-100 (PFA-100™) assay or by flow cytometry [13]. 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 [145, 150].

The MYH-9-related disorder is a syndrome caused by a mutation within the *MYH9* gene that is inherited in an autosomal dominant fashion [151, 152]. The syndrome includes the previously classified disorders May–Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome [145, 153]. It is characterized by macrothrombocytopenia and mucocutaneous bleeding in early life, with the development of hearing loss, glomerulonephritis, and cataracts with aging [154, 155]. Life-threatening bleeding is rare, but can occur with trauma [145]. Diagnosis should be strongly considered in a patient with macrothrombocytopenia in addition to glomerulonephritis, sensorineural hearing loss, and cataracts [145]. 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 [154]. Definitive diagnosis is achieved with demonstration of a mutation in the *MYH9* gene.

Gray platelet syndrome (GPS) is a very rare hereditary platelet function disorder secondary to decreased alpha granule content [156]. There are case reports of autosomal dominant and autosomal recessive inheritance, but it can also be sporadic [145, 154]. The syndrome is characterized by normal or low platelet count, large/giant platelets, and mucocutaneous bleeding of variable severity [154]. Platelets appear agranular and thus gray on peripheral smear, and platelet aggregation studies may be abnormal to one or more agonists [145].

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 [154, 157]. Patients present with

mucocutaneous bleeding that is usually mild-to-moderate in severity [154]. 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 [154]. Platelet-type vWD is similar to type 2B vWD, but is different in that the genetic defect affects the platelet rather than vWF [158].

Treatment of the giant platelet function disorders include antifibrinolytic agents or desmopressin for mild-to-moderate bleeding and platelet transfusions and/or recombinant factor VIIa for severe bleeding [145].

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 [154]. XLT presents with isolated thrombocytopenia, whereas WAS presents with a severe immunodeficiency leading to recurrent infections, allergies, autoimmunity, and lymphoid malignancy [154, 159]. The disorders are caused by mutations in the gene encoding the Wiskott-Aldrich syndrome protein (WASp) [160–162]. The incidence of WAS is 1/250,000 and usually occurs in patients of European decent [154]. Patients present at birth with bleeding and frequent illness related to the immune dysregulation, which worsens with age [162]. Bleeding may range from mild mucocutaneous bleeding to severe intracranial or gastrointestinal hemorrhage [154]. Immune dysfunction may present with frequent infections or other signs of dysregulation, including eczema, concurrent autoimmune disorders, IBD, vasculitis, arthritis, or lympoproliferative disorders [154, 162]. 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 [154, 160]. Treatment includes prophylactic antibiotics against *Pneumocystis jirovecii* pneumonia in infants and children, and platelet transfusions to treat severe bleeding [162]. IVIG is indicated for patients with antibody deficiency [162]. Splenectomy has been successful at correcting thrombocytopenia, but the risks of severe infection often outweigh the benefits [162]. The only curative treatment is hematopoietic stem cell transplantation [163, 164].

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 [165], leading to a defective platelet integrin $\alpha_{IIb}\beta_3$ receptor [166–168]. This integrin is present in high concentrations on platelets, and when functionally intact, allows strong bonds to form between the platelet and vWF and/or fibrinogen [145, 169]. Absence results in inefficient platelet aggregation [145]. 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 [169]. Although the degree of bleeding is variable among patients [165, 170], it has been observed that the greater the deficiency of the $\alpha_{IIb}\beta_3$ receptor, the more severe the bleeding symptomatology [167]. Patients typically present with mucocutaneous bleeding beginning in childhood, often before 5 years of age [167, 169]. The most common clinical features are purpura, epistaxis, gingival bleeding, and menorrhagia [167]. GT can be diagnosed with prolonged closure time of the PFA-100, with a prolonged bleeding time, with 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 [145, 157, 169, 171]. Treatment of GT involves antifibrinolytics or tranexamic acid for mild-to-moderate mucocutaneous bleeding and platelet transfusion and/or recombinant FVIIa for severe bleeding [145]. Menorrhagia can be treated with oral tranexamic acid and/or hormone therapy [145]. In cases of severe, recurrent bleeding, hematopoietic stem cell transplantation can be considered [172].

CAMT, characterized by severe thrombocytopenia, is an autosomal recessive disorder affecting the *MPL* gene [173]. Mutations in this gene result in altered expression or function of the thrombopoietin receptor [173]. 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 [145, 174]. 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 [145]. Bleeding symptoms are treated with platelet transfusions, but progression of aplasia requires hematopoietic stem cell transplantation [145, 175].

TAR is an autosomal recessive disorder with uncertain genetic basis [176]. 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 [176–178].

Unlike in CAMT, the severe thrombocytopenia generally improves through childhood [145, 154]. Diagnosis is suggested by congenital thrombocytopenia and the associated clinical abnormalities [145]. Bleeding in infancy may be severe and require platelet transfusions, but with aging, treatment is rarely needed [145].

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Bleeding in Acute and Chronic Liver Disease

11

Esther Paula Soundar and Jun Teruya

The liver plays a central role in hemostasis. A majority of coagulation factors and their inhibitors are synthesized in the hepatocytes with the exception of factor VIII and a subunit of factor XIII. Liver disease in general 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. Multiple hemostatic abnormalities may coexist in an individual patient with liver disease. Different pathophysiological mechanisms form an underlying basis for bleeding in acute and chronic liver disease. In acute liver failure (ALF), there is a lower incidence of thrombocytopenia but more severe reductions in circulating procoagulant and anticoagulant factors. On the other hand, patients with chronic liver failure have thrombocytopenia as well as coagulopathy. Approximately a third of patients with chronic liver disease also exhibit systemic hyperfibrinolysis proportional to the degree of liver dysfunction that could be attributed to elevated tissue plasminogen activator (tPA) levels and low levels of alpha-2-antiplasmin (α2AP), factor XIII, and thrombin-activated fibrinolysis inhibitor (TAFI).

Acute Liver Failure

ALF is a severe liver dysfunction presenting with encephalopathy and coagulopathy within 26 weeks of hyperbilirubinemia in previously healthy patients. The incidence of fulminant hepatic failure is low in the United States and estimated to be approximately 2000 cases per year [1]. Drug-related hepatic failure including acetaminophen toxicity contributes to approximately 50 % cases of ALF [2]. Other common etiologies seen in the United States are hepatitis A and B, ischemia, other hepatotoxic drugs, and autoimmune hepatitis (Fig. 11.1). According to the US Acute Liver Failure Study Group (ALFSD), about 5 % of ALF patients present with very severe coagulopathy with INR > 10 on admission [3].

It has been known that all hepatic procoagulant factors except factor VIII and anticoagulant factors such as protein C, protein S, and antithrombin are significantly reduced very early in the disease process. Particularly, factor VII and factor V show considerable decline and have short half-lives [4] (Table 11.1). In severe liver injury, fibrinogen levels may even be increased as an acute phase reactant, and although hypofibrinogenemia is uncommon, it could be due to increased fibrinogenolysis [5]. Factor XIII deficiency in this setting may contribute to a weak clot. Dysfibrinogenemia may coexist and could be due to defective posttranslational assembly or excess sialic acid content, however, by itself, does not increase bleeding risk. A decrease in fibrinogen levels along with declining factor VIII may represent evolving disseminated intravascular coagulation (DIC). Impediment to the clearance of plasmin or plasmin activators by the hepatic reticuloendothelial cells along with the decreased synthesis of fibrinolytic inhibitors such as plasminogen activator inhibitor type 1 (PAI-1) and α2AP may enhance fibrinolysis and clinically present as hyperfibrinolysis syndrome [6].

Modest thrombocytopenia occurs in ALF. Although thrombopoietin is synthesized in the liver, the role of thrombopoietin does not seem to be plausible owing to the fact that there are either normal or increased levels in patients with ALF. Alternatively, it may possibly be associated with increased platelet activation followed by clearance [4]. Circulating platelet microparticles laden with tissue factor may be responsible for coagulation activation and resulting consumption of platelets and thereby thrombocytopenia [7, 8]. It is still not known whether the activation/consumption

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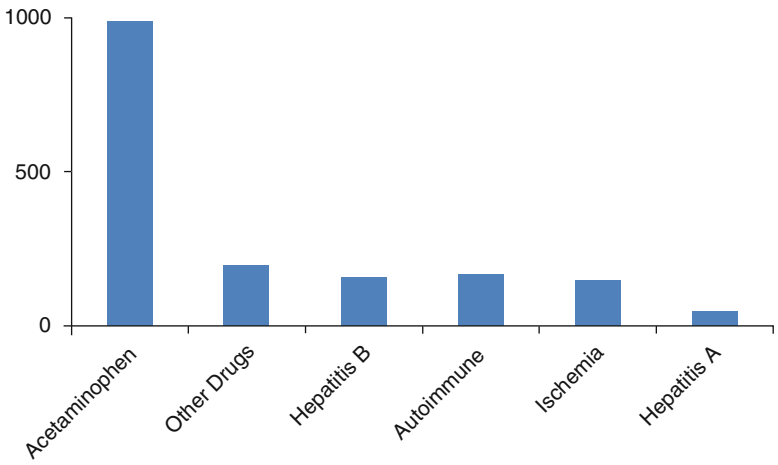

Fig. 11.1 Etiology of acute liver failure in the United States

Table 11.1 *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 11.2 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

process is systemic or locally confined to the liver. Recent studies on the decreasing trend of platelet counts in patients with ALF support the platelet activation consumption pathway [9] (Table 11.2).

Even if there are severe derangements in coagulation profile, clinically significant spontaneous bleeding may not happen and therefore measures to decrease the bleeding risk by blood component therapy or otherwise is not always recommended [10]. However, if the patient is bleeding even a minor bleeding such as oral bleeding, appropriate therapeutic interventions including transfusions of blood products are indicated. It is important to consider correction of coagulation

parameters before invasive procedures involving high bleeding risk such as implantation of intracranial pressure (ICP) monitors [11]. Prophylactic administration of fresh frozen plasma (FFP) and cryoprecipitate followed by recombinant activated factor VII (rFVIIa) has improved prothrombin time (PT)/international normalized ratio (INR) compared to FFP alone, but concerns for thrombotic complications remain [12, 13].

Spontaneous unprovoked hemorrhage is mostly mucosal in nature presenting as hematemesis, hemoptysis, epistaxis, and hematuria. Rarely, spontaneous intracranial hemorrhages have been reported. Invasive procedures such as venous and arterial catheter placement or ICP monitors may provoke severe bleeding in 10% of patients undergoing such procedures [11]. 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, poor oral intake, and cholestasis could affect vitamin K absorption, and therefore severe vitamin K deficiency may be present [15]. Sepsis induced DIC, and multiple prior transfusions of 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. First of all, 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. Alternatively, fibrinogen concentrates can be rapidly administered without the need for thawing and ABO typing. Similarly prothrombin complex concentrate (PCC) could replace FFP to provide vitamin K-dependent hemostatic factors that help in thrombin generation. Both these agents provide necessary hemostasis without volume expansion but should be used with extreme caution and preferably as rescue therapeutics due to potential thrombotic complications. 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 [18]. The dosage and indications are found in Table 11.3. It should

Table 11.3 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 1st 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
ALF acute liver failure, *FFP* fresh frozen plasma, *FXIII* factor XIII, *rFVIIa* recombinant activated factor VII

be noted that rapid lab testing for hyperfibrinolysis is not available in most coagulation laboratories. Viscoelastometry (TEG™ or ROTEM™) may show hyperfibrinolysis; however, it is known that it is not sensitive enough to detect clinically significant medical hyperfibrinolysis.

Finally, therapeutic plasma exchange (TPE) is very effective in temporarily preventing life-threatening bleeding in volume-overloaded children and adults with severe coagulopathy associated with ALF, although not useful in alleviating the neurologic complications of liver failure [19, 20]. It can act as a bridge to liver transplantation until a donor organ is identified. Patient plasma is replaced with donor plasma without increasing total blood volume and thus preventing increases in ICPs.

Chronic Liver Disease

Cirrhosis and chronic liver disease were the twelfth most common cause of death in the United States in 2013, accounting for 36,427 [11.5 per 100,000 persons] deaths [21]. The incidence of chronic liver disease is estimated to be 360 cases per 100,000 of population per year, and chronic hepatitis B, hepatitis C, and alcoholic and nonalcoholic liver disease are the major causes. In most cases, liver-related mortality results from complications of chronic liver disease including advanced cirrhosis [22]. Despite multiple etiologies, common pathophysiological characteristics are evident such as hepatocyte necrosis, fibrosis, nodular regeneration, and ultimate loss of functional liver parenchyma. Chronic liver disease is accompanied by different levels of changes in the hemostatic system proportional to the degree of disease. More severe the disease, greater is the reduction of the coagulation factors. This is in contrast to healthy individuals who normally have an excess plasma pro- and anticoagulant levels to provide a cushion during any consumptive event [23].

Platelets are the main players in the primary hemostatic plug formation and inducers of thrombin generation. In end-stage liver disease, reduced thrombopoietin levels cause thrombocytopenia, hence leading toward a bleeding tendency. This is counterbalanced by an increase in high von Willebrand factor (VWF) and low ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). Considering the secondary hemostasis stage, low hepatic procoagulation factors I, II, V, VII, IX, X, and XI are balanced by reduced hepatic anticoagulant factors such as protein C, protein S, and antithrombin and increased VWF and factor VIII which are not produced by the hepatocytes. The serine proteases of the fibrinolytic system including plasminogen and α2AP are of hepatic origin and therefore are also reduced in cirrhosis. Antifibrinolytic factors such as low plasminogen and high PAI-1 maybe equalized by hyperfibrinolytic factors like high tPA, low thrombin-activatable fibrinolysis inhibitor (TAFI), and reduced α2AP [24]. Thus, hemostasis is precariously balanced by comparable reductions of all the proanticoagulants and anticoagulants as well as the fibrinolytic system.

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 [25] to maintain fibrinogen levels to about 150 mg/dL and platelet count of 100,000/mm^3. In general, critically ill patients with chronic liver disease 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.

Unprovoked spontaneous variceal bleeding is often a severe complication of liver cirrhosis secondary to portal hypertension, and 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 [26]. In addition, resuscitation measures should include blood products intending to restore hemodynamic stability and hemoglobin of 8 g/dL and a platelet count of >56,000/mm^3 [27, 28]. This should be done with extreme caution because volume resuscitation may result in comparatively higher portal venous pressure and resultant re-bleeding episodes. Correction of hemostatic abnormalities should be attempted in these patients, if they present with severe coagulopathy [29].

Several laboratory tests help physicians to assess hemostasis and are listed with their advantages and disadvantages in Table 11.4. PT is a quick and 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 levels may suggest either consumption or an underlying hyperfibrinolysis

Table 11.4 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
PTT	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 not known
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, *PTT* activated partial thromboplastin time, *VWF* von Willebrand factor

during a variceal bleed. Finally, dynamic functional laboratory tests like viscoelastometry (TEG™ or ROTEM™) and thrombin generation assays are efficient tools for assessing global hemostasis and to guide hemotherapy.

Parenteral administration of vitamin K can alleviate deficiency generally seen in decompensated liver cirrhosis secondary to bile salt deficiency and broad-spectrum antibiotic usage. There is definitely 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 [30]. Although there is no published data on the use of fibrinogen and PCC, it is still preferable over FFP due to smaller volumes. 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.

Summary

Hemostasis is rebalanced in patients with acute and chronic liver disease and unprovoked spontaneous bleeding due to coagulopathy is not common. Prophylactic administration of blood products to patients with high bleeding risk prior to invasive procedures such as implantation of ICP monitors can be considered. Several laboratory tests can be useful and help physicians guide hemotherapy in patients with bleeding. Different blood products and factor concentrates are administered to achieve hemostasis in acute and chronic liver disease depending on the pathophysiology and the clinical condition of the patients.

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Bleeding and Hyperfibrinolysis

12

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Acquired Systemic Hyperfibrinolysis

Thrombolytic Therapy

Hyperfibrinolytic bleeding may occur for a variety of reasons (Table 12.1). 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 2–6 % of patients receiving tPA for ischemic stroke, 0.6–2 % 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 5000–10,000 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 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 the plasminogen activator is only 2–4 min. 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].

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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. 12.1) [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 50–250 ng/mL during CPB with the majority in the active form [8]. The level 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 monitored using viscoelastometry (see Chap. 4, Fig. 4.3). Hyperfibrinolysis on viscoelastometry is almost always associated with bleeding and usually requires treatment with an antifibrinolytic medication. Since

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Table 12.1 Mechanisms of systemic hyperfibrinolytic bleeding

	Production		Intravascular fibrin	Inhibition of tPA	Inhibition of Plasmin	Clearance of tPA
	tPA	uPA				
Acquired disorders						
Thrombolytic therapy[a]	↑ ↑	↑ ↑	**N**	**N**	**N**	**N**
Cardiopulmonary bypass	↑ ↑	**N**	↑ ↑	**N**	**N**	**N**
Liver transplantation	↑ ↑	**N**	↑ ↑	↓ ↓	↓ ↓	↓ ↓
Trauma	↑ ↑	**N**	↑ ↑	**N**	↓ ↓	+/–
DIC	↑ ↑	**N**	↑ ↑	**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

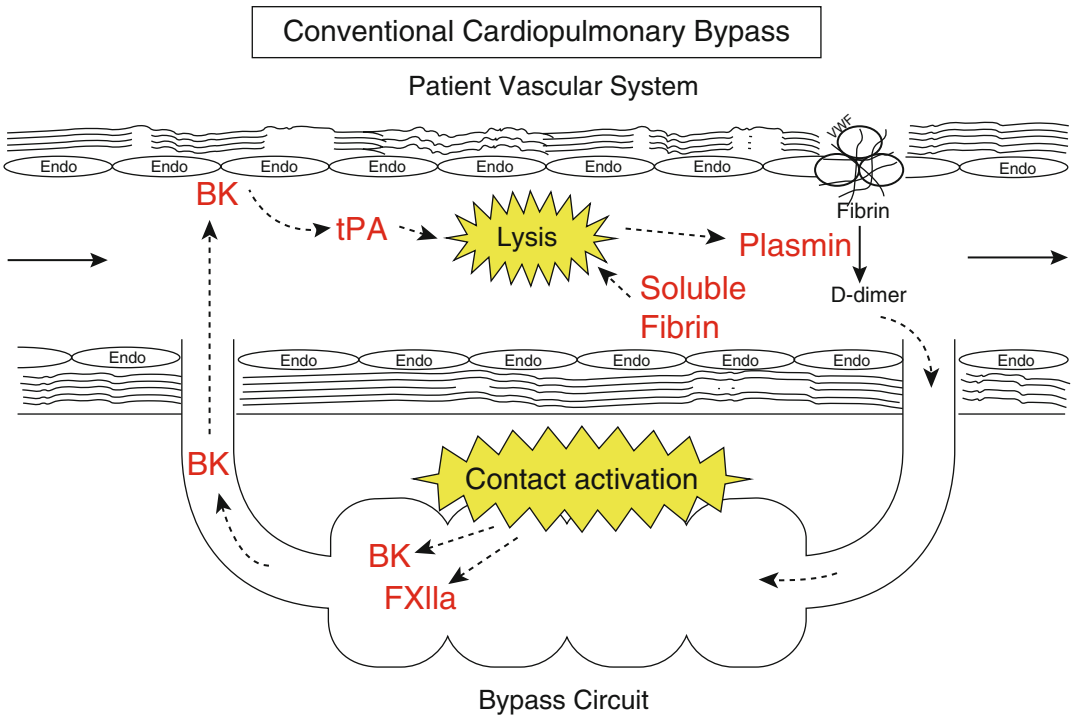

Fig. 12.1 *Hyperfibrinolysis during cardiopulmonary bypass.* Circulation of blood across the artificial surface of the pump/oxygenator circuit leads to activation of the contact system including formation of bradykinin (BK) and activated factor XII (FXIIa). Bradykinin formed in the bypass circuit flows back into the patient's vascular system stimulating release of tissue plasminogen activator (tPA) from the 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

about two-thirds of patients show hyperfibrinolysis during CPB [8], many patients routinely receive antifibrinolytics during open heart surgery to suppress fibrinolysis and reduce blood loss [10]. Two types of antifibrinolytics have been used: aprotinin and lysine-binding site antagonists like ε-aminocaproic 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].

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 [12, 13]. In adults on ECMO, excessive bleeding occurs in more than 30 % of patients [14], with evidence of ICH often found in those that died [13]. 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 [15]. 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 [12].

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 tPA 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 min) and inhibition by PAI-1. Liver cirrhosis increases fibrinolytic activity due both to decreased clearance of tPA and decreased production of PAI-1 by the liver. In severe cirrhosis this can lead to an increased risk of hyperfibrinolytic bleeding. 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 no 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 [16]. In severe cases, tPA levels can rise to 400 ng/mL during the anhepatic and reperfusion phases [16]. 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 [17]. 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 [16]. Approximately 30 % of liver transplant patients show fibrinolysis severe enough to increase bleeding and transfusion requirements [16, 18]. 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 the surgery [18, 19]. The coagulopathy of liver transplantation is complex and involves far more than hyperfibrinolysis [19]. 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 [19].

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 [18]. While some studies have reported a reduction in blood loss with antifibrinolytic therapy, data from controlled trials is limited [20].

Trauma

Increased fibrinolysis in trauma patients has some of the same multifactorial mechanisms seen in CPB and liver transplantation: increased levels of tPA combined with increased intravascular fibrin resulting in clinically significant hyperfibrinolysis and bleeding [21]. The cause of elevated tPA levels in severe trauma is unknown but may be associated with increased secretion of tPA from endothelium injured by shock/hypoxia/ischemia [22]. tPA levels may reach 30–60 ng/mL with reduced antiplasmin in severe trauma [23–25]. 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 (2–11 % of cases), but associated with a high mortality rate (54–76 %) [26–28]. 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 [23]. Treatment of trauma patients with antifibrinolytic agents has been shown to reduce bleeding and mortality [29].

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) and other consumptive coagulopathies are a complex set of disorders associated with many different diseases including sepsis, cancer, trauma, 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 [30–32]. 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 [30]. 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 acute promyelocytic leukemia and trauma as discussed above. In a recent study, low-dose heparin and EACA were used to treat patients with acute promyelocytic leukemia with evidence of coagulopathy, bleeding, and hyperfibrinolysis as indicated by low antiplasmin activity (<50 % of normal) [33].

Transient Hyperfibrinolysis

Massive but transient release of tPA leading to bleeding has been described associated with electric shock, complicated labor, heat stroke, surgery, and other procedures [34]. 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 using viscoelastic testing.

Amyloidosis

Hyperfibrinolytic bleeding in amyloidosis has primarily been associated with the monoclonal light-chain form of the disease [35]. 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. The endometrium from women with menorrhagia produced higher levels of tPA and relatively lower levels of PAI-1 than control subjects without menorrhagia [36]. Menstrual fluid fibrinolytic activity was higher in women with menorrhagia and correlated with total blood loss [37]. 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 [38]. The fibrinolytic inhibitor tranexamic acid has been shown to be a safe and effective treatment for women with menorrhagia, with a 40–50 % reduction in blood loss and improvement in quality of life [39, 40]. While not as effective as intrauterine administration of levonorgestrel in reducing blood loss (up to 97 % reduction), tranexamic acid had less side effects [39, 41]. 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 [41].

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 [42]. Topical antifibrinolytic therapy applied at the time of joint or spine surgery has also been shown to reduce blood loss in some studies [43].

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. The euglobulin clot lysis time is often reduced in hereditary hyperfibrinolysis but is nonspecific and cannot determine the underlying cause; specific measurement of fibrinolytic activators and inhibitors is required for diagnosis. The standard therapy is treatment with an antifibrinolytic agent.

Plasminogen Activator Inhibitor 1 Deficiency

Plasminogen activator inhibitor 1 (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 [44]. 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. 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).

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 [45]. 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 [46]. 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 requires antifibrinolytic agents.

Increased tPA Levels

An unusual cause of hereditary hyperfibrinolytic bleeding is persistent elevation of tPA levels [47–49]. 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.

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Bleeding of Unknown Etiology

13

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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, 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 (PTT), fibrinogen, and platelet count, included in complete blood count (CBC), as first-tier (Table 13.1) testing. In the setting of anemia, if both the MCV and MCH are decreased and RDW is increased, it suggests chronic iron deficiency anemia. If PT, PTT, 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 13.1).

Unclassified bleeding disorders may be defined as within normal limits in all tests listed in Table 13.1. Even in tertiary care hospitals, tests shown in Table 13.1 may not be performed in-house. If the tests listed in Table 13.1 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]. 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 [3].

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 [4, 5]. However, unless the factor XIII level is below 10–15%, TEG™ or ROTEM™ may be normal. 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 day 5–7 following birth. Still, patients with heterozygous factor XIII deficiency may not bleed until surgical procedure or dental extraction is performed [6]. If the patient has no bleeding history, but has developed new onset of bleeding such as intramuscular bleeding, a factor XIII inhibitor should be suspected [7]. 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 [8].

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Table 13.1 Lab tests related to hemostasis

First tier
PT
PTT
Fibrinogen
Platelet count
Second tier
Thrombin time
Coagulation factor assay
Factor XIII assay
Viscoelastometry (ROTEM™ or TEG™)
PFA-100™
Von Willebrand panel (factor VIII, ristocetin cofactor activity, VWF antigen, activity/antigen ratio, VWF multimer assay) Glycoprotein Ib binding as say or 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

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. Since AVWS is under-recognized, knowledge of underlying conditions associated with AVWS is necessary (Table 13.2).

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 disease [9]. 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™ or TEG™ are useful for moderate to severe platelet function defects seen in entities such as Glanzmann's thrombasthenia or Bernard–Soulier syndrome [10]. Since they are not sensitive to mild to moderate platelet dysfunction, they cannot be used to monitor antiplatelet medication.

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, PTT, 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 cells should also be transfused in order to prevent hemorrhagic shock or ischemic organ damage if bleeding is continuous. Table 13.4 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 Chap. 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 [11]. Individual lab tests for hyperfibrinolysis may not be readily available. Of note, antifibrinolytics may be beneficial without significantly increasing thrombotic risk (see Chap. 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 PTT 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 [12], since PT reagent contains a heparin neutralizer such as polybrene.

Table 13.2 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

Table 13.3 Examples of rare bleeding disorder

Disease condition	Management
East Texas bleeding disorder [43]	
Factor V Amsterdam [44]	
Thrombomodulin (p.Cys537Stop) mutation [45]	Protein C concentrate
Antithrombin Pittsburgh [46]	
Ehlers–Danlos syndrome (connective tissue disorders) [47, 48]	DDAVP, antifibrinolytics
Quebec platelet disorder [49]	Antifibrinolytics
Scott syndrome [50]	Platelet transfusion

Table 13.4 Available blood components

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

Table 13.5 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

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 13.3 shows examples of rare bleeding disorders. Finding the etiology of bleeding requires consultation with specialized laboratories, usually research laboratories. Tables 13.4 and 13.5 show available blood components and medications used to treat these disorders.

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 [13] or antibody against factor V [14, 15]. Likewise, platelet transfusions may be also effective for AVWS since von Willebrand factor is also stored in α-granules [16].

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, PTT, 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 [17]. There is not much data regarding the use of plasma exchange in order to remove direct oral anticoagulant.

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. 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. It is usually seen in suicide attempts. Mild bleeding may be corrected with oral vitamin K1 at 25–100 mg daily; however, sometimes up to 400 mg is required [18]. 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 to 30 mL/kg), plus intravenously 10–15 mg of vitamin K1 [19]. Rarely paradoxical thrombosis complicates superwarfarin bleeding, and the management in these cases is very challenging [20]. Thrombotic episodes were attributed to the administration of PCC, or if concomitant thrombosis and hemorrhage happened prior to any blood product infusion, thrombotic phenomenan 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 [21], 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 seen in the setting of hematologic malignancy and liver disease [22]. 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 [23]. It is structurally similar to unfractionated heparin, though its anticoagulant effects are mediated mostly via complexing with antithrombin to inhibit factor X [24]. 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 [24]. Both heparan and dermatan are less potent inhibitors of coagulation than pharmaceutical heparin, which is likely due to decreased sulfation of saccharide units [25, 26].

Table 13.6 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

The heparin-like effect of endogenous glycosaminoglycans has been associated with multiple myeloma, B-cell and T-cell lymphomas [22], systemic mastocytosis [27, 28], suramin therapy [29], metastatic transitional cell carcinoma [30, 31], metastatic breast cancer [32], systemic candidiasis [33], and renal cell carcinoma [34]. More recently, this effect has been described in the setting of bacterial infection in cirrhotic patients [35], liver transplantation [36, 37], and in patients receiving extracorporeal membrane oxygenation therapy (ECMO) [38, 39]. Heparan 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 [38, 40]. Like heparin, heparan is metabolized by the liver and may build up in the setting of liver disease [29]. 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 13.6. Laboratory identification of heparin-like inhibitors is difficult. Though we often identify heparin in association with a prolonged PTT, 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 [41]. 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 [41] (see Table 13.7). 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 lab, 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 [29]. Prolongation of the clotting time on TEG™ or ROTEM™ can also demonstrate the heparin-like effect [34, 35, 39] (Fig. 13.1).

Appropriate treatment for heparin-like effect is not well defined. Some patients have been successfully treated with protamine sulfate [41]. We have found that a slow continuous infusion of protamine at 1 mg/min has resolved bleeding in our patients; however, protamine therapy does not always appear to work [33]. Plasma exchange in this setting has been described, but is of questionable benefit [41]. The only reliable treatment appears to be eradication of the underlying disorder [41]. 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 [38, 39]. Ongoing research indicates that circulating glycosaminoglycans may be a marker for the development of critical illness [39, 42]. A high index of suspicion is critical to identify this disorder.

Table 13.7 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
PTT with Hepzyme	Normal (may only see partial correction)
TEG/ROTEM	Prolonged clotting time
Anti-Xa	Normal or elevated

Summary

Occasionally, patients present with bleeding without any apparent cause. Laboratory testing algorithms may be used to help guide treatment and determine the underlying etiology. 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 workups and expert consultation may be necessary to identify rare bleeding disorders.

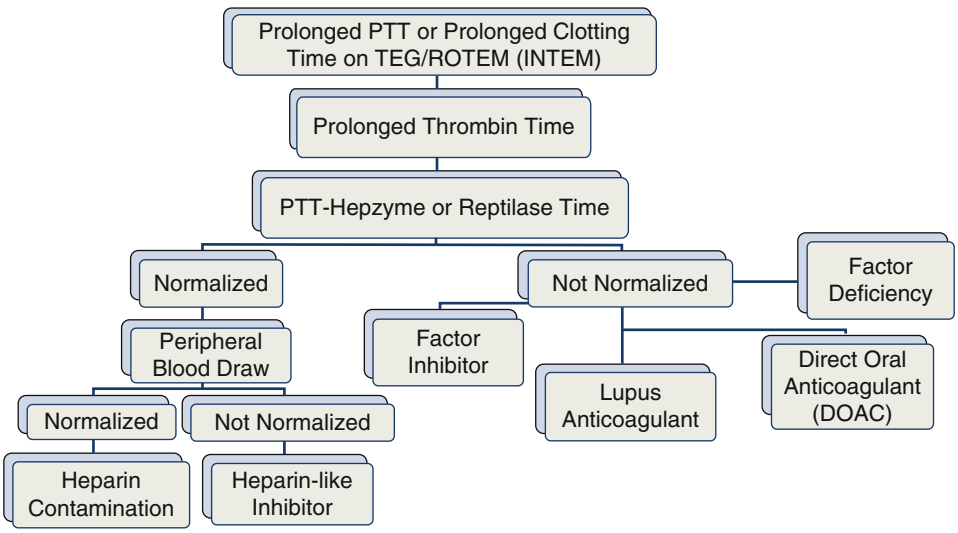

Fig. 13.1 Diagnostic algorithm. *PTT* partial thromboplastin time, *TEG* thromboelastography, *ROTEM* rotational thromboelastometry

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Bleeding Associated with Disseminated Intravascular Coagulation

14

Charles S. Eby

Abbreviations

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

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 [2]. 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, laboratory, and vascular consequences of DIC include preexisting morbidities, organ system vulnerability to injury, and the tempo of 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 and sometimes counterintuitive.
7. Excessive fibrin(ogen)olysis is an uncommon subtype of DIC which requires different management approaches.

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

Pathophysiology of DIC

Hemostasis involves many complex cellular functions (endothelial cells, platelets, leukocytes) and protein activation pathways (coagulation, fibrinolysis, complement, inflammation). When diseases or insults perturb these processes, the consequence is often excess generation of thrombin which may be clinically undetectable or disastrous. 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 [2]. Table 14.1 lists the major clinical disorders complicated by DIC.

Tissue factor activates factor VII to VIIa which proceeds to activate factor X to Xa activating prothrombin (factor II) to thrombin. Thrombin targets multiple substrates, most of which are prothrombotic: conversion of fibrinogen to fibrin; activation of platelets; activation of factors XI, VIII, V, and XIII and one substrate which negatively feeds back on thrombin generation; and activation of protein C. Thrombin also initiates fibrinolysis by stimulating release of tissue plasminogen activator from endothelial cells which activates plasminogen to plasmin, and plasmin degrades fibrin polymers into soluble fibrin degradation fragments including the

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Table 14.1 Clinical disorders complicated by DIC

Acute process	Chronic process
Sepsis	Solid neoplasms
Major trauma, brain injury, major burns	Retained dead fetus
Heat stroke	Chronic liver disease (controversial)
Obstetric emergencies	Hemangiomas producing Kasabach-Merritt syndrome
Amniotic fluid embolism	Aortic aneurysms, often with extensive dissection
Abruptio placentae	
Leukemias—acute promyelocytic most common	
Acute on chronic liver failure	
ABO-incompatible hemolytic transfusion reaction	

neo antigen D-dimer. Acute, overwhelming thrombin generation, from a localized site of trauma or diffusely throughout the vasculature due to infection, 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. Activated platelets, neutrophils, and monocytes and dysfunctional endothelial cells contribute to destabilizing hemostasis checks and balances by suppressing protein C activation and inhibiting fibrinolysis [1, 4, 5].

Clinical Consequences of DIC

The clinical consequences range from mild laboratory abnormalities to end-organ ischemia (necrosis of adrenal glands and skin; renal, pulmonary, liver, and gastrointestinal dysfunction; suppression of consciousness) and diffuse bleeding from mucous membranes, phlebotomy sites, and major organ systems. 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 potential DIC situation is patients with chronic advanced liver disease who acutely decompensate due to bacterial infection or renal failure. 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 abrupt declines in fibrinogen are due to primary fibrinolysis or decreased protein synthesis [6].

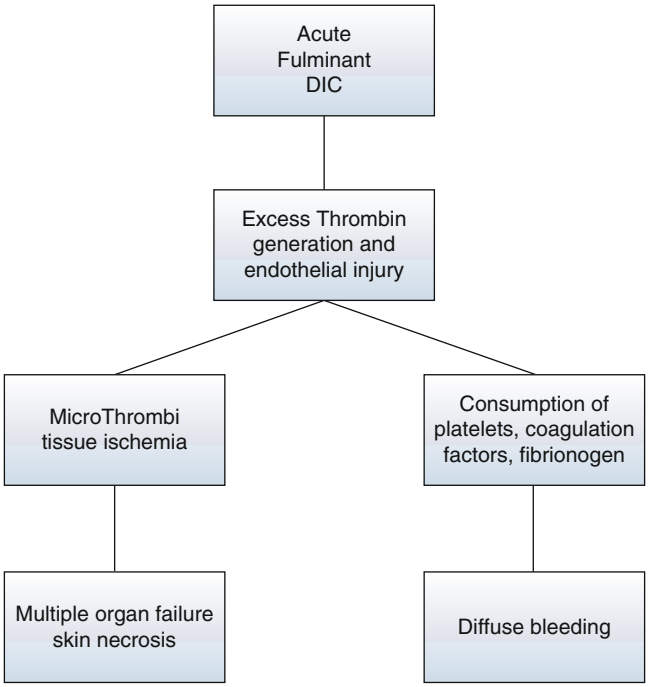

Fig. 14.1 Clinical consequences of acute and overt DIC

Subtypes of DIC and Common Underlying Causes

Acute and overt DIC is a common companion to many sudden, life-threatening events (Fig. 14.1). The most common category is sepsis due infectious diseases, predominantly gram-negative and gram-positive bacteria. Overt skin necrosis, multiorgan function failure, and abnormal bleeding are signs of DIC complications. Other infectious agents which can initiate DIC include fungi, malaria [7], dengue hemorrhagic fever [8], and Ebola [9]. Recognition of the early onset of coagulopathy due to blood loss and tissue hypoperfusion has changed initial management of massive trauma cases [10]. Uncommon obstetric emergencies like amniotic fluid embolism and placenta abruption can cause DIC and severe bleeding [11]. Acute promyelocytic leukemia (APL) is also uncommon, and patients typically have laboratory signs of overt DIC at presentation and are at high risk of major bleeding complications from release of tissue factor, cysteine proteases, and other activators from the immature malignant cells [2].

The conditions causing "smoldering" activation of the coagulation system which is recognized as chronic DIC are outlined in Fig. 14.2. Chronic DIC is common in patients with solid tumors [12]. Solid malignancies generate tissue factor as well as other procoagulant activators and mucin. Depending upon the degree of TF shedding, cancer-associated DIC may be asymptomatic; provoke venous or

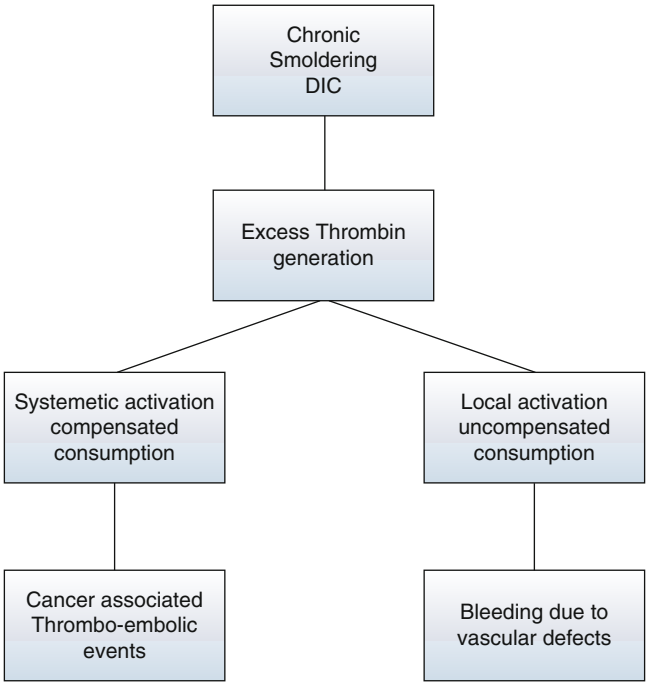

Fig. 14.2 Clinical consequences of chronic smoldering DIC

arterial thromboembolic events when combined with other hypercoagulable risk factors including chemotherapy, surgery, and central venous catheters; or cause migratory thromboembolic events consistent with Trousseau syndrome. Bleeding is rarely a complication of cancer-associated chronic DIC with the exception of DIC with hyperfibrinolysis, most often associated with metastatic prostate cancer [13].

Two types of vascular abnormalities, congenital hemangiomas [14] and aortic aneurysms [15], can cause sufficient chronic local consumption of platelets, coagulation factors, and fibrinogen with secondary fibrinolysis 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 complex interactions a patient's premorbid health status and an acute or chronic process capable of activating thrombin have on the nonspecific tests which are routinely used to assess DIC [16, 17]. Therefore clinicians must determine the likelihood that DIC is occurring and is an important complication by synthesizing information from a patient's diagnosis, history, medications, physical exam findings, and all available laboratory, pathology, and imaging data. There are five practical laboratory tools 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 [16]. 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, the presence of fragmented red cells (schistocytes) is both insensitive and nonspecific for DIC. The International Society for Thrombosis and Hemostasis (ISTH) scientific subcommittee on DIC developed a scoring system to evaluate patients at risk for overt, acute DIC [18] (Table 14.2). A score of ≥ 5 is highly supportive for DIC in acutely ill patients. Validation studies have confirmed its clinical utility for diagnosing DIC and for predicting patient's survival [19]. Serially monitoring one, or all of the five hemostasis tests, may demonstrate trends consistent with resolving or persistent acute DIC and can be particularly useful 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 [16]. Serial fibrinogen levels over several days may demonstrate a downward trend consistent with excess consumption by thrombin leading to a decision to intervene.

Table 14.2 Scoring system for overt DIC adapted from [18]

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)	____
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 $<10\times$ upper limit of reference range; strong D-dimer if $>10\times$ 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

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 [17, 20]. Monitoring the 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 [17, 20]. Unfractionated heparin or low molecular weight heparin chemoprophylaxis against large vessel thromboembolic complications is usually appropriate unless bleeding risk is judged to be prohibitive. Therapeutic anticoagulation, if the risk of bleeding is acceptable, is reserved for documented thromboembolic events and skin necrosis [17, 20].

DIC-Induced Multiple Organ Failure and Thrombosis

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 [21], restoring natural anticoagulants by infusing antithrombin [22] or recombinant activated protein C in moderately septic patients [23], and blocking TF with infusion of recombinant tissue factor pathway inhibitor (TFPI) [24]. While it is discouraging to observe a lack of clinical utility for promising strategies to reduce thrombin generation and improve outcomes for septic patients in DIC, research with novel therapeutics is continuing. In Japan recombinant soluble thrombomodulin is used to treat patients with sepsis and DIC [1], but this has not been widely adopted by clinicians in other countries.

Prevention and treatment of venous thromboembolic events with anticoagulants patients in solid cancer patients are in effect treating chronic DIC due to tumor-associated prothrombotic risk factors [25].

DIC-Induced Bleeding

Bleeding is the dominant complication of obstetric-related overt DIC due to placenta abruption or amniotic fluid embolism precipitated by tissue factor entering the maternal circulation [11]. Both complications require emergent surgical and medical procedures to stabilize the mother and fetus including aggressive transfusion with red cells, platelets, plasma, and cryoprecipitate to replace components lost due to consumption and hemorrhage [26].

Laboratory signs of DIC occur in most patients presenting with APL, and there is ample evidence for thrombin generation from activators released from malignant promyelocyte to generate thrombin, induce endothelial cell dysfunction, and increase fibrinolysis. Hemorrhagic complications dominate the clinical signs and symptoms of APL DIC, but microthrombi-induced organ ischemia is also occurring. An elevated PT may be the most accurate predictor of bleeding events [27]. To prevent bleeding-related morbidity and mortality, APL patients should receive transfusion support for thrombocytopenia and hypofibrinogenemia while initiating all-trans-retinoic acid to induce maturation of malignant APL cells with resolution of hemorrhagic complications [27].

Severe bleeding due to hypofibrinogenemia, coagulopathy, and thrombocytopenia is a rare complication of cancer-related chronic DIC, almost always due to refractory metastatic prostate cancer. 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 [13, 28].

Research into major trauma-induced coagulopathy has shown an extremely complex and incompletely understood derangement of multiple cellular, enzymatic, inflammatory, and signaling pathways [4, 29]. Excess fibrinolytic activity is a consistent initial finding. Early treatment with tranexamic acid improved survival in the CRASH-2 randomized study of major trauma patients [30] which lead to routine use of antifibrinolytics, in addition to aggressive transfusion support rather than waiting for overt signs of coagulopathy to develop, at many trauma centers.

Very rarely, a sustained, local activation and consumption of platelets and a subsequent activation of coagulation pathway, fibrin deposition, and fibrinolysis produce a generalized bleeding diathesis in pediatric patients with hemangiomas, called Kasabach–Merritt syndrome (KMS) [14] and in elderly patients with complex, and frequently inoperable and dissecting, aortic aneurysms [15]. 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. The possible benefit or risks from the use of antiplatelet, anticoagulant, or antifibrinolytic drugs have been inadequately investigated [14]. A severely atheromatous or dissecting aortic aneurysm exposes sufficient tissue factor to create a systemic depletion of platelets, fibrinogen, coagulation factors, elevated D-dimer, and 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 [15, 31].

Summary

Disseminated intravascular coagulation represents a spectrum of disruptions and injuries to the microvascular system initiated by various acquired systemic or localized disorders

culminating in accelerated activation and deregulation of coagulation. The consequences range from nonspecific alterations in routine tests and organ functions 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

15

Charles S. Eby

Abbreviations

VKDB	Vitamin K deficiency bleeding
DIC	Disseminated intravascular coagulation
APTT	Activated partial thromboplastin time
PT	Prothrombin time
INR	International Normalized Ratio
PIVKA-II	Protein induced in vitamin K absence-prothrombin

Vitamin K is a cofactor for human glutamic acid carboxylase enzymes in multiple tissues and organs [1] (Table 15.1). 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 and S (Fig. 15.1) 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. 15.2). 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 (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 prolonged prothrombin time (PT) and International Normalized Ratio (INR) which correct after performing a PT/INR mixing study (patient plasma: normal 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 extremely 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 coagulopathy is severe. The

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Table 15.1 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 and S	Formation and regulation of fibrin clot
Bone	Osteocalcin	Bone remodeling
Bone, soft tissue, blood vessel walls	Matrix Gla Protein	Inhibit soft tissue calcium deposition

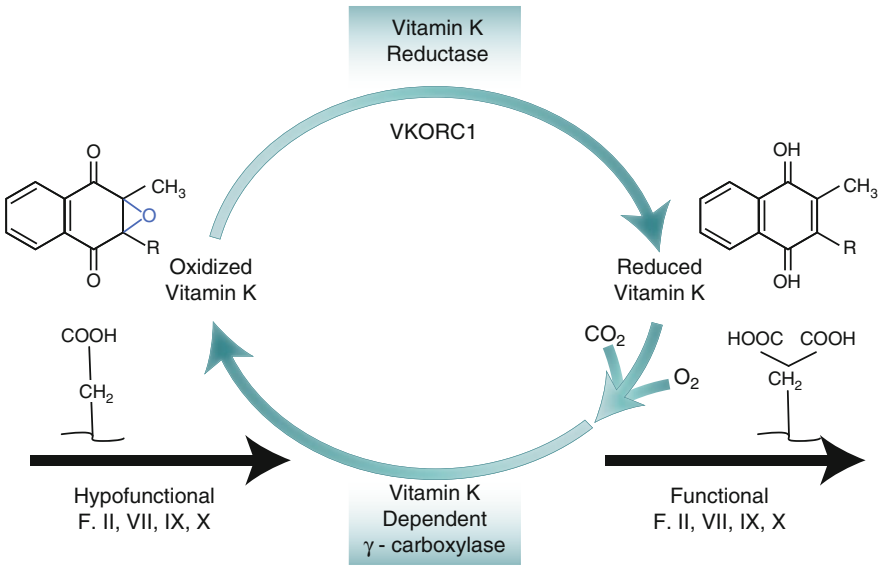

Fig. 15.1 Hepatic vitamin K cycle. Posttranslational gamma-carboxylation of selected glutamic acid residues converts hypofunctional proteins to functional coagulation factors (X, IX, VII, II) and regulators (proteins C and S), while the cofactor, reduced vitamin K, is converted to an oxidized epoxide. Vitamin K epoxide is recycled to reduced vitamin K by vitamin K reductase (VKOR)

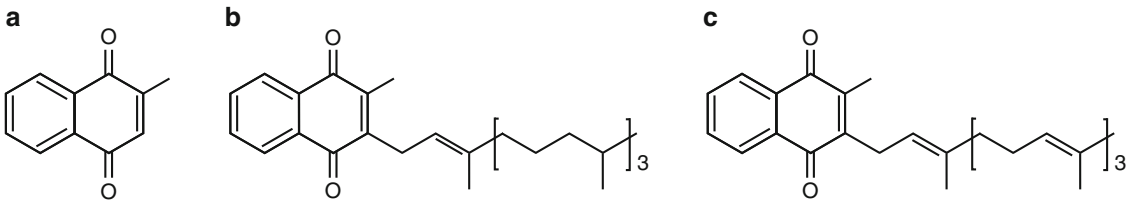

Fig. 15.2 Members of the vitamin K family have a common naphthoquinone ring and side chains of varying length and saturation. (**a**) Synthetic menadione, (**b**) plant-derived phylloquinone, and (**c**) an example of bacteria-derived menaquinone (MK4 with 4 isoprenyl units)

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 under carboxylated prothrombin proteins induced in 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 under carboxylated osteocalcin [8] and matrix Gla protein without convincing evidence to date of clinical consequences for bone and blood vessel homeostasis [9]. 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.

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 15.2) is a rare hemorrhagic complication with potential devastating consequences and can

Table 15.2 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
Typical	1–7 days	GI, skin, circumcision, umbilicus,	Idiopathic or 2nd low breast milk intake, no vitamin K prophylaxis
Late	2–8 weeks	Intracranial, skin, GI	Idiopathic or 2nd to poor nursing, temporary or disease-related malabsorption, no vitamin K prophylaxis

Table 15.3 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

be prevented by oral or intramuscular (IM) vitamin K prophylaxis at birth [10]. Placental transfer of vitamin K from mother to fetus is inefficient causing all newborn infants to be relatively vitamin K deficient [11]. 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 new born vitamin K deficiency. Table 15.3 outlines the three recognized presentations of newborn VKDB and associated causes [10]. 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 [10].

Prevention of newborn VKDB requires prophylactic vitamin K administration to all newborn infants since there are no reliable risk stratification guidelines. Either a single IM injection of 0.5–1.0 mg or multiple oral doses of vitamin K between weeks 1 and 8 are very effective [12]. Formulas provide 10 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 and is not a valid reason to defer vitamin K prophylaxis [13].

During childhood, adolescence, and adulthood, acquired abnormal bruising or bleeding due to vitamin K deficiency-induced coagulopathy is rare and not predictable. However, in populations at high risk for vitamin K deficiency, such as anorexic cancer patients [14], asymptomatic elevated PIVKA-II and PT/INR prolongation are common. 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 environments, and they are not mutually exclusive (Table 15.3).

There are many reports of acquired coagulopathies in part attributed to antibiotic-induced depletion of intestinal bacteria leading to acquired vitamin K deficiency [15, 16]. However, the extent of bacterial vitamin K_2 bioavailability to the human host remains controversial [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 [17, 18]. Patients suffering from prolonged malnutrition due to eating disorders [19], cancer-related anorexia [20], and perioperative limited intake [21] can become vitamin K deficient and have major bleeding complications in the absence of antibiotic therapy. Anecdotal reports linking vitamin K deficiency-induced coagulopathy to the beta-lactam class of antibiotics with a thiol side chain may be due to drug inhibition of hepatic reduction of oxidized vitamin K instead of alterations in gut microbes [22, 23]. However, patients who experience antibiotic-related signs or symptoms of vitamin K deficiency usually have additional risk factors including poor nutrition.

There are several options for reversal 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 h. 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. In the United States, Kcentra™ is only approved to reverse warfarin-induced coagulopathy. Fresh frozen plasma would be the least efficient replacement therapy due to the large transfusion volume (10–20 mL/kg) required to partially and 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 [24, 25], and there are no randomized controlled trial data to assess the risk or benefit of this routine practice [26]. While there are no documented dose-dependent acute or chronic adverse consequences from vitamin K supplements, the risk of anaphylaxis during IV vitamin K administration is approximately 3 per 10,000 doses [27].

Accidental or surreptitious ingestion of vitamin K antagonist rodenticides can result in a life-threatening coagulopathy [28]. To combat warfarin resistance mutations in rat and mouse VKOR genes, biochemists synthesized "superwarfarin" molecules with greater potency for VKOR inhibition to prevent recycling of oxidized vitamin K. Table 15.4 provides brand names of some rodenticides and VKOR 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 factor V (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 include immediate infusion of Kcentra™ starting with doses recommended for a markedly prolonged INR due to warfarin antagonism of vitamin K, transfusion with fresh frozen plasma, and IV vitamin K_1. 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 [28].

Table 15.4 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

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 it's bioavailability to the human host appears to be limited based on incomplete investigations to date.
3. Neonates are the most vulnerable population to vitamin K deficiency bleeding complications. Parenteral or oral vitamin K supplementation at birth dramatically reduces this risk.
4. During childhood and adulthood, regional or systemic disorders affecting 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 the more biologically active K1, inadequate oral intake, and malabsorption. The impact of antibiotic-induced vitamin K deficiency due to alterations in intestinal microbiome is unclear.
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

16

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 a ~twofold increased risk of bleeding in patients with renal failure [6]. 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].

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Pathophysiology of Bleeding in Patients with Uremia

Platelets

Platelet function is heavily disturbed in uremia [1, 8]. 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 [9–11] although a correlation between the bleeding time and the concentration of the dialyzable uremic metabolites was not detected so far [12]. However, dialysis improves platelet function and reduces the bleeding risk [13–17]. Urea itself does not seem to interfere with platelet function [18]. Platelet components such as α-granules [14, 19] 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 [14]. 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 [14, 20], which can be reversed by dialysis [21]. In addition, ultrafiltrates collected from uremic patients inhibited platelet-activating factor synthesis that could account for the decreased platelet activity [22]. 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 [23]. Oxidative stress and inflammation also have a profound effect on platelet function [24].

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Platelet–Vessel Wall Interactions

A decreased amount of GP Ib on platelets [4] together with the insufficient binding of vWF and fibrinogen to activated platelets from uremic patients can reduce the function of the GP IIb/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 [25, 26].

Moreover, vasoactive substances such as nitric oxide (NO), inhibiting platelet aggregation through the formation of cGMP, or prostacyclin, 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 [27, 28].

Anemia

Anemia can promote bleeding episodes in uremic patients as it directly influences the bleeding time [29–31]. In anemia platelets flow in the middle of the blood stream due to the lower number of erythrocytes, which impairs the interaction between platelets and the vessel wall resulting in a prolonged bleeding time. Furthermore, the low number of erythrocytes with a reduced hemoglobin amount leads to a reduced scavenging of NO [32] thus decreasing ADP and thromboxane A2 release via an enhanced activation of guanylyl cyclase [33] with increased cGMP levels. This inhibits platelet aggregation and inactivation of PGI_2 [34].

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 [35, 36]. β-Lactam antibiotics interact with platelets through an interference with ADP receptors. These effects are related to dose and duration of the therapy. ASS has been shown to significantly prolong the bleeding time in patients with renal failure [37]. 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 [38].

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 16.1). 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).

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 [13–17]. 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 [16, 39, 40]. Furthermore, an activation defect of the platelet glycoprotein IIb–IIIa complex could be involved in the bleeding tendency of some patients related to hemodialysis [13] as the expression of the GP IIb–IIIa receptor on thrombocytes is higher in peritoneal dialysis [41], which has been shown to maintain in vitro platelet aggregation better as compared to hemodialysis [42]. Moreover, peritoneal dialysis was associated with better platelet aggregation as compared to hemodialysis [43]. 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 [44]. Furthermore, a better elimination of middle molecules could be responsible for the advantages of peritoneal dialysis with respect to hemodialysis [42]. However, it is not known how actual dialysis procedures such as hemodiafiltration (HDF) compare to peritoneal dialysis as also HDF

Table 16.1 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 bags	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.	

effectively eliminates middle molecules. Of note, hemodialysis and peritoneal dialysis could also promote coagulation [45, 46].

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 [47] or erythropoietin [48, 49] 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 [49–51]. Furthermore, the number of reticulated platelets with an increased metabolic activity is higher after the administration of erythropoietin [52, 53], the platelet aggregation and the platelet interaction with the sub-endothelium is higher [49–51], and erythropoietin improves platelet signaling through tyrosine phosphorylation [54]. 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) [32].

EPO at a dose of 40–150 U/kg intravenously three times a week has been studied in uremic bleeding [49, 51, 52]. A hematocrit greater than 30 % is associated with a normalization of the bleeding time [49–51]. 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 [50, 51, 54]. Thus, it can be used in acute bleeding episodes but also as a prophylaxis.

However, problems exist with the target parameter: the 2012 KDIGO 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 [55]. 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 [26]. 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 [56]. Furthermore, it can be also used as a prevention of bleeding episodes in such patients (i.e., renal biopsies, endoscopy, operations). 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 [57]. 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 [44]. However, its effect reaches its maximum after 4–6 h and has nearly vanished after 8–24 h [26]. Even after one dose, tachyphylaxis might occur; thus its duration of activity is rather short [44] and treatment should not be repeated after one dose [44]. In patients with antiplatelet drugs [58] as well as heparin, desmopressin can also reduce the prolonged bleeding time [59]. Its mechanism of action is related to a reduction of protein c and PAI-1 and an increase of vWF and factor VIII from storage sites mediated via the action of vasopressin 2 receptors on endothelial cells [5, 60, 61]. Furthermore, it increases the expression of GP Ib on platelets [60]. This minimizes the effects of dysfunctional vWF and leads to larger vWF-factor VIII multimers that reduce bleeding time [62, 63].

Conjugated Estrogens

Bleeding episodes can be also treated with conjugated estrogens in patients with uremia [64–68]. 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 [69]. 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 [60, 70]. Furthermore, a transdermal estradiol patch with a dose of 50–100 μg/day can be applied twice a week [71]. This approach is also suitable for longer treatment periods as it was used for 2 months during this study. Successful treatment of nasal bleeding has also been achieved with topical intranasal estrogens in patients with von Willebrand disease and hemophilia [72].

An increase of thrombocyte 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 [73], which can be prevented by estrogens [74]. Estrogens need more time until the therapeutic effect begins, while its duration is substantially longer in comparison to desmopressin [64].

Fresh Frozen Plasma, Cryoprecipitate, and Factor VIIa

Cryoprecipitate contains substantial amounts of vWF, factor VIII, fibrinogen, and fibronectin and thus can immediately correct defects in primary hemostasis. However, this effect will last for only 4–12 h [5, 25, 34]. It should be used only in emergency situations were a rapid correction of hemostatic defects is needed, particularly, if hypofibrinogenemia with fibrinogen levels < 1 g/L is present [60]. However, the effect in patients with end stage renal disease is difficult to predict [25, 26, 75]. Infections, anaphylactic reactions, and volume overload could be adverse reactions in patients with renal failure [5, 60]. In contrast to cryoprecipitate, FFP contains all coagulation factors and should be used in patients with severe bleeding due to warfarin or phenprocoumon therapy where cryoprecipitates are not effective due to their low content in vitamin K-dependent coagulation factors [76].

Moreover, some case reports describe the use of recombinant activated factor VIIa (rFVIIa) for treatment of bleeding in uremic patients [77–80]. This approach seems attractive, as it should act only locally at the site of bleeding [81]. Thus it has been successfully used also in a patient with bleeding after a kidney biopsy [81]. However, due to the lack of studies, only little experience exists with the use of factor VIIa 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 [60, 82]. Tranexamic acid effectively stopped cerebral, gastrointestinal, or angiodysplasia-associated bleedings of the colon in patients on hemodialysis [83–85]. 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. [60]. 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, also 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 erythropoietin 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 factor VIIa 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 16.1).

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Bleeding Associated with Trauma

17

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. 17.1). 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 activity 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 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

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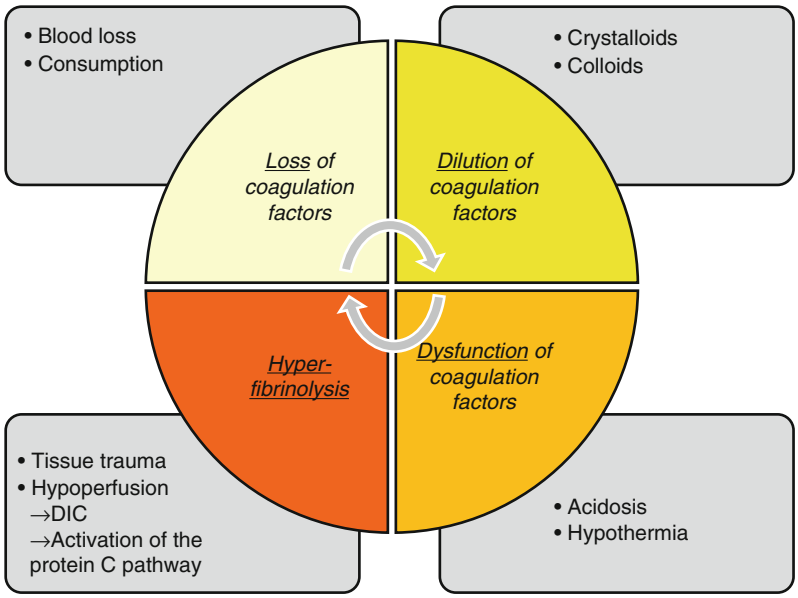

Fig. 17.1 Typical contributors to acquired coagulopathy in bleeding trauma patients. *DIC* disseminated intravascular coagulation

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 packed red blood cells, plasma, and platelets in a fixed ratio. The 1:1:1 mixture of packed 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 17.1) [19]. 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 [28]. Together with the use of viscoelastic tests for goal-directed coagulation management, the use of fibrinogen concentrate and prothrombin complex concentrate has been shown to be effective in treating major trauma patients [29, 30].

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, but is not recommended for use in patients with intracerebral hemorrhage caused by isolated head trauma (Table 17.1) [19].

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 [31]. Tranexamic acid has also been used successfully in the military trauma setting, resulting in reduced mortality, which is further reduced when combined with cryoprecipitate [32, 33]. Tranexamic acid must be given early (less than 3 h) in the course of trauma (Table 17.1) [34].

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 [19].

Calcium should be supplemented to maintain ionized calcium levels within the normal range during massive transfusion [19].

Desmopressin may be administered in patients treated with platelet-inhibiting drugs or with von Willebrand disease

Table 17.1 Recommendations for systemic hemostatic therapy in addition to or instead of the 1:1:1 massive transfusion packages, as per currently published guidelines [19]

Agent	Recommendation
Antifibrinolytic agents	*Within 3 h after injury*
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 50 mg/kg (approximately equivalent to 15–20 single donor units in a 70 kg adult)
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
Recombinant activated coagulation factor VII	Use may be considered if major bleeding and traumatic coagulopathy persist despite standard attempts to control bleeding and best-practice use of conventional hemostatic measures
	NO use in patients with intracerebral hemorrhage caused by isolated head trauma

but should not be administered routinely in the bleeding trauma patient (Table 17.1) [19].

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 packed 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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18 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, 9]. 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) [6]. 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 [7]. 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 [8]. 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 [9].

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 strongly associated with a set of clinical manifestations such as arterial and venous thrombosis, recurrent fetal loss and other obstetric complications, or thrombocytopenia and, less commonly, with hemolytic anemia, neuropsychiatric complications, or livedo reticularis, the antiphospholipid antibody syndrome (APAS) [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 "postinfectious") 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 the 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 complexes 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 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, the "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 have 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 shows 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 postinfectious 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 BaSO4 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 LA, 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 describes hematomas of the bilateral gluteus maximus muscles and subclavian area in a patient with Bence-Jones protein k-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 perioperative 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 three out of the 21 cases (14 %) needed supportive treatment (e.g., fresh frozen plasma, red blood cells, and/or vitamin K), with the remaining two 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 PTs 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 intravenous immunoglobulin (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 four weekly doses of 375 mg/m^2, (b) no improvement after two courses of rituximab 1 g/dose, and (c) relapse after corticosteroids and IVIg, improved after four weekly doses of 375 mg/m^2 with prothrombin levels up to 74 % [60].

Finally, other treatments, such as plasma exchange, hydroxychloroquine and the androgen 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 the androgen 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 data available, 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 prothrombotic 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

19 Intracerebral Hemorrhage: An Overview of Etiology, Pathophysiology, Clinical Presentation, and Advanced Treatment Strategies

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 Apo lipoprotein 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].

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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. 19.1) [4–6].

Regional cerebral blood flow is also affected during ICH and occurs in specific phases (Fig. 19.1).

- 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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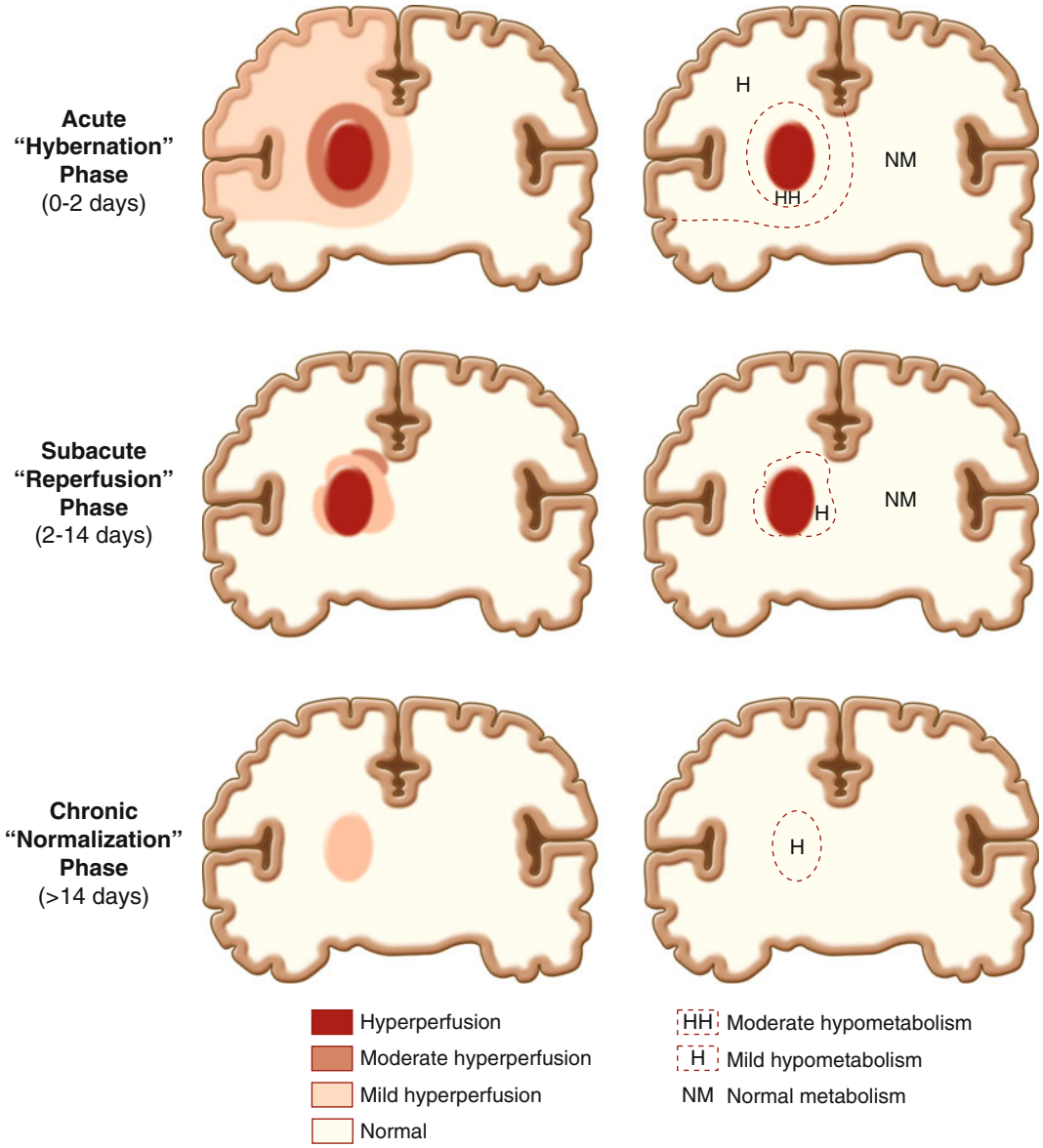

Fig. 19.1 Diagrammatic representation of the three phases of cerebral blood flow and metabolism changes in the acute, subacute, and chronic phases after intracerebral hemorrhage [6]

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 Apo lipoprotein 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. 19.2) 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 byproducts 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

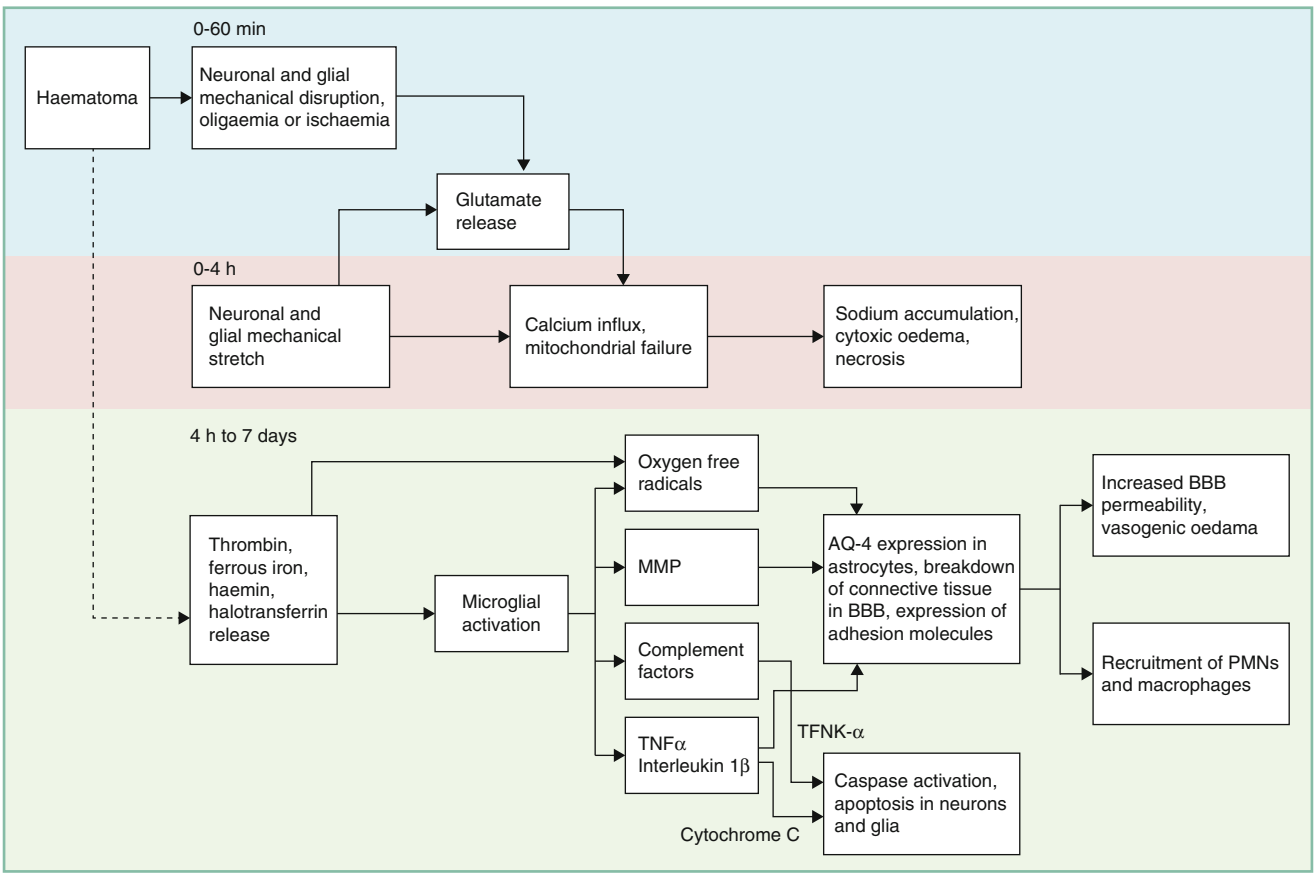

Fig. 19.2 Cascade of neural injury initiated by intracerebral hemorrhage. The initial process in the first 4 h are related to the direct effect of the hematoma, while later steps are accounted for through the release of products from the hematoma. *BBB* blood–brain barrier, *MMP* matrix metallopeptidase, *TNF* tumor necrosis factor, *PMN* polymorphonuclear cells. From Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009 May 9;373(9675):1632–44. With permission from Elsevier

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 19.3 illustrates the progression of hematoma and edema on computed tomography (CT) [4–6].

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.

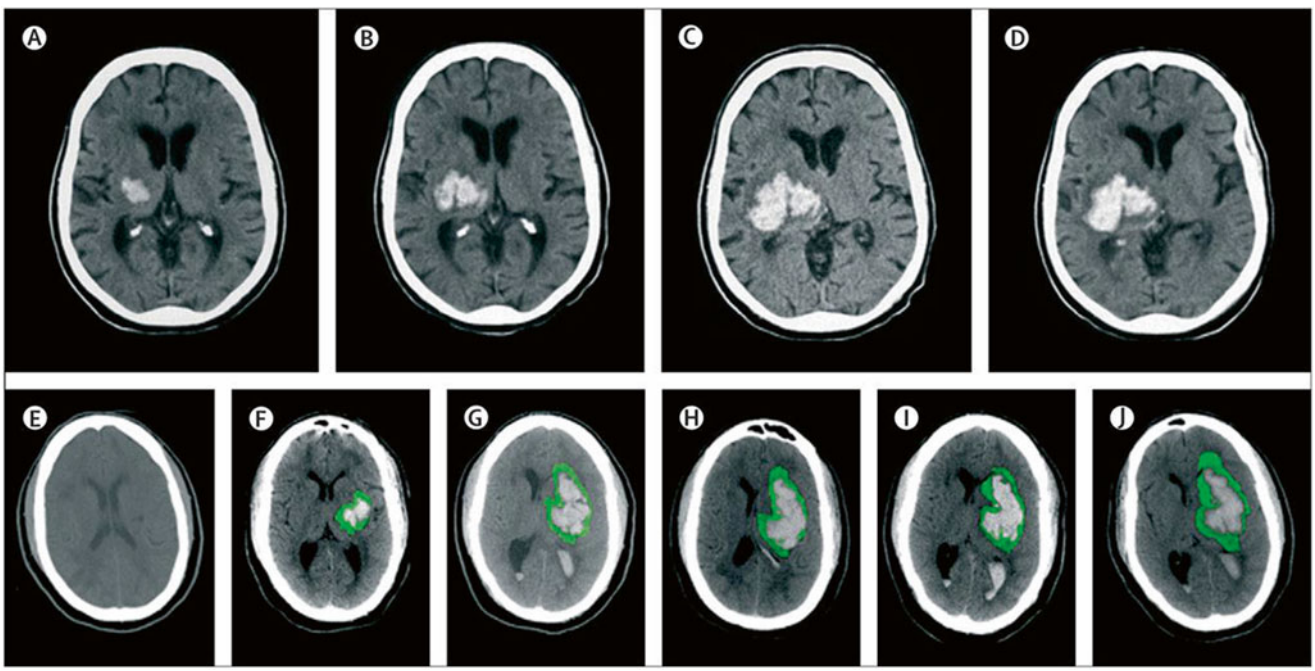

Fig. 19.3 Progression of hematoma and edema on computed tomography (CT): hyperacute expansion of hematoma in a patient with intracerebral hemorrhage on serial CT scans. Small hematoma detected in the basal ganglia and thalamus (**a**). Expansion of the hematoma after 151 min (**b**). Continued progression 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**)

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 prehospital 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 underscores 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 noninvasive 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 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 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 U.S. 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 19.1 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 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 >60 to 80 mmHg. If a patient presents with an SBP of >180 mmHg or MAP of >130 mmHg with no increase in ICP, 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

Table 19.1 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)		• Both Bebulin and Profilnine are three-factor PCCs that have approximately 1/10th the factor VII activity relative to factor IX activity. The amounts of factor II and X relative to IX is variable, but for Bebulin X II IX and for Profilnine II X IX	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 g/kg every 2 h	Congenital factor VII deficiency
		• For factor VII-deficient patients, 15–30 g/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 serum 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			Wilate is not indicated for hemophilia A
(Baxter)			
• Monarc-M (Baxter)			
• Monoclate-P (CSL-Behring)			
Recombinant			
• Advate (Baxter)			
• Helixate FS (CSL-Behring)			
• Kogenate FS (Bayer)			
• Recombinate (Baxter)			
• Xyntha (Wyeth)			

(continued)

Table 19.1 (continued)

Product	Factor(s)	Dose (consultation with a hematologist is recommended for specific dosing)	Uses
Factor IX concentrates			
Plasma-derived	IX	Each factor IX unit/kg raises the serum 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 serum level by 0.83 %, so 120 U/kg raises the activity to 100 %
• BeneFix (Wyeth)			

From Morgenstern LB, Hemphill JC, 3rd, Anderson C, Becker K, Broderick JP, Connolly ES, Jr., et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2010 Sep;41(9):2108-29

vWD von Willebrand disease, *FDA* U.S. Food and Drug Administration, *PCCs* prothrombin complex concentrates

[a]Also contains von Willebrand factor

[b]Indicated for von Willebrand disease (dose by ristocetin cofactor units; ratio of fVIII to ristocetin cofactor unit varies by product)

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 outcomes is being evaluated in the ongoing phase III ATACH II and INTERACT 2 trials [15–21].

Figure 19.4 illustrates the importance of aggressive SBP control. Table 19.2 provides the major trials looking at BP management in ICH.

Seizure in ICH

Eight percent of patients with ICH have clinical seizures within one 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 two 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 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

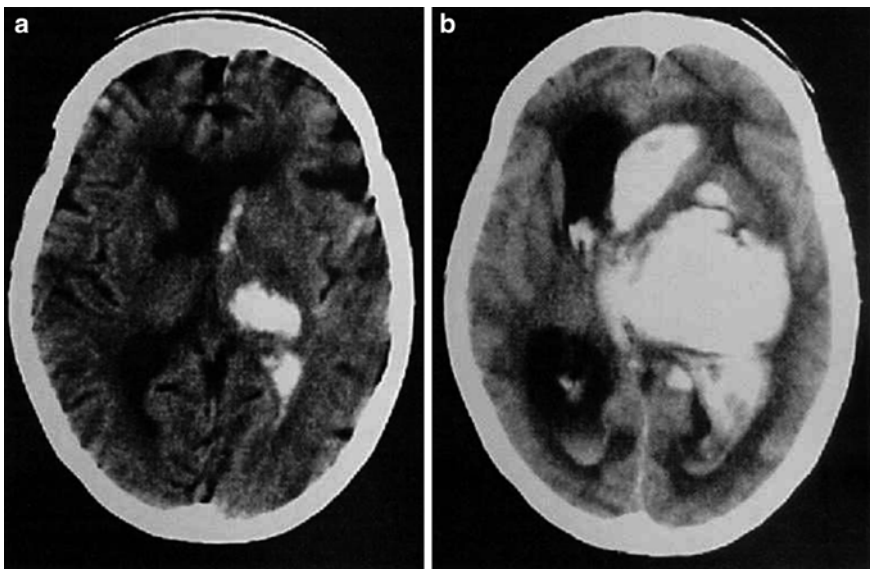

Fig. 19.4 Illustrates lack of BP control. (**a**) Initial head CT, (**b**) head CT in the same patient whose SBP was consistently more than 140 mmHg

Table 19.2 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

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, 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. 19.5).

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].

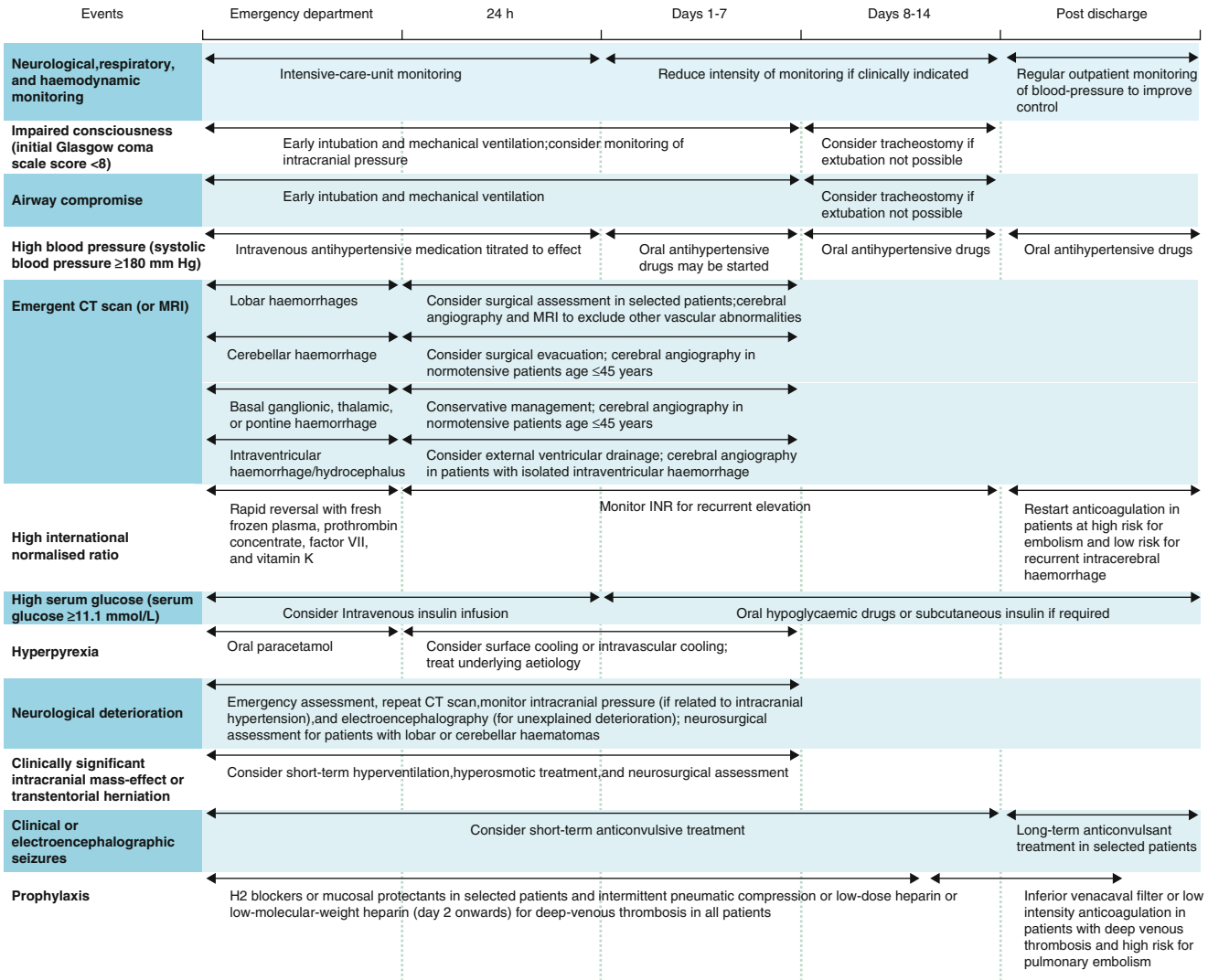

Fig. 19.5 Management algorithm for patients with intracerebral hemorrhage

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Epistaxis

20

Elton M. 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]. Most cases of nosebleeds are not life threatening, are simple, are not complicated, and are not associated with an underlying disorder. 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 20.1.

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 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

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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 or not 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.

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

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Table 20.1 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	

carotico-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 anticoagulation factor medication such as warfarin, heparin, 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). Associated cranial nerves or vision problems are more worrisome for the presence of a lesion. Headaches can be also associated with skull base lesions, but many adults with hypertension can also present with headaches. 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 synthe-

Table 20.2 Curacao criteria for the diagnosis of hereditary hemorrhagic telangiectasia [6]

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

sis of procoagulant proteins II, VII, IX, and X, as well as factor V and factor XI, as well as a qualitative platelet deficiency [2]. Patients with chronic kidney disease especially those with uremia have decreased platelet aggregation. Those on dialysis are exposed to heparin on a regular basis [3].

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 [4].

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. HHT affects 1 in 5,000 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. 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 [5]. Its diagnosis can be suggested or confirmed by the Curacao criteria (Table 20.2). The recognition of familial causes of epistaxis is important, since both the workup and management of epistaxis can vary in these cases.

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 [7].

Nasal endoscopy allows for a closer examination of the intranasal structures. The middle meatus may be swollen or have purulence in acute or chronic rhinosinusitis. Nasal masses can be seen on nasal endoscopy. 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. 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 counts (CBC), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and bleeding time may be ordered to screen for anemia, thrombocytopenia, and other coagulation disorders. Fibrinogen levels are occasionally helpful, especially in the case of disseminated intravascular coagulation (DIC). Some centers have used thromboelastography (TEG) as an adjunct to evaluate the coagulation cascade, but its utility is still being questioned [8]. von Willebrand's 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. Heparin can be reversed with FFP or protamine. Newer antithrombin inhibitor agents such as argatroban and fondaparinux 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 infusions may be necessary in patients with thrombocytopenia, while FFP 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. 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 [9]. 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. 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 out of 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.

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 [10].

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 [11]. There are 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.

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. The treatment of nasal masses is beyond the scope of this chapter. Many of the conservative measures described above can be utilized to manage the nosebleeds until the mass is treated appropriately.

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), and intranasal bevacizumab (anti-vascular endothelial growth factor). 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. Antiestrogen agents and bevacizumab can be used systemically in HHT patients as well [12].

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.

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Bleeding Disorders Related to Lung Disease

21

Timothy J. Vece and George B. Mallory Jr.

Introduction

Extravasation of blood elements within the lung may manifest dramatically as hemoptysis or more subtly 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 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 also 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.

There are many classifications by which bleeding disorders in the lungs can be categorized. Table 21.1 shows a simplified list of categories and prominent examples that span the lifespan from infancy through adulthood. There are many 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.

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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 quite uncommon, but multifocal ground glass densities on chest CT radiography are quite 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.

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Table 21.1 Causes of hemoptysis by category

Cardiopulmonary disorders
Congenital heart disease
Pulmonary hypertension
Left heart disease
Hematologic disorders
Complication of anticoagulant therapy
Thrombocytopenia
Von Willebrand disease
Complication of bone marrow transplantation
Pulmonary embolism
Hematologic disorders
Disseminated intravascular coagulation
Thrombocytopenia
Von Willebrand disease
[pulmonary embolism]
Neoplastic disorders
Carcinoid tumors
Neoplastic disorders, especially endobronchial carcinomas
Other pulmonary vascular disorders
Pulmonary immune-mediated vasculitis
Pulmonary arteriovenous malformations
Lung disease
Necrotizing pneumonia
Angioinvasive fungal infection
Chronic bronchiectasis
Diffuse alveolar damage as in adult respiratory distress syndrome
Pulmonary hemosiderosis
Trauma
Transbronchial biopsy or bronchoscopic needle aspiration
Blunt or penetrating trauma with injury to pulmonary vascular bed
Airway foreign body
Miscellaneous
Cocaine
Nitrogen dioxide toxicity
Complications of biologic therapies

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's 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. 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].

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].

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 present with chronic respiratory symptoms including small amounts of hemoptysis, worsening exercise intolerance, and, often, significant hypoxemia [18, 19]. Even though massive, life-threatening pulmonary hemorrhage is rare, 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 granulo-

matosis [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's 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 abnormal 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 extra-pulmonary malformations, people with HHT can present with cerebral vascular accidents or recurrent,

severe nosebleeds, which is the most common symptom 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 associated digital clubbing. The 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. 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.

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. The most common 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. Due to 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 idiopathic pulmonary capillaritis. Patients present

with a classic triad of anemia, hypoxemia, and pulmonary infiltrates on imaging [46]. Histopathology 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].

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 [49, 50].

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 [51]. Nonsurgical techniques to ablate endobronchial tumors can inadvertently lead to pulmonary hemorrhage [52]. Transbronchial biopsies via the flexible bronchoscope carry a low but important risk of pulmonary hemorrhage [53, 54]. Although the newly introduced technique of transbronchial cryobiopsies has been introduced with some enthusiasm, pulmonary hemorrhage is not entirely obviated [55].

Miscellaneous

A variety of drug therapies excluding anticoagulation have been associated with pulmonary hemorrhage including new biologic agents like alemtuzumab [56] and abciximab [57]. Environmental exposures like nitrogen dioxide can rarely manifest with hemoptysis [58]. Recreational drug use, most commonly cocaine, can lead to pulmonary hemorrhage [59].

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. Initial evaluation begins with a thorough history and physical examination. The volume of blood, its character, 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 hearts and the palpation of the abdomen for organomegaly is mandatory. The skin should be evaluated for bleeding sites, petechiae, or excessive ecchymosis.

A CBC and an initial superficial coagulation profile with prothrombin time, activated partial thromboplastin time, and fibrinogen. 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 spirometric lung function testing are reasonable. 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 computed tomography with contrast may be helpful. Although not as frequently diagnostic, flexible bronchoscopy is occasionally helpful in evaluating the location and appearance of the bleeding source [60, 61]. 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 [62].

If etiology is unclear, in some patients a lung biopsy by the open or thoracoscopic techniques 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 including 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 [63] followed by bronchial artery embolization may be the therapeutic approach of choice [64]. In adults, 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, topical

iced saline [65], topical epinephrine [66], or topical thrombin may be applied [67]. In some situations, laser or electrocautery via bronchoscopy can be used. If bleeding is repetitive, tranexamic acid may be useful in some patients [68]. 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 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

22

Lakshmi V. Srivaths, Jennifer L. Bercaw, and Jennifer E. Dietrich

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 and affecting an estimated 18 million women worldwide [4, 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 anovulation to fibroids or cancer [8]. A commonly overlooked etiology of HMB is a bleeding disorder or risk factor for bleeding 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 [9, 10]. Although anovulatory bleeding is frequently seen in adolescents after menarche [11], bleeding disorder can exacerbate HMB in females with anovulation.

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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 [9]. 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 [12]. The recent recommendations of the International Federation of Gynecology and Obstetrics Menstrual Disorders Working Group are to replace confusing terminologies with clear and simple terms [13]; thereby, the terms menorrhagia, metrorrhagia, and menometrorrhagia are to be discarded. The term HMB is recommended to define excessive menstrual blood loss ≥80 mL of blood loss 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.

Prevalence of HMB and Bleeding Disorders

Among women with bleeding disorder, HMB is the most common symptom, reported in 32–100 % of women with von Willebrand disease (vWD), 51–95 % with severe platelet dysfunction, 10–57 % of hemophilia carriers, and 35–70 % with coagulation factor deficiencies [3]. Surveillance of 319 female patients with inherited BD 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].

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Table 22.1 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

Among adolescents and adult women experiencing HMB, there is also an increased prevalence of BD. In adult women with HMB, several studies have reported increased prevalence of vWD, platelet dysfunction, and coagulation factor deficiencies including hemophilia carrier state [3] (Table 22.1). During the past 2 decades, several studies have evaluated adolescent females with HMB and reported prevalence rates of various bleeding disorder as illustrated in Table 22.1 [2, 15]. The prevalence rate for the disorders varied among these studies depending on the medical setting and how the bleeding disorders were defined. 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 [16]. 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. Underlying thyroid dysfunction can result in HMB in women of all ages [17]. As some studies have shown an association between hypothyroidism and low vW 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.

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, 19]. History of pad or tampon change hourly, passage of clots >1 in. 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, postpartum or postoperative hemorrhage, anemia requiring transfusion, and family history of bleeding or bleeding disorder [20]. Several bleeding scores [21] and HMB-specific short screening tools [22] 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 [23]. 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. 22.1). A score of >100 was found to be sensitive for a diagnosis of HMB, equivalent to blood loss of >80 mL [24]. 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 [25].

Laboratory Evaluation for Bleeding Disorders: In patients who require a bleeding disorder workup, the clinician should consider evaluation for vWD, platelet disorders, factor deficiency, and lastly fibrinolytic pathway defects.

Despite the cost-effectiveness of screening adolescents with HMB for vWD [26], a recent study demonstrated that <15 % of adolescents with HMB were screened for vWD [27]. Initial vW testing includes vWF antigen, vWF activity, and factor VIII (FVIII) assays [28] (Table 22.2). Further tests including vW multimer, assays for evaluating increased clearance of vWF, ristocetin-induced platelet aggregation (RIPA), 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). Platelet function analyzer (PFA-100) does not have utility as a screening test to detect vWF deficiency [35]. 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 [36]. Patients with low vWF levels between 30–50 IU/dL and clinically significant bleeding may be treated similar to those with type 1 vWD. Knowledge about vW exon 28 polymorphisms and their impact on vWF levels is important

NAME:
DAY START: SCORE:

TOWEL	DAY 1	2	3	4	5	6	7	8
								
								
								
Clots/Flooding								
TAMPON								
								
								
								
Clots/Flooding								

Fig. 22.1 PBAC chart

Table 22.2 Evaluation of heavy menstrual bleeding and bleeding disorder [3, 28–34]

	Bleeding disorder	Tests	Supplementary tests
Tier 1 [1–3, 28, 32]	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 and clotting factor deficiencies
Tier 2 [29–31]	Platelet function defect Inherited/acquired thrombocytopenia	Platelet aggregometry Platelet secretion analysis	Platelet electron microscopy Flow cytometry for platelet glycoprotein analysis Platelet antibody assay Genetic tests for congenital platelet disorders
Tier 3 [33, 34]	Fibrinolytic pathway defects Factor 13 deficiency	Fibrinolytic pathway analysis Coagulation factor 13 analysis	Thromboelastography/ROTEM analysis Euglobulin clot lysis time Specific assays (if available)

vWD: von Willebrand disease

while interpreting test results [37]. Specific precautions to be undertaken include repeating borderline values to rule out false negative results, onsite 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 recent study on healthy women did not show statistically significant change in vWF levels between contraceptive and control group [38]. 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 recommended for vWD diagnosis [28].

In females with platelet disorders comprising of thrombocytopenia and platelet function defects, HMB is the most common bleeding symptom [29, 30, 39]. Thrombocytopenia is predominantly due to immune etiology but can be also due to malignancy, chemotherapy, aplastic anemia, hypersplenism, and congenital/hereditary causes. Inherited platelet disorders encompass Bernard–Soulier syndrome (BSS), Glanzmann thrombasthenia (GT), MYH-9 related disorders, Scott syndrome, primary secretion, signal transduction, and receptor agonist defects [29, 31]. The initial steps in evaluating for platelet disorders include 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 [31]. The reference standard for diagnosing mild platelet function defect is the light transmission aggregometry [40]. Avoiding platelet function-impairing medications 10–14 days prior to testing and using freshly drawn, nonthrombocytopenic specimens that are not activated by tubing the sample 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, and flow cytometry for detecting platelet glycoprotein Ib-IX-V (BSS) and IIb–IIIa (GT) defects.

Carriers of hemophilia with low factor VIII and IX levels can present with HMB as a predominant complaint. [41, 42] Other rare coagulation factor deficiencies (factors II, V, VII, X, XI, and XIII) in isolation or in combination can cause significant HMB [32]. The screening tests include prothrombin time, activated partial thromboplastin time, fibrinogen activity, thrombin/reptilase time with specific factor analysis, fibrinogen antigen, and genetic testing as needed. Fibrinolytic pathway defects such as plasminogen activator inhibitor-1 (PAI-1) deficiency [33] can be difficult to detect due to the rarity, lack of availability of optimal tests, and variation in assay results. PAI-1 activity 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 [34].

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 [32]. 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. Herein, it is important to detect and manage the underlying cause in addition to evaluation of the bleeding defect.

A tiered, stepwise evaluation for bleeding disorders in females with HMB done in conjunction with a hematologist (Table 22.2) is necessary for accurate diagnosis. 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

Hemostatic Therapy: For vWF deficiency, elevation of vWF level can be accomplished in two ways [28]. Intranasal or intravenous (IV) administration of desamino-D-arginine vasopressin (DDAVP) (subcutaneous (SC) preparation available only in Europe) will lead to 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 moderate bleeding for short duration 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 United States (Humate-P, Alphanate-SD, and Wilate). The dosing for acute and severe bleeding typically is 40–60 units/kg and for maintenance therapy and moderate bleeding including HMB is 20–40 units/kg. A highly purified vWF concentrate (Wilfactin™) is available in Europe, and recombinant vWF has been approved for clinical use in US.

Thrombocytopenia other than due to immune etiology can be managed with platelet transfusion for severe bleeding [29]. Due to the risk of platelet refractoriness in patients with severe platelet function defects, recombinant 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 [32]. 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 [33]. These include epsilon-aminocaproic acid (EACA/Amicar™; recommended dose, 50 to 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), also used as adjunct therapy to other hemostatic agents or hormonal therapy [43]. TXA has been used effectively as standalone agent in HMB in European countries and Canada [44], and the FDA approval of the oral formulation in 2009 has increased its use in the United States. Vascular anomalies may be managed with general hemo-

static therapy and hormonal therapy as needed but may need major interventions such as endometrial ablation and hysterectomy [33].

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 [45]. Multiple hormonal options exist but 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 [46]. IV estrogen is typically dosed as 25 mg every 4–6 h until bleeding stops [46–48]. Adolescents requiring IV estrogen should be transitioned to maintenance therapy via a tapering regimen following control of acute bleeding [45]. Side effects of estrogen include nausea, headache, elevated blood pressure, potential for blood clot formation, rare risk for causing hepatic adenomas, and breast discharge. For patients with a contraindication to estrogen products, 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 [45]. Progesterone side effects mainly include breast tenderness, mood change, and breakthrough bleeding. In patients who fail all other treatments for severe HMB, GnRH analogs such as depo-leuprolide acetate (LA) may be considered. LA induces a hypoestrogenic environment in approximately 4 weeks with resulting amenorrhea [49]. 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 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 [50]. As maintenance therapy, combined oral contraceptives (COC) are very effective. Adolescents with HMB may benefit from extended cycle regimens instead of more traditional monthly withdrawal bleeds [48]. 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 [51].

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 [50, 52]. 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. [53] The LNG-IUD has also been effective in treating HMB among adolescents with bleeding disorder that are refractory to other treatments [54]. Other 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 [55]. 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 [56]. 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 [50, 56]. Although amenorrhea rates are as high as 20 % in the first year, the etonogestrel implant may result in more episodes of unscheduled bleeding [45, 56].

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 a therapy tailored to the patient's needs is chosen, with either one administered as primary or supplemental therapy for HMB.

Supportive and Other Therapies: Anemia and iron deficiency secondary to HMB are frequent complications [57, 58]. These can be managed with iron supplementation or with red blood cell transfusion when severe. Platelet transfusion and FFP transfusion may be needed in patients with PD 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 underlying etiology and the desire for fertility maintenance. Endometrial balloon tamponade can be an effective means of controlling acute HMB and allowing stabilization of the patient in anticipation of further medical (hemostatic, hormonal) therapy [59–62]. Ultrasound can be helpful during placement to diagnose intrauterine pathology and to confirm adequacy of balloon placement [59–62]. 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 female [63, 64]. While successful pregnancies have been reported after this procedure [65], 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 life-saving measure in young women as pregnancy is contraindicated in women who have undergone UAE [64, 65]. An endometrial ablation and hysterectomy are more definitive surgical treatments for menorrhagia but are not first-line options for management in the adolescent due to the resulting infertility and can often be avoided by employing one or more of the above measures [66–68]. Nonetheless, in a patient with acute, life-threatening hemorrhage, hysterectomy should not be delayed in favor of potentially less effective measures [66–68]. To prevent excessive bleeding during surgery and procedures including IUD placement, tailored therapy with general and/or specific hemostatic agents is needed perioperatively.

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 [69–72]. Our institution recently 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 [73].

Complications of HMB

More than Menorrhagia: Among women and girls with HMB and an established blood dyscrasia, other gynecologic conditions such as endometriosis and hemorrhagic ovarian cysts (HOC) are more commonly reported [74]. Nonetheless, a number of hormonal medical treatments can aid in the control of these secondary concerns to keep endometriosis under control or 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: Excess menstrual blood loss can lead to anemia and iron deficiency [57, 58] and hypotension, necessitating hospitalization and PRBC transfusion. As iron deficiency can cause fatigue and impaired learning, accurate diagnosis and iron supplementation can correct anemia and also positively impact concentration, verbal learning, and memory [57, 58].

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, 75–77].

Collaborative Approach

While managing females with HMB, it is essential to have collaborative management by hematology and gynecology providers; in addition, a comprehensive approach by nursing staff, patient educator, genetic counselor, and social worker will provide the patients with wholesome care. Patient-centered efforts such as small group meetings and patient camps can go a long way to improve patient education and to provide emotional support and increase awareness through social networking.

Conclusion

HMB is a common condition among females. Systematic evaluation for underlying bleeding disorder and other causes will aid to establish a correct diagnosis. Utilizing hormonal and/or hemostatic therapy for acute management and maintenance therapy of HMB and bleeding disorder, keeping in mind fertility preservation for women of reproductive age, and a collaborative approach among gynecology and hematology providers will ensure a holistic approach to restore the overall well-being of the patient.

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Gross Hematuria

23

Monica Gabrielle 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. Depending on the etiology, it can be seen at the start of the urinary stream, the end of the stream (terminal hematuria), or throughout the urinary stream. It can present with no additional symptoms or a range of ancillary symptoms including dysuria, pain, obstruction, or hypotension. Gross hematuria 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 physicians and advanced practice practitioners, 87 % were unaware of guidelines regarding the management of microscopic or gross hematuria, and 93 % agreed that a clinical care pathway for the evaluation and management of hematuria 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 (which contains data from ED visits for over 950 hospitals and represents a 20 percent sample of US hospital-based ED registries) 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 emergency room were estimated to be as high as $238,000,000 a year [2].

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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 guidelines on microscopic hematuria [3].

Gross Hematuria: Initial Management and Referral

While the initial presentation of gross hematuria may be alarming to both the clinician and patient, it is rarely a clinical emergency. 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 in clinical evaluation, as 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 the urine they are able to produce, 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

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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 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 is a triphasic CT scan with noncontrast, parenchyma-enhanced, and delayed imaging. This is commonly referred to as a CT urogram. It may be performed prone to allow small distal ureteral calculi to be distinguished from bladder stones and to aid in the visualization of ureteral contrast. The initial noncontrast phase from the kidney to pelvis allows for the evaluation of renal or ureteral stones that may be effaced by the administration of contrast. 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 distension and opacification of the collecting system, ureter, and bladder. This is the phase that is most prone to limited results, due to differences in the rate of contrast excretion into the ureters and bladder, as well as peristalsis.

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 first, 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 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 opacification of the ureter is also less reliable. Single-phase CT scan is being studied but is not yet the standard of care.

Ultrasound and intravenous pyelography (IVP) have both been found to be not as sensitive as multiphase CT scan in evaluating for nephrolithiasis [6] and renal or transitional cell lesions [7]. However, some investigators suggest that combining the two modalities is more sensitive than either alone in the detection of malignancy [8]. There are no data comparing the effectiveness of magnetic resonance imaging (MRI) to CT scan. 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.

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.

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.) One-shot IVP in adults is in limited use intraoperatively and in most cases is able to determine only that there is a functioning contralateral kidney prior to consideration for urgent renal exploration.

Ureteral injury from acute trauma is rare—80 % of ureteral injuries are iatrogenic, which is important to consider after gynecologic, urologic, and bowel surgery [9]. Bladder evaluation is necessary after penetrating pelvic injury, pelvic surgery with gross hematuria, or blunt external trauma with pelvic fracture and gross hematuria. Bladder distension with saline irrigation prior to ruling out a rupture could prove disastrous. Rupture is uncommon in the setting of patients with gross hematuria without pelvic fracture or pelvic fracture without gross hematuria. The bladder filling phase of a CT urogram is not sufficient for evaluation 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 [10]. 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 [11]. 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. 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 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 [12].

If renal, ureteral, bladder, or urethral injuries are suspected either through mechanism of injury, physical exam, or imaging, urgent urologic consultation is indicated.

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, and 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 or clots does not require catheterization or bladder irrigation.

Prior to deciding on catheter placement, however, it is important to understand their design: the size of a Foley catheter, 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) [13].

Well-meaning 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 burden 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 [14].

If urine clears with manual irrigation and removal of clots, aggressive oral and intravenous hydration should be instituted 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 should be obtained to rule out the presence of continued clot in the bladder. In the setting of physical or lab evidence of continued bleeding, depending on the etiology of the bleeding, urologic intervention may be considered.

The urologist may recommend a number of treatments 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 (Amicar), 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 [15]. However, adverse systemic thrombotic events have been reported in the literature.

The use of Amicar in upper tract (renal or ureteral) bleeding may also result in ureteral clot obstruction [16]. Tranexamic acid (another reversible inhibitor of plasminogen) has been used to control intractable upper tract hematuria in some case studies [17]. However, it is more thrombogenic than Amicar and has been shown to reliably cause upper tract clot obstruction when used for upper tract gross hematuria and lower tract clot obstruction when used in patients with even microscopic levels of hematuria [18]. It is not currently recommended as a treatment for gross hematuria [19].

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 23.1 lists the various etiologies 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 [8, 20]. The rate of recurrence in such patients is unknown.

Hematuria After Urologic Procedures

Gross hematuria is a feature after virtually all procedures with instrumentation of the urinary tract, and in general is both expected and transient, requiring only timed voiding and the encouragement of hydration. Recent instrumentation can, however, make a urinalysis difficult to interpret whether pyuria is due to recent instrumentation or inflammation, such as from an indwelling ureteral stent, or due to infection, of which patients are at higher risk after urologic surgery. However, severe gross hematuria 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 bladder resection is at higher risk for bladder perforation during irrigation than a recent transurethral resection of the prostate. The risk of bladder perforation during manual irrigation is especially high during recent procedures where a section of the bladder is opened and closed, such as a partial cystectomy, diverticulectomy, or ureteral reimplant. In these cases, manual irrigation should ideally only be performed by a urologist. The risk of bladder perforation during manual irrigation is not as high after prostatic procedures such as a transurethral resection of the prostate, where the bladder wall was not thinned or violated. It is not uncommon for patients to present with transient 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.

Table 23.1 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 malignancy	Pseudoaneurysm Ureteroileal fistula Nutcracker syndrome
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 malignancy Invasion or metastasis by other malignancy	Hemorrhagic cystitis Arteriovenous malformation

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 [21]. 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 [15].

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 [22].

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% [8, 15]. 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: contrast imaging 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.

There is an especially strong causal association between cigarette smoking and bladder cancer, with smokers having a threefold risk of invasive bladder cancer compared to nonsmokers, and smoking cessation can reduce this risk [23]. One study found that there was an association between patients meeting NLCST criteria (55 to 75 years old with more than 30-pack-year smoking history and less than 15 years since smoking cessation) who present with gross hematuria and the risk of initial tumors being high grade and muscle invasive [24].

Patients who are on anticoagulant therapy are not exonerated from a necessary workup for gross hematuria. A recent retrospective analysis of ER 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 [25]. The majority of cancer diagnosed in the setting of gross hematuria is urothelial, primarily the bladder; several large studies showed less than three percent of patients presenting with gross hematuria had upper tract urothelial carcinoma or renal cell carcinoma (RCC) [7, 14]. The classic triad of flank mass, hematuria, and pain is now overwhelmingly uncommon in RCC and presents in less than ten percent 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.

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 [26]. Prostatic hyperplasia demonstrates hypervascularity with fragile microvessels, as well as an increase in acinar cells and stromal cells [27]. 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 large-volume catheter balloon (30 cc balloon) 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%) [28]. 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 [29].

Ultimately, if gross hematuria has been recurrent or persistent, cystoscopy with the patient under anesthesia may be necessary to evacuate clot and cauterize prostatic bleeding. In such a situation electrocautery resection or laser photocoagulation/vaporization are often performed for prostatic debulking. Should this fail or should life-threatening hemorrhage occur, selective arterial prostatic angioembolization under interventional radiology remains a means of last resort [30].

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 from nephrolithiasis almost never requires 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 [31]. 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 radiation cystitis in the long term. 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 [32].

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. Urinary diversion with or without cystectomy is a method of last resort and has a high rate of perioperative morbidity (over 80 %) [33].

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 outpatient 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

24

Jose Vega Peralta and Martin L. Freeman

Epidemiology

Upper gastrointestinal bleeding (UGIB) is defined as bleeding that occurs from the mouth to the duodenum, proximal to the ligament of Treitz [1]. UGIB is routinely divided into nonvariceal UGBI (NVUGBI) or portal hypertensive-related bleeding. This distinction is important due to significant differences in therapy. Upper GI bleeding remains a major medical emergency, leading to nearly 300,000 hospitalizations per year in the United States [2], and is associated with mortality rates as high as 5 % [2, 3] major morbidity high costs. In 2004 the direct costs attributable to the diagnosis of peptic ulcer disease were $1.4 billion in the United States [4].

Worldwide, the incidence of UGIB has decreased, likely secondary to the increased use of acid-suppressing medications and decreased prevalence of *H. pylori* [1]. Even though the incidence of upper GI bleeding has decreased, in a 2012 US study, UGIB was ranked as the seventh most common gastrointestinal and hepatology principal hospital discharge diagnosis and as the tenth leading cause of death from gastrointestinal and liver disease [3].

Peptic ulcer disease is the predominant cause of NVUGBI [4]. The population presenting with peptic ulcer disease tends to be older, male, with the use of nonsteroidal anti-inflammatory drugs or aspirin, and from areas with a higher prevalence of *Helicobacter pylori* [2, 5].

Portal hypertension can be complicated by bleeding, which can be caused by varices in the esophagus, stomach, duodenum, or elsewhere in the GI tract, and also by portal hypertensive gastrointestinal enteropathy. Portal hypertension is most commonly associated with cirrhosis, but there are multiple other causes of portal hypertension that can lead to UGIB.

Risk Factors

The most common risk factors for acute NVUGBI are *H. pylori* infection; the use of NSAIDS, aspirin, or antiplatelet/anticoagulant medications; and the use of selective serotonin reuptake inhibitors (SSRIs) [1, 3].

H. pylori is a well-established risk factor for developing peptic ulcer disease. *H. pylori* is found in over 40 % of patients with peptic ulcer disease [2] and in perhaps even as many as 70 %, based on a meta-regression analysis of 71 studies which included 8496 patients [6].

H. pylori and NSAID use are known to be independent and synergistic risk factors for the development of uncomplicated and bleeding peptic ulcer disease [7]. SSRIs have also been associated with increased risk of upper GI bleeding, especially when used in combination with an NSAID [8].

Risk factors for portal hypertensive-related bleeding include known varices, known portal hypertensive enteropathy, and decompensating acute or chronic liver disease.

Causes

UGIB can be divided into variceal and nonvariceal UGBI. The most common cause of NVUGBI is peptic ulcer disease (Figs. 24.1 and 24.2), followed by erosive disease, esophagitis, malignancy, and Mallory-Weiss tears (Fig. 24.3) [2]. There are multiple less common causes of NVUGBI including Dieulafoy lesions, Cameron ulcers, gastric antral vascular ectasia, angiodysplasias, gastrointestinal stromal tumors, hemobilia, hemosuccus pancreaticus, and vascular-enteric fistulas.

Portal hypertension-related bleeding can be caused by esophageal, gastric (Fig. 24.4), or ectopic varices and also by portal hypertensive gastrointestinal enteropathy.

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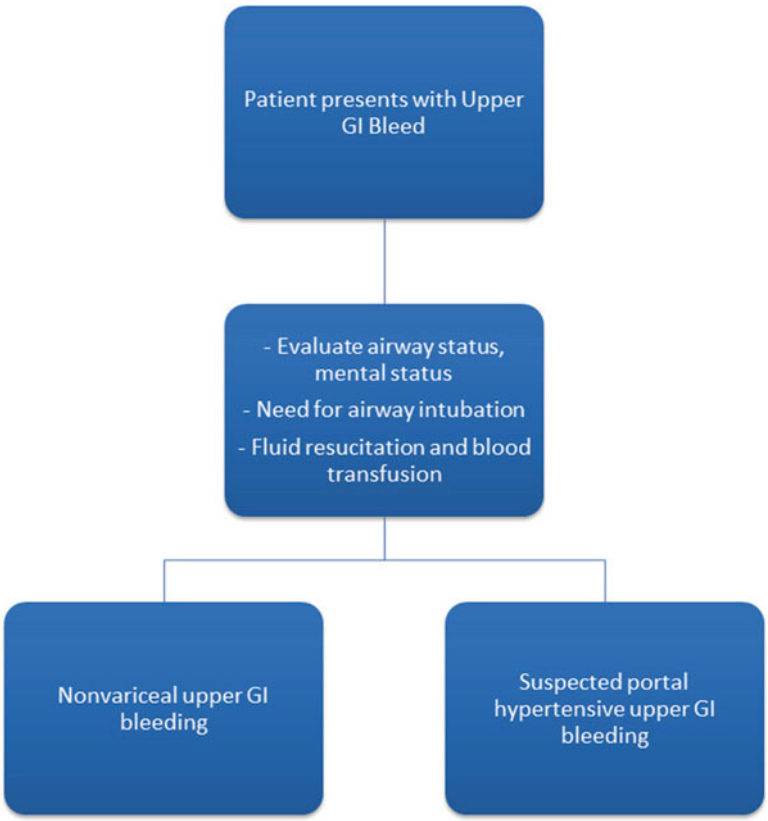

Fig. 24.1 Initial assessment of patient with upper GI bleeding

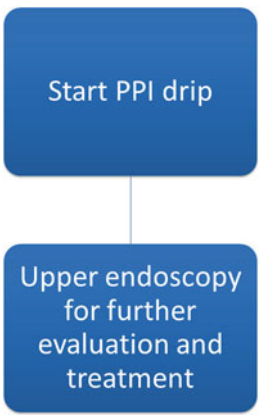

Fig. 24.2 Management of patient with nonvariceal upper GI bleeding

Initial Assessment

The initial assessment of patients with upper GI bleeding is crucial as adequate risk stratification will lead to improved patient outcomes. Evaluation should start with the 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 determined as prompt volume resuscitation can treat or avoid shock. A directed history and physical exam will help determine the location of the bleeding source, which will help guide the decision on which initial tests to order. It is also important to determine if the patient is at risk of portal hypertensive-related bleeding as there are important differences in management, specifically with respect to medications and fluid replacement.

If the patient does not present with hematemesis, the color of the stools will help determine if the bleeding is from an upper or lower source. Black tarry stools, referred to as melena, are caused by bleeding most commonly originating proximal to the ligament of Treitz. As little as 100 mL of hemorrhage can lead to melena. In addition, slow bleeding from the small intestine or right side of the colon may lead to melena or dark maroon-colored stools. Bright red- or maroon-colored stools in a hemodynamically unstable patient could also be caused by brisk upper GI bleeding. Coffee ground appearance in the emesis may represent a slow upper GI bleeding or old blood from a source that may not be actively bleeding.

It is important to know the patient's past medical history and medications, as they may suggest the cause of the bleeding, such as NSAID and peptic ulcer disease, history of DVT filter, or other vascular prostheses which may result in vascular-enteric fistula. Specifically a history of bleeding disorders, previous bleeding events, smoking, alcohol use, liver disease and use of aspirin, NSAIDs, and anticoagulants

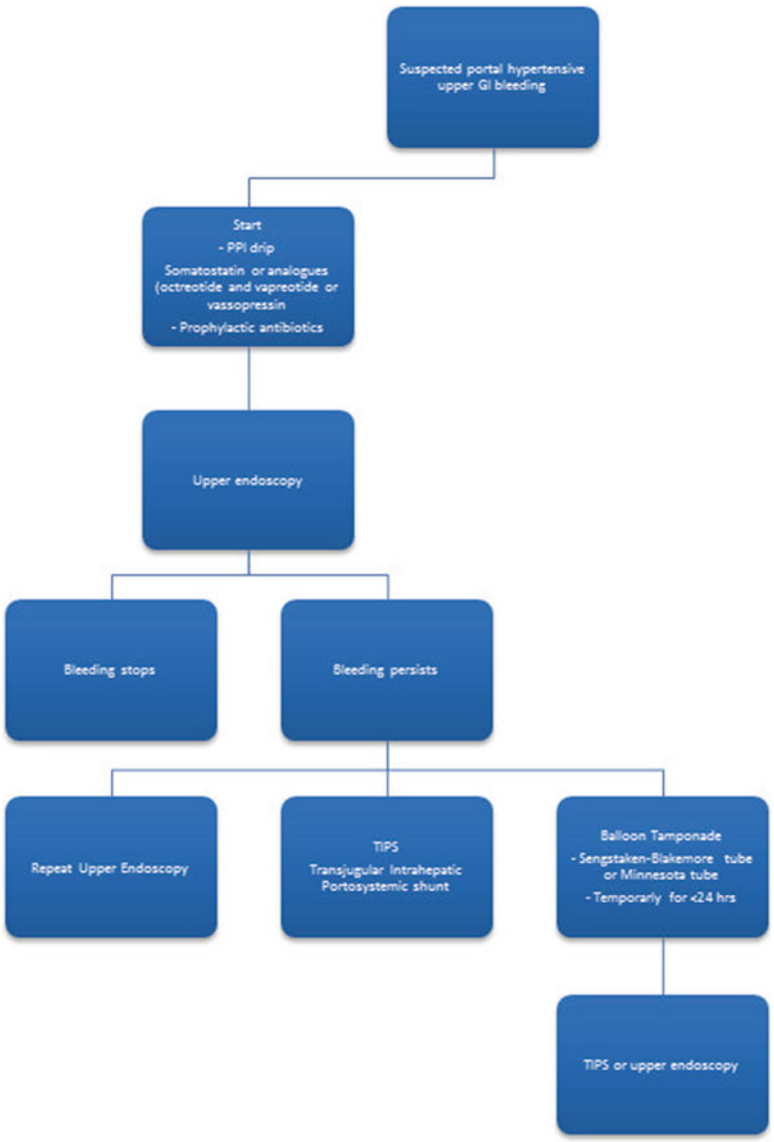

Fig. 24.3 Management of patient with suspected portal hypertensive upper GI bleeding

should be sought. Presenting symptoms will also help determine the severity of the bleed. Common symptoms of upper GI bleeding include epigastric pain, shortness of breath, dizziness, lightheadedness, and syncope.

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 markers of hypovolemia [9]. Laboratory studies in the initial assessment of any patient with upper GI bleeding should include a complete blood count (CBC), 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 time such that leveling off of the hemoglobin may not occur for up to 72 h, even after bleeding has stopped. Therefore the hemoglobin and hematocrit should be checked periodically, as often as every 6 h, depending of the severity of the bleeding.

Once the initial assessment has been done, this 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 h of presentation unless they are considered to be at low risk for rebleeding [10, 11].

There are several pre-endoscopic risk assessment scores designed to risk 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

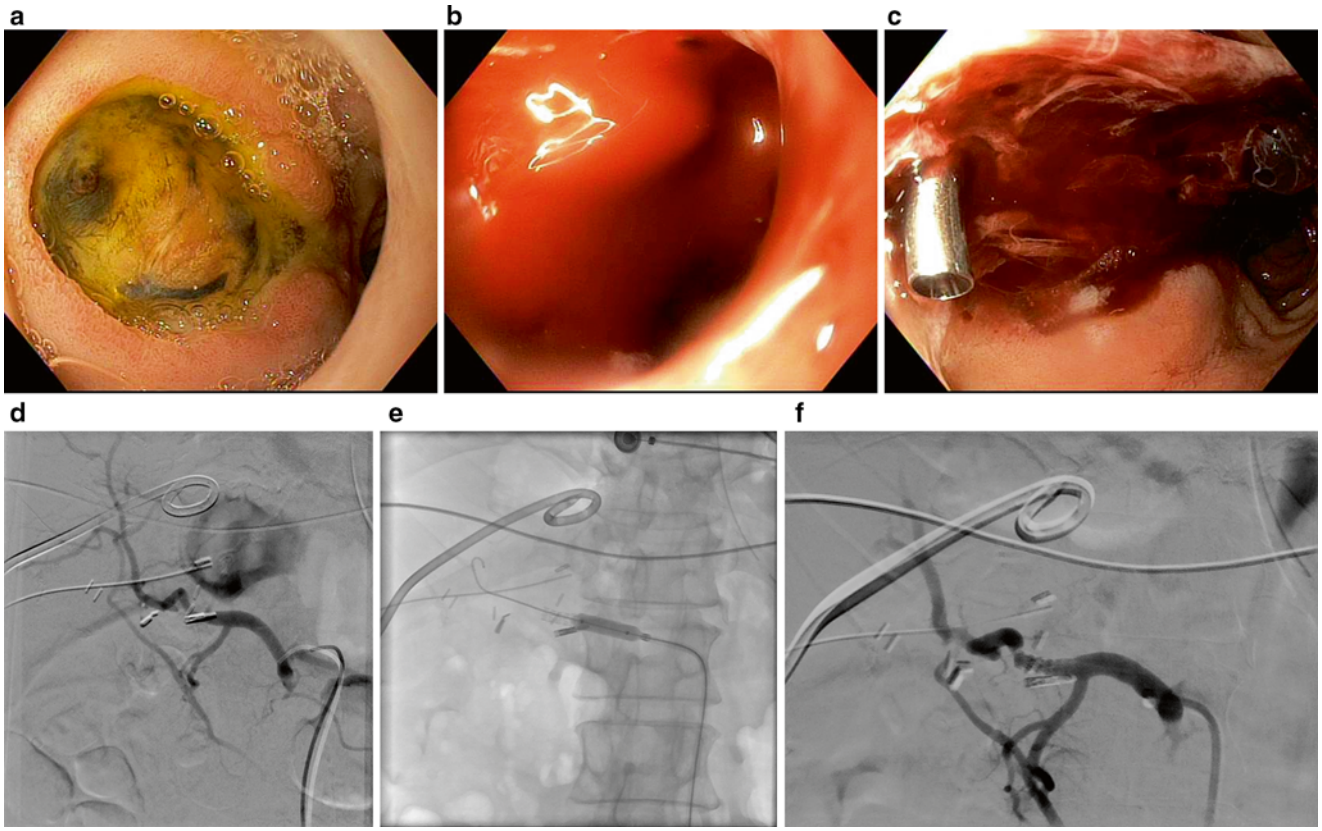

Fig. 24.4 (**a**) Duodenal bulb ulcer eroded into common hepatic artery. (**b**) Active bleeding from common hepatic artery. (**c**) Endoscopic treatment of hepatic artery with endoscopic clip with cessation of bleeding. (**d**) Repeat bleeding from common hepatic artery requiring angiographic therapy by interventional radiology. (**e**) Very large artery requiring placement of covered vascular stent across rent to control bleeding. (**f**) Repeat injection of angiographic contrast demonstrating bridging of rent in artery by stent with control of bleeding

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.

Medical Management

Medical management is integral to the management of upper GI bleeding and includes airway control, volume resuscitation, blood transfusion, prokinetics, proton pump inhibitors (PPIs), and eventually treatment of *Helicobacter pylori*. See Figs. 24.5, 24.6, and 24.7. If portal hypertensive bleeding is suspected, specific medical therapies such as octreotide and other vasoactive medications improve outcomes.

A secure airway should be maintained in every patient with major GI bleeding, with a low threshold for endotracheal intubation to prevent aspiration of blood and respiratory failure. 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, therefore treating or avoiding shock and resulting end-organ damage. The need for 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. For patients with a history of coronary artery disease or presenting with acute hemorrhage or evidence of organ hypoperfusion, a goal hgb of 10 g/dL may be needed. Excessive transfusion has been associated with increased mortality in at least one large study [12].

Guidelines recommend that a PPI should be started in patients presenting with upper GI bleeding. PPI therapy has been proven to decrease the number of patients found at endoscopy to have higher-risk stigmata of hemorrhage, such as active bleeding, nonbleeding visible vessel, and adherent clot. PPIs have been shown to reduce rates of rebleeding, need for surgical intervention, and mortality [13].

Erythromycin is an antibiotic with prokinetic effects that, when given prior to endoscopy, has been shown to improve gastric emptying and increase visibility at endoscopy, leading to 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

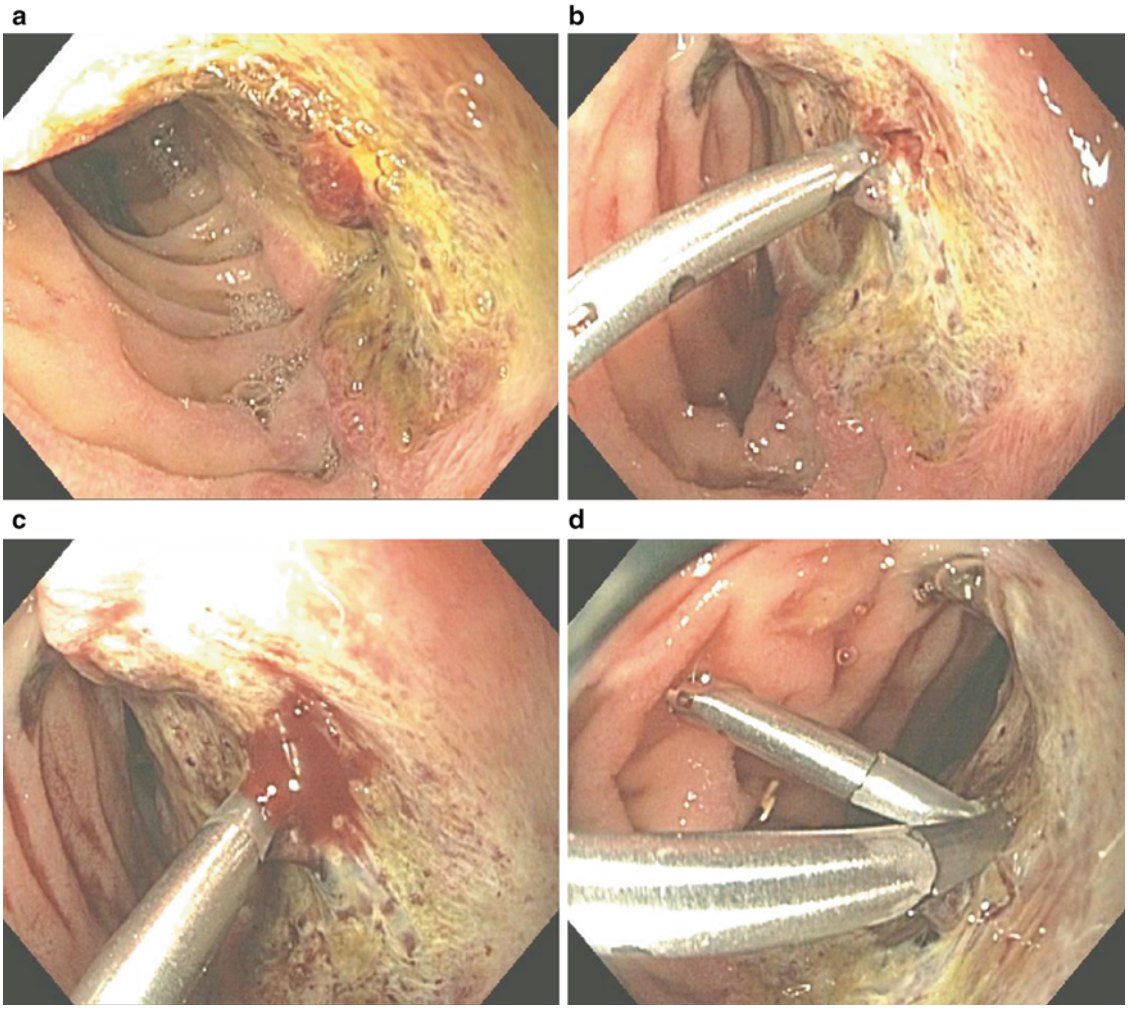

Fig. 24.5 (**a**) Nonbleeding visible vessel in duodenal ulcer. (**b**) Treatment of visible vessel in duodenal bulb ulcer with hemostatic clip. (**c**) Further bleeding despite single clip placement. (**d**) Successful hemostasis after second endoscopic clip placement

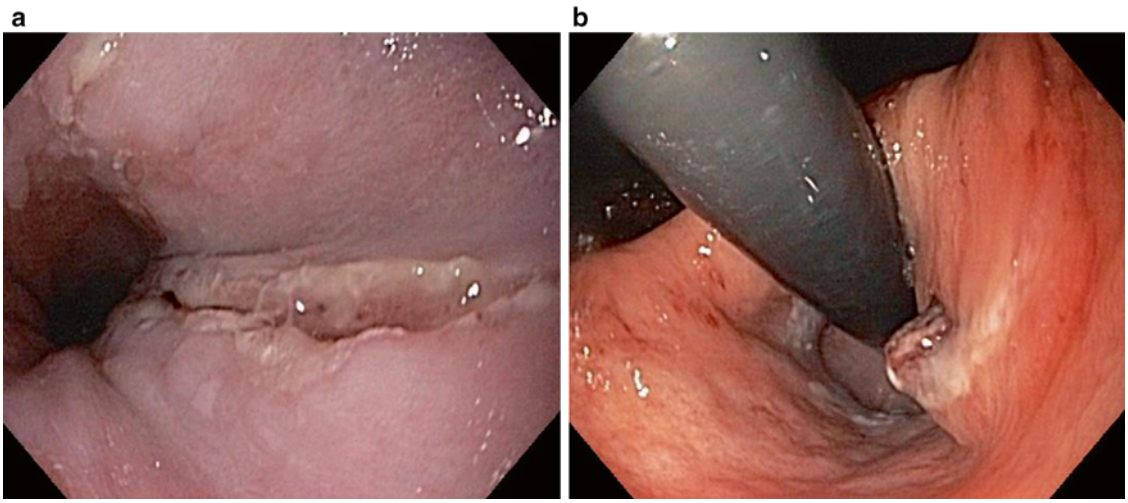

Fig. 24.6 (**a**) Mallory-Weiss tear in distal esophagus. (**b**) Visible vessel in Mallory-Weiss tear seen at retroflexed view of gastroesophageal junction

interval), a 250-mg bolus of erythromycin can be administered 30–45 min prior to emergency endoscopy [10].

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 NG lavage [14, 15].

If portal hypertensive bleeding is suspected (Fig. 24.7), the following medications should be considered: somatostatin and analogues (octreotide and vapreotide), vasopressin, antibiotics, and nitrates (see Table 24.1). Somatostatin and analogues cause splanchnic and mesenteric vasoconstriction by inhibiting the release of glucagon. Vasopressin leads to systemic and splanchnic vasoconstriction. When vasopressin is used in conjunction with nitrates, there is an additive effect in decreasing the portal pressure. Nitrates also decrease the side effects of vasopressin's vasoconstriction. In practice, in the United States, octreotide, a somatostatin analogue, is the primary agent used to reduce risk of portal hypertensive rebleeding. Antibiotics also have a role; they 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 [16, 17].

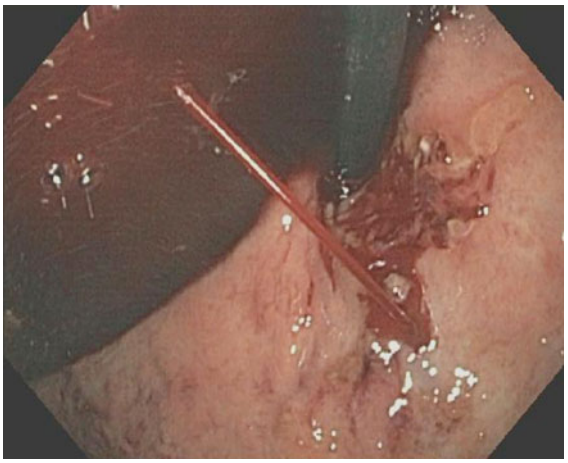

Fig. 24.7 Bleeding gastric varix

Endoscopic Management

The role of upper endoscopy in the management of upper GI bleeding has evolved from diagnostic to therapeutic. Patients presenting with significant upper GI bleeding should undergo endoscopic evaluation within 24 h of presentation [10, 11]. Adequate resuscitation and stabilization of hemodynamics should be achieved prior to any endoscopic intervention. Great advancements have been made in hemostatic techniques, and more are currently being developed. Multiple modalities are available.

Several substances can be injected through using retractable needles. The most commonly used is epinephrine. 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 the only therapy in most circumstances due to high risk of rebleeding. Other substances that can be injected for nonvariceal bleeding, but are rarely used, include sclerosing agents and fibrin glues.

Thermal therapy includes coaptive coagulation probes such as bipolar and heater probes. These are highly effective at treating smaller caliber vessels in nonvariceal sources such as ulcers, Mallory-Weiss tears, and angiodysplasias (Figs. 24.8 and 24.9). These devices are often used in combination with epinephrine injection. Argon plasma coagulation can also be used for thermal therapy involving a spark-induced ionization of the gas that will lead to delivery of thermal energy.

The most commonly used device for therapy of visible vessels, tears, and perforations is endoscopic clips placed through the endoscope channel (Figs. 24.1 and 24.2). Larger over-the-scope clips (OTSC) are occasionally used for treatment and closure of larger lesions, especially when perforation is suspected.

Band ligation is the treatment of choice for treatment of esophageal variceal bleeding. It has also been proven to be highly successful in treating Dieulafoy lesions, Mallory-Weiss tears, gastric angioectasias, and postpolypectomy bleeding. Cyanoacrylate glue injection is widely used outside the United States for treatment of gastric varices (Figs. 24.4 and 24.10). Additionally, endoscopic ultrasound-guided placement of angiographic coils is increasingly used for bleeding gastric varices.

Table 24.1 Medications for Portal Hypertensive Bleeding

Vasopressin	0.4 unit bolus followed by an infusion of 0.4–1 units/min
Octreotide	50 μg bolus followed by a continuous infusion of 50 μg/h and is continued for 3–5 days
Somatostatin	250 μg bolus followed by a continuous infusion of 250 μg/h and is continued for 3–5 days

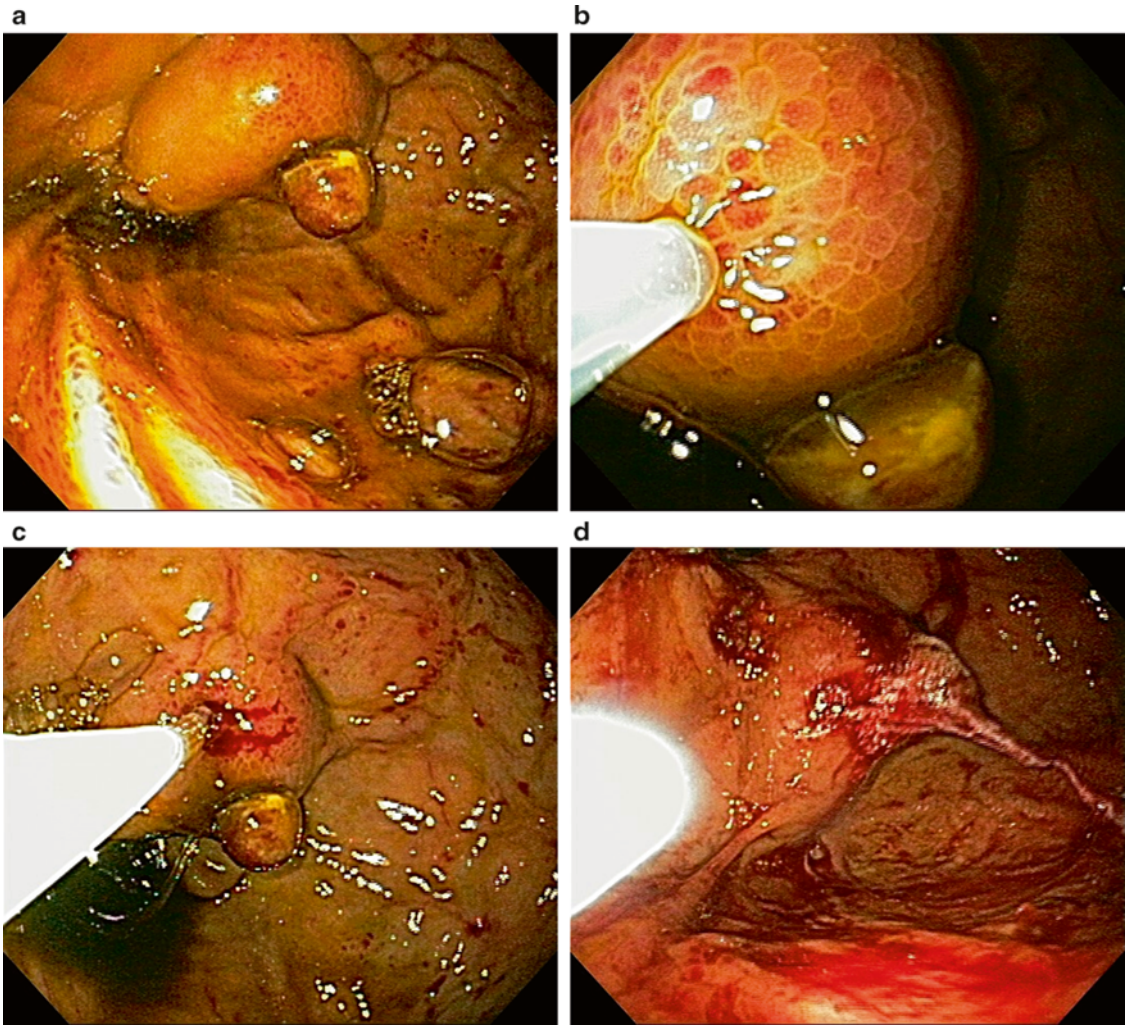

Fig. 24.8 (**a**–**d**) Cyanoacrylate glue injection into bleeding gastric fundic varices

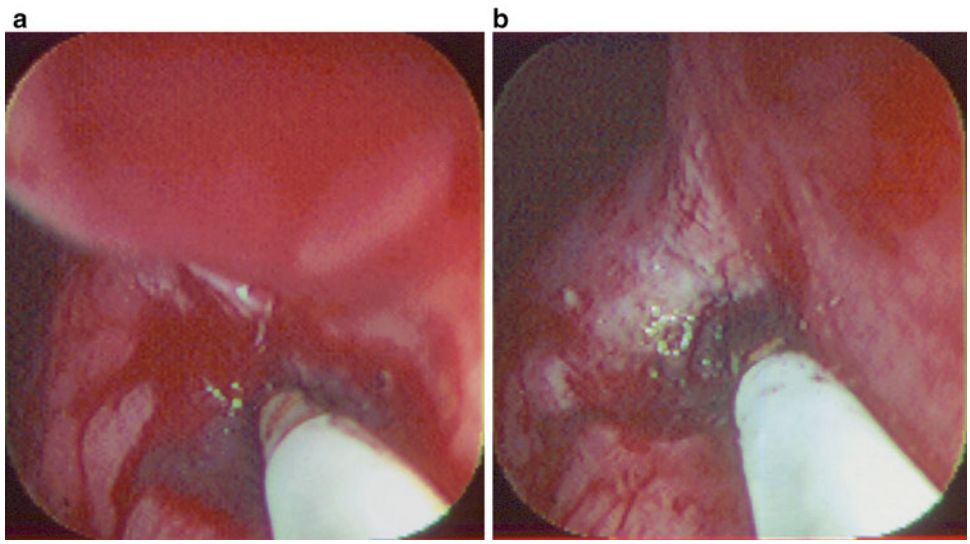

Fig. 24.9 (**a**, **b**) Bipolar probe coagulation of actively bleeding ulcer

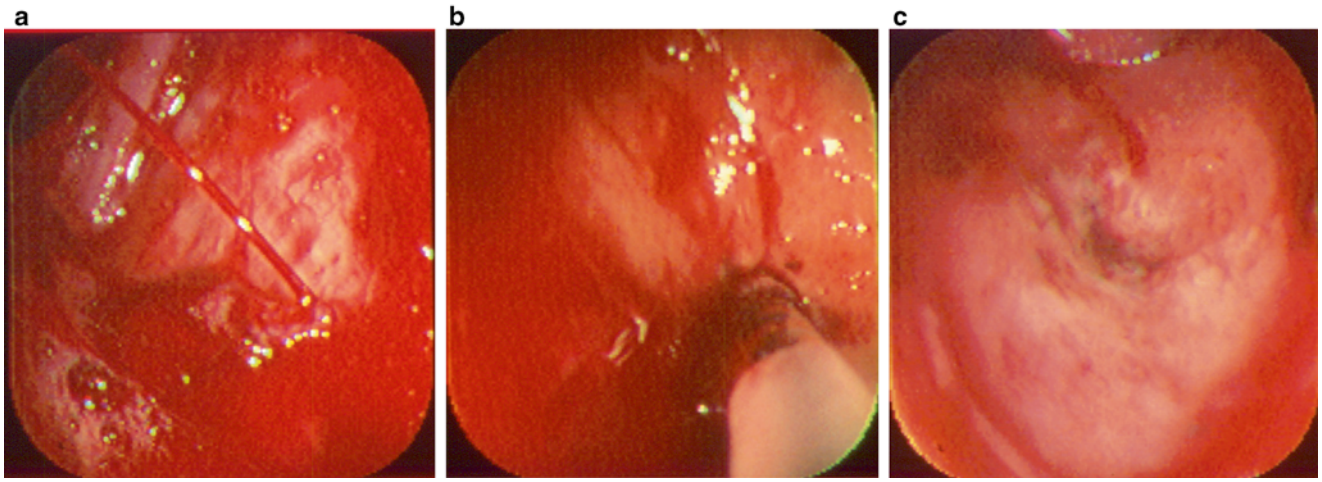

Fig. 24.10 (**a–d**) Combination of epinephrine injection followed by bipolar probe coagulation of spurting bleeding gastric ulcer

In the setting of variceal upper GI bleeding, when endoscopy treatment has failed to stop the bleeding, the options to consider are the temporary use of balloon tamponade or 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.

Conclusion

Even though the incidence of upper GI bleeding has decreased, it still continues to be a major medical emergency with significant morbidity, mortality, and cost. There have been great advancements in the diagnosis, management, and endoscopic treatment options for upper GI bleeding, which has led to the need for a multidisciplinary approach to guarantee the most up-to-date and appropriate management.

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Part IV

Bleeding Associated with Medication

Antiplatelet and Anticoagulant Agents

25

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 oral anticoagulants (NOACs) and newer and more potent antiplatelet drugs, questions about safety and practical use of these agents arise as they are more routinely incorporated into clinical practice (Table 25.1).

Anticoagulant medications are one of the most commonly prescribed medications in the United States, with 4.2 million Americans taking anticoagulants in 2007 [1]. 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.

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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 NOACs given their rapid onset and offset as compared to traditional vitamin K antagonists (VKAs). The purpose of periprocedural bridging (Tables 25.2 and 25.3) 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 [2, 3].

The use of all anticoagulants carries an inherent risk of bleeding and bleeding complications. The bleeding profile of NOACs, as compared with VKAs, is better, especially concerning rates of intracranial and fatal hemorrhage [4]. However, the lack of availability of an antidote for most of the NOACs is of concern to some clinicians and patients. At the time of publication of this book, however, several promising reversal agents are undergoing clinical trials and one reversal agent idarucizumab has gained FDA approval for the reversal of the direct thrombin inhibitor dabigatran [5–7].

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,

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Table 25.1 Anticoagulant agents: pharmacokinetic/pharmacodynamic properties [50, 51]

Agent	Effect	Half-life (route)	Elimination	Antidote
Warfarin	Reduces factors II, VII, IX, X	36–42 h (PO)	Renal (92 %, primarily as metabolites)	Vitamin K
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
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—(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 %	None
Apixaban	Direct Xa inhibitor	8–15 h (PO)	Renal—25 %, hepatic—75 %	None
Edoxaban	Direct Xa inhibitor	8–10 h (PO)	Renal—50 %	None
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

Table 25.2 Risk stratification for perioperative thromboembolism [10]

		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. [10]
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 25.3 Perioperative anticoagulation and bridging protocol [10]

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 (Hgb, platelet count, creatinine, INR)
−7	Stop aspirin or other antiplatelet agent
−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

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 procedure. Observational studies have suggested that brief interruption of warfarin therapy for a procedure is associated with a very low rate of postoperative thromboembolism [8, 9]. 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 [2]. 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 25.2) 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 25.4).

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 [10]. For patients with arterial indications for anticoagulation, the $CHADS_2$ score (Table 25.2) is a validated clinical prediction score to estimate stroke risk in patients with non-valvular atrial fibrillation [11]. Additionally, data suggests that the $CHADS_2$ score may predict postsurgical stroke risk [12, 13]. 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 [14].

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

Table 25.4 Elective procedures by bleeding risk [10, 52]

Low bleeding risk		High bleeding risk
Anticoagulation could be continued	Anticoagulation discontinued	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
Cutaneous biopsies	Angiography	Abdominal surgery
Pacemaker and cardiac defibrillator insertion	Minor orthopedic surgery	Major orthopedic surgery

deemed suitable for systemic anticoagulation. Therefore, patients with very high bleeding risks are not well represented [15]. 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 [16]. 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 [10].

The patients' estimated thromboembolic risk is what determines an aggressive periprocedural antithrombotic strategy (such as bridging anticoagulation) versus a more conservative one (Table 25.2). 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 [17–21].

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 25.5). The thienopyridines, aspirin, dipyridamole, cilostazol, and nonsteroidal anti-inflammatory agents are irreversible inhibitors. Ticagrelor is a reversibly binding $P2Y_{12}$ receptor antagonist that exhibits a rapid onset and offset of antiplatelet effect [22]. 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 $P2Y_{12}$ receptor antagonist that exhibits a rapid onset and offset of antiplatelet effect with a half-life of only minutes [23]. 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 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 a drug-eluting stents. Whether 12 months of antiplatelet therapy is required for newer second-generation drug-eluting stents is unknown. Therefore, based on currently available data and guidelines, it is reasonable to defer elective surgery for at least 12 months after a drug-eluting stent [24, 25].

Most antiplatelet medications have short half-lives; however the most frequently used agents (aspirin, clopidogrel) irreversibly inhibit platelet function (Table 25.5). 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 [10]. 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 [10]. For patients undergoing coronary artery bypass grafting (CABG), continuing aspirin would be appropriate, although recent guidelines from the American College of Chest Physicians suggest that thienopyridine therapy should be held before CABG [10].

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 25.5). Cangrelor, a nonthienopyridine adenosine triphosphate analogue, was investigated as a bridging agent in a prospective trial involving patients receiving a thienopyridine who underwent CABG [26]. 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 [27]. 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 [28]. However, the use of platelet transfusion in reversing newer antiplatelet agents such as ticagrelor has recently been called into question [29]. Clinical trials are needed to ascertain the efficacy of this strategy.

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,

Table 25.5 Antiplatelet drugs [22, 23, 53–56]

Name	Mechanism of action	Time to maximum level	Elimination half-life	Notes
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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ ADP receptor	30 min	7 h	Antiplatelet effect lasts 5–7 days
Ticagrelor	Reversible inhibition of $P2Y_{12}$ ADP receptor	1.5 h	7 h	Residual antiplatelet effect decreased to 30 % after ~2.5 days
Cangrelor	Reversible inhibition of $P2Y_{12}$ 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	Inhibits platelet aggregation
Cilostazol	Inhibitor of phosphodiesterase III	3 h	11–13 h	Reversible inhibition of platelet aggregation

COX cyclooxygenase, *PAR* protease-activated receptor-1

Table 25.6 FDA-approved indications for NOACs

Condition	Dabigatran (Pradaxa™)	Rivaroxaban (Xarelto™)	Apixaban (Eliquis™)	Edoxaban (Savaysa™)
Stroke prevention in atrial fibrillation	✓	✓	✓	✓
VTE treatment	✓[a]	✓	✓	✓[a]
Prophylaxis of VTE in knee and hip arthroplasty	–	✓	✓	–

FDA Food and Drug Administration; as of September 2015, *VTE* venous thromboembolism
[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

cataract surgery, and minor skin procedures do not need interruption of warfarin (Table 25.4). 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 [2, 3].

The approach to perioperative warfarin cessation and bridging anticoagulation is detailed in Table 25.3. 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 initiated after 72 h [30]. 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 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 [10, 31].

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 warranted with renal biopsy, liver biopsy, prostate biopsy, endoscopic sphincterotomy, and pacemaker placement given the higher bleeding risk association with these minor procedures [31].

Non-vitamin K Antagonist Oral Anticoagulants

The NOACs include direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban) and the direct thrombin inhibitor dabigatran (Table 25.6). The timing of discontinuation of these agents before high-risk procedures depends on the creatinine clearance (Fig. 25.1) with dabigatran being the most renally dependent and apixaban being least renally dependent [10, 32]. 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 [33].

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, NOACs can be safely resumed 24 h postoperatively. Higher bleeding risk procedures may require 48–72 h. Importantly, an assessment of the stability of renal function has critical given its impact on drug clearance [10]. Thus far the only protocol involving NOACs devised that has been studied in a prospective manner involves the perioperative management of dabigatran [34].

Bridging therapies have a limited role with NOACs 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

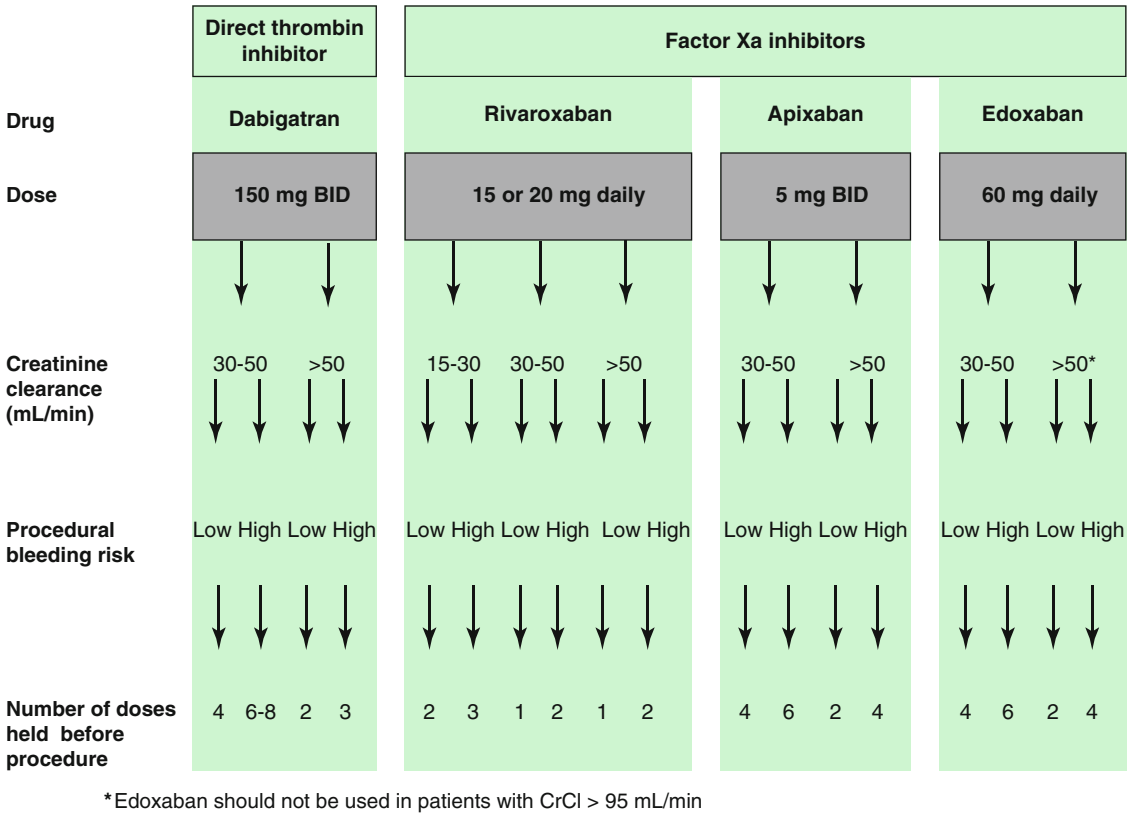

Fig. 25.1 Preoperative interruption of NOACs [10, 32]

NOAC bioavailability may be affected over a prolonged period. Several randomized trials involving NOACs 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 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 NOACs as well.

Parenteral Anticoagulants: Heparin, Heparin Derivatives, and Direct Thrombin Inhibitors

Intravenous UFH has a half-life of 60–90 min (Table 25.1), 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 25.1), and the last dose should be given 24 h before the anticipated procedure [1]. 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 [31].

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 [4]. 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 25.7 and Fig. 25.2). 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 25.7 Interventions for bleeding cessation [50, 51]

Agent	Dose	Comments
Blood product derivatives		
Platelets	1 apheresis unit 5–8 whole blood units	• Used in patients receiving antiplatelet therapy • Raise platelet count by 30×10^9/L
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
Hemostatic agents		
Aminocaproic acid	4–5 g IV/PO over 1 h, 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

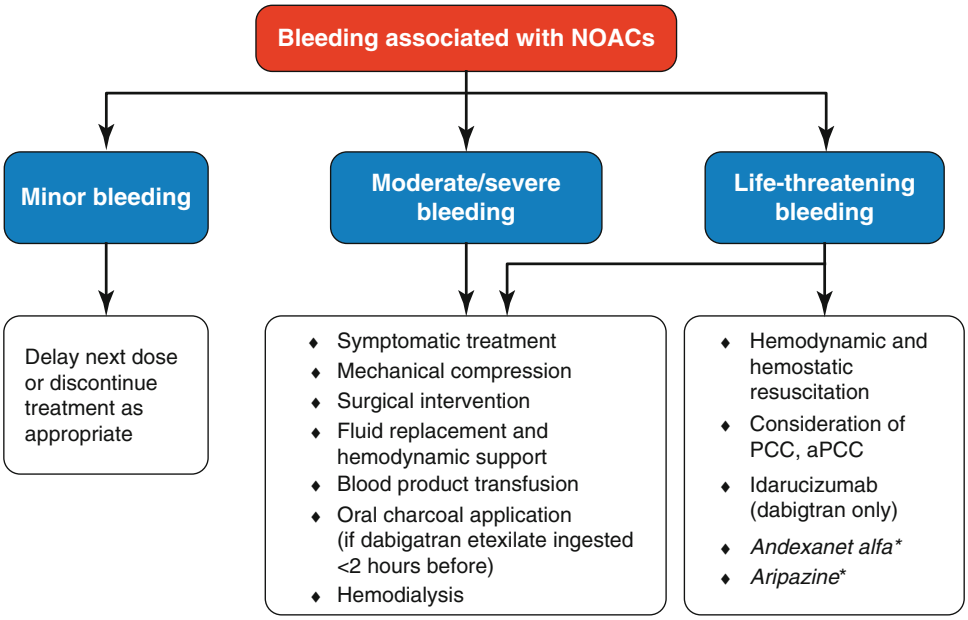

Fig. 25.2 Management of bleeding associated with NOACs [49]

aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate
*These agents are currently being studied in clinical trials and are not available for clinical use.

Antiplatelet Drugs

Aspirin, nonsteroidal anti-inflammatory drugs, dipyridamole, ADP receptor (P2Y12) inhibitors, and PAR-1 antagonists (Table 25.5) 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 appears to be the best option [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].

The use of desmopressin (DDVAP) in patients with normal renal function who have active bleeding on antiplatelet agents has limited data. However, randomized data, albeit limited, is available in the setting of patients requiring urgent cardiovascular surgery [38, 39]. Nonetheless, these cases can be complex, and an individualized approach based on the complete clinical picture is required.

Heparin and Derivatives

Protamine sulfate, a protein derived from fish, can fully neutralize heparin's effect. Because of the relatively short half-life of intravenously administered heparin (Table 25.1), 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 [40]. However agents under current development such as andexanet alfa and aripazine (PER-977, ciraparantag) may have a future role in the reversal of heparin derivatives [41].

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 [42, 43]. 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.

Non-vitamin K Antagonist Oral Anticoagulants: Dabigatran and Direct Xa Inhibitors

Given the short half-lives of NOACs, 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 NOAC used and the degree of renal function of the patient (Table 25.1). 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 NOACs, 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.

Targeted reversal agents are not currently in wide use to reverse the anticoagulant effects of NOACs. However, numerous agents are currently under investigation, and one, idarucizumab, has been approved by the Food and Drug Administration (FDA) in the United States at the time of this book's publication but is not yet widely available [5]. Additionally, it is unclear whether the effect of these reversal agents on laboratory endpoints leads to improved clinical outcomes. This has yet to be proven. Nonetheless, there is a clear need to quickly and reliably reverse direct oral anticoagulants given the efficacy data with PCCs, and other factor concentrates are limited and in some cases conflicting [44, 45].

Activated charcoal and hemodialysis have demonstrated some reversal effect in dabigatran-associated bleeding (Fig. 25.2). Conversely, rivaroxaban and apixaban are too highly protein bound and therefore not readily dialyzable. Ultimately, it is not clear that hemodialysis or activated charcoal will have any role in the future if targeted reversal agents and antidotes are proven to be effective.

Future Directions

There are three intravenous antidotes at different stages of human clinical trials for the reversal of direct oral anticoagulants. Idarucizumab is the furthest along in development and has received approval by the FDA. 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 [5].

Andexanet alfa is a modified recombinant factor Xa decoy molecule that reverses direct oral anticoagulants and parenteral indirect factor Xa inhibitors (e.g., enoxaparin, fondaparinux). Its efficacy of reversal was demonstrated within minutes in healthy older participants who took apixaban and rivaroxaban [46]. The 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 efficacy of this compound with normalization of laboratory parameters in healthy edoxaban-treated volunteers within minutes of administration [47].

Other novel reversal agents have also being evaluated in vitro and in animal studies [45, 48]. 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

26

Jennifer C. 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 Neurologic 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 three hours of stroke symptom onset [2]. tPA now holds FDA approval for acute arterial stroke, ST elevation myocardial infarction, 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 parapneumonic 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 life saving.

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]. After injury to the brain such as ischemia, tPA is thought to potentially up-regulate 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, exposes the brain to a higher risk of bleeding [10]. Recently, matrix metalloproteinases (MMP) have been identified as contributors to the neurotoxicity that occurs after stroke, ultimately affecting blood brain barrier integrity and neuronal injury. tPA itself may play a role in worsening or triggering these processes via its proteolytic properties affecting the neurovascular matrix [11].

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 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 hemor-

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rhage 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 intracerebral hemorrhage increased to 7.9 % [3].

ST Elevation Myocardial Infarction

Recombinant tPA is frequently used in the treatment of ST elevation myocardial infarction within 12 h of symptom onset when percutaneous coronary intervention cannot be performed within 120 min of arrival to the hospital [12]. 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 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 [13].

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 PE, 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 GI 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]. Shimohata et al. suggested that consideration for dose adjustments in patients at high risk for hemorrhagic conversion be undertaken [14]. 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 [15]. 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

If hemorrhage is suspected during administration of tPA, 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. Neurosurgery should be consulted. Initial screening blood tests should be drawn including PT, PTT, coagulation profile, fibrinogen levels, CBC with platelets, PFA-100, and ABO/Rh typing and red cell antibody screening test. For patients with tPA-related ICH, there is limited data to support best practice. However, having a treatment protocol in place and readily available is important for rapid evaluation and treatment of this potentially lethal complication. Guidelines for the management of spontaneous ICH have been developed by the AHA and are typically applied to this unique situation.

As in all ICH, AHA recommendations include admission to a neurosciences intensive care unit which has been associated with improved clinical outcomes. 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, EEG should be performed to assess for subclinical seizures and electrographic seizures should be treated. Prophylactic treatment of seizures should not be administered, as in previous studies it was associated with higher rates of death and disability. 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 [16].

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 propose that it is safe to lower systolic blood pressure <140 mmHg suggesting it may improve functional outcome and reduce chances of hemorrhage expansion [16]. In spontaneous ICH, the ischemic penumbra is limited in size and maintaining perfusion to it may not make a significant difference clinically [17]. 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.

Management of Coagulopathy

Management of coagulopathy after thrombolysis is variable. Goldstein et al. reviewed current 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 aminocaproic acid (5 %) [18]. 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 [19]. 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 [20]. tPA may also affect platelet activation and function [21]. Therefore, treatment modalities that target these mechanisms of hemorrhagic transformation may be most beneficial in this setting.

The Neurocritical Care Society and the Society of Critical Care Medicine recently developed a new evidence-based guideline to aid in the management of ICH after tPA. This guideline recommends treating patients immediately with 10 units of cryoprecipitate. However, the quality of evidence supporting this recommendation was reported as low. 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. The quality of evidence supporting this recommendation was reported as very 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 [22].

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 [23]. The intrinsic pathway of the coagulation system is also activated by cryoprecipitate as it contains factor VIII [24]. 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 [23]. 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 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 MCA 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 [25]. 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 [18]. Although the mechanism of action of these agents remains promising, quality of evidence for the clinical use of these products remains very low.

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 [21]. 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 [21]. Data in spontaneous ICH suggests that decreased platelet function may be associated with early hematoma expansion and worse functional clinical outcome at three months based on modified Rankin scores [26]. It is known that many patients receiving tPA are taking antiplatelet medication, resulting in known baseline platelet dysfunction. However, the Neurocritical Care Society and the Society of Critical Care Medicine 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 [22].

Factor VIIa 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 [27]. It is not recommended in the newest guideline. Factor VIIa binds to factor X on activated platelets initiating a cascade of events resulting in thrombin formation and clot formation at the site of bleeding [28]. Phase II trials in spontaneous ICH were initially promising; however, phase III trials found that although factor VIIa minimized hematoma expansion, there was no clear difference in clinical outcome between patients who received factor VIIa and those who did not. There were also higher numbers of arterial thrombotic events in the group treated with factor VIIa compared to placebo [29]. Subgroup analysis suggested an improved outcome with factor VIIa 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 [30]. Overall, due to high risk of serious thrombotic complications, Factor VIIa is not currently recommended for bleeding after tPA [22].

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 factor II, IX, and X along with protein 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 [31]. 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 [32]. PCC agents have not been adequately studied for this use and are not included in the newest guideline for the management of tPA-related hemorrhage [22].

Finally, Vitamin K needed for the ɣ-carboxylation of factors II, VII, IX, and X should be considered [33]. 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 [24].

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 [34, 35]. Smaller retrospective studies indicate there may not be an increased risk of hemorrhage with decompressive craniectomy surgery after receiving tPA [36]. 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 [37].

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 [38]. STICH II was then undertaken to clarify this and again there was no clear benefit from surgery [39]. In both studies, however, there were high rates of crossover from the medical man-

Table 26.1 Management of thrombolysis-related bleeding concern for symptomatic intracerebral hemorrhage [22]

• 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 PT, PTT, fibrinogen, CBC with platelets, PFA-100, ABO/Rh typing and red cell antibody screening test
• Order 2–4 units PRBC on hold
• Correct coagulopathy (per Neurocritical Care Society and Society of Critical Care Medicine recommendations)
– 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 or
E-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 EEG

agement 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 [16].

Neuroprotection

Finally, it has been shown that MMP contribute 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 [11]. There is some data that suggests that MMPs may be beneficial in the recovery phase [40]. 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 [41].

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. 26.1).

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Part V

Bleeding Associated with Procedure

Bleeding Associated with ECMO

27

Jun Teruya and Cole Burgman

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) has been more and more commonly performed for patients with respiratory failure and cardiorespiratory failure. Extracorporeal cardiopulmonary resuscitation (ECPR) is also commonly performed in some hospitals. The recent improvement of technology made the circuit, oxygenator, and pump more biocompatible. However, bleeding and thrombotic complications are still ongoing problems especially for patients on ECMO for a long time.

ECMO can be used to support both the circulatory and/or the respiratory systems. The two modalities are venous–venous (VV) used to support the lungs and venous–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 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. Postoperative cardiac repair whether in the catheterization lab or cardiac operating room can cause the heart to have poor function. 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 up until the last decade. With improvements in catheter technology, VV ECMO has become the main modality to support newborns up to adult in respiratory failure. Indications for 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 support is only for respiratory support, a patient must have good cardiac function and may need inotropic support during ECMO. The goal with VV ECMO is to increase O_2 and decrease CO_2 to maintain a balanced acid/base. Respiratory support has allowed patients to remain on ECMO for much longer time than they ever had when using VA support. Due to the length of time of patients on ECMO, the management of the patients has needed to evolve. Physical and physiological therapies are now becoming very important especially since recovery can take weeks if not 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, reduced circuit pressures, and clotting. All of these were major complications prior to these improvements. 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 surface. By reducing inflammation, patients have less early clotting and less third spacing of volume into their tissues. These manufactures are still working to improve tubing coatings. The goal is to make the circuit appear invisible to the body's defiance mechanisms.

Other developments that have improved the ECMO circuitry are cannula strength, more efficient oxygenators, and

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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 causes stress to the blood. Turbulent flow within the ECMO circuit is a source for clot and hemolysis. The oxygenator used to be the biggest source of turbulent flow causing clotting, hemolysis, and increased pressures within the circuit. It wasn't 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 pediatric and adult ECMO, but in neonatal ECMO there are still many questions about its performance. Only with more time will we know if the centrifugal pump be a good option for neonates.

Finally the renal support devices are routinely used during ECMO. These devices are a porous membrane that cannot have biocompatible coating and are a source of clotting within the ECMO circuit. The membrane is 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 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 the same as they were when it was started in 1976.

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, thrombin inhibitor 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 (PTT), fibrinogen, anti-Xa, and platelet count. Monitoring methods and the target ranges vary among hospitals. ACT has been used for many years; however, the utility has been criticized in order to monitor coagulation and heparin effect in the setting of ECMO. It has no or little correlation with PTT or anti-Xa [2]. Therefore, ACT alone is not enough to monitor heparin effect [3, 4]; Table 27.1 shows an example of monitoring panel. There is always debate which test is the best to monitor the heparin effect. When ACT, PTT, and anti-Xa are performed at the same time and show discrepant results, it is the question which result is most reliable, in other words, how to change the heparin dose based on three different results. ACT and PTT are affected not only by heparin but also underlying coagulable state and lupus anticoagulant. Anti-Xa values represent overall anticoagulant effect of heparin, which are similar to anti-IIa values. It is interfered by a high bilirubin and plasma hemoglobin, but not affected by underlying coagulable state. Therefore, once underlying hypocoagulable state is appropriately corrected, heparin dose should be adjusted based on anti-Xa values. Table 27.2 shows advantages and disadvantages of anti-Xa, PTT, and ACT. Of note, some reputable hospitals have stopped using ACT to monitor anticoagulant effect in ECMO (personal communication). Table 27.3 shows other important parameters that affect hemostasis during ECMO. See below for individual explanation.

Table 27.1 Monitoring hemostasis parameters at Texas Children's Hospital

Test	Desired target/range	Comments
PT	<16.0–17.0 s	To assess underlying coagulable state
PTT hepzyme	<38.0 s	
Fibrinogen	>200 mg/dL	
PTT	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	80–100 %	To maximize heparin therapy

Table 27.2 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 bilirubin and free hemoglobin • Not available at all hospitals
PTT	• Global test for intrinsic coagulation factors • Readily available at most hospitals • By removing heparin using heparinase (Hepzyme™), baseline PTT 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 • Can be performed at bedside	• Neither precise nor accurate. • Affected by coagulation factors, heparin, lupus anticoagulant, and many others

Table 27.3 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, ristocetin cofactor activity, von Willebrand factor antigen, von Willebrand factor multimer)		Weekly

Etiology of Bleeding and Management

Heparin Overdose

Overall anticoagulant action of heparin is anti-Xa and anti-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 makes 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 by two- to fourfolds, which is released from endothelial cells [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 level 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 FV 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 cause 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; 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.

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 even if anti-Xa level is within the target range, there is 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, fibrinogen level may go up as an acute phase reactant, which is a risk factor for thrombosis. There are reports of decrease in factor XIII level 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. Therefore, potentially factor XIII concentrate, recombinant factor XIII, or cryoprecipitate may be given if bleeding persists without efficacy of antifibrinolytic and/or von Willebrand factor concentrate.

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 count varies 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. It was reported that tissue plasminogen activator and plasmin–anti-plasmin 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. It can happen within 24 h after ECMO initiation [15]. Lab finding shows decreased von Willebrand factor (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 study (Figs. 27.1 and 27.2). In the setting of ECMO, ristocetin cofactor activity may be normal or only mildly decreased [18]. Table 27.4 shows an example of lab 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. 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 has to be given repeatedly. It should be noted that cryoprecipitate 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 a risk of thrombosis if factor VIII is already increased.

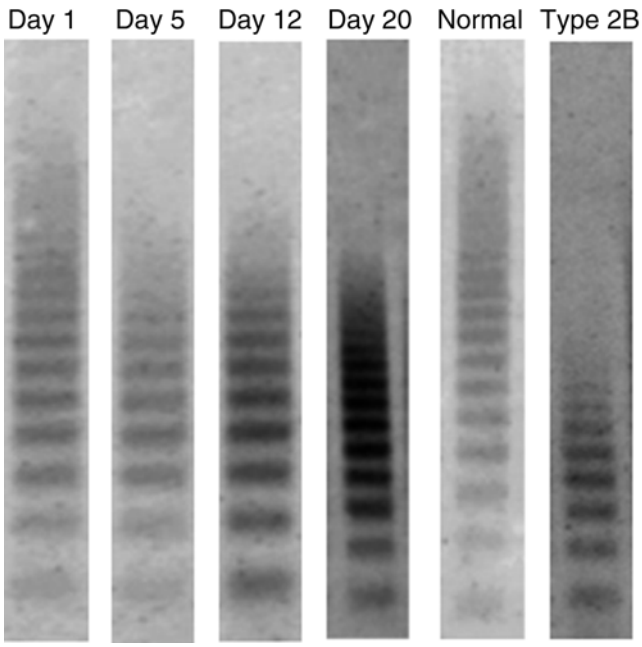

Fig. 27.1 Von Willebrand factor multimer pattern during ECMO

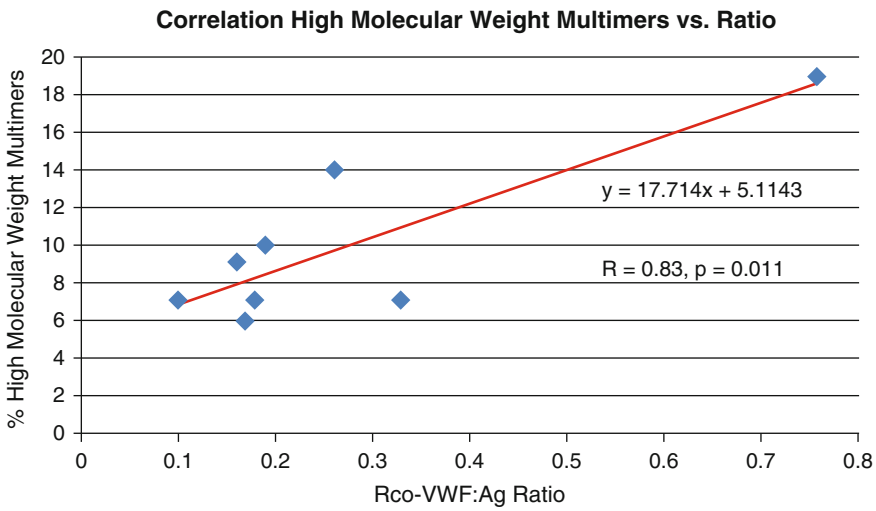

Fig. 27.2 VWF:RCo/VWF:Ag ratio with high molecular weight multimers

Table 27.4 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:RCo (%)	27	31	47	40
VWF:Ag (%)	81	302	278	225
VWF:RCo/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

Hemolysis

Intravascular hemolysis is another cause of derangement of hemostasis and renal damage. Plasma-free hemoglobin (≥50 mg/dL) increases von Willebrand factor-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 accounted for by 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 tried 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.

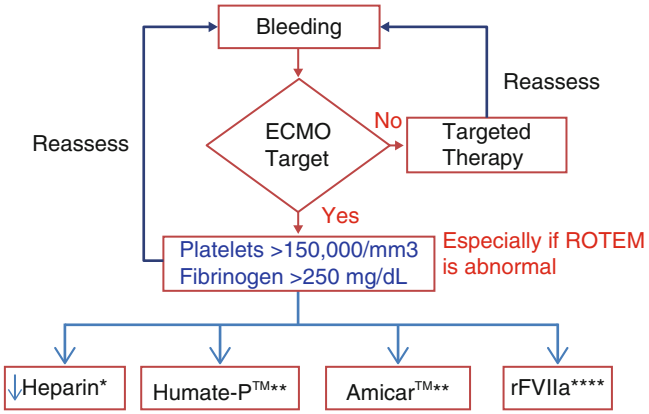

Fig. 27.3 Algorithm-based management (courtesy of Dr. Shiu-ki Hui, modified). *anti-Xa 0.1–0.2 units/mL or hold heparin up to 12 h, **15–25 units/kg, ***10–30 mg/kg/h until bleeding improved, ****Although there are reports of using recombinant activated factor VII, it induces a significant risk of thrombosis and clotting the circuit

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 deficiency, thrombocytopenia, platelet dysfunction, hyperfibrinolysis, and acquired von Willebrand disease. Regular monitoring and targeted management are needed to prevent major fatal bleeding such as in the brain or lung (Figs. 27.3 and 27.4).

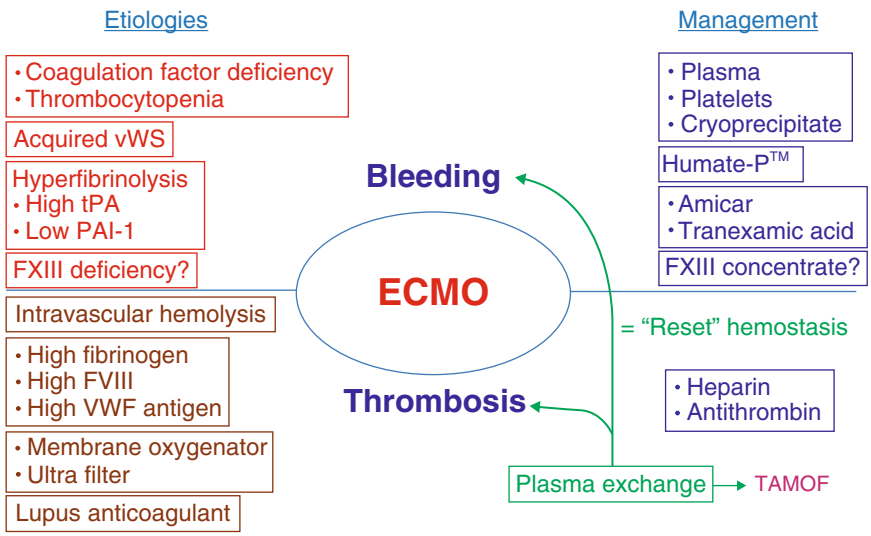

Fig. 27.4 Etiology and management of bleeding and thrombosis during ECMO. *VWS* von Willebrand syndrome, *tPA* tissue plasminogen activator, *PAI-1* plasminogen activator inhibitor 1, *FXIII* factor XIII, *FVIII* factor VIII, *VWF* von Willebrand factor, *TAMOF* thrombocytopenia-associated multiorgan failure

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Bleeding Related to Cardiac Surgery

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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 (CPB) 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 nonsurgical coagulopathic bleeding. Notably, alterations in coagulation experienced during CPB 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

1. Anticoagulants. The underlying conditions for which a patient may need cardiac surgery often require anticoagulation. All anticoagulant agents are risk factors for bleeding.
   (a) Warfarin

   Warfarin competitively inhibits the subunit 1 of the multiunit vitamin K epoxide reductase (VKOR) complex, depleting functional vitamin K reserves and reducing 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 reversibility, 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 MI [5–8].

   (b) Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)

   Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are antithrombin activators that 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 extracorporeal membrane oxygenation, CPB, and for bridging therapy in patients

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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 for venous thromboembolism (VTE) prophylaxis and bridging therapy in valve replacement patients [5–8].

(c) Bivalirudin

Bivalirudin acts as a specific and reversible direct thrombin inhibitor. Bivalirudin binds both circulating and clot-bound thrombins and inhibits coagulant effects by preventing thrombin-mediated cleavage of fibrinogen to fibrin monomers and activating of factors V, VIII, and XIII. 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)/heparin-induced thrombocytopenia thrombosis syndrome (HITTS), and thus may be encountered in urgent surgeries following cardiac catheterization [5–8].

(d) 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 and VTE prophylaxis. Though at present not commonly encountered, availability of the reversal agent idarucizumab could potentially increase perioperative use of dabigatran [5–9].

(e) Rivaroxaban and apixaban

Both drugs are factor Xa inhibitors and were designed not to require routine monitoring, with the aim of making them more desirable choices than warfarin. Rivaroxaban is FDA approved for VTE prophylaxis after hip and knee surgery, risk reduction for VTE occurrence in those with recurrent VTE, treatment of VTE, and for risk reduction of stroke in nonvalvular AF. Apixaban is FDA approved for VTE prophylaxis after hip and knee surgery, for treatment of VTE, and for risk reduction of stroke in nonvalvular AF. Increasing in use, there is at present no reversal agent for either of these drugs, though an antifactor Xa antidote is currently in development [5–8].

2. Antiplatelet agents. As with anticoagulant agents, cardiac patients are often candidates for antiplatelet therapy. All antiplatelet agents are risk factors for bleeding.

(a) Aspirin

Aspirin reduces platelet aggregation by nonselectively 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 reexploration [10–15]. In patients undergoing 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 transfusion, when compared to controls. The STS (Society of Thoracic Surgeons) 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.

(b) 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 reexploration for bleeding [5, 7].

(c) Ticagrelor

Ticagrelor 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.

(d) 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 CPB [16, 17], and thus may contribute to intraoperative and postoperative bleeding.

3. 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 [18–20].

4. 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 are found with advanced liver failure [18, 19, 21, 22]. Decreased baseline factors will increase the likelihood of intraoperative dilutional coagulopathy.

5. 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 [18, 23].

6. 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 [18].

7. 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 dysfunction, 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 [18, 24, 25].

8. 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 CPB, hepatic dysfunction, and trauma patients [18, 21].

9. 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 h or more than 4 units of RBCs within 1 h. 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 [18, 26, 27].

10. 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 phospholipid 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 fibrin to thrombin [18, 25]. If massive transfusion is required during cardiac surgery, ionized calcium levels should be frequently monitored, and calcium adequately replaced, usually with calcium chloride IV.

Management of Bleeding in Cardiac Surgery

1. Risk assessment

    Assessment of the risk of major perioperative bleeding should include 1) an understanding of the type of surgery, including the use of CPB and hypothermia, 2) a comprehensive history and physical, including noting of personal or family history of bleeding and personal history of renal dysfunction, hepatic dysfunction, active cancer, and chemotherapy, and 3) laboratory evaluation of residual effects of antithrombotic agents, as well as an understanding of any need for reinitiation of antithrombotic therapy within 24 h after the surgery. To some degree, all cardiac surgeries must be considered high risk for bleeding [28].

    More than 6 million patients in the United States receive long-term anticoagulation therapy for the prevention of thromboembolism due to atrial fibrillation and placement of a mechanical heart valve prosthesis, VTE, or MCS device. After the placement of a coronary artery stent, use of dual antiplatelet therapy (combination of treatment with aspirin and a thienopyridine) has dramatically increased [29]. Approximately 10 % of patients taking antithrombotic agents undergo surgical or other invasive procedure annually [30]. The goal in these patients is to minimize both thromboembolic events and major hemorrhage in the perioperative period [19]. Management involves balancing the risk of perioperative bleeding with continued treatment or use of bridging anticoagulation therapy against the thrombotic risk with the 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 high risk for thromboembolism when anticoagulation therapy is suspended and to minimize the risk of bleeding after high-risk surgery. In most cases, bridging anticoagulation therapy is used in patients receiving warfarin [5, 6, 8], although cangrelor, a reversible P2Y12 inhibitor, was investigated as a bridging antiplatelet agent in CABG patients receiving a thienopyridine [31]. 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 on complex cases requires a multidisciplinary discussion (Table 28.1).

2. Reversal of antithrombotic agents

    When urgent or emergent surgeries are required, there are various options 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 28.2).

3. 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 [18]. Uncontrolled hemorrhage and, by way of consequence, massive transfusion is a frequent complication of trauma and surgery [27]. After transfusion of more than 4 units of RBCs within 1 h, transfusion of blood products has been advocated to be kept as red blood cell, plasma, and platelet in a 1:1:1 ratio [32]. However, the study showed non-difference in mortality rate at 24 h or at 30 days despite the fact that the 1:1:1 ratio group achieved a better hemostasis. 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 [33]. Calcium supplementation to keep ionized calcium >1 mmol/L and avoidance or correction of hypothermia may be critical in patients receiving massive transfusion [27].

4. Hemostatic agents

    (a) 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

Table 28.1 Overview of antithrombotic agents [5–9, 26]

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
Unfractionated heparin	Antithrombin activation (inhibition of factors IIa, IXa, XIa, and XIIa)	IV, 2–6 h, depending on dose. Subcutaneous, 12–24 h, depending on dose
LMWH	Antithrombin activation (inhibition of factors IIa, IXa, XIa, and XIIa)	24 h
Fondaparinux	Antithrombin activation (factor Xa inhibitor)	2–6 days, depending on dose and creatinine clearance
Bivalirudin	Direct thrombin inhibitor	2–6 h, depending on dose and creatinine clearance
Dabigatran	Direct thrombin inhibitor	1–2 days with creatinine clearance rate of ≥ 50 ml/min; 3–5 days with creatinine clearance rate of <50 mL/min
Rivaroxaban	Direct factor Xa inhibitor	≥1 day with normal renal function; 2–4 days with creatinine clearance rate of <90 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
Desirudin	Direct thrombin inhibitor	2 h
Antiplatelet agents		
Aspirin	Irreversible cyclooxygenase inhibitor	7–10 days
Dipyridamole	Phosphodiesterase inhibitor	7–10 days
Cilostazol	Phosphodiesterase inhibitor	7–10 days
Thienopyridine agents (clopidogrel, ticlopidine, prasugrel, ticagrelor)	ADP receptor antagonist	5 days (clopidogrel and ticagrelor), 7 days (prasugrel), or 10–14 days (ticlopidine)

Table 28.2 Reversal of antithrombotic agents [5–9, 45]

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 and time for correction
Unfractionated heparin	PTT, thrombin time, TEG™, or ROTEM™	Protamine sulfate	If time permits, hold intervention for 4 h to avoid the need for protamine
LMWH	Anti-Xa activity	Protamine sulfate	Protamine is only partially effective. LMWH clearance should be gauged with GFR in mind
Fondaparinux	None, consider fondaparinux-specific anti-Xa assays	None, FVIIa in patients with major bleeding	Elimination is impaired in stage IV/V chronic kidney disease
Bivalirudin	PTT, thrombin time for residual effect	None, FVIIa in patients with major bleeding	Clearance is impaired with renal dysfunction
Dabigatran	PTT, thrombin time for residual effect	Idarucizumab (Praxbind)	Consider holding medication for longer period before surgery
Rivaroxaban	Prothrombin time or anti-Xa activity	None, but consider 4-factor PCC	Consider holding medication for longer period before surgery
Apixaban	Anti-Xa activity	None, but may consider 4-factor PCC	–
Desirudin	PTT, thrombin time, ecarin clotting time	None	–
Antiplatelet agents			
Aspirin	LTA-arachidonic acid, PFA-100™, VerifyNow™	Platelet transfusion, desmopressin	Laboratory assays need clinical validation
Thienopyridine agents (clopidogrel, ticlopidine, prasugrel, ticagrelor)	LTA-ADP, VerifyNow™	Platelet transfusion, consider FVIIa in patients with major bleeding	Precise FDA indications vary according to specific drug

LTA light transmittance aggregation

half-life of around 2 h and are excreted in urine. The most commonly used regimen for TXA is 10 mg/kg bolus followed by 1 mg/kg/h as a continuous infusion, whereas for Amicar™ a 5 g bolus is followed by 1 g/h 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 [19, 26, 34].

Aprotinin is a bovine-derived serine protease inhibitor which has powerful antiplasmin and antikallikrein effects. In high doses, it reduces bleeding in cardiac surgery. Despite a positive effect on red cell 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 [26].

(b) Desmopressin

Desmopressin (DDAVP) is a vasopressin analogue which releases endogenous von Willebrand factor 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 h. It 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 [18, 26, 35].

(c) 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 CPB [6]. rFVIIa may lead to thrombotic complications, especially in patients at high risk [35–38]. 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 [39]. However, patients receiving lower doses (10–20 μg/kg) may have a lower incidence of thromboembolic events [40].

(d) Prothrombin complex concentrates (PCCs)

4-Factor PCCs contain a high concentration of lyophilized clotting factors II, VII, IX, and X and proteins C and S [41]. 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, 42]. Compared with FFP, 4-factor PCCs 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 the concern of right ventricular dysfunction and the risk of lung injury [42, 43]. PCC use may be associated with increased risk for thromboembolic events, usually in patients with other prothrombotic risk factors [42]. 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) [44].

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 CPB.
- Medications that prevent coagulation such as heparin (unfractionated heparin, low-molecular-weight heparin), vitamin K antagonists (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), adenosine diphosphate (ADP) 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 a history of 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, hypokalemia, and hypothermia, which can result in intraoperative coagulopathy. Additionally, hypothermia and the bypass circuit itself can result in platelet dysfunc-

tion. 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 include 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 PCC for reversal of the effects of warfarin. Reversal agents for other anticoagulants may soon be available.
- 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 TXA 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 PCC and/or recombinant factor VIIa can be considered. 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

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Hemostasis in Cirrhosis and Liver Failure

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 protein 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 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 [5–8]. 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 [9]. 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 [10, 11]. 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 porto-pulmonary hypertension [12–14]. Notably, platelet dysfunction and acquired dysfibrinogenemia may also occur in cirrhosis [1, 15, 16]. 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 is common in patients with cirrhosis or during and after liver transplantation [12]. Therefore, infection and sepsis can quickly result in alterations in hemostasis in cirrhotic patients by inducing disseminated intravascular coagulation (DIC) [17, 18]. Similar, but more pronounced changes of pro- and anticoagulant factors are observed in acute liver injury and failure [19]. However, data regarding fibrinolysis in acute liver dysfunction are inconclusive [19, 20]. Recent studies showed

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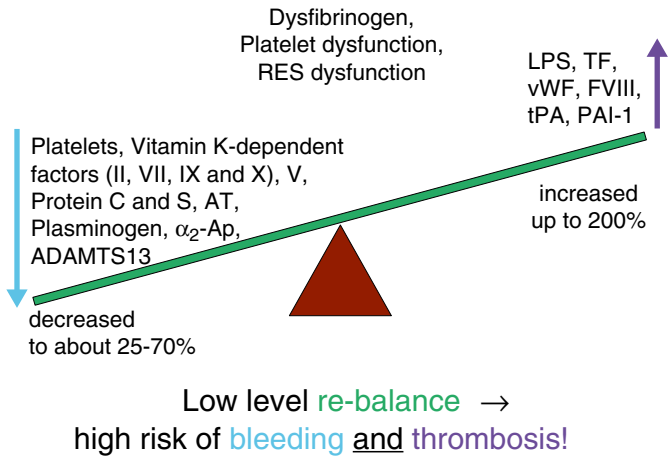

Fig. 29.1 Hemostasis in cirrhosis. In cirrhosis hemostasis is rebalanced at a low level associated with a high risk of bleeding and thrombosis. Courtesy of Klaus Görlinger, Tem International

evidence for a shutdown of fibrinolysis rather than hyperfibrinolysis in acute liver failure, similar to the early phase of sepsis [20–22]. 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. 29.1) [1–4, 23]. 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, 24]. Therefore, prophylactic correction of laboratory results by transfusion of blood products may have a deleterious effect on cirrhotic patients [1, 2, 25].

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, VHT and point-of-care (POC) platelet function testing is essential.

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) [26]. Thromboplastins of different origin are added to recalcified, citrated plasma and the time until coagulation starts is measured. This test only reflects the activity of vitamin K-dependent procoagulant factors in plasma 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, 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 [27–30]. This has been demonstrated in patients with cirrhosis and patients undergoing liver transplant as well [1, 25, 31–39]. In particular, no correlation could be observed between PT and the bleeding time observed directly on the liver surface during laparoscopic liver biopsy [40, 41]. However, the validity of the INR as a prognostic parameter in liver dysfunction is not affected by this finding [31, 37].

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, 20, 41]. 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 [19, 42–44]. Furthermore, the results of TG assays are modified by the presence or absence of platelets [45–47]. 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 [48]. 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 a standard laboratory tests.

Viscoelastic Hemostatic Testing (Thromboelastometry/Thromboelastography)

VHT such as thromboelastometry (ROTEM™, Tem International GmbH, Munich, Germany) and thrombelastography (TEG™, Haemonetics, Niles, IL) are performed on whole blood, reflecting the interaction between blood cells (platelets, leukocytes, and erythrocytes) and plasmatic coagulation factors (pro- and anticoagulants). In addition to the dynamics of clot formation (CT, CFT, alpha angle and r-time, k-time, alpha angle), they provide essential information about clot firmness (A5, A10, MCF, and MA) and clot stability (ML, CLI30, CLI60) [38, 49, 50]. 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 [51, 52]. 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 [53–55]. 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 [56–59]. 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 [56, 57, 60]. 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. 29.2, and Chap. 5, Figs. 5.4 and 5.5c) [49, 52, 55, 56, 61–68]. 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

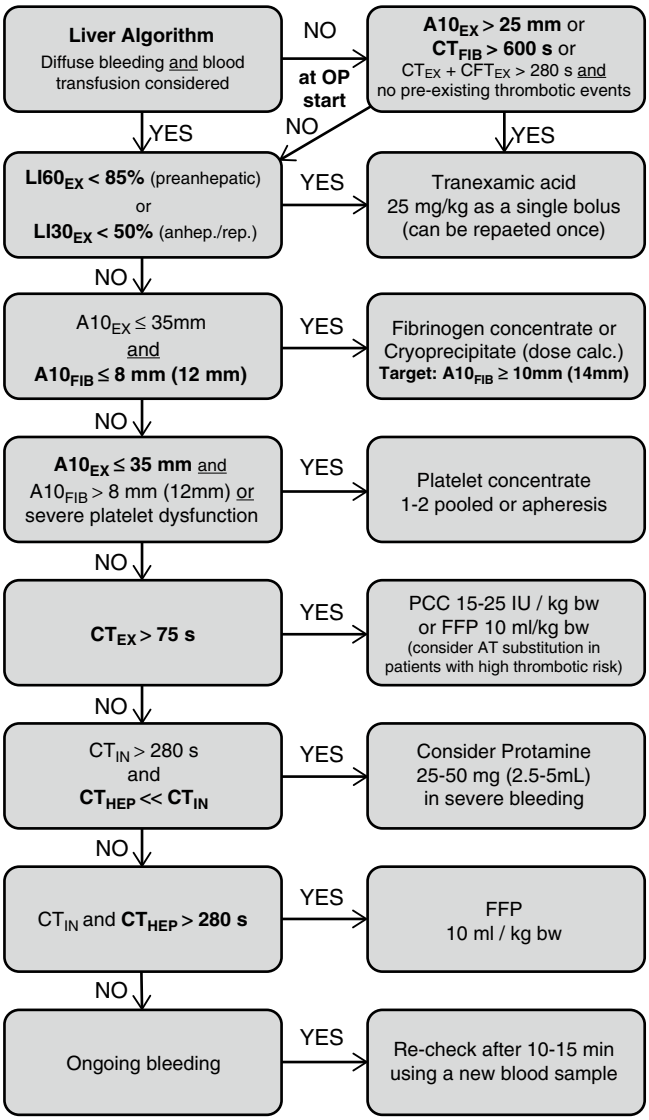

Fig. 29.2 Evidence-based ROTEM™ A10 bleeding management algorithm in liver transplantation. $A10_{EX}$ amplitude of clot firmness 10 min after CT in EXTEM; $A10_{FIB}$ amplitude of clot firmness 10 min after CT in FIBTEM; *bw* body weight in kg; CT_{EX} coagulation time in EXTEM; CT_{FIB} coagulation 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; *dose calc.* dose calculation; *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; *PCC* 4-factor prothrombin complex concentrate. Courtesy of Klaus Görlinger, Tem International

[69]. 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 [12, 13, 70, 71]. Notably, viscoelastic tests showed normo- [31, 72–75] or even hypercoagulability [19, 76–78] in patients after liver resection or with 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 Chap. 5, Fig. 5.5e) [46]. Furthermore, tissue factor expression on monocytes, detected by thromboelastometry in septic patients as well as in patients undergoing liver transplantation or extracorporeal organ support, may play an important role in hypercoagulability and thrombosis in liver cirrhotic patients (see Chap. 5, Fig. 5.5e) [12, 21, 79–81].

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 [49, 50, 82–89]. For more details on thromboelastometry, see Chap. 5 [49].

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 [90–93]. Here impedance aggregometry has been shown to be the most reliable and reproducible POC test, providing a high predictive value for bleeding and thrombosis [94–97]. 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 [6, 12–14, 71]. Furthermore, platelet adhesion and aggregation seems to be increased in cirrhosis due to a disbalance of high vWF and low ADAMTS13 levels [5–8]. In liver transplant patients at risk of hepatic artery thrombosis, impedance aggregometry can be used to assess the effect of antiplatelet drugs [98–105]. Notably, impedance aggregometry results may be influenced by platelet counts $<150 \times 10^3/mm^3$ [106]. This may limit the value of platelet function testing in patients with cirrhosis and severe thrombocytopenia $<50 \times 10^3/mm^3$. However, sparse data are available in this setting. For more details on impedance aggregometry, see Chap. 5 [49].

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 Chap. 5 [49].

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 overload (TACO). Therefore, a restrictive transfusion strategy has been shown to be superior compared to a liberal transfusion concept in this setting [25, 107–109]. 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 [108]. 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 [110, 111]. Furthermore, therapy with prothrombin complex concentrate (PCC) was superior to plasma transfusion in gastrointestinal hemorrhage due to warfarin therapy [109]. 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 [25, 38].

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, 19]. Nevertheless, plasma and platelet transfusions are still used for pre-procedural prophylaxis in cirrhosis patients [28, 29, 112–114], and in the UK, cirrhosis is one of the factors associated with a greater use of prophylactic plasma transfusion [115]. However, a high proportion of current plasma transfusion is of unproven clinical benefit and has to be considered as inappropriate [28, 29, 114–122]. 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 [25, 33–36, 76].

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, 50, 82–89]. 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, 63–66, 70, 83, 85, 123–129]. In these studies, the transfusion requirements for red blood cells, 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 % [127]. 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 [127]. 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™) [128]. 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 [130]. 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. Actually, at least one prospective observational study (Massicotte L. Montreal, Canada, NCT02356068, 2015) and three randomized controlled trials (RCTs) are running to assess the predictivity, efficacy, and safety of a ROTEM™-guided bleeding management algorithm in patients undergoing liver transplantation (Yamauchi LHI. Sao Paulo, Brazil, NCT02239991, 2014 and Bonnet A. Lyon, France, NCT02311985, 2015) or in cirrhotic patients undergoing central venous catheterization (Rocha L. Sao Paulo, Brazil, NCT02352181, 2015).

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, 62–64]. 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 [33, 34]. 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 [63–66]. Our evidence-based ROTEM™ A10 liver transplant bleeding management algorithm is displayed in Fig. 29.2 and discussed in the following paragraphs. Outside of the USA, the algorithm is most often guided already by the amplitude of clot firmness 5 min after CT (A5 in EXTEM and FIBTEM) allowing for an earlier decision-making.

Since the amount of blood transfusion is 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 [29, 39, 69, 128, 131–145].

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) [146]
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 [147]. 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 the acidosis, hyperkalemia, and hypocalcemia after reperfusion, hypothermia can aggravate coagulopathy and can result in severe hypotension, bradycardia, and even cardiac arrest [148, 149]. Acidosis can also enhance fibrinolysis [150]. In particular during the anhepatic phase, rapid transfusion of high amounts of plasma can result in citrate intoxication [151–153]. High amounts of calcium gluconate or calcium chloride may be needed to antagonize this effect [148, 154]. 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 drug such as aprotinin, epsilon-aminocaproic acid (EACA), or tranexamic acid (TXA). At that time, transfusion requirement in patients undergoing liver transplantation was very high, and the administration of antifibrinolytic drugs reduced these transfusion requirements significantly [155–162]. 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 [163–168]. Furthermore, implementation of POC VHT allowed for a timely and specific detection of hyperfibrinolysis in this setting [61, 62, 85, 155, 166–172]. 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 [63, 173].

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) [58, 62, 167, 171–174]. 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) [150, 175–178]. Accordingly, this complex interaction can only be assessed by VHA but not by coagulation tests using plasma.

Notably, patients with acute liver failure present with a fibrinolytic shutdown rather than hyperfibrinolysis as shown for patients with sepsis, too [20, 21]. Therefore, prophylactic administration of antifibrinolytic drug might rather be harmful than beneficial in this patient population.

According to our algorithm, TXA (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™ $A10_{EX}$ ≤ 25 mm [170, 179]. Furthermore, a flat-line in FIBTEM (CT_{FIB} > 600 s) and prolonged coagulation initiation and prolongation phase (CT_{EX} + CFT_{EX} > 280 s) seems to be associated with a very high incidence of hyperfibrinolysis during liver transplantation (Fig. 29.2) [180]. 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 [58, 174, 181]. However, the prophylactic administration of antifibrinolytics should strictly be avoided in patients with preexisting thrombotic events [164–168].

Notably, tPA activity is increasing during the anhepatic phase, whereas PAI-1 activity is decreasing. Accordingly, the fibrinolytic activity achieves a peak level after reperfusion of the liver graft [169, 182]. 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 in severe trauma) [62, 167, 171, 172, 183, 184]. 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. 29.2 and Chap. 5, Fig. 5.5b). In the absence of severe bleeding, ROTEM™ is rechecked after detecting 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. This is crucial in the management of bleeding in liver transplant and other settings. EXTEM A5 can reliably identify a platelet count below $50 \times 10^3/mm^3$ and $30 \times 10^3/mm^3$ 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 Chap. 5, Table 5.4) [51, 55]. FIBTEM A5 and A10 can identify a plasma fibrinogen concentration below 100 mg/dL with a cutoff value 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 [52]. 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; $p=0.04$) [55]. 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, colloids effects, and factor XIII deficiency, as well as about platelet dysfunction affecting the thrombin receptor (PAR = protease activatable receptor) pathway. Accordingly, EXTEM and FIBTEM A5/A10 have been shown to better predict bleeding than platelet count and plasma fibrinogen concentration [27, 185] 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 [62, 146, 186]. 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 [186]. This is in line with our experience and data published by other authors in this setting [3, 62, 124, 125, 128, 187–189]. 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 are provided in Chap. 5 and Fig. 5.6a–f) [49]. Using the before mentioned ROTEM™, cutoff values in interventional trials resulted in a significant reduction in transfusion requirements in patients undergoing liver transplantation [63–66, 126–128]. Accordingly, these cutoff values for EXTEM and FIBTEM A5/A10 are used in our algorithm (Fig. 29.2 and Chap. 5, Fig. 5.5c), 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 ≤ 7/8 mm. The dose of fibrinogen concentrate (Haemocomplettan™ P, CSL Behring GmbH, Marburg, Germany; marketed in the US under the tradename RiaSTAP™) or cryoprecipitate can be calculated based on the targeted increase in FIBTEM A10 or A5 (Table 29.1) [65, 190]. Instead of the table presented in Table 29.1, the following formula can be used for fibrinogen dose calculation [191, 192]:

$$\text{Fibrinogen dose(g)} = \text{targeted increase in A10}_{\text{FIB}}\text{(mm)} \times \text{body weight(kg)} / 160$$

Table 29.1 FIBTEM-guided fibrinogen substitution

Targeted increase in FIBTEM A10 (A5) (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)

Here, fibrinogen dose calculation is based on the targeted increase in FIBTEM A10 (A5) in mm [65, 190]. In case of severe bleeding, the achieved increase in FIBTEM A10 (A5) may be lower than the calculated increase. Courtesy of Klaus Görlinger, Tem International

Here, the correction factor (140–160 mm kg g^{-1}) is depended on the actual plasma volume, and it has to be considered that the FIBTEM A10/A5 increase reached finally can be lower than the calculated increase in severe bleeding.

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 [190]. 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 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 [8]. 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 > 7/8 mm (Fig. 29.2 and Chap. 5, Fig. 5.5d). Here, one pooled or apheresis platelet concentrate can increase EXTEM A5/A10 by at maximum 8–10 mm [47, 193, 194]. Therefore, transfusion of one platelet concentrate may be sufficient to reach an EXTEM A10 target of >35 mm if EXTEM A10 was between 25 and 35 mm before platelet transfusion. In case of a pre-transfusional EXTEM A10 between 15 and 25 mm, usually two platelet concentrates are necessary to reach this target, whereas a pre-transfusional EXTEM A10 < 15 mm usually requires the combined administration of platelets (two pools or apheresis) 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 $50 \times 10^3/mm^3$ [70]. This concept has a high potential to reduce platelet transfusion-related complications in patients undergoing liver transplantation [25, 66, 69, 195].

Furthermore, a shift to higher fibrinogen levels in case of bleeding after reperfusion by using a higher FIBTEM A5/A10 cutoff (≤11/12 mm) and targeted value (≥13/14 mm) might be reasonable to avoid potential harmful platelet transfusion and is considered in our algorithm (Fig. 29.2) 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 [69, 195]. Several studies could prove the concept that higher fibrinogen levels can be compensated for low platelet counts [191, 192, 196]. 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]. In bleeding patients undergoing liver transplantation, an EXTEM CT > 75 s seems to be the best cutoff value to trigger a therapeutic intervention [146]. 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 recombinant activated factor VII (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 15–25 IU/kg body weight in this constellation without an increase in thrombotic/thromboembolic events (Fig. 29.2 and Chap. 5, Fig. 5.5j) [25, 62–66, 198]. 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 [90, 91, 199]. 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 in particular [66, 200–204]. 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 [25, 33, 34, 66, 109, 205, 206]. 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 [25, 62–66, 198]. 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 4.3.7). However, antithrombin administration may be considered in

patients presenting a 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 but the evidence for that is low. Notably, 4F-PCC (Kcentra™, CSL Behring GmbH) is actually FDA approved for warfarin reversal, solely, whereas Octaplex™ is licensed in Canada for the same broad spectrum of indications as in Europe [207–210]. Nevertheless, broader use of 4F-PCC is under debate in the USA, too [92, 190, 211, 212].

Whereas PT/INR were designed and work 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 [66, 198, 213–215]. 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, 25, 28, 29, 33, 34]. Nevertheless, this concept is just under investigation in a RCT in patients undergoing liver transplantation [216].

Even high amounts of plasma (10–20 mL/kg body weight) are quite ineffective to correct coagulopathy in cirrhosis [114, 217]. 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 [98, 107, 110, 111, 134, 136, 140–144, 218–220]. 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 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 have 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 [220–223]. Keeping the increased risk of thrombosis in mind, the off-label use of rVIIa (45–90 µg/kg body weight) in patients with severe bleeding that is unresponsive to other hemostatic interventions (cryoprecipitate, platelet, and plasma transfusion) might be considered—in particular if 4F-PCCs are not available [84, 92, 224, 225]. However, the off-label use of rFVIIa was not any more necessary after implementation of our ROTEM™-guided liver transplant bleeding management algorithm [63–66].

Management of Endogenous (Auto-) Heparinization (Protamine)

During liver graft reperfusion, liberation of heparinoids (glycosaminoglycans) from the glycocalyx of the damaged liver endothelium often occurs [17, 226]. This is associated with a prolongation of the aPTT, the kaolin-TEG r-time, and the INTEM CT. Here, a heparin-like effect can be confirmed by a shortening of the r-time in the heparinase-TEG or of the CT in HEPTEM, respectively (Fig. 29.2 and Chap. 5, Fig. 5.5f–h) [62, 85, 169, 180, 226–230]. In severe bleeding, this heparin-like effect can be antagonized by small amounts of protamine (25–50 mg in an adult) (Fig. 29.2) [169, 231, 232]. 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 (see Chap. 5, Fig. 5.5i) [233–235]. Therefore, the administration of protamine should be considered carefully and an overdose should strictly be avoided. Similar endogenous heparin-like effects have been recently reported in severe trauma [235, 236].

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, 237, 238]. In contrast, global coagulation assays such as thromboelastometry and ETP show more hypercoagulability with an inherent risk of thrombosis [19]. 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 [239–242]. 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 [5–9, 238]. 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 [243]. Accordingly, venous thromboembolism (VTE) prophylaxis is required during the hospitalization of patients with liver dysfunction [244]. Nevertheless, 75 % of these patients do not receive any VTE prophylaxis [245, 246].

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 [247]. 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. A recent 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 [248]. Prophylactic use of low-molecular-weight heparins (LMWH) in patients with cirrhosis appears to be safe [249]. 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 [249].

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 [250, 251]. Since argatroban is mainly metabolized in the liver, it should be used with caution in patients with liver dysfunction and/or hyperbilirubinemia [252, 253]. 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 [254].

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Percutaneous Image-Guided Interventions Including Solid Organ Biopsies

30

Shiraz Rahim, Indravadan J. Patel, and Jon C. Davidson

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 (See Table 30.1)

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.

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

Partial thromboplastin time (PTT) measures the intrinsic pathway and can be elevated by liver disease, lupus anticoagulant, and medications such as heparin and argatroban (thrombin inhibitor). Although certain causes of an elevated PTT can increase bleeding risk, such as the use of heparin, a single elevated lab value often reverts to a normal value on repeated testing when other etiologies, such as lupus anticoagulant, cause the elevation. A single elevated value therefore is not 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 levels 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.

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Table 30.1 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

Table 30.2 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 for full details and more management recommendations

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 numbers 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 (See Table 30.2)

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 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 procedure 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. 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 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. This form of heparin does not affect PTT, and monitoring levels is more expensive and difficult. Both types have a half-life of only a few hours (unfractionated heparin 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 heparin. 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 heparin 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 similarly 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, apixaban, and lepirudin (withdrawn from US market) block thrombin directly, allowing for more predictable anticoagulation compared to indirect inhibition from medications like heparin. There is no effective antidote to these anticoagulants in patients presenting with bleeding. 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].

Newer Anticoagulants

Dabigatran (Pradaxa™) is a direct thrombin inhibitor similar to the ones described above [24]. Rivaroxaban (Xarelto™) is a direct factor Xa inhibitor [25]. Both are approved for deep venous 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]. There are no specific antidotes for either medication; however, increasingly 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 once [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].

A special note should be made about recombinant factor VIIa, 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 aggregation and activation. 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 Chap. X).

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 numbers 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 counts 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 counts 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 interventionist 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 (See Table 30.3)

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.

Angiography (See Fig. 30.1)

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 were 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.

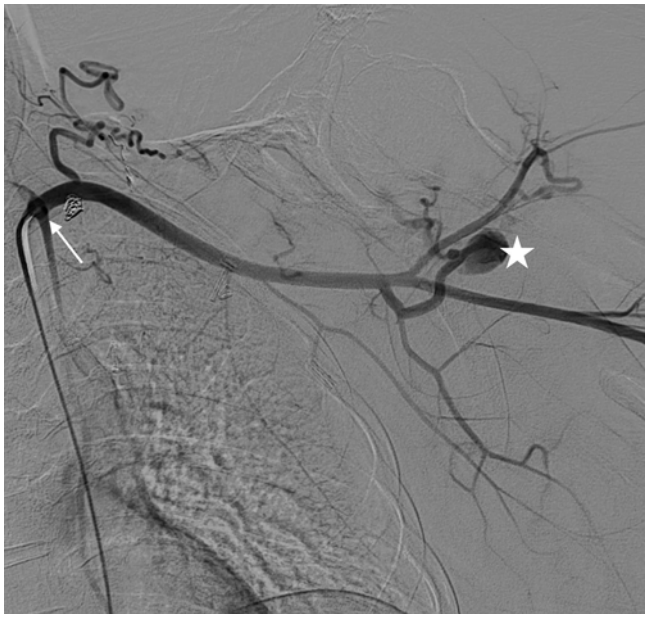

Fig. 30.1 Angiography of the left subclavian artery. A catheter was threaded into the femoral artery, is passed up through the abdominal and thoracic aorta, and is seen ending in the left subclavian artery (*white arrow*). After contrast opacification of the artery, a pseudoaneurysm is visualized in the artery (*white star*)

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. 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

Table 30.3 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	

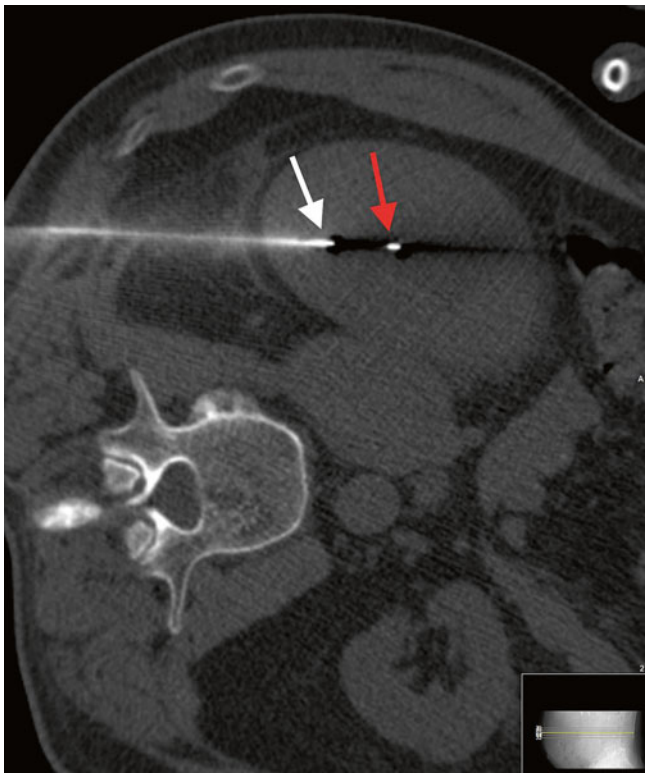

Fig. 30.2 CT-guided renal biopsy. The image demonstrates a biopsy needle being placed percutaneously through the right posterior of the patient and into the inferior pole of the right kidney. The red arrow denotes the end of the biopsy needle. Note the dark spot between the part of the needle denoted by the red arrow and the white arrow. This indicates the section of tissue that will be biopsied

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 (See Fig. 30.2)

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 seven 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) is an alternative method of measuring bleeding time and has started to be studied as a method of predicting bleeding complications. A PFA measures closure time or total time of undergoing a normal platelet and von Willebrand factor interaction in vitro. PFA can therefore identify clinically relevant platelet-binding disorders and deficiencies of platelet membrane receptors. Closure times are measured using a PFA 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 or 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 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 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

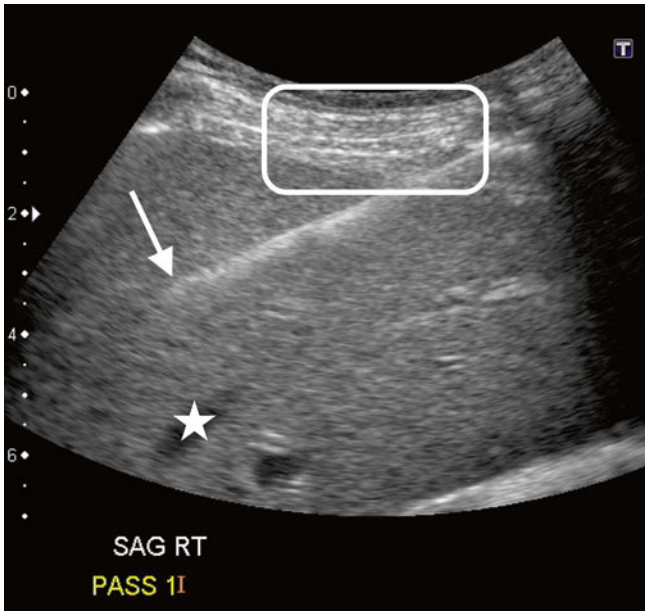

Fig. 30.3 Ultrasound-guided liver biopsy. The image shows a bright echogenic needle being guided under a curved array ultrasound transducer for a random liver biopsy. The needle tip is denoted by the white arrow. This was a random liver biopsy. Ultrasound allows the radiologist to visualize the needle 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)

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 (See Fig. 30.3)

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 counts [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].

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, micro hemorrhage is a very common complication, occurring in 4 to 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 (See Fig. 30.4)

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 greater 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].

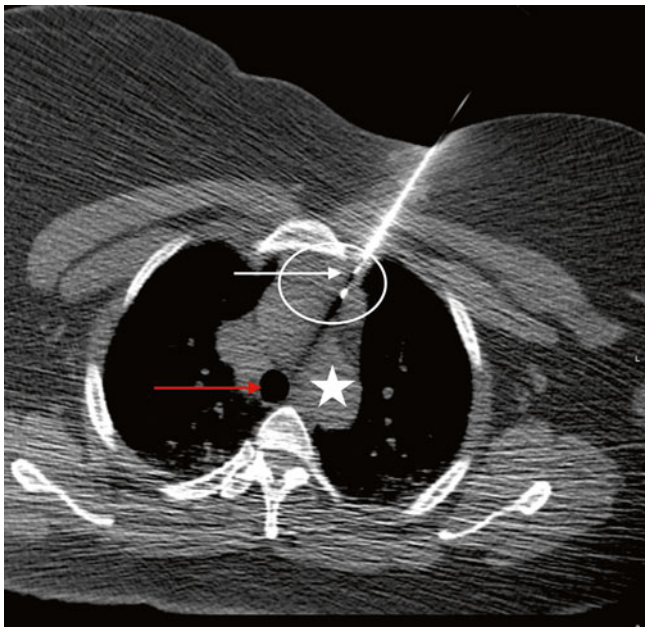

Fig. 30.4 CT-guided mediastinal mass biopsy. This image shows needle (*white arrow*) placement within an anterior mediastinal mass (*white circle*). Note the proximity of the mass and the needle to the aortic arch (*white star*) and the trachea (*red arrow*). Active imaging guidance during such a procedure 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]. 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 counts above 25,000/mm^3 and INR up to 2.0 [84].

For non-tunneled catheters, some studies showed that platelet counts 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, six 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)

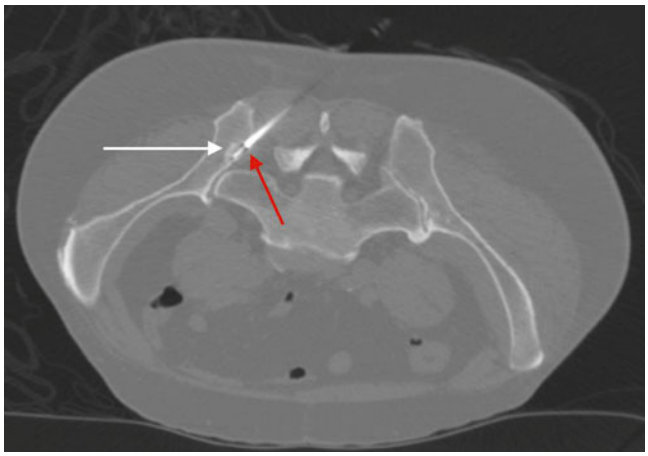

Fig. 30.5 CT-guided bone biopsy. This figure shows biopsy of the right ischial tuberosity with an 18 gauge biopsy needle. The white arrow denotes a sclerotic lesion within the bone. The red arrow points to the needle. As in Fig. 30.2, there is a gap between the end of the needle and the area of the needle denoted by the red arrow. This is the portion of the needle that procures the sample tissue

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 (See Fig. 30.5)

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. 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 extrapolate. 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 is 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 three 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.

Conclusions

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

31

Julia A.M. Anderson and Andrew K. 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].

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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 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 (FVIII) concentrate rich in vWF is necessary. Currently this is derived from human plasma as no recombinant vWF concentrate is yet available [2].

Hemophilia A and B are X-linked recessive conditions with identical clinical manifestations [3]. Depending on the plasma levels of FVIII or factor IX (FIX) activity, hemophilia is defined as "mild," "moderate," or "severe" (see Table 31.1). 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

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Table 31.1 The severity of hemophilia, clinical manifestations, and recommendations for dental procedures

Degree of hemophilia	Factor percentage (normal range 50–100 %)	Clinical features	Dental treatment
Severe	<1 %	Frequent spontaneous bleeds	Enhanced preventive advice and treatment with general dental practitioner or community dentist Should have all dental treatments except for prosthetics carried out in a hospital setting with specialist dental unit, unless prior arrangements made with the hemophilia center and general dental practice or community dental practice
Moderate	2–5 %	May have spontaneous bleeds	Enhanced preventive advice and treatment with general dental practitioner or community dentist Manage as for severe hemophilia
Mild	6–40 %	Bleed after trauma or surgery	Enhanced preventive advice and treatment with general dental practitioner or community dentist Do not require all treatments carried out at the hospital; should be seen 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

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bleeding [2]. Although it is important to measure clotting factor levels before dental procedures in all carriers and potential carriers of hemophilia, the factor levels have weak correlation with clinical bleeding in hemophilia carriers [5, 6].

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].

The development of antibodies or "inhibitors" to factor therapies is a serious complication, and patients then require concentrates known as "by-passing therapies" to enable hemostasis to be achieved [7]. 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 FVIII or FIX therapy should be managed by good prevention and minimally invasive techniques since the administration of local anesthesia is almost never required.

Factor XI (FXI) 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 FXI levels by administration of fresh frozen plasma or FXI concentrate and by the use of antifibrinolytic agents [8]. FXI 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. Factor concentrate replacement therapy should be administered as close to the time of the dental procedure as possible. Patients with severe hemophilia, or with inhibitors, may require postprocedural 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.

Table 31.2 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	

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Wisdom Teeth

The removal of wisdom teeth is a more complex problem since although many teeth are relatively easy to remove, a number posess 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 [9, 10]. 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, 9] (see Table 31.2).

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 [9]. 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 [11, 12].

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 non-steroidal 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 [13].

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 further 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 [14]. In 2009, the UKHCDO 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 (Desamino-8-D-arginine Vasopressin (DDAVP))

Desmopressin stimulates release of endogenous FVIII 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 [15]. 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 [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 [16, 17]. There is a small 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 [18, 19].

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 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, 9, 20]. Resorbable and non-resorbable sutures are acceptable.

Dental Extractions in Patients With Inhibitors to FVIII and FIX

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. By-passing 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].

Dental Extractions in Patients With Acquired Bleeding Disorders

Anticoagulants

Warfarin and the oral VKAs (e.g., acenocoumarol (Sintrom™)) have been the mainstay of oral anticoagulation for several decades, 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 are currently the optimal antithrombotic treatment in patients with active malignancy undergoing treatment for venous thromboembolism and are the anticoagulant of choice in pregnant women.

An array of new oral anticoagulants, known as 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 [21].

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 tranexamic acid mouthwash in primary care has been recommended in some guidelines [22] but is felt by others to be expensive, difficult to obtain, and of no more benefit than other local hemostatic measures [23].

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 [24]. 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 [22, 23]. 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 deferred 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 fail-

ure, hypertension, age over 75 years, diabetes mellitus, prior stroke, or transient ischemic attack and for the treatment and prevention of venous thromboembolism. Currently there are no licensed reversal agents but Specific antidotes are in development. There is emerging evidence on the efficacy of prothrombin complex concentrates and activated prothrombin concentrates on reducing the effect of DOACs in the setting of emergency bleeding, but their role remains unclear.

Currently there are no clinical trials of DOACs in the dental care setting to guide the management around 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 [25]. The study protocol involved cessation of the study drug with patients assigned to dabigatran taking the last dose of drug 49 (35–85) hours before the procedure compared with 114 (87–144) hours in patients receiving warfarin. The analysis showed no difference in the rates of periprocedural bleeding between the dabigatran and warfarin patients [25] .

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 [26]. There are also general surveillance reports and communications that advise interruption of DOACs for patients with minor bleeding risk is not necessary [27].

Based on this limited evidence, two differing approaches may be suggested and there is controversy about best practice [28]. One approach recommends the avoidance of invasive treatment until 24 h following the last dose of rivaroxaban and 12 h following the last dose of dabigatran or apixaban, assuming normal renal function. This approach takes into account the low thromboembolic risk associated with discontinuation of the DOAC for a short period of time; that the bleeding risk can sometimes be difficult to gauge, and there is a lack of reversal agents at the present time, especially relevant in patients who live 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 [28]. It is important to note that oral absorption takes around 4 h for time to peak effect.

An alternative approach for patients with minor bleeding risk defined as less than a total of three simple dental extractions, and surgery lasting less than 45 min, continues the DOAC without interruption, as long as the patient 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. For patients requiring multiple extractions (more than three) and surgery lasting more than 45 min, or for patients requiring significant oral maxillofacial surgical procedures, the DOAC should 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 [29].

Consensus guidelines are being published [30], but the optimal strategy is currently uncertain and differs from one institution to the next. Further research 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 70,000/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 and this will 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. It is probably easier to divide the patients into three groups depending on the results of the platelet count and the prothrombin time ratio (Table 31.3).

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.

Patients with a severe form of the disease have a significant risk of bleeding following a dental extraction. The

Table 31.3 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/mm3 PT ratio <1.7
Severe	Platelet count less than 100,000/mm3 PT ratio >1.7

[a]Prothrombin time (PT)

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

32

Rebecca Barton and Paul Monagle

Introduction

Thrombocytopenia, defined as a confirmed platelet count of less than 150,000/mm^3, 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-birthweight or premature infants [1–3]. Thrombocytopenia is further classified as severe if the platelet count is less than 50,000/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 32.1).

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) [2].

The majority of neonatal thrombocytopenia is mild to moderate, does not cause any bleeding and resolves without treatment or intervention.

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Fetal/Neonatal Alloimmune Thrombocytopenia

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].

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) cross the placenta and act via the human platelet alloantigens (HPAs) 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

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Table 32.1 Causes of neonatal thrombocytopenia

Acquired	Congenital
Immune mediated - Neonatal alloimmune - Maternal autoimmune 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 - Intrauterine growth retardation (IUGR) Kasabach-Merritt syndrome Thromboembolism Liver failure Hypersplenism	No or minor platelet dysfunction - Fanconi anaemia - Thrombocytopenia-absent radius (TAR) syndrome - Congenital amegakaryocytic thrombocytopenia - von Willebrand disease type 2B - Thrombotic thrombocytopenic purpura (ADAMTS13 deficiency) Platelet dysfunction - Wiskott-Aldrich syndrome - X-linked macrothrombocytopenia - Chediak-Higashi syndrome

maximum is reached late in the third trimester [8]. The resultant severe thrombocytopenia can present from as early as 14 weeks of gestation in at least 50 % of first pregnancies [1, 2, 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 fetal/neonatal alloimmune thrombocytopenia (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, 9, 11] (see Table 32.2). Population studies have demonstrated that 2 % of the female population is HPA-1a negative; however, only 10 % of these women will develop an antibody during pregnancy [12, 13].

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].

Table 32.2 Comparison between two large case series of the most common single HPA-specific alloantibodies identified in the mother of patients with FNAIT

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. [9]
Listed in order of frequency

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, and potentiate the severity of the haemorrhage by causing endothelial damage [18].

The mechanism by which FNAIT causes thrombocytopenia is considered to be the platelet equivalent of haemolytic disease of the fetus and newborn (HDFN) [7, 19]; 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, 20]. 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, melaena, 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, 20, 21]. Intraparenchymal haemorrhages are the most common site of ICH; however, intraventricular and extra-axial haemorrhages are reported [4, 21], and if intrauterine death does not occur, then subsequent porencephaly or hydranencephaly and ventriculomegaly develop 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 [22].

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 crossmatch between samples to identify rare antigens and lastly antigen detection by polymerase chain reaction (PCR) techniques [22]. 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) [23]. Maternal serum is tested against both the paternal platelets and a panel of blood group type O platelets [6]. See Table 32.3 for suggested diagnostic workup.

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, 23]. 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, 23]. 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 32.3 Suggested diagnostic workup 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 crossmatch (MAIPA)	Maternal serum vs. paternal platelets Maternal serum vs. donor group O-matched platelets
HLA crossmatch (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.

Risk Stratification

Recurrence rates of FNAIT have been reported to range from 75 to 90 % in subsequent pregnancies [2, 4, 24].

With the addition of new maternal non-invasive 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 <20,000/mm^3, then the fetus is considered to be 'high risk' [20, 25]. A proposed treatment algorithm based on this risk stratification is shown in Fig. 32.1.

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.

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 %

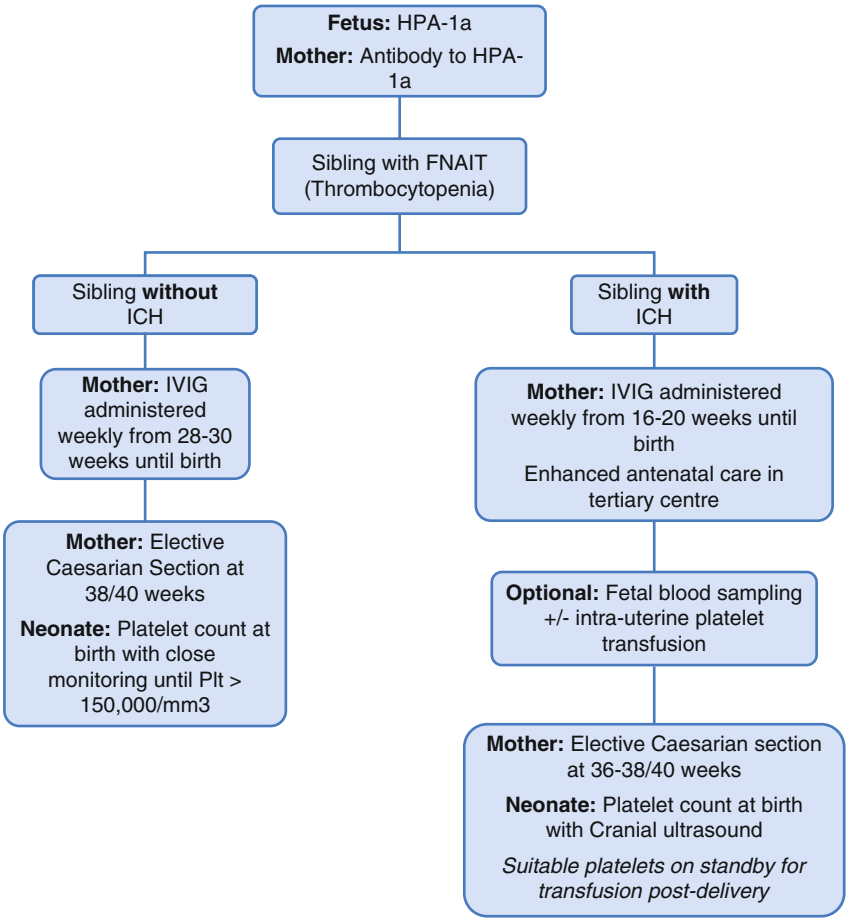

Fig. 32.1 Proposed treatment algorithm (adapted from Porcelijn et al. [25])

per procedure, largely due to haemorrhage, with additional risks associated with premature delivery [14, 23, 26].

Maternal Therapy

Current maternal antenatal therapy may be based on risk stratification and includes the use of high-dose intravenous immunoglobulin (IVIG), with or without the use of corticosteroids. 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, 21, 27].

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 30–50,000/mm^3 in the first 24 h 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, 28]. 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 Caesarian 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 [29].

If only random donor platelets are available, the addition of IVIG, at a dose of 1 g/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 h following transfusion; however, it is often recommended as a complementary treatment strategy [30].

Regardless of the treatment, monitoring the neonate closely for any clinical signs of bleeding, routine regular cranial ultrasounds and regular platelet counts is required.

If there is no sign of bleeding or the platelet count is above 50,000/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, 22]. 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 [2].

Screening

A good screening programme 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 programmes, including cost analysis, with the majority of groups concluding that a screening programme consisting of HPA-1a typing and screening for antibodies in HPA-1a-negative women may reduce mortality and serious morbidity [13, 31, 32]. Recent research is also recommending HLA-DR genotyping to further identify mothers with fetuses at risk of FNAIT [16]. 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 sensitisation and standardisation of treatment, are required to assist in reducing the morbidity and mortality associated with FNAIT.

Maternal Thrombocytopenia

There are a 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 immune thrombocytopenia (ITP) and systemic lupus erythematosus (SLE) [33]. 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 these children. A major point of difference from FNAIT is that in FNAIT, 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 are required.

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Bleeding in the Neonate

33

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 haemostasis 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. 33.1. 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 stabilises 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 haemorrhage and thrombosis.

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 [28]. 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 [32]. The assessment of platelet function however is difficult, regardless of the age of the patient since it demands large volumes and specialised laboratory expertise, and is also a poor surrogate for in vivo primary hemostasis [13, 29]. Studies examining neonatal platelet function have mostly been performed on cord blood rather than infant blood, and whilst sampling cord blood has the advantage of larger volumes, it is not equivalent in function to peripheral blood [26]. Overall these studies have demonstrated that the platelet function in neonates compared with adults is hyporeactive in some regards and hyperreactive in others [13, 29]. In vivo tests of platelet function such as bleeding time and platelet function analyser (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 [24, 26].

Coagulation factor production can be detected from 10 weeks of gestation [22]. Concentrations of coagulation proteins increase with age and are consequently lower in preterm compared with term infants [29]. Reference ranges for coagulation assays in neonates and infants vary with laboratory analyser and reagent system, and this needs to be taken into consideration when comparing abnormal results from different laboratories.

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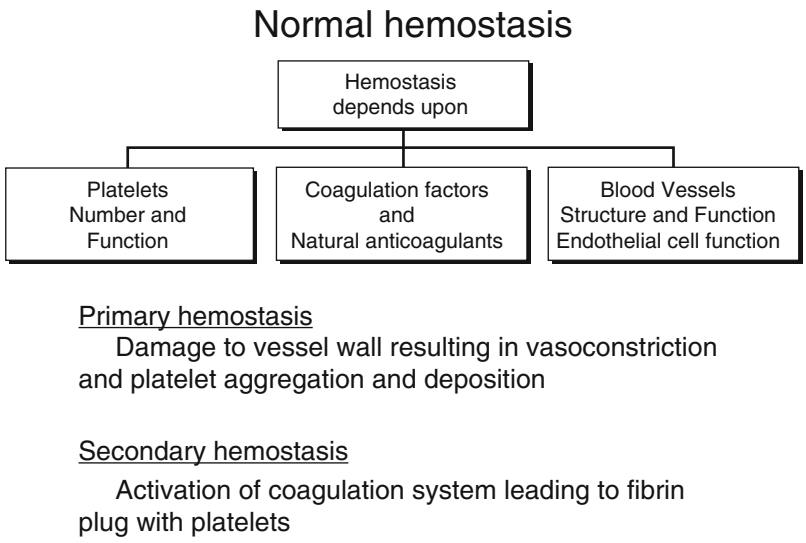

Fig. 33.1 Normal hemostasis

Table 33.1 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
Fibrinogen activity	Unknown
Regulation of coagulation	
Antithrombin	Decreased
Protein C	Decreased
Total protein S	Decreased
Free protein S	Increased
Alpha 2 macroglobulin	Increased

Neonates have lower levels of most coagulation factors compared with adults [4]. See Table 33.1. 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 (XI, 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 [15].

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 C4-binding protein [21, 27]. Plasminogen levels of the newborn are also lower than in adults, demonstrating reduced fibrinolytic activity [3].

This functional immaturity of neonatal pro- and anticoagulant proteins demonstrates that the haemostatic system is set differently to adults, and under normal circumstances, the infant is not at increased risk of either haemorrhage or thrombosis.

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 immunisations).
- Upper and lower gastrointestinal tract.
- Bleeding from umbilical stump.
- Extracranial (subgaleal haemorrhage, cephalohaematoma).
- 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 venepuncture 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 (PTT). 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 analyser and reagents. In practice this is difficult to achieve and the use of published ranges may be required [4]. Neonates with polycythaemia 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 Chap. 7. However, Fig. 33.2 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. Paediatricians and haematologists 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 (II, VII, IX and X, due to mutations in genes controlling the vitamin K pathway).

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 FVII, FX, FXIII 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. FXIII 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 [10]. 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.

VWD is characterised by a qualitative or quantitative defect in von Willebrand factor (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 remained 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 [18].

Congenital Platelet Disorders

These are many and complex and have been reviewed [7, 23] and are discussed in more detail in Chap. 10. 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 characterised by severe bruising and purpura at birth. The diagnosis may be difficult but is urgent since platelet transfusions may be life-saving.

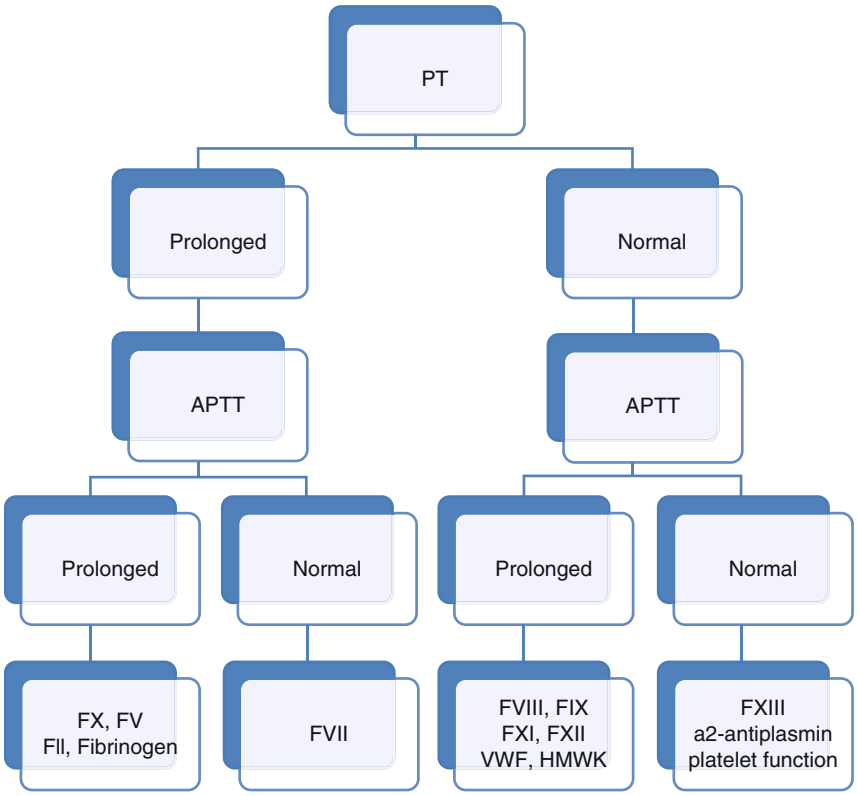

Fig. 33.2 Inherited causes of prolonged coagulation tests

Glanzmann thrombasthenia (GT) is the most serious of these with recessive inheritance and a normal platelet count. The platelets do not function as they are missing essential surface glycoproteins and are unable to bind coagulation factors.

Acquired Hemorrhagic Diseases

DIC is a complex disorder triggered by many conditions, including severe hypoxia, trauma, generalised 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 haemodynamic 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 [20].

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 INR, PTT and fibrinogen; and D-dimer. Table 33.3 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 whilst providing tailored product support.

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 33.2) 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 Chap. 15.

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

Table 33.2 Interpretation of coagulation tests in the bleeding neonate with normal platelet count

		Differential diagnoses
PT prolonged	PTT normal	Acquired conditions • Vitamin K deficiency Inherited conditions • FVII deficiency
PT prolonged	PTT prolonged	Acquired conditions • DIC[a] • Liver disease • Vitamin K deficiency Inherited conditions • Deficiency of II, FV, FX or fibrinogen • Combined factor deficiency
PT normal	PTT prolonged	Acquired conditions • Heparin administration • Lupus anticoagulant[b] Inherited conditions • Deficiency of FVIII, FIX, XI or XII
PT normal	PTT normal	Inherited conditions • FXIII deficiency

PT prothrombin time, *PTT* activated partial thromboplastin time
[a]DIC is characterised 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 33.3 Comparison of DIC and liver disease

	DIC	Liver disease
INR	↑	↑
PTT	↑	↑
Fibrinogen	↓/Normal	Normal
D-dimer	↑	Normal
Platelet count	↓	Normal or ↓*
Bilirubin	Normal	↑

*The reduced platelet count in liver disease is usually due to associated hypersplenism

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, hypoglycaemia, oedema with or without ascites and oliguria [31]. The pattern of coagulopathy and laboratory tests is shown in Table 33.3. The differential diagnosis for this rare disorder includes five major entities: intrauterine insult, bacterial or viral sepsis, haematological disorders, inborn errors of metabolism and primary liver disease [25]. One such example of primary liver disease is neonatal haemochromatosis (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. [17] 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 oligohydramnios) and premature birth [31].

A haematological condition that can present as neonatal liver failure is haemophagocytic lymphohistiocytosis (HLH), which is caused by excessive immune activation. Affected neonates have fever, haepatosplenomegaly, 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 [14].

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 [9]. 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 necrotising 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 Chap. 32.

Intraventricular Hemorrhage

The role of developmental haemostasis in the development of intraventricular haemorrhage (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 the MRI used once the infant approaches term age to help aid assessment of white matter injury [8]. 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 [5].

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 NICU patients and 70 % of those born with a birthweight less than 1000 g [13]. Major morbidities, such as

chronic lung disease, sepsis, necrotising enterocolitis and postnatal steroid therapy, are significantly more common in infants with IVH [6]. Anaemia (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 [28].

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 centres, from restrictive (active haemorrhage 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, alloimmunisation, 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 [11]. Currently, the PLANET-2 study is using a randomised controlled trial designed to compare restrictive versus liberal platelet transfusions in neonates <34 weeks, which will hopefully give further guidance to this area.

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 in unknown [19]. Symptomatic intracranial bleeding in the term neonate is estimated at 4 per 10,000 live births [12]. 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 labour, as well as deliveries requiring instrumentation [30]. Other differential diagnoses in the term neonate with intracranial bleeding to consider include arteriovenous malformations, inherited and acquired coagulation disorders and finally nonaccidental injury.

Differentiating Nonaccidental Injury from Inherited Bleeding Disorders

When an infant presents with bruising or bleeding, there is often concern that this is due to nonaccidental injury (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 [16].

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Part VII

Hemostatic Agents and Blood Components Used to Stop Bleeding

Hemostatic Agents Used to Stop Bleeding

34

Rachel S. Beaty

Hemostatic Agents Used to Stop Bleeding

Tranexamic Acid

Brand Names (USA): Lysteda™, Cyklokapron™
Description: Tranexamic acid is a synthetic amino acid that is classified as antifibrinolytic. It is a competitive inhibitor of plasminogen activation, which becomes a noncompetitive inhibitor at higher concentrations. Tranexamic acid displaces plasminogen from fibrin and results in the inhibition of fibrinolysis. Tranexamic acid is approximately ten times more potent than aminocaproic acid, and its elimination half-life is 2–11 h [1, 2]. Tranexamic acid is available in an intravenous solution and an oral tablet. In addition, an oral solution may be compounded. If 10 mL of the compounded oral 5 % solution is swallowed, this provides 500 mg of tranexamic acid orally [3]. However, this oral solution is mostly studied for topical use.

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].

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], blood loss reduction in hemophilia patients undergoing tooth extraction [25], treatment of hemoptysis in cystic fibrosis patients [26–28], and prevention of perioperative bleeding associated with spinal surgery and craniosynostosis surgery [29–32].

Adverse Effects and Monitoring Parameters: Orally administered tranexamic acid can cause gastrointestinal upset, headache, abdominal pain, muscle pain, and thrombosis (Table 34.1). Visual defects may occur; thus, patients should undergo routine ophthalmologist examinations. Intravenous tranexamic acid can also cause hypotension with rapid administration [33]. The dose and frequency of tranexamic acid should be adjusted in patients with renal dysfunction (see Table 34.2). Importantly, tranexamic acid should not be used when there is evidence of active intravascular thrombosis [1, 2]. Caution is advised if antifibrinolytics are used together with prothrombin complex concentrates (PCC) or activated prothrombin complex concentrates (APCC) because of the risk of thrombosis. If treatment with both agents is deemed necessary, it is recommended to wait 4–6 h after the last dose of PCC or APCC before administering antifibrinolytics [34].

Aminocaproic Acid

Brand Name (USA): Amicar™
Description: Aminocaproic acid is an antifibrinolytic that binds competitively to plasminogen, which reduces the conversion of plasminogen to plasmin, resulting in the inhibition of fibrin degradation. The main difference between aminocaproic acid and tranexamic acid is that tranexamic binds more strongly to plasminogen; thus, aminocaproic acid is less potent than tranexamic acid. Aminocaproic acid has an elimination half-life of 2 h and may accumulate in patients with renal dys-

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Table 34.1 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 min 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 h 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 min	Repeat 4 times daily for 2 days after procedure. *Patient shouldn't eat or drink for 1 h after using oral rinse*
Prevention of perioperative bleeding associated with cardiac surgery	• 30 mg/kg IV prior to incision, followed by 16 mg/kg/h IV until sternal closure • 10 mg/kg IV prior to incision followed by 2 mg/kg/h IV continued for 2 h after surgery • 10–15 mg/kg IV followed by 1–1.5 mg/kg/h IV	
Prevention of perioperative bleeding associated with spinal surgery	• 2000 mg IV prior to incision followed by 100 mg/h IV during surgery and for 5 h postoperatively • 10 mg/kg IV prior to incision followed by 1 mg/kg/h 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 min before skin incision • The preoperative dose may be followed by 10 mg/kg IV administered 3–12 h after the operation • Postoperative doses ranged from a 10 mg/kg IV bolus (or 1000 mg) to a 1 mg/kg/h IV infusion over 10 h	
Blood loss reduction in total knee replacement surgery	10 mg/kg (or 1000 mg) IV approximately 10 min before deflation of the first tourniquet with a second dose (10 mg/kg) 3 h after the first dose	
Trauma-associated hemorrhage	1000 mg IV followed by 1000 mg IV over the next 8 h	
Prevention of bleeding associated with ECMO during surgery for CDH	4 mg/kg IV before repair, followed by 1 mg/kg/h IV for 24 h	
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/h IV infusion	
Prevention of bleeding associated with cardiac surgery in children	6.4 mg/kg IV followed by 2–3 mg/kg/h IV infusion	
Prevention of perioperative bleeding associated with spinal surgery in children	20 mg/kg IV and 10 mg/kg/h IV infusion OR 10 mg/kg IV and 1 mg/kg/h IV infusion	
Prevention of perioperative bleeding associated with craniosynostosis surgery in children	• 50 mg/kg IV prior to incision, followed by 5 mg/kg/h IV infusion until skin closure OR • 15 mg/kg IV prior to incision, followed by 10 mg/kg/h IV infusion until skin closure	
Treatment of hemoptysis in cystic fibrosis patients	• 60 mg/kg/day IV every 6 h × 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	
Usual dosing: 15–25 mg/kg PO every 8 h or 10 mg/kg IV every 8 h		

Adapted from references [1–32]

Table 34.2 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 h • 5 mg/kg/dose IV once daily

Adapted from references [1, 24, 33]

Table 34.3 Aminocaproic acid dosing

Indication	Dose and frequency	Duration
Acute bleeding	4–5 g PO/IV during the first hour, followed by 1 g/h for 8 h (or 1.25 g/h 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 min, followed by 1–4 g IV/PO every 4–8 h or 1 g/h (max daily dose: 24 g)	
Control of oral bleeding in congenital and acquired coagulation disorder	50–60 mg/kg PO every 4 h	
Prevention of dental procedure bleeding in patients on oral anticoagulant therapy	Oral rinse: Hold 4 g/10 mL in mouth for 2 min then spit out	Repeat every 6 h for 2 days after procedure
Prevention of perioperative bleeding associated with cardiac surgery	• 10 g IV followed by 2 g/h 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, and100 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/h for up to 72 h	
Prevention of perioperative bleeding associated with spinal surgery pediatric patients	100 mg/kg IV after induction, followed by 10 mg/kg/h for the remainder of the surgery; discontinue at time of wound closure	
Usual dosing: 60–100 mg/kg PO every 6 h (up to 24 g/day in adults)		

Adapted from references [35–47]

function. Thus, a reduced dose may be necessary in anephric patients or those with renal dysfunction. Aminocaproic acid is available as an intravenous solution, oral solution, and oral tablet [35, 36].

Adult Use: Aminocaproic acid can be used to enhance hemostasis when fibrinolysis contributes to bleeding [35], control of acute bleeding [35], control of bleeding with severe thrombocytopenia [37, 38], control of bleeding in congenital and acquired coagulation disorder [39], blood loss reduction in patients on oral anticoagulant therapy undergoing dental procedures [40], and prevention of perioperative bleeding associated with cardiac surgery [41, 42].

Pediatric Use: Aminocaproic acid can be used in children for the prevention of perioperative bleeding associated with cardiac and spinal surgery [42–44] and prevention of bleeding associated with ECMO [45–47].

Adverse Effects and Monitoring Parameters: The most common adverse effect of aminocaproic acid is gastrointestinal upset (Table 34.3). 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, creatine phosphokinase (CPK) should be monitored, 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 [35].

Fibrinogen Concentrate (Human)

Brand Name (USA): RiaSTAP™

Description: Fibrinogen concentrate (coagulation factor I) is generated from pooled human plasma and is a physiological substrate of thrombin, factor XIIIa, and plasmin. Soluble fibrinogen is converted to insoluble fibrin. Fibrin is stabilized by factor XIIIa, which induces cross-linking of fibrin polymers to provide strength and stability to the blood clot. The cross-linked fibrin is the end result of the coagulation cascade. Human fibrinogen concentration has a fairly long elimination half-life of 61–97 h; however, this half-life may be decreased in children and adolescents. Fibrinogen concentrate is available as intravenous powder, for reconstitution [48].

Adult Use: Fibrinogen concentrate can be used in the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia) [48], supportive therapy in trauma patients who are bleeding [49–53], blood loss reduction in cardiovascular surgery [49, 54, 55], blood loss reduction in postpartum hemorrhage [56], and improvement in clot firmness after orthopedic surgery [57].

Pediatric Use: Fibrinogen concentrate can be used in children for the treatment of congenital fibrinogen deficiency [58, 59] and reduction of blood loss after surgical craniosynostosis repair [60].

Adverse Effects and Monitoring Parameters: Fibrinogen concentrate may cause hypersensitivity reactions, thrombosis,

Table 34.4 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 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 references [48–60]

and headache (Table 34.4). Similar 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. A target fibrinogen level of 100 mg/dL should be maintained until hemostasis occurs and wound healing is complete. The reference range for normal fibrinogen is 200–450 mg/dL [48].

Factor VIIa (Recombinant)

Brand Name (USA): NovoSeven™ RT
Description: Recombinant factor VIIa 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 converts prothrombin to thrombin, a key step in the formation of a fibrin-platelet hemostatic plug. Recombinant factor VIIa has a short terminal half-life of 2.6–3.1 h, thus a need for frequent dosing. Recombinant factor VIIa is available as an intravenous solution [61].

Adult Use: Recombinant factor VIIa is indicated for use in patients with hemophilia A or B with inhibitors [61], congenital factor VII deficiency [61], acquired hemophilia [61], and Glanzmann's thrombasthenia [61]. There have been numerous studies and reports on the unlabeled use of recombinant factor VIIa in bleeding patients. The paragraph below is not an exhaustive list but rather a general summary of the use of this product in different patient populations. Recombinant factor VIIa has been reported to be used in patients with warfarin-related intracerebral hemorrhage (ICH) [62, 63], refractory bleeding after cardiac or liver surgery in nonhemophilic patients [63–67], anticoagulation reversal [68–70], blood loss reduction after cardiac surgery [71], coagulopathy reversal in isolated traumatic brain injury (TBI) [72], diffuse alveolar hemorrhage in bone marrow transplant (BMT) patients [73], bridge to transplant in end-stage liver disease patients [73], trauma-related coagulopathy [73], refractory perioperative bleeding in noncardiac patients [73], life-threatening refractory hemorrhage of any cause in severely coagulopathic patients [63, 73], blood loss reduction in abdominal trauma patients [74], and esophageal varices [63].

Pediatric Use: Recombinant factor VIIa can also be utilized in the pediatric population for reduction in blood loss and requirement for blood products after cardiac surgery [75, 76], coagulopathies [77], treatment of severe bleeding associated with dengue hemorrhagic fever [78], liver impairment [79, 80], and nonhemophilic hemorrhages [81].

Adverse Effects and Monitoring Parameters: Recombinant factor VIIa may cause antibody formation, hypersensitive reactions, thromboembolic events, and hyper- or hypotension (Table 34.5). Monitoring parameters include evidence of hemostasis. The prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (PTT), and factor VII may also be useful as adjunct tests to evaluate efficacy [61].

Desmopressin

Brand Names (USA): DDAVP™, Stimate™
Description: Desmopressin is a synthetic analogue of vasopressin, but the molecular structure is modified from vasopressin to reduce its vasoactive actions; vasopressin activates both V1 and V2 receptors where desmopressin only stimulates V2 receptors. Desmopressin increases plasma levels of von Willebrand factor (VWF), factor VIII (FVIII), and tissue plasminogen activator (t-PA) contributing to a shortened PTT 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 [82–86]. The secreted t-PA is inactivated by plasminogen activator inhibitor and thus does not seem to promote fibrinolysis or bleeding. Most patients with type 1

Table 34.5 Factor VIIa dosing

Indication	Dose, frequency, and duration
Warfarin-related ICH	• 10–100 mcg/kg IV administered concurrently with IV vitamin K *Lower doses (10–20 mcg/kg) are generally preferred given the higher risk of thromboembolic complications with higher doses*
Treatment of refractory bleeding after cardiac surgery in nonhemophilic patients	• 35–70 mcg/kg IV • 10–20 mcg/kg in patients with a left ventricular assist device, to reduce thromboembolic events
Reduction in blood loss after cardiac surgery	40 mcg/kg IV
Reverse coagulopathy in patients with isolated TBI	20 mcg/kg IV *(in addition to other blood products)*
Diffuse 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 mcg/kg IV repeated every 15 min to a maximum dose of 90 mcg/kg
Blood loss reduction in abdominal trauma patients	24–72 mcg/kg IV, repeat in 3 h if no clinical improvement
Reduction in blood loss after cardiac surgery in pediatrics	90–180 mcg/kg IV after cardiac surgery 40 mcg/kg IV during surgery
Coagulopathies in pediatrics	5 mcg/kg IV initial, followed by 10, 20, 40, or 80 mcg/kg IV
Treatment of severe bleeding associated with dengue hemorrhagic fever in pediatrics	100 mcg/kg IV × 1 (or repeated doses every 4 h as needed)
Chronic liver disease in children	38–118 mcg/kg IV × 1
Nonhemophilic hemorrhage in pediatrics	90 mcg/kg IV × 2
Usual dose range 40–90 mcg/kg IV	

Adapted from references [61–81]

von Willebrand disease (VWD) and FVIII/VWF levels greater than 10 units/mL will respond to desmopressin, but patients with type 2 VWD have a more variable response. Prior to utilizing desmopressin for therapy, a therapeutic trial should be conducted to determine a patient's response. To test responsiveness, blood samples are taken 30–60 min and 4 h after an intravenous injection of desmopressin to obtain a reliable figure on recovery and clearance of FVIII and VWF [87]. Desmopressin has an elimination half-life of 2–4 h; however, the half-life is prolonged to 9 h in patients with renal impairment (See Table 34.7) [35].

Formulations: Desmopressin is available as a 4 mcg/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 [83].

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 [34, 88, 89], uremia associated with acute or chronic renal failure [90], prevention of surgical bleeding in patients with uremia [91], stabilization of platelet function in intracranial hemorrhage [92], blood loss reduction after cardiac surgery [93, 94], blood loss reduction in dental procedures [83], and blood loss reduction in patients with liver cirrhosis [95–98]. It is recommended to utilize VWF in addition to desmopressin if the postsurgical treatment is necessary for more than three days [83].

Pediatric Use: In the pediatric setting, desmopressin is utilized for heavy menstrual bleeding in adolescent females [99, 100], congenital VWD in patients who respond to a desmopressin challenge [82], congenital platelet defect disorders in patients who respond to a desmopressin challenge [82], circumcision in combined factor V and VIII deficiency [101], tonsillectomy and adenoidectomy [83], and otologic surgery [83]. Studies have shown that desmopressin administered as a one-time dose after cardiopulmonary bypass failed to reduce blood loss after cardiovascular surgery in pediatrics [102–104]. Of note, children under two years of age tend to have a lower response to desmopressin in comparison to older children [83].

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) (Tables 34.6 and 34.7). Monitoring parameters include fluid intake, urine volume, and signs/symptoms of hyponatremia [83]. 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 [105–109].

Table 34.6 Desmopressin dosing

Indication	Dose, frequency, and duration
Uremic bleeding associated with acute or chronic renal failure	0.4 mcg/kg IV once
Prevention of surgical bleeding in patients with uremia and reduction in bleeding time in patients with liver cirrhosis	0.3 mcg/kg IV once
Reduction of blood loss in intracranial hemorrhage	24 mcg IV once • Patients 20 kg= 8 mcg • Patients 50 kg= 20 mcg • Patients 100 kg= 40 mcg or 0.3 mcg/kg
Blood loss reduction after cardiac surgery	0.3 mcg/kg IV once after coming off cardiopulmonary bypass
Dental procedure	0.3 mcg/kg IV daily for 1–2 days
Heavy menstrual bleeding in adolescent females	Intranasal desmopressin: 1.5 mg/mL or 150 mcg 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 mcg per spray Patients < 50 kg: 150 mcg (1 spray) Patients ≥ 50 kg: 300 mcg (1 spray each nostril) If using preoperatively, administer 2 h before surgery
Congenital VWD and congenital platelet defect disorders in pediatrics	0.3 mcg/kg IV once, if used preoperatively administer 30 min before procedure; may repeat dose if needed
Tonsillectomy, adenoidectomy, and otologic surgery in pediatrics	0.3 mcg/kg IV once or twice daily for 1–7 days
Generally, 0.3 mcg/kg of desmopressin can increase the level of FVIII and von Willebrand factor for two- to sixfold. Peak effect occurs 1 h after injection. Recommended not to use more than once daily due to development of tachyphylaxis [34]	

Adapted from references [34, 83, 88, 101]

Table 34.7 Desmopressin dosing in renal impairment

Creatinine clearance	Dose
<50 mL/min	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 references [34, 90, 91]

Due to the risk of hyponatremia, some institutions adopt sodium limits associated with desmopressin administration, i.e., avoid desmopressin if sodium is less than 130 meq/L. Tachyphylaxis can occur with consecutive dosing of desmopressin; thus, it is recommended to use specific factor concentrates or platelet transfusions, depending on the underlying disease, if hemostasis after major trauma or surgery is desired [110].

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Brand Name (USA): Humate-P™
Description: Humate-P™ is a factor product that is derived from human plasma and contains FVIII, VWF, and small amounts of fibrinogen and albumin [111]. Its use is 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 (VWF:RCo) activity. The average ratio of VWF:RCo to FVIII in Humate-P™ is 2.4:1, which is more similar to the ratio in normal human plasma in comparison to other VWF/FVIII products. The elimination hale-life of VWF:RCo in Humate-P™ has a wide range of 3–34 h 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 [111]); treatment of spontaneous or trauma-induced bleeding and prevention of excessive bleeding during and after surgery in patients with severe VWD [111, 113, 114], including mild or moderate disease where use of desmopressin is known or suspected to be inadequate [111]); reduction of postpartum blood loss in VWD type 3 patients [115]; and development of acquired von Willebrand disease after ventricular assist device implantation [112]. When used for surgical prophylaxis, target levels of VWF:RCo should be approximately 100 units/dL and, at

Table 34.8 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 h for three doses; then 60 units/kg IV every 12 h; then 40 units/kg IV every day and unfractionated heparin started to maintain PTT 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 h [34]	

Adapted from references [83, 111–117]

Table 34.9 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 references [83, 118–120]

least for the first 3 days of treatment, a nadir of 50 units/dL VWF:RCo, as well as similar targets for FVIII [83]. Humate-P™ administered as a continuous infusion has also been reported to be successful for surgical prophylaxis [83].

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 (Table 34.8). 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 FVIII:C daily. Humate-P™ can also transmit infections since it's derived from human plasma [111].

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Brand Name (USA): Alphanate™
Description: Alphanate™ is derived from human plasma and contains FVIII, VWF, and other plasma proteins. Alphanate™ is used to replace endogenous factor VIII and VWF. The average ratio of VWF:RCo to FVIII in Alphanate™ is not provided by the manufacturer but is approximately 1:1. 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 h). Alphanate™ is available as an intravenous powder for reconstitution [83].

Adult Use: Alphanate™ is utilized for the prevention and treatment of hemorrhagic episodes in patients with hemophilia A [118] and prophylaxis with surgical and/or invasive procedures in patients with VWD when desmopressin is either ineffective or contraindicated [118, 119]. Alphanate™ is not indicated for surgical prophylaxis in patients with severe VWD, type 3 [83, 118].

Pediatric Use: Alphanate™ is used in pediatric patients with VWD for the treatment of bleeding episodes [120] and prophylaxis prior to surgery [118, 120].

Adverse Effects and Monitoring Parameters: Alphanate™ can cause antibody formation, hypersensitivity, thrombotic evens, rash, face edema, headache, dizziness, and nausea (Table 34.9). 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™.

Phytonadione (Vitamin K)

Brand Name (USA): Mephyton™
Description: Phytonadione is a vitamin that is necessary for the liver to synthesize factors II, VII, IX, and X. These vitamin-K dependent coagulation factors are γ-carboxylated by the action of vitamin K and glutamyl carboxylase. Phytonadione is available as an intravenous aqueous colloidal solution and an oral tablet [121].

Table 34.10 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 h 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 references [121–126]

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 [121], hypoprothrombinemia due to drugs or factors limiting absorption or synthesis [121], vitamin K deficiency secondary to VKA [122–124], and preprocedural/surgical INR normalization in patients receiving warfarin [122, 125].

Pediatric Use: Phytonadione is used in pediatric patients to treat vitamin K deficiency secondary to vitamin K antagonist administration [121] and bleeding in patients with chronic cholestasis [126].

Adverse Effects and Monitoring Parameters: Phytonadione can cause hypersensitivity reactions, flushing, dizziness, and abnormal taste (Table 34.10). PT, INR, and hypersensitive reactions should be monitored following phytonadione administration [121].

Four-Factor Prothrombin Complex Concentrate (Human)

Brand Name (USA): Kcentra™
Description: Kcentra™ is derived from human plasma and contains factors II, VII, IX, and X proteins C and S. Coagulation factors II, IX, and X are part of the intrinsic coagulation pathway, while factor VII is part of the extrinsic coagulation pathway. Ultimately, these 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 enzymes 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 that inactivates factors Va and 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 h; factor VII, 1.5–6 h; factor IX, 20–24 h; factor X, 24–48 h; protein C, 1.5–6 h; and protein S, 24–48 h. Kcentra™ is available as an intravenous powder for reconstitution [127]. Three-factor prothrombin complex concentrates (Bebulin™ and Profilnine™) differ from Kcentra in that they do not contain factor VII but only contain factors II, IX, and X (see Tables 34.12 and 34.13) [128–130].

Adult Use: Kcentra™ is indicated for VKA reversal in patients with acute major bleeding or need for an urgent surgery/invasive procedure [127]. Reports have also shown Kcentra™ to be effective in the reversal of direct factor Xa anticoagulants [131, 132], an alternative agent to fresh frozen plasma (FFP) in patients with serious/life-threatening bleeding related to vitamin K antagonist therapy [133], and in acquired, non-warfarin-related coagulopathy in major trauma and surgery [134–137].

Pediatric Use: Data supporting four-factor prothrombin complex concentrate use in pediatric patients is limited to case reports or case series. These data show prothrombin complex concentrate can be used for prophylaxis in patients with severe congenital factor X deficiency [138, 139] and in dilutional coagulopathy [140]. 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 (Tables 34.11, 34.12, and 34.13). Infection can also be transmitted since Kcentra™ is derived from human plasma. The INR should be monitored at baseline and at 30 min post dose, and a patient's clinical response should be monitored during and after treatment [127].

Table 34.11 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 h in perioperative period, 20 units/kg IV every 72 h for prophylaxis • 25 units/kg IV every 72 h • 30 units/kg IV every 72 h • 30 units/kg IV twice per week	
Dilutional coagulopathy in pediatrics	30 units/kg IV	Once

Adapted from references [127, 131–140]

Table 34.12 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 reference [127]

Table 34.13 Comparison of three- and four-factor prothrombin concentrations

	Kcentra™ 500 unit vial	Bebulin™ 200–1200 unit vial	Profilnine™[a] 500 unit vial
Factor II	380–800 units	480–760 units	NMT 150 units/100 units factor IX
Factor VII	200–500 units	<100 units	NMT 35 units/100 units factor IX
Factor IX	400–620 units	480–760 units	100 units
Factor X	500–1020 units	480–760 units	NMT 100 units/100 units factor IX
Heparin	8–40 units	≤72–114 units	
Protein C	420–820 units		
Protein S	240–680 units		
Antithrombin	4–30 units		

Adapted from references [127–130]
NMT not more than
[a]Also contains polysorbate 80

Thrombin Powder

Brand Name (USA): Recothrom™
Description: Thrombin is a topical product that is made through recombinant DNA technology. Thrombin 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 [141].

Adult Use: Thrombin is utilized for hemostasis [141]; control of localized, accessible bleeding from lacerated tissues [34]; con-

trol of bleeding after dental extractions or at surgical sites [34]; and reduction of blood loss in total knee arthroplasty [142].

Pediatric Use: Thrombin powder has been studied in pediatric patients and is approved to aid in hemostasis, specifically in burn patients [141].

Adverse Effects and Monitoring Parameters: Patients who receive thrombin powder should be monitored for abnormal hemostasis (Table 34.14). Thrombin powder may also cause pruritus. Of note, this product is for topical use only [141].

Protamine Sulfate

Brand Name (USA): Not applicable
Description: Protamine is a strongly alkaline substance and is 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 lost. Protamine has a very rapid onset of action (5 min), and the elimination half-life is approximately 7 min. However, when protamine is administered, it neutralizes the heparin; therefore, subsequent doses are not usually required. Protamine is available as an intravenous solution [143].

Adult Use: Protamine is utilized in adults for the reversal of heparin and low molecular weight heparins [143, 144]. When heparin is given as a continuous IV infusion, only heparin given in the preceding several hours should be considered when administering protamine [145]. Protamine can also be utilized for low molecular weight heparin (LMWH) overdose, but the anti-Xa activity is never completely neutralized [146–148]. Protamine is also used to neutralize heparin in patients previously on cardiopulmonary bypass, the most effective dosing being individualized management [149], and to reduce bleeding complications after carotid endarterectomy [150].

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 [151, 152], and to treat severe post-reperfusion coagulopathy in liver transplant patients [153].

Adverse Effects and Monitoring Parameters: Severe hypotension can occur with rapid administration of protamine; thus, protamine should be administered over at least a 10-min period (Table 34.15). Transient hypotension can still be expected within 3–4 min after administration [154]. There is also a risk for anaphylaxis with protamine administration

Table 34.14 Thrombin powder dosing

Indication	Dose, frequency, and duration
Hemostasis	Apply powder directly to the site of bleeding or on oozing surfaces

Adapted from References [34, 141, 142]

Table 34.15 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 h	The dose of protamine should equal the dose of enoxaparin
	>8 h 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 PTT is prolonged 2–4 h 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 h	The dose of protamine should equal the dose of LMWH. If the PTT is still prolonged 2–4 h after the initial dose, a second dose of 0.5 mg protamine per 1 mg LMWH may be administered
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 references [143–153]

secondary to histamine release, which has been reported mainly during cardiac surgeries [155]. 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 min to 18 h following the reversal of heparin with protamine [143].

Anti-inhibitor Coagulant Complex (Human)

Brand Name (USA): 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 unitages 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 PTT 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 h. Anti-inhibitor coagulant complex is available as an intravenous powder for reconstitution [156].

Adult Use: Anti-inhibitor coagulant complex is utilized in adults for control and prevention of bleeding episodes in hemophilia patients with inhibitors [156] and moderate to severe bleeding in patients with acquired hemophilia [157, 158]. Anti-inhibitor coagulant complex is also used for perioperative management in hemophilia patients with inhibitors, life-threatening bleeding associated with dabigatran use [159–165], and life-threatening bleeding associated with rivaroxaban use [166]; reversal of warfarin-related bleeding [167]; and management of refractory bleeding in cardiac surgery [168].

Pediatric Use: Anti-inhibitor coagulant complex is utilized in pediatrics for control and prevention of bleeding episodes in hemophilia patients with inhibitors [156], prevention of bleeding episodes in factor X deficiency [169], and treatment of hemothorax in children with congenital coagulopathy [170].

Adverse Effects and Monitoring Parameters: Thrombotic and thromboembolic events can occur following anti-inhibitor coagulant complex use, especially with doses ≥ 100 units/kg (Table 34.16). Therefore, caution is advised in patients with atherosclerotic disease, crush injury, septicemia, or concomitant treatment with factor VIIa or antifibrinolytics due to increased risk of developing thrombotic events from circulating tissue factor or predisposing coagulopathy. Infection can also be transmitted since anti-inhibitor coagulant complex is derived from human plasma. Monitoring parameters include

Table 34.16 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 h until pain improves (max 200 units/kg/day)
Mucous membrane bleeding in adult and pediatric hemophilia patient inhibitors	50–100 units/kg IV every 6 h 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 h 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 h 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 h until bleeding is 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 every 12 h for 3 days, then 100 units/kg IV every 24 h for 4 days

Adapted from references [156–170]

signs of symptoms of DIC, hemoglobin, and hematocrit. Of note, PTT and thromboelastography (TEG) should not be utilized to monitor response; DIC can occur when practitioners attempt to normalize these values with anti-inhibitor coagulant complex [156].

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Blood Components

35

Lisa Hensch

Red Blood Cells

Etiology of Anemia

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 35.1. When there is clinical suspicion for hemolysis, a series of laboratory tests may be necessary for confirmation [1]. Laboratory tests used in the identification of hemolysis can be found in Table 35.2. 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 lowering hemoglobin/hematocrit, but no external bleeding is observed. These patients may require an extensive workup to determine the exact cause of their anemia in order to initiate appropriate treatment.

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 primarily 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 particular 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. 35.1).

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].

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Table 35.1 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	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	

Table 35.2 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]

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.

Preparation, Dosage, and Administration

Pretransfusion testing: A pretransfusion sample is used for type and screen or type and crossmatch. 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 generally 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.

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 [14]. 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 [15].

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 [16]. RBCs are transfused through a 170–260 μm filter to remove clots and macroaggregates [16]. 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

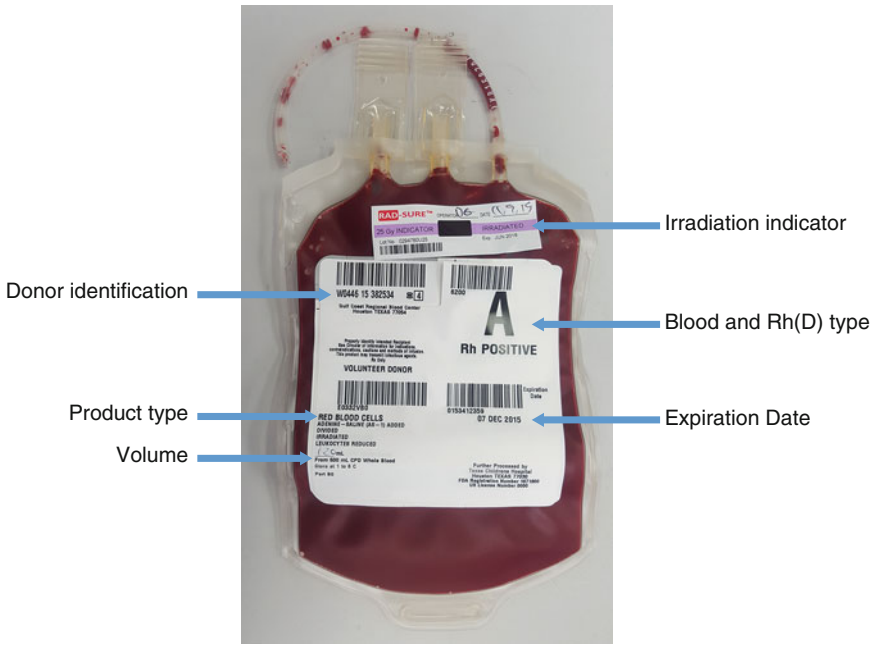

Fig. 35.1 Red blood cell unit

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 [16]. Transfusion with solutions containing dextrose can be associated with hemolysis, while the calcium in Ringer's lactate may lead to clotting [17]. Some studies have reported that infusion with Ringer's lactate is safe in rapid transfusion settings [18, 19]; however, this is not a universally accepted practice [17].

Alternatives to Allogeneic Red Cell Transfusion

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. These 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 [20]. 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 [21]. These units are stored in citrate solution and, at room temperature, can be held for up to 8 h [21]. 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 [21]. ANH is associated with fewer allogeneic red cell, platelet, and plasma transfusions as well as improved outcomes [22]. 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 [21]. 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, obstetrics, 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 [23].

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 multiple 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 RBCs and the transfusion requirement for the patient. Each hospital blood bank should have a policy regarding when to switch 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 the sensitization of Rh is not high in acutely bleeding patients with hemorrhagic shock when Rh-positive RBCs are transfused to Rh-negative patients [14].

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 [24]. In 2010, 83 % of institutions surveyed provided some degree of phenotype-matched red cells, yet alloimmunization rates remain high [25]. Whenever possible, transfusion services should provide Rh (DCE)- and K-compatible units for patients with sickle cell disease [26]. In patients who have already developed 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. Bleeding in these patients typically results in mucocutaneous bleeding, such as petechiae, purpura, ecchymosis, epistaxis, or gum bleeding. Common causes of thrombocytopenia are listed in Table 35.3. Platelet dysfunction is seen in the setting of renal disease (uremic thrombocytopathy), various medications (aspirin, clopidogrel, ticlodipine, dipyridamole, etc.), mechanical intervention (cardiac bypass, extracorporeal membrane oxygenation (ECMO), ventricular assist devices), and congenital diseases (Glanzmann's thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc.).

Table 35.3 Causes of thrombocytopenia

Causes of thrombocytopenia
Splenomegaly
Disseminated intravascular coagulation (DIC)
Dilutional coagulopathy
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)

Table 35.4 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

Indications

Platelet transfusion is indicated when the patient has thrombocytopenia or platelet function defect. Platelet transfusion in the consumptive disorders heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura (TTP) is generally contraindicated due to the risk of arterial thrombosis and increased mortality rates [27]. 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 35.4.

General Features

There are two general types of platelets: 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

Fig. 35.2 Apheresis 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 [28, 29]. Currently, platelets expire after 5 days as a result of the risks for bacterial contamination [9], but the expiration date can be extended to 7 days with additional bacterial testing or pathogen inactivation strategies. When whole blood-derived platelets are pooled for transfusion, the new expiration time becomes 4 h from the time of pooling (Fig. 35.2).

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.

Table 35.5 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
$\frac{\text{Platelet increment} \times \text{weight (kg)} \times 75\ \text{mL/kg} \times 100\,\%}{\text{Number of platelets transfused} \times 10^{11}}$

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 [15]. It is important to assess for adequate platelet increment. A sample for testing should be obtained 10–60 min after transfusion. The corrected count increment (CCI) can be used to determine if the patient has had an adequate response to transfusion. A CCI of less than 5,000 on two occasions [30] or a percent platelet recovery of <30 % [31] may indicate platelet refractoriness. These calculations are given in Table 35.5.

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 [32]. 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 [33]. When an HLA or HPA antibody is identified, patients can be managed with HLA- or HPA-matched platelets to help achieve adequate platelet recovery [34]. However, obtaining matched platelets can be time-consuming and costly. Platelet cross-matching can also be used to find compatible platelets for transfusion and has been shown to significantly improve the CCI [35] 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 [36].

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 [37]. 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 [38].

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 of the 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 plasmapheresis.

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 [39]. In fact, some studies show that the reduction in procoagulants such as protein C and antithrombin is more significant than the reduction in clotting factors [40]. 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. The 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 [41]. Plasma transfusion simply to correct a minimally elevated INR is not indicated. (See Chapter 11 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 for Thrombosis and Hemostasis if the INR is >1.5 or fibrinogen is less than 150 mg/dL [42]. 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 [43].

Vitamin K Deficiency

Vitamin K deficiency results in deficiency 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 [44]. If Kcentra™ is not available for reversal, plasma may be used. (See Chapter 15 for additional information regarding vitamin K deficiency and Chapter 34 for additional information about Kcentra™.)

Plasma Exchange

TTP is a category I indication for plasma exchange [45]. Even if a patient with TTP is actively bleeding, platelets should not be given due to the potential risk for exacerbating TTP [27]. 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

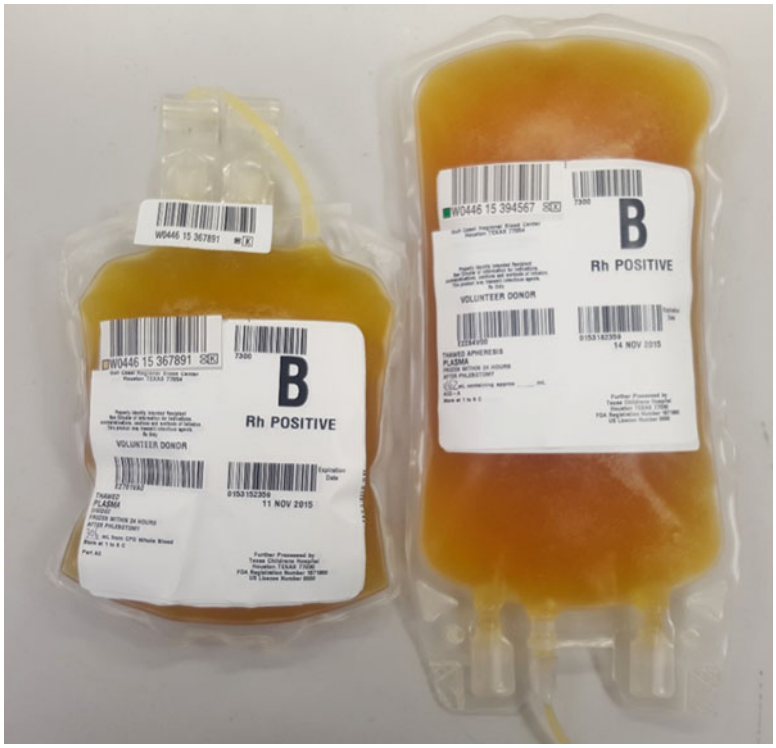

Fig. 35.3 Thawed plasma, whole blood derived (left) vs. apheresis (right)

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 [45].

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 may have volumes up to 500–800 mL [7]. FFP is expected to contain 1 IU/mL of each clotting factor (Fig. 35.3).

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. After 24 h of 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, although still therapeutic, amounts of factors V and VIII [46].

Liquid plasma: After plasma is separated from cellular component (red cells and platelets), it is not frozen and is stored at 1–6 °C. 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 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 [47]. However, a separate study showed liquid plasma had better hemostatic ability than thawed plasma when evaluated by thromboelastography and thrombin generation assay [48].

Pretransfusion Testing

Plasma may contain significant amounts of anti-A and anti-B antibodies. 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 35.6 gives the approximate half-life of each factor.

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 [16]. Plasma is transfused through a 170–260 μm filter.

Table 35.6 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. [49]

Cryoprecipitate

General Features

Cryoprecipitate is produced from human plasma. When 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 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 [50], 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 [16]. In the pediatric setting, it may be appropriate to use single units of cryoprecipitate; however, for adults, cryoprecipitate is frequently made into 5-unit pools (Fig. 35.4).

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

Fig. 35.4 Cryoprecipitate, single-unit (left) vs. 5-unit pool (right)

have >150–200 mg/dL [51], and obstetric patients should have >300 mg/dL of fibrinogen at the time of delivery [52].

Factor XIII deficiency: Congenital factor XIII deficiency is a rare disease that is associated with a lifelong bleeding tendency and abnormal wound healing [53]. It is not frequently detected on routine tests of coagulation, such as the PT or 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 [54] 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 since recombinant factor VIII is readily available. Likewise, it is not used to treat von Willebrand disease since von Willebrand factor/factor VIII concentrates (Humate-P™, Alphanate™) 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 [55], though it appears that the response is variable [56] (see Chapter 16).

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 5–10-unit pool of cryoprecipitate. A more exact calculation of the appropriate dose is shown below in Table 35.7.

Administration

Cryoprecipitate is administered through a 170–260 μm filter as rapidly as tolerated [16].

Table 35.7 Calculation for cryoprecipitate dosing

Dose of cryoprecipitate
$\text{Units} = \frac{(\text{desired fibrinogen} - \text{initial fibrinogen}) \times 70\ \text{mL/kg} \times \text{weight(kg)} \div 100}{250\ \text{mg/unit}}$

Massive Transfusion

Massive transfusion is traditionally defined as >10 units of RBCs transfused within 24 h [57]. 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 [58]. 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 [58]. 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 [59]. Early support with FFP improves survival in these patients [60]. 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 [61]. 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 [62]. (See Chapter 5 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 [63]. Infusion of greater than 3 L of crystalloids, or only 500 mL of colloids, can lead to increased postoperative bleeding [64]. 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

Table 35.8 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

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 [65]. Conversely, alkalosis may develop the day after massive transfusion due to the metabolism of citrate to bicarbonate.

Hyperkalemia: Massive and rapid transfusion of RBCs can lead to the development of hyperkalemia. Hyperkalemia may lead to the development of 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 [66]. 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 [67]. 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 35.8 aimed at reducing cardiac toxicity, removing potassium from the extracellular compartment as well as increasing elimination [68].

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 [69]. At this temperature, platelet activity and enzyme activity are impaired [70]. Prevention of hypothermia involves warming the room, warming the patient with blankets or heat lamps, using blood warmers for all fluids [71]. 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, rapid transfusion of citrated blood components can lead to hypocalcemia. Severe hypocalcemia is associated with depressed circulatory function [72] and alterations in the coagulation cascade. It is 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.

Component Modifications

A summary of general features of each of the components used to maintain hemostasis is provided in Table 35.9. 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 [73, 74]. Latent 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 [75, 76]. 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 [77]. 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 some 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-

Table 35.9 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 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 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]

making regarding CMV-safe versus CMV-seronegative components in these 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 [78].

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 35.10. 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 [79]. There is increased release of potassium from RBCs into the extracellular fluid following irradiation [80]. Washing may be considered to remove excess potassium if the red cell unit has been irradiated to prevent hyperkalemia in neonates and infants [81].

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 35.11. Unfortunately, washing also results in loss of RBCs and platelets as well as decreased red cell survival after transfusion. Washing is indicated to prevent severe allergic reactions including anaphylaxis [6]. It should be noted that in the presence of anti-IgA in the recipient, washing should be more thorough than usual washing. Literature

Table 35.10 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)

Table 35.11 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 [86, 87]
ABO-incompatible organ transplantation
Maternal platelet transfusion in neonatal alloimmune thrombocytopenia

suggests that two washes with 2 L of saline are needed to completely remove trace amounts of IgA [82]. 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 [83]. 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 [84]. However, a clear association has not been established, and emergent transfusion should not be delayed for washing of the red cell unit [85].

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]. 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 [88]. 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] for certain procedures, such as in intrauterine transfusion [88].

Whole blood: Currently, the use of whole blood is mostly limited to military operations [89, 90]. Whole blood components must be ABO identical [4].

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 ten 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 [91, 92], 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 [93]. 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 [93]. 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 [94]. 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 antigen or human neutrophil antigen. 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 donors for plasma products, have been shown to decrease the incidence of TRALI [95]. Nonetheless, TRALI is the most common cause of fatal transfusion reactions, accounting for 41 % of fatal reactions reported to the FDA between 2010 and 2014 [96].

Transfusion-associated circulatory overload (TACO): TACO is currently the second most common fatal transfusion reaction, accounting for 22 % of fatal reactions reported to the FDA between 2010 and 2014 [96]. Despite this, TACO is commonly under recognized. 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 [94]. 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 [97]. 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.

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 35.12 [94]. 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 [98]. New information technology such as bar

Table 35.12 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 [94]

Table 35.13 Allergic transfusion reactions

Causes of allergic transfusion reactions
Peanut allergens [107]
Shellfish [108]
Latex [108]
IgA deficiency [109]
C4 deficiency [110, 111]
Haptoglobin deficiency [112]
Methylene blue [113]

coding and radio-frequency 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 [99]. AHTRs from ABO-incompatible transfusions lead to intravascular hemolysis. It is critical that AHTRs be identified as quickly as possible. Clinical manifestations are related to the volume transfused [98]. 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 [94]. 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 [100]. Pretransfusion treatment with acetaminophen may reduce febrile transfusion reactions [100]; however, they may also mask symptoms of an acute hemolytic transfusion reaction. The practice of universal leukocyte reduction has been found to decrease the incidence of febrile transfusion reactions in some centers [73, 101].

Delayed hemolytic transfusion reactions (DHTRs): Delayed hemolytic transfusion reactions typically occur 3–14 days following transfusion and are associated with extravascular hemolysis [102]. The hemovigilance protocol defines DHTR as a newly identified alloantibody occurring between 24 h and 28 days after transfusion associated with hemolysis or spherocytes [94]. DHTRs are most commonly caused by Rh (DCE), K, Kidd, and Duffy antibodies. Of these, Jk^a is the most commonly implicated [103]. 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 [104] and a drop in reticulocytes below the patient's baseline. The risk of hyperhemolysis in this setting has been reported to be 4 % [105]. Additional transfusion may exacerbate the degree of hemolysis. Successful treatment with plasma-to-RBC replacement, corticosteroids, IVIG, and rituximab has been reported [106].

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 [102]. 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 [94]. 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 35.13.

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 [114]. However, actual recipient infection is more commonly seen with *Staphylococcus aureus* and *Serratia marcescens* [96]. *Babesia microti* infections are transmitted by RBC transfusion and were the most commonly reported cause of transfusion-transmitted fatal infections between 2010

Table 35.14 Estimated risks for transfusion-transmitted viral infection in the United States

Infection	Risk per unit
Hepatitis B	1:765,000–1:1,006,000 [117]
Hepatitis C	1:1,149,000 [118]
HIV	1:1,467,000 [118]
HTLV I/II	1:2,679,000 [118]

and 2014 [96]. New testing strategies aimed at detecting *Babesia* in the blood supply are being investigated [115]. *Yersinia enterocolitica* infection is also associated with RBC transfusion [116]. Transfusion-transmitted bacteremia is reported to occur as a result of 1:100,000 platelet transfusions and 1:5,000,000 red cell transfusions [116].

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*. The approximate risk for transfusion-transmitted viral infections in the United States is listed in Table 35.14. Additional infectious disease risks include malaria, prion disease, and Zika virus.

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 transfusion occurs only in the setting of an appropriate indication and at a dose that is 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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