INTRODUCTION

This chapter focuses on a variety of pathophysiologic conditions associated with abnormal hemostasis or abnormal laboratory measurements of hemostasis. In order to understand how to approach a patient with a bleeding problem, this chapter will start with a brief overview of our current understanding of coagulation including an overview of the processes involved in the regulation of hemostasis and a brief discussion of the interactions of coagulation and inflammation. The coagulopathic conditions frequently encountered in the intensive care unit (ICU) can be arbitrarily divided into three categories: conditions associated with serious bleeding or a high probability of bleeding; thrombotic syndromes or conditions associated with a higher probability of thrombosis; and systemic diseases associated with acquired selective coagulation factor deficiencies. In addition, there are a few conditions associated with abnormal coagulation screening tests that represent laboratory phenomena that are not associated with an increased risk of bleeding. A topical listing of these conditions is included for review in Table 143.1. The order in which these categories are listed suggests their relative importance to the critical care practitioner. This chapter will then end by noting future directions in research and care of the critically ill patient with a hemostatic abnormality. While space limitation will not allow for a comprehensive discussion of all aspects of pathophysiology, clinical presentation, and management of hemorrhagic and thrombotic disorders encountered in the ICU, the goal is to provide a framework that will allow the reader to garner a basic understanding of the issues and direct him/her toward additional sources of information.

OVERVIEW OF COAGULATION

Traditionally, medical students have been taught that the process of blood clotting is divided into the “intrinsic,” “extrinsic,” and “common” pathways (Fig. 143.1), and students often come away with the thought that clotting occurs as the result of an orderly, sequential process. While this arbitrary segmentation of the clotting process may allow for a basic level of understanding, it obscures the fact that once initiated, clot production and clot destruction (fibrinolysis) occur simultaneously, and also minimizes the role platelets and the endothelium play in the overall process. This section of the chapter will try to clarify some of the newer thoughts on coagulation and the overall process of hemostasis.

While previously it was thought that the “intrinsic” pathway beginning with the activation of factor XII (F.XII) to activated factor XII (F.XIIa) in contact with some biologic or foreign surface was physiologically most important in the initiation of clot formation, we now know that the activation of F.X to F.Xa through the action of the F.VIIa/tissue factor (TF) complex is paramount in this regard (1,2). It is also evident that the various elements of the clotting cascade frequently act in concert; hence the use of the term “tenase” to describe the action of F.VIIa /TF complex along with the F.IXa/F.VIIIa complex on the activation of factor X to Xa, and the use of the term “prothrombinase” to describe the factor Xa/Va complex which cleaves prothrombin (factor II) to form thrombin (factor IIa). In addition, we now know that there is both “cross-talk” between the two arms of the clotting cascade and downstream effects of several clotting factors. Chief among these is the ability of F.VIIa to enhance the activation of F.IX (to F.IXa) and F.XI (to F.XIa) (further pointing out the central role F.VIIa and TF play in vivo) and the procoagulant effect of F.VI in activating F.V and F.VIII to their active forms (F.Va and factor VIIa) (3) (Fig. 143.2). Furthermore, there are various “feedback” loops, principally involving thrombin, that enhance the “upstream” activation and inhibition of the clotting process.

Tissue factor is present not only in the subendothelial matrix, but is also present circulating freely in plasma as soluble tissue factor and can be identified on cellular elements such as monocytes. However, clotting does not occur in free flowing blood but rather on surfaces. Platelets, endothelial cells, the subendothelial matrix, and biologic polymers (e.g., catheters, grafts, stents, etc.) can provide these surfaces for clot formation and all play a critical role in clot formation.

Platelets not only initiate the clot formation through the formation of a platelet plug, but, more importantly, they bring specialized proteins that regulate the clotting response (e.g., F.VIII, inhibitors of fibrinolysis, etc.) to the area of bleeding, and provide a surface for the colocalization of clotting factors for efficient clot formation (Fig. 143.3). Platelets do not ordinarily adhere to the vascular endothelium, but when the endothelium is mechanically disrupted (e.g., cut) or activated by inflammation, platelets will then bind to the endothelial cell or subendothelial matrix via a von Willebrand factor (vWF)-dependent mechanism. Once adherent, the platelets become activated and secrete various molecules that further enhance
Blood coagulation and platelet activation and modulates vascular tone and permeability. Endothelial cells also synthesize and secrete the components of the subendothelial extracellular matrix including adhesive glycoproteins, collagen, fibronectin, and vWF. When disrupted, bleeding occurs. However, when injured, the endothelium often becomes a prothrombotic rather than an antithrombotic organ and unwanted clot formation may occur. The final phase in hemostasis, fibrinolysis, is also dependent on both plasma and endothelial cell factors (Fig. 143.5). None of these are measured in the traditional tests of coagulation (i.e., PT, aPTT) and, consequently, these tests will be normal unless the pace of fibrinolysis is such that clotting factor consumption is greater that replacement (i.e., a consumptive coagulopathy, DIC) (7). Fibrinolysis is initiated once thrombin is generated and will result in an increase in fibrin and fibrinogen fragments (D-dimer or FSPs/FDPs, respectively). Thrombin binding to thrombomodulin on the endothelial surface is a critical step in the thrombin-mediated activation of protein C (to produce activated protein C; aPC) and for the activation of thrombin-activatable fibrinolysis inhibitor (TAFI). However, activation or injury to endothelial cells frequently results in a shedding of surface expressed thrombomodulin (and an increase in plasma soluble thrombomodulin) and, therefore, a decrease in intrinsic anticoagulation (i.e., decrease in aPC) and fibrinolysis inhibition (i.e., decreased TAFI), both of which will increase the risk of microvascular thrombosis and development of multiorgan dysfunction (8,9).

There are multiple points of intersection between the biochemical events of inflammation and those of coagulation and fibrinolysis (10–12). While a full discussion of these points is beyond the scope of this chapter, the “cross-talk” between inflammation and coagulation likely takes place at the level of the endothelium, and is bidirectional wherein activation
of either pathway affects the functioning of the other (10). While many different inflammatory cytokines have been identified as promoters of a procoagulant milieu, the interconnection of TF and tissue necrosis factor-α (TNF-α) may potentially be the most important of these (13). During sepsis, tissue factor expression is upregulated in activated monocytes and endothelial cells as a response to endotoxin, with the consequence being both the secretion of pro-inflammatory cytokines (e.g., IL-6, TNF) from activated mononuclear cells, and the activation of coagulation. This results in increased thrombin production which plays a central role in coagulation and inflammation through the induction of procoagulant, anticoagulant, inflammatory, and mitogenic responses (12). Thrombin results in the activation, aggregation and lysis of leukocytes and platelets, activation of endothelial cells with resultant increase in pro-inflammatory cytokines IL-6 and TNF expression. The net result of thrombin generation is to produce a pro-inflammatory and procoagulant state leading to the formation of fibrin and microvascular thrombosis. However, these pro-inflammatory effects of thrombin are counterbalanced by the anti-inflammatory effects of activated protein C (aPC) (see Fig. 143.4) (12).

![Diagram of clotting pathways](image)

**FIGURE 143.2** Modified clotting cascade indicating cross-talk between the intrinsic and extrinsic pathways by the action of Villa/tissue factor (TF) enhancing the conversion of factor XI to activated factor XI (Xla) (dotted lines).

**FIGURE 143.3** The role of platelets in mediating primary hemostasis at sites of vascular injury. Platelets are initially activated and express specific adhesion receptors on their surface followed by adhesion to activated endothelial cells and exposed subendothelial components (e.g., collagen, von Willebrand factor). Subsequent platelet aggregation occurs with the development of a primary platelet plug. Coagulation occurs on the developing platelet plug with the creation of a fibrin clot.
The second important point of connection of coagulation and inflammation is through the protein C system (14–16). While the anticoagulant effects of aPC and its cofactor protein S are well known, only recently have the anti-inflammatory roles of these proteins been appreciated. In experimental models, aPC has been shown to increase the secretion of anti-inflammatory cytokines, reduce leukocyte migration and adhesion, and protect endothelial cells from injury. Additionally, the balance between the anticoagulant and anti-inflammatory roles of aPC may be mediated by the relative distribution of free and C₄BP bound protein S (15,16). *In vitro*, aPC inhibits TNF-α elaboration from monocytes and blocks leukocyte adhesion to selectins, as well as influences apoptosis (12). The protein C pathway is engaged when thrombin binds to thrombomodulin on the surface of the endothelium. Binding of PC to the endothelial cell protein C receptor (EPCR) augments protein C activation by the thrombin–TM complex more than 10-fold *in vivo*. EPCR is shed from the endothelium through the action of inflammatory mediators and thrombin thereby down regulating aPC generation in sepsis and inflammation.

The third important link between inflammation and coagulation occurs at the level of fibrinolysis and also involves the protein C system. aPC is capable of neutralizing the fibrinolysis inhibitors plasminogen activator inhibitor type-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI). Consequently, depressed levels of aPC not only promote clot for-
mation by reducing the inactivation of the procoagulant molecule–activated factors V and VII (FV,V, FVIIIa) leading to increased generation of thrombin and fibrin clots, but also by limiting the fibrinolytic response needed to degrade clots. TAFI (also known as carboxypeptidase R) has also been shown to inactivate inflammatory peptides such as complement factors C3a and C5a which can play a role in the contact activation of coagulation. In addition, polymorphisms of the promoter region of the PAI-1 gene which lead to differences in PAI-1 production have been demonstrated to affect the prognosis in meningococcal sepsis and multiple trauma pointing out the important role of this regulatory system (17). This finding points out the importance of our developing knowledge of how common polymorphisms of genes encoding important molecules affect our response to infection and injury. The importance of these interactions between coagulation and inflammation, the central role of protein C, and the importance gene polymorphisms play in host responses and clinical outcomes is further reinforced by a recent report demonstrating increased mortality and organ dysfunctions and increased inflammation in patients who exhibited a specific polymorphism (1641AA) of the protein C gene (18).

AN APPROACH TO THE PATIENT WITH AN ACTUAL OR SUSPECTED COAGULATION DISORDER

Clinical History

Diagnostic assessment begins at the bedside. The medical history, both past and present, may lend some insight into the risk for significant bleeding (19,20). A prior history of prolonged or excessive bleeding or of recurrent thrombosis is important to elicit. Specific questions regarding bleeding should investigate the occurrence of any of the following: spontaneous, easy, or disproportionately severe bruising; intramuscular hematoma formation (either spontaneous or related to trauma); spontaneous or trauma-induced hemorrhrosis; spontaneous mucous membrane bleeding; prior problems with bleeding related to surgery (including dental extractions, tonsillectomy, and circumcision); the need for transfusions in the past; menstrual history; and, finally, current medications. There are innumerable aspirin-containing medications available to the consumer, all of which can potentially interfere with platelet-mediated primary hemostasis. Many other drugs used in the ICU also are associated with bleeding abnormalities and are discussed later in this chapter. In situations involving trauma (either surgical or accidental), it is important to determine the severity of injury relative to the magnitude of bleeding that followed. A prior history of significant thrombosis (e.g., deep venous thrombosis, pulmonary embolus, and stroke) also suggests the possibility that a hypercoagulable condition may be present. As thrombotic events are generally uncommon in younger adults, the occurrence of thrombotic events, particularly early cardiovascular events such as myocardial infarction, in young adult relatives should cause the clinician to consider the presence of a congenital thrombophilic abnormality in his patient. These include deficiencies of antithrombin III, protein C or protein S, the presence of the factor V Leiden R506Q mutation, and the prothrombin G20210A polymorphism/mutation. While the C677T mutation/polymorphism of the MTHFR (methylene tetrahydrofolate reductase) gene has previously been identified as a thrombotic risk factor, more recent evaluation of the available data suggests that the thrombophilic risk of this genetic may principally derive from the increase in serum homocysteine that can result from this mutation. Consequently, it may be that only in the presence of an elevated serum homocysteine is the C677T mutation of the MTHFR gene clinically relevant (21–23). In addition, vasculitis associated with an “autoimmune” disorder such as systemic lupus erythematosus (SLE) must always be considered in the evaluation of an individual with an unexplained pathologic clot. In all cases, the family history is important in trying to separate congenital from acquired disorders.

In a general sense, one can segregate defects into those involving primary or secondary hemostasis according to the nature of the bleeding. Patients with primary hemostatic defects tend to manifest “platelet- or capillary-type bleeding”—oozing from cuts or incisions, mucous membrane bleeding, or excessive bruising. This type of bleeding is seen in patients with quantitative or qualitative platelet defects or von Willebrand disease. In contrast, patients with deficits in secondary hemostasis tend to display “large-vessel bleeding” characterized by hemarthroses, intramuscular hematomas, and the like. This type of bleeding is most often associated with specific coagulation factor deficiencies or inhibitors.

Physical Examination

Development of generalized bleeding in critically ill ICU patients presents a special problem. Such bleeding is often associated with severe underlying multiple organ system dysfunction. Thus, correction of the coagulopathy usually requires improvement in the patient’s overall clinical status. Supportive evidence or physical findings of other concurrent organ system dysfunction (e.g., oliguria or anuria, respiratory failure, hypotension) often are readily apparent. With the exception of massive transfusion syndrome (discussed later), generalized bleeding in critically ill patients is often caused by sepsis-related DIC (24,25). However, the clinician must also consider the coagulopathy of severe liver dysfunction, undiagnosed hemophilia, or, in the elderly or debilitated, vitamin K deficiency in the differential diagnosis (24-26).

The physical examination of the patient with a bleeding disorder should answer several basic questions. Is the process localized or diffuse? Is it related to an anatomic or surgical lesion? Is there mucus bleeding? And finally, when appropriate, are there signs of thrombosis (either arterial or venous)? These answers may give clues to the cause of the problem (primary vs. secondary hemostatic dysfunction; anatomic bleeding vs. generalized coagulopathy).

During the course of the examination, particular attention should be paid to the presence of several specific physical findings that may be helpful in determining the etiology of a suspected hemostatic abnormality. For example, the presence of an enlarged spleen coupled with thrombocytopenia suggests that splenic sequestration may be a contributor to the observed thrombocytopenia. Further, evidence of liver disease (e.g., portal hypertension, ascites) points to decreased factor synthesis as a possible etiology of a prolonged PT or aPTT. When lymphadenopathy, splenomegaly, or other findings suggestive of disseminated malignancy are detected, acute or chronic DIC should be suspected as the cause of prolonged coagulation times, hypofibrinogenemia, and/or thrombocytopenia. Purpura that are palpable suggest capillary leak from vasculitis, whereas purpura associated with thrombocytopenia or qualitative
platelet defects are generally not elevated and cannot be distinguished by touch. Finally, venous and arterial telangiectasia may be seen in von Willebrand disease and liver disease, respectively. When selective pressure is centrally applied to an arterial telangiectasia, the whole lesion fades, whereas a venous telangiectasia requires confluent pressure across the entire lesion (as with a glass slide) for blanching to occur.

**Diagnostic Laboratory Evaluation**

This section focuses on selecting appropriate tests to enable the clinician to sort out information from the history, physical examination, or previously obtained (and often confusing) laboratory data. Before we proceed, however, the importance of correct specimen collection for hemostatic evaluation must be emphasized. In the ICU, it is common for laboratory samples to be drawn through an indwelling arterial or central venous cannula, often because other access is no longer available. Heparin is, therefore, commonly present, either in solutions used to flush the cannula, to transduce a waveform, or as a component of the intravenous infusion. Depending on the concentration of heparin in the infusing fluid and the volume of blood withdrawn, several tests can be influenced. Fibrin degradation products (FDPs) can be falsely elevated and fibrinogen can be falsely low. Likewise, the PT, aPTT, and thrombin time (TT) can be spuriously prolonged. A minimum of 20 mL of blood in adolescents and adults (10 mL of blood in younger children) should therefore be withdrawn through the cannula and either discarded or used for other purposes before obtaining a specimen for laboratory hemostasis analysis (27). This practice should minimize any influence of heparin on the results. In some clinical situations, it may not be reasonable to withdraw this volume of blood and a peripheral venipuncture may be necessary. Because the aPTT is sensitive to the presence of small amounts of heparin, the presence of an unexpected prolonged aPTT obtained through a heparinized catheter should raise the suspicion of sample contamination. In this setting, the TT also will be prolonged but will normalize if the contaminating heparin is neutralized (e.g., with toluidine blue or protamine sulfate).

The presence of most suspected bleeding disorders can be confirmed using routinely available tests. These include evaluation of the peripheral blood smear (including an estimate of the platelet count and platelet and red blood cell morphologic features); measurement of the PT, aPTT, and the TT; and, finally, assays for fibrinogen or the presence of FDPs or the D-dimer fragment of polymerized fibrin. This latter test is more specific for the fibrinolytic fragment produced when polymerized fibrin monomer, produced through the action of thrombin on fibrinogen, is cleaved by the proteolytic enzyme plasmin (8). In contrast to the older assays for fibrin degradation or fibrin-split products (FDPs and FSPs) which will be positive even if fibrin is not produced and the fragments are the result of proteolytic degradation of native fibrinogen, the D-dimer assay is positive only if fibrinogen has been cleaved to fibrin by the action of thrombin. Discretion should be used in determining which of these tests are most appropriate for assessment; they need not be ordered as a blanket panel on all patients with known or suspected bleeding disorders. Table 143.2 summarizes several major categories of hemorrhagic disorders and the tests that are characteristically abnormal in each. In most instances, measurement of the platelet count, fibrinogen level, PT, aPTT, and TT should provide sufficient information for determining the correct diagnosis—or at least making an educated guess. By using these five screening tests and assessing other more specific tests only when an absolute diagnosis is necessary, inappropriate use of laboratory resources may be avoided. The use of thromboelastography as tool to both assess hemostasis and guide transfusion of blood products in patients is frequently employed in Europe but less often in North America. While this methodology (thromboelastography [TEG] or rotational thromboelastometry [ROTEM]) offers potential benefits over...
plasma-based tests (e.g., aPTT, PT, TT), by simultaneously assessing the multiple elements of hemostasis in whole blood, adoption of this testing methodology has been sporadic as it has not yet been shown to be superior to the more traditional plasma-based tests of coagulation (28–30).

**Evaluation of Thrombosis**

Patients who present with a thrombotic event will generally not display abnormalities of usual “clotting” studies, that is, their PT, aPTT, TT, and fibrinogen will usually be within normal ranges. While hyperfibrinogenemia and persistent elevations of FVIII have been associated with an increased risk of thrombosis, both may be elevated by acute inflammation and consequently the finding of elevations of these clotting factors is of limited usefulness in the evaluation of a thrombotic event in an acutely ill individual. Other studies such as TEG, ROTEM, measurement of endogenous thrombin potential (ETP), indirect markers of thrombin generation (e.g., prothrombin fragment F1+2, thrombin–antithrombin complexes [TAT], and markers of fibrinolysis activation and inhibition (e.g., plasmin–antiplasmin complexes [PAP], PAI-1 activity) may be more useful in identifying those patients most at risk for thrombotic events (31). However, most of these studies do not fall into the category of “routine” tests readily available with a rapid turnaround time that would facilitate acute care decision-making. Several inherited or acquired abnormalities that place an individual at increased risk for thrombosis have been identified and determination of these factors should be undertaken when a thrombotic event is suspected or documented. Prior to initiation of anticoagulation, plasma levels of protein C (antigen and activity), protein S (antigen and activity; total and free), and antithrombin III (antigen and activity) should be obtained. In addition, PCR analysis for mutations in the factor V (factor V Leiden; [Arg]R506Q[Gln]), and prothrombin ([Gly]G20210A[Ala]) genes should be performed; determination of the methylenetetrahydrofolate reductase (MTHFR; [Cys]C677T[Thr]) mutation can be deferred unless serum homocysteine is found to be elevated. Acquired thrombosis risk factors include the presence of “Lupus” anticoagulants, antiphospholipid and anticardiolipin antibodies which may be associated with underlying autoimmune disorders or with acute inflammation. In adult populations, approximately 40% of patients with thrombosis will not display one of the known thrombophilic risk factors. The intensivist must look for confounding clinical conditions such as severe dehydration with marked hemoconcentration (in the case of central venous sinus thrombosis), indwelling catheters, vascular compression (e.g., cervical ribs), type-II heparin-induced thrombocytopenia (see below), etc. in their evaluation of a patient with thrombosis.

**CONDITIONS ASSOCIATED WITH SERIOUS BLEEDING OR A HIGH PROBABILITY OF BLEEDING**

**Disseminated Intravascular Coagulation**

**Pathogenesis**

Because it often occurs in conjunction with more serious, life-threatening disorders, DIC is one of the most serious hemostatic abnormalities seen in the ICU. The clinical syndrome itself results from the activation of blood coagulation, which then leads to excessive thrombin generation. The final result of this process is the widespread formation of fibrin thrombi in the microcirculation, with resultant consumption of certain clotting factors and platelets. Ultimately, this consumption generally results in the development of significant bleeding as the rate of consumption outpaces the rate at which the clotting factors and platelets are produced (32). Table 143.3 reviews several specific conditions associated with the development of DIC. In general, the conditions associated with DIC are the same for either adult or pediatric populations. These include a wide variety of disorders that share as their common feature the ability to initiate coagulation to varying degrees. The mechanisms involved generally can be considered in two categories: (1) those intrinsic processes that enzymatically activate procoagulant proteins; and (2) those that cause the release of tissue factor, which then triggers coagulation. These are complex events that can lead to significant bleeding and often complicate the management of an already critically ill patient.

Fibrinolysis invariably accompanies thrombin formation in DIC (32). Thrombin generation or release of tissue plasminogen activator usually initiates this process. Plasmin is generated which then digests fibrinogen and fibrin clots as they form. Plasmin also inactivates several activated coagulation factors and also impairs platelet aggregation. DIC represents an imbalance between the activity of thrombin, which leads to microvascular thrombi with coagulation factor and platelet consumption, and plasmin, which degrades these fibrin-based clots as they form. Therefore, thrombin-induced coagulation factor consumption, thrombocytopenia, and plasmin generation all contribute to the presence of bleeding.

In addition to bleeding complications, the presence of fibrin thrombi in the microcirculation also can lead to ischemic tissue injury. Pathologic data indicate that renal failure, acrocyanosis, multifocal pulmonary emboli, and transient cerebral ischemia may be related clinically to the presence of such thrombi. The fibrinopeptides A and B (resulting from enzymatic cleavage of fibrinogen) lead to pulmonary and systemic

**TABLE 143.3 Underlying Diseases Associated With Disseminated Intravascular Coagulation**

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Severe liver disease</td>
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<tr>
<td>Shock</td>
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<tr>
<td>Penetrating brain injury</td>
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<tr>
<td>Necrotizing pneumonitis</td>
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<tr>
<td>Tissue necrosis/crush injury</td>
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<tr>
<td>Intravascular hemolysis</td>
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<tr>
<td>Acute promyelocytic leukemia</td>
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<tr>
<td>Thermal injury</td>
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<tr>
<td>Freshwater drowning</td>
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<td>Fat embolism syndrome</td>
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<tr>
<td>Retained placenta</td>
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<tr>
<td>Hypertonic saline abortion</td>
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<tr>
<td>Amniotic fluid embolus</td>
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<tr>
<td>Retention of a dead fetus</td>
</tr>
<tr>
<td>Eclampsia</td>
</tr>
<tr>
<td>Localized endothelial injury</td>
</tr>
<tr>
<td>Acrocyanosis, giant hemangiomata, angiography</td>
</tr>
<tr>
<td>Disseminated malignancy (prostate, pancreatic)</td>
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</tbody>
</table>
vasoconstriction, which can potentiate an existing ischemic injury. In a given patient with DIC, either bleeding or thrombotic tendencies may predominate; in most patients, bleeding is usually the predominant problem. In up to 10% of patients with DIC, however, the presentation is exclusively thrombotic (e.g., pulmonary emboli with pulmonary hypertension, renal insufficiency, altered mental status, acrocyanosis) without hemorrhage. Whether the presentation of DIC is thrombotic, hemorrhagic or “compensated” (i.e., laboratory results consistent with DIC without overt bleeding), microthrombosis probably contributes to the development and progression of multiorgan failure.

Clinical Presentation and Diagnosis

The suspicion that DIC is present usually stems from one of two situations: (1) unexplained, generalized oozing or bleeding; or (2) unexplained abnormal laboratory parameters of hemostasis. This usually occurs in the context of a suggestive clinical scenario or associated disease (see Table 143.3). While infection and multiple trauma are the most common underlying conditions associated with the development of DIC, certain other organ system dysfunctions predispose to DIC, including hepatic insufficiency and splenectomy (24,25). Both of these conditions are associated with impaired reticuloendothelial system function and consequent impaired clearance of activated coagulation proteins and fibrin/fibrinogen degradation fragments which may inhibit fibrin polymerization and clot formation.

The clinical severity of DIC frequently has been assessed by the severity of bleeding and coagulation abnormalities. Recently, scoring tools employing a panel of laboratory tests along with severity of illness scores to assess the likelihood and severity of DIC have been proposed in an attempt to determine diagnosis and direct initial therapy at the time of diagnosis. A listing of the tests most commonly employed in many of these scoring systems for the diagnosis of DIC are found in Table 143.4. The use of these scoring systems for the early diagnosis and treatment of DIC does appear to have prognostic value, particularly in patients with sepsis (33–35). The systems suggested by Leclerc (36) (for children) and those developed by the International Society on Thrombosis and Hemostasis (ISTH) (37) and Japanese Association for Acute Medicine (JAAM) (38) are three of the more commonly employed scoring systems and may serve as a template for the diagnosis of DIC: a qualitative score (three out of tests positive; Leclerc) or a quantitative score (five points ISTH, four points JAAM) are strongly suggestive of a diagnosis of DIC. The combination of a prolonged PT, hypofibrinogenemia, and thrombocytopenia in the appropriate clinical setting is sufficient to suspect the diagnosis of DIC in most instances. Severe hepatic insufficiency (with splenomegaly and splenic sequestration of platelets) also can yield a similar laboratory profile and must be ruled out.

In addition to liver disease, several other conditions have presentations similar to DIC and must be considered in the differential diagnosis:

- Liver disease
- Massive transfusion
- Primary fibrinolysis
- Thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS)
- Heparin therapy
- Dysfibrinogenemia

With the exception of massive transfusion syndrome, these disorders generally have only two of the three characteristic laboratory findings of DIC; a comparison of the laboratory findings in these disorders is noted in Table 143.2. In order to confirm a diagnosis of suspected DIC, confirmatory tests indicating increased fibrinogen turnover (i.e., elevated FDPs or D-dimer assay) may be necessary. The D-dimer assay for the D–D fragment of polymerized fibrin has been shown to be both highly sensitive and specific for proteolytic degradation of polymerized fibrin (fibrin clot that has been produced in the presence of thrombin). Consequently, this test is being employed with increasing frequency in patients with suspected DIC. However, remembering that thrombin is produced whenever coagulation is activated in the presence of bleeding, the clinician must interpret a modest elevation of D-dimer in a postoperative or trauma patient with some degree of caution.

The presence of a marked elevation of D-dimer in a nonbleeding patient essentially excludes primary fibrinogenolysis as the sole cause of measurable FDPs in the serum. The TT is a less sensitive test for DIC, but may be useful in cases of suspected heparin overdose because it corrects in the test tube with the addition of protamine sulfate or toluidine blue. Similarly, the euglobulin clot lysis time may not be sensitive to fibrinolysis associated with DIC but is significantly shortened in most cases of primary fibrinolysis. Other tests of purported value, such as soluble fibrin monomer or thrombin–antithrombin complex formation, either have problems with sensitivity or are impractical for widespread use outside of research settings.

TTP and HUS

Specific mention of TTP and HUS should be made. While neither generally produces a coagulopathic state, both are characterized by marked microangiopathy and microvascular thrombosis. While their similar clinical presentation suggests that these two diseases may represent different ends of the spectrum of end-organ dysfunction possible in microangiopathic states, our improved understanding of the pathophysiology in these two entities confirms that they are not merely differing clinical manifestations of a single-disease entity (39). TTP is characterized by the pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurologic symptoms, fever, and renal dysfunction. While only 40% of patients will display the full pentad, up to 75% will manifest a triad of MAHA, neurologic symptoms, and thrombocytopenia. This disorder is felt to be due to the congenital or acquired (often antibody-mediated) absence of a vWF cleaving protease (ADAMTS13) resulting in the circulation of unusually large vWF multimers which can induce or enhance the pathologic adhesion of platelets to the endothelium. The therapy of choice for TTP is plasma exchange by apheresis. While the literature is not consistent regarding routine (prophylactic) platelet transfusions in TTP.
Management of DIC

The primary treatment for DIC is correction of the underlying problem that led to its development. Specific therapy for DIC should not be undertaken unless the patient has significant bleeding or organ dysfunction secondary to DIC, significant thrombosis has occurred, or treatment of the underlying disorder (i.e., acute promyelocytic leukemia) is likely to increase the severity of DIC.

Supportive therapy for DIC includes the use of several component blood products (45). Packed red blood cells are given according to accepted guidelines in the face of active bleeding. Fresh whole blood (i.e., less than 24 to 48 hours old) also may be given to replete both volume and oxygen-carrying capacity, with the additional potential benefit of providing coagulation proteins, including fibrinogen, and platelets. Fresh frozen plasma (FFP) is of limited value for the treatment of significant hypofibrinogenemia because of the inordinate volumes required to produce any meaningful increase in plasma fibrinogen concentration. Infusion of fibrinogen concentrate, or if concentrate is not available, cryoprecipitate is the preferred product for the correction of significant hypofibrinogenemia (46). FFP infusions, however, may effectively replete other coagulation factors consumed with DIC such as protein C although the increase in these proteins may be quite small unless large volumes of FFP are infused. The use of cryoprecipitate, FFP, or other blood products in the treatment of DIC has, in the past, been open to debate because of concern that these products may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and "turn off" ongoing coagulation so that repletion of coagulation factors.
XIII activity also is often decreased in the setting of hepatocellular disease. However, the clinical significance of this decrease in factor XIII is uncertain because levels as low as 3% provide for normal fibrin clot stabilization. Although factor VIII (i.e., factor VIII-C, AHF) is synthesized in the liver, recent data shows it to be in hepatic sinusoidal cells rather than hepatocytes (58). Consequently, synthesis seems to be independent of the state of hepatic function. Indeed, factor VIII levels may be increased in some types of liver disease. Plasma protein C and antithrombin III levels are low in many conditions of hepatic insufficiency, with variable effects.

In addition to these deficiencies in plasma coagulation protein synthesis, many patients with liver disease, particularly cirrhosis, have increased fibrinolytic activity. The mechanism for this heightened fibrinolytic state is not clear but may be related to the increased amounts of plasminogen activator often noted in these patients. It may be difficult to discern whether fibrinolysis occurs solely because of underlying severe liver disease or as a result of a concurrent DIC as patients with cirrhosis are at increased risk for the development of DIC. The clinical distinction between primary DIC and a secondary hemostatic defect resulting from liver disease can be virtually impossible to make if active bleeding is present. In liver disease, levels of FDPs can be increased by both increased fibrinolysis and by decreased hepatic clearance. Finally, clinically significant fibrinolysis is a frequent occurrence in patients who undergo portacaval shunt procedures.

Thrombocytopenia may be present to a variable degree in patients with hepatic dysfunction. This is usually ascribed to splenic sequestration. It is rarely profound and generally does not produce clinically significant bleeding as a solitary defect. *In vitro* platelet aggregation may also be affected, however. Increased plasma concentrations of FDPs are a possible cause of these qualitative platelet abnormalities. The thrombocytopenia of liver disease in conjunction with other coagulation or hemostatic defects secondary to liver disease may result in bleeding that is difficult to manage clinically, particularly if all aspects of the problem are not addressed.

Patients with hepatocellular liver disease may also exhibit decreased synthesis of the vitamin K-dependent anticoagulant proteins, protein C and protein S, as well as antithrombin III (56). Decreased levels of these natural anticoagulants may increase the risk of thrombosis. Neither the PT, aPTT, nor TT will be affected by the levels of any of these naturally occurring anticoagulants.

**Presentation**

The hemostatic defect in liver disease is multifactorial, and each patient should be approached accordingly. The most common scenario is a patient with liver disease and a prolonged PT without overt bleeding in whom the potential for bleeding is a concern. In patients with liver disease and impaired synthetic capabilities, particularly those who are critically ill, factor VII activity levels are usually the first to decrease due to its short half-life of 4 to 6 hours and increased turnover. This results in a prolonged PT, and can be noted even when usual markers of hepatocellular injury or hepatic insufficiency remain relatively normal (56, 57). A prolonged TT in the setting of liver disease may indicate the presence of dysfibrinogenemia as a result of altered hepatic fibrinogen synthesis, or may indicate an acquired defect in fibrin polymerization (e.g., increased FDPs). As the severity of liver disease increases, the aPTT also may be affected, reflecting more severely impaired synthetic function. In this setting, plasma concentrations of the vitamin K-dependent coagulation proteins decrease, as do those of factor V (which is not vitamin K–dependent). Although fibrinogen synthesis occurs in the liver, plasma levels of fibrinogen are generally maintained until the disease approaches end-stage. When fibrinogen levels are severely depressed, liver failure has typically reached the terminal phase. In contrast to the hypofibrinogenemia noted with consumptive coagulopathies, hypo-fibrinogenemia noted in liver disease is the result of decreased synthesis and is not accompanied by a marked increase in either FDPs or D-dimers.

In more severe forms of liver disease, fibrinolysis may complicate clinical management. The differentiation between concomitant DIC and fibrinolysis attributable to liver disease alone may be difficult (57). The D-dimer assay result should be negative in the patient who has liver disease and elevated FDPs but no active bleeding. Further clinical distinction usually is not possible.

**Management**

If the patient is not actively bleeding, no specific therapy is required, with certain provisos. In patients with a markedly prolonged PT who are in a postoperative state or are scheduled for an invasive procedure, correction of the PT should be attempted. FFP or a prothrombin complex concentrate (PCC) provides the most immediate source of specific coagulation factors (i.e., factors II, VII, IX, and X). While FFP usually corrects an isolated mild PT prolongation, it is less effective in correcting a more profound prolongation of the PT. Consequently, consensus is moving toward the use of a PCC, preferably a 4-factor PCC (4PCC) as the initial choice to correct a markedly prolonged PT due to the greater amount of F.VII contained in 4PCCs. For this reason, 4PCCs are also preferred over the use of rhFVIIa to correct a prolonged PT (59). Fibrinogen support in the form of fibrinogen concentrate or cryoprecipitate is required if fibrinogen levels are <50 to 100 mg/dL, or if there is documentation of a significant dysfibrinogenemia. The routine correction of prolonged PT/INR in patients who are to undergo minor invasive procedures has not been shown to affect procedural blood loss (60).

Vitamin K deficiency is also relatively common in this patient population, and replacement may be needed. In contrast to patients with dietary vitamin K deficiency and normal liver function, correction of the PT in vitamin K–responsive critically ill patients typically requires longer than 12 to 24 hours. Patients with significant hepatic impairment may manifest a partial response or may not respond at all. Individuals with severe liver disease, or marked prolonged vitamin K deficiency, will demonstrate a prolongation of the aPTT in addition to a prolonged PT. This prolongation of the aPTT is the result of other clotting factors besides F.VII being low. In this setting, the use of rhFVIIa will not provide adequate hemostatic support. If the prolongation of the aPTT is due solely to decreases in the vitamin K–dependent factors (II, VII, IX, X), infusion of a 4PCC is the treatment of choice. However, if other clotting factor deficiency is suspected, plasma (either FFP or commercial solvent/detergent-purified commercial product) is preferred. While recombinant human activated factor VII (rhFVIIa) infusions have been shown to control the bleeding in severe liver disease, reduced reduction in mortality has not been demonstrated (51, 59). The use of rhFVIIa should
be reserved for patients with poorly controlled bleeding that is
unresponsive to other more established therapeutic modalities
such as infusion of plasma or 4PCCs.

A comprehensive therapeutic approach is needed in the
patient with active bleeding as a result of liver disease. Ini-
tially, a 4PCC at a dose calculated to increase F.VII to ≥50% of
normal (i.e., 0.5 units/mL) should be administered. If a 4PCC
is not available, plasma, 10 to 15 cc/kg body weight, may be
given. Doses of 4PCC or plasma should be repeated every 6
to 8 hours until bleeding slows significantly, and should then
be continued at maintenance levels as dictated by clinical sta-
 tus and coagulation studies. Recombinant human activated
factor VII may be used in those patients unresponsive to FFP
infusions (60). Cryoprecipitate should be infused for fibrino-
gen levels <50 to 100 mg/dL. Platelet transfusions also may
be required if the platelet count is <40 to 80,000/μL, depend-
ing on the clinical situation. Vitamin K should be empirically
administered on the presumption that part of the synthetic
defect may result from a lack of this cofactor. However, one
must anticipate a poor response to vitamin K in the presence
of severe liver disease. Transfusions of packed cells are given
as deemed appropriate by the clinician.

**Vitamin K Deficiency**

The most common cause of a prolonged PT in the ICU is vita-
mamin K deficiency. Vitamin K is necessary for the gamma-car-
boxylation of factors II, VII, IX, and X, without which these
factors cannot bind calcium and are not efficiently converted
into their activated forms. Factor VII has the shortest half-life
of these coagulation proteins; accordingly, the PT is the most
sensitive early indicator of vitamin K deficiency.

Vitamin K deficiency is relatively common in critically ill
patients for several reasons including the use of broad-spec-
trum antibiotics, poor nutrition preceding or subsequent to
ICU admission, and the use of parenteral nutrition without
vitamin K supplementation. Many of the second- and third-
generation cephalosporins directly interfere with vitamin K
absorption from the gut lumen. The metabolites of some of
these antibiotics may even act as competitive inhibitors
of vitamin K. In addition, these and other antibiotics may
kill or inhibit the growth of gut bacteria and thus limit the
amounts of vitamin K they normally produce and excrete into
the gut lumen. While malnutrition also may contribute to the
development of vitamin K deficiency, this usually requires 1
to 2 weeks to develop in the complete absence of vitamin K
intake. However, the use of parenteral alimentation without
vitamin K supplementation coupled with antibiotic use may
result in rapid vitamin K depletion and prolongation of the PT
can occur within only 2 to 3 days. Finally, fat malabsorption
states, including cystic fibrosis, may be associated with vitamin K
deficiency. Vitamin K is fat soluble and is not absorbed well
in some conditions of biliary tract and intrinsic small bowel
disease. In the ICU, vitamin K deficiency usually results from
the interaction of several of these factors and is rarely lim-
ited to one of the conditions mentioned. It is the responsi-
bility of the clinician to maintain an awareness of the potential
for vitamin K deficiency and to treat accordingly.

The differential diagnosis of an isolated prolongation of
the PT, with or without bleeding, includes both vitamin K
deficiency and liver disease. The clinical presentation of these
patients is often quite similar. In fact, the distinction sometimes
can be made only on the basis of the response (or lack thereof)
to empirical vitamin K therapy. Warfarin administration
(either overt or covert) also should be excluded as a cause of
a prolonged PT. Newer, long-acting vitamin K antagonist
(VKA) rodenticides (so-called “super-warfarin”), which, when
ingested, produce a profound, prolonged, vitamin K–resistant
reduction in vitamin K–dependent clotting factors may pro-
duce an isolated prolongation of the PT initially. Treatment of
poisoning with these agents requires aggressive prolonged use
of vitamin K, and, in the bleeding patient, infusions of FFP or
rH.F.IIa. Confirmation of warfarin exposure as the cause of a
prolonged PT is possible by toxicologic methods to detect the
drug and/or its metabolites, or one can identify the presence
of noncarboxylated forms of vitamin K–dependent clotting
factors in plasma (proteins induced by vitamin K antagonist;
PIVKAs). In addition, the presence of a specific inhibitor or
genentinal deficiency of factor VII will also result in an iso-
lated prolongation of the PT. Acquired inhibitors of factor VII
are rare, and homozygous deficiency of factor VII has not been
described. Individuals heterozygous for factor VII deficiency
and those with certain polymorphisms of the promoter region
of the factor VII gene tend to have factor VII levels in the 25%
to 50% range and do not appear to be at significant increased
risk for bleeding. Lupus-like anticoagulants resulting from
inflammation may also result in an isolated prolongation
of the PT; these are generally of no clinical significance and
are not associated with an increased risk of bleeding. These
patients are not at increased risk for bleeding.

The laboratory findings of an isolated vitamin K deficiency,
in addition to a prolonged PT, include a normal fibrinogen level,
platelet count, and factor V level. Factor V is not a vitamin K–
dependent protein and should therefore be normal except in
cases of DIC (consumption) or severe liver disease (decreased
production). Prolongation of the aPTT from vitamin K defi-
ciency, warfarin therapy, or from liver disease is a relatively
late event and occurs initially as a result of factor IX depletion.

**Management**

The management of vitamin K deficiency consists primarily of
its repletion, usually by intravenous or subcutaneous routes in
critically ill patients. Therapy should not await the develop-
ment of bleeding or ooze but should be administered when
the PT abnormality is detected and vitamin K deficiency is
thought to be responsible. As with other drugs administered
subcutaneously (e.g., insulin), adequate blood pressure and
subcutaneous perfusion are needed to ensure reliable absorp-
tion from the soft tissues. Concern about the possibility of
anaphylactoid reactions with the intravenous use of vitamin K
exists. This risk is almost completely negated when the drug is
given as a piggyback infusion over 30 to 45 minutes in a small
volume of fluid rather than as a bolus or “slow-push” dose.
This is the preferred method of drug administration in hemo-
dynamically unstable patients. The usual dose of vitamin K in
adults is 10 to 15 mg intravenously or subcutaneously (1 to
5 mg in young children, up to 10 mg in larger children). In an
otherwise healthy person, the PT should correct within 12 to
24 hours after this dose. Serial dosing of critically ill patients is
often utilized, however, and the PT may require up to 72 hours
to normalize. If the PT does not correct within 72 hours after
three daily doses of vitamin K, intrinsic liver disease should be
suspected. Further administration of vitamin K is of no addi-
tional benefit in this setting.
When the patient is actively bleeding, it is not sufficient to give vitamin K alone. A more immediate restoration of coagulation is required. FFP has traditionally been employed in this setting. To restore hemostasis to an acceptable level (30% to 50%) of normal enzyme activity, 10 to 15 cc/kg body weight of FFP is typically required. A similar approach is used in patients previously given warfarin. Recombinant human activated factor VII (rhFVIIa) has been used with success to reverse the bleeding noted in vitamin K deficiency and in warfarin overdose (60,61).

**Massive Transfusion Syndrome**

Transfusion of large quantities of blood can result in a multifactorial hemostatic defect. The genesis of this problem is related to the “washout” of plasma coagulation proteins and platelets, and it may be exacerbated by the development of DIC with consequent factor consumption, hypothermia, acidosis or, rarely, by citrate toxicity or hypocalcemia. These variables often act in combination to cause a coagulopathic state (62). A washout syndrome can result from the transfusion of large amounts of stored blood products devoid of clotting factors and platelets. This develops exclusively in patients who receive large volumes of packed RBCs (e.g., trauma victims, patients with massive gastrointestinal hemorrhage or hepatectomy, or those undergoing cardiopulmonary bypass) without also receiving FFP and platelets. Factors V and VII have short half-lives and are often deficient in blood that has been banked longer than 48 hours. In addition, a qualitative platelet defect can be demonstrated in whole blood within hours of its storage, especially if an acid–citrate–dextrose solution is used. Consequently, transfusion of large quantities of stored whole blood may produce limited benefit in controlling the bleeding resulting from decreased clotting factors and platelets.

Massive transfusion had generally been defined, in adults, as the transfusion of >10 units of RBCs within 24 hours, >4 units of RBs in 1 hour, or >50% blood volume replacement within 3 hours. The development of a washout coagulopathy is directly dependent on the volume of blood transfused relative to the blood volume of the patient. As a general rule, residual plasma clotting activity after one-blood volume exchange falls to 18% to 37% of normal; whereas after a two-blood volume exchange, residual activity is only 3% to 14%; and after a three-blood volume exchange, less than 5% of normal clotting function remains. As previously discussed, DIC may develop in many clinical settings, including some associated with major hemorrhage or massive transfusion. In the presence of hypotension associated with hypovolemia or hemorrhagic shock, DIC is a common sequela. Major trauma itself, especially with the release of tissue factors into the plasma, also can result in the development of DIC. Exsanguinating hemorrhage sometimes requires blood replacement faster than a type and crossmatch of each unit can be performed, and unmatched blood is given as a lifesaving measure. Donor–recipient incompatibility—even when the mismatch is only of the minor blood group systems—can lead to DIC. Human error resulting in major incompatibility can produce severe hemolysis and be lethal. Finally, microaggregates of blood cells that form within stored blood products also can cause DIC. The advent of smaller pore, more effective filtering systems for blood product administration, however, has essentially eliminated this as a source of problems.

The patient who is bleeding as a consequence of massive transfusion or washout presents with diffuse ooze and bleeding from all surgical wounds and puncture sites. Laboratory abnormalities include prolonged PT, aPTT, and TT. Fibrinogen levels and platelet counts are typically decreased; FDPs are not usually increased unless concurrent DIC is present (see Table 143.2). The likelihood that the clinical laboratory picture is a direct result of the massive transfusion can be estimated from the amount of bleeding that has occurred and the blood volume administered relative to the patient’s blood volume (i.e., the number of blood volume exchanges that have been given). The more stored blood (e.g., packed RBCs) transfused relative to the patient’s blood volume, the greater the chance of the development of coagulopathy due to massive transfusion.

**Management**

The therapeutic approach to patients who develop a coagulopathy from massive transfusion is supportive. Platelets and FFP are given to replete the components of coagulation that are typically lacking (40). Platelet administration may help stem bleeding from anatomic wounds. Severe bleeding associated with thrombocytopenia alone is uncommon unless counts fall below 20,000 to 30,000/µL of blood. Because of the complex nature of bleeding seen with massive transfusion, patients may benefit from platelet transfusion at counts even as high as 80,000 to 100,000/µL. FFP is preferred over cryoprecipitate because it has a more complete coagulation protein composition. However, cryoprecipitate may be specifically given when fibrinogen depletion is thought to be a major contributor to the observed bleeding. Over the past 2 to 3 decades, the approach to transfusion support to individuals who require multiple blood transfusions acutely for the treatment of trauma or massive surgical hemorrhage has evolved from a policy of 1 unit of FFP and 1 unit of platelets for every 4 to 5 units of pRBCs transfused to a current 1:1:1 ratio of pRBC:FFP:platelets (63,64). However, the increased patient exposure to plasma with these new transfusion algorithms has also increased the risk for transfusion-related acute lung injury (TRALI) (65). Use of a commercially prepared solvent/detergent virally purified plasma produced form pooled fresh plasma has been shown to result in a decreased risk of TRALI in comparison to that with traditional single-donor plasma, and has also been shown to have a more consistent clotting factor profile than does the various forms of “fresh frozen” plasma available at hospitals (66,67).

Prospective identification of those at risk to develop a coagulopathy from massive transfusion is important. When the magnitude of the insult and the anticipated need for blood are large, both platelets and FFP should be given before a coagulopathy develops. Many institutions have developed infusion algorithms that include activating a “massive transfusion” protocol with their Transfusion Medicine service. These programs have generally resulted in more efficient utilization of blood products in the setting of trauma care (68,69). Use of a higher pRBC:plasma:platelet ratio transfusion regimen should prevent washout and its attendant bleeding. If the patient continues to bleed despite what should be adequate therapy for massive transfusion syndrome, other causes should be considered. Specifically, anatomic bleeding and the possibility of DIC should be investigated. Therapy in this setting may include rhFVIIa infusion (49).
Anticoagulant Overdose

Anticoagulant therapy is not unusual in the ICU, and the possibility of errors in administration exists. Methods of prophylactic anticoagulant use, systemic anticoagulation, and thrombolytic therapy are sometimes poorly standardized and can lead to overdose.

Heparin

Heparin is a repeating polymer of two disaccharide glycosaminoglycans and is commercially prepared from either porcine intestinal mucosa or bovine lung. Heparin is currently found in two forms, unfractionated heparin (UH) and low–molecular-weight heparin (LMWH). It is important to understand the differences between these two forms of the drug as they have different mechanisms of action and associated precautions. Unfractionated heparin has an immediate effect on coagulation that is mediated primarily through its interaction with antithrombin III. The resulting heparin–antithrombin III complex possesses a much greater affinity for thrombin than does AT III alone and inactivates thrombin, thereby damping-down clot formation. In addition, heparin also has a direct effect inhibiting activated factor X (EXa). This anticoagulant effect of UH is relatively minor. Consequently, achieving a therapeutic aPTT with UH is very difficult in the face of low levels of AT III. The degree of anticoagulation produced by heparin has traditionally been monitored by the prolongation of the aPTT. In contrast, LMWH, produced by controlled enzymatic cleavage of heparin polymers, produces anticoagulation almost exclusively through inhibition of EXa. This produces a more stable degree of anticoagulation, and due to its longer half-life (approximately 3 to 5 hours) and biologic activity (approximately 24 hours), allows for intermittent bolus therapy (i.e., every 12 or 24 hours) while still maintaining steady-state effect. However, LMWH does not produce consistent prolongation of the aPTT and requires assay of anti-Xa activity for monitoring (if desired). Recently, a therapeutic range for the anti-Xa level achieved with UH infusions has been developed. As most hospital labs now routinely measure anti-Xa levels, some institutions/clinicians monitor UH therapy and adjust doses accordingly.

Heparin is metabolized in the liver by the “heparinase” enzyme in a dose-dependent fashion with excess heparin then being excreted through the kidneys. As the rate of heparin administration is increased, the half-life of the drug is prolonged due the increase in the percentage of the drug being excreted by the kidney. For example, when a 100 U/kg bolus of heparin is infused intravenously, the average half-life of the drug is 1 hour. If the bolus is increased to 400 or 800 U/kg, however, the half-life is prolonged to 2.5 and 5 hours, respectively. The nonlinear response results in greater drug effects on coagulation with smaller dosage increments. When one “reboluses” or increases a heparin infusion rate in response to insufficient anticoagulation (i.e., inadequate prolongation of the aPTT or anti-Xa level), a point will be reached when further small increments in the heparin infusion rate may result in a substantially greater prolongation of the aPTT. The risk of pathologic bleeding associated with heparin increases when the prolongation of the aPTT is beyond the therapeutic window (generally considered to be 1.5 to 2.5 times the patient’s baseline aPTT, corresponding to a plasma heparin concentration of 0.2 to 0.4 units/mL, or 0.3 to 0.7 anti-Xa units/mL).

As a corollary, administration of heparin as a continuous infusion rather than in an intermittent bolus dose regimen is less likely to be associated with pathologic bleeding.

Management

Serious bleeding associated with heparin overdose can be rapidly reversed by protamine sulfate. Protamine binds ionically with heparin to form a complex that lacks any anticoagulant activity. As a general rule, 1 mg of protamine neutralizes approximately 100 U of heparin (specifically, 90 USP units of bovine heparin or 115 USP units of porcine heparin). The dose of protamine needed is calculated from the number of units of active heparin remaining in the patient’s system. This, in turn, is estimated from the original heparin dose and the typical half-life for that infusion rate. The aPTT is used to gauge the residual effects of heparin. Protamine itself potentially has anticoagulant effects, and precautions are necessary during its administration. The drug should be given by slow intravenous push over 8 to 10 minutes. A single dose should not exceed 1 mg/kg (50 mg maximum dose). This dose may be repeated, but no more than 2 mg/kg (100 mg maximum dose) should be given as a cumulative dose without rechecking coagulation parameters. The dose of protamine should always be monitored by coagulation studies. Significant side effects are most commonly seen in situations of overly rapid drug administration and include hypotension and anaphylactoid-like reactions. LMWH is not consistently neutralized by protamine, so invasive procedures should not be performed within 24 hours of administration. Bleeding following LMWH therapy has been treated effectively with rhF.VIIa.

Warfarin

Warfarin and vitamin K are structurally similar in their respective 4-hydroxycoumarin nucleus and naphthoquinone ring. The mechanism of action of warfarin is through inhibition of vitamin K epoxide reductase (VKOR; specifically the C1 subunit VKORC1) which is necessary to maintain a reduced form of vitamin K (vitamin K hydroquinone). Vitamin K hydroquinone is a necessary substrate of the postsynthetic modification is necessary to produce a calcium-binding site on the vitamin K–dependent clotting factors (factors II, VII, IX, X). This postsynthetic modification is necessary to produce a calcium-binding site on the molecule which, when occupied, allows for the efficient activation of the zymogen clotting factor into its enzymatically active form. When warfarin is present in sufficient plasma concentrations, there is depletion of reduced vitamin K (vitamin K hydroquinone) and consequent depletion of the active forms of vitamin K–dependent factors.

The PT, or more precisely the international normalized ratio (INR) calculated from the PT, is an accurate indicator of the intensity of anticoagulation with warfarin when its use has continued beyond 2 or 3 days. Factor VII has a half-life of only 4 to 6 hours and (the active form) is rapidly depleted after one or two doses of warfarin. The remainder of the vitamin K–dependent factors may take up to a week to become depleted. The PT becomes prolonged, and INR elevated, with factor VII depletion alone but does not reflect an overall state of anticoagulation until an equilibrium period of several days has passed. Over this time, the other vitamin K–dependent factors are depleted and PT prolongation (INR elevation) can then be used to assess the anticoagulant effects of warfarin. In severe cases of warfarin overdose, the aPTT also becomes prolonged as a result of deple-
tion of the active forms of factors II, IX, and X. While the INR is calculated from the PT and is frequently used as a surrogate for the PT and in this manner used to assess bleeding risks, the INR has only been validated as an indicator of anticoagulant intensity with VKA therapy. While some retrospective studies have identified an INR 1.5 as being associated with an increased risk of bleeding, INR alone has not been shown to be a consistent indicator of bleeding risk with invasive procedures, in liver disease or other medical conditions (70–72).

Several drugs and pathophysiologic conditions are associated with potentiation of warfarin’s effects on coagulation. Table 143.5 lists many of the drugs known to prolong the effects of warfarin. These drugs have a variety of mechanisms, which generally include either inhibition of function or competitive binding of the enzymes responsible for active warfarin metabolism. Aspirin does not seem to have any direct influence on warfarin metabolism but can so profoundly influence qualitative platelet function that it must be considered as a potentiator of warfarin’s anticoagulant effects. The same is true for clofibrate. Ingestion of large quantities of aspirin may also impair prothrombin (factor II) synthesis, further increasing the effects of warfarin administration. Warfarin is metabolized by the liver. Conditions of acute and chronic hepatic dysfunction can alter warfarin metabolism and vitamin K–mediated γ-carboxylation of the vitamin K–dependent coagulation proteins. Broad-spectrum antibiotics also may limit vitamin K availability through their alteration of the gut flora (in addition to any direct effect on vitamin K metabolism). All of these factors may ultimately influence a patient’s response to warfarin.

A clinical syndrome referred to as “warfarin (coumadin) necrosis” has been noted during the initial stages of anticoagulation with a VKA. It is characterized clinically by the development of skin and subcutaneous necrosis, particularly in areas of subcutaneous fat, and pathologically by the thrombosis of small blood vessels in the fat and subcutaneous tissues. This syndrome is caused by the rapid depletion of the vitamin K–dependent anticoagulant protein C prior to achieving depletion of procoagulant proteins and occurs predominantly in individuals heterozygous for protein C deficiency. While anticoagulation generally requires a decrease in procoagulant protein levels to approximately 20% to 25%, a prothrombotic milieu is created with protein C levels of 40% or less. Consequently, individuals who are heterozygous for protein C deficiency and have baseline protein C levels of 50% to 60% may develop a prothrombotic environment during the first few days of warfarin therapy. The risk of developing warfarin necrosis appears to be greater when an initial dose of warfarin greater than 10 to 15 mg is administered. The development of this syndrome generally can be avoided if heparin and warfarin therapy are overlapped until “coumadinization” is complete, and if large loading doses of warfarin are avoided.

Management

When over-anticoagulation with warfarin presents with bleeding, immediate reversal is usually mandated (38). Infusion of FFP or 4PCCs, which provide prompt restoration of the deficient vitamin K–dependent coagulation proteins, is preferred over rhFVIIa infusions for the restoration of hemostatic function in patients on VKA therapy. The routine correction of prolonged PT/INR in patients who are to undergo minor invasive procedures has not been shown to affect procedural blood loss (59,73,74). A typical dose of 4PCC for correction of a prolonged INR secondary to VKA therapy in 15 IU FVII/kg body weight; for correction with FFP, 10 to 15 cc/kg is usually sufficient to produce significant correction of the PT although repeat infusions of FFP may be needed to effect continued correction of the PT due to the short half-life of factor VII (40). Vitamin K also may be administered, particularly in situations that are less acute (see section “Vitamin K Deficiency”) although this will make it more difficult to “re-coumadinize” the patient afterwards. For severe bleeding or bleeding not controlled by 4PCC or FFP infusions, an activated PCC or rhFVIIa may be given.

**Platelet Disorders**

Platelets are necessary for efficient clot formation. They not only produce a physical barrier at the site of vascular injury (the so-called “platelet plug”), they also serve to focus the clotting process at the point of bleeding by delivering vasoconstrictors, clotting factors, and a surface on which clot development occurs to the bleeding site (see Fig. 143.3). Quantitative and qualitative platelet disorders are a common cause of clinical bleeding in the ICU. Table 143.6 presents an overview of platelet disorders based on this classification scheme.

**Quantitative Platelet Disorders**

A decrease in the number of circulating platelets reflects the presence of increased peripheral destruction/sequestration, decreased marrow production, or a combination of these factors. Examples of increased peripheral destruction include immune-mediated processes (both autoimmune and drug-induced), abnormal consumption (as in DIC), and mechanical destruction (e.g., cardiopulmonary bypass, hyperthermia). Autoimmune processes such as idiopathic thrombocytopenic purpura (ITP), SLE, or acquired immunodeficiency syndrome (AIDS) can result in increased peripheral destruction and increased splenic sequestration of platelets. Autoimmune destruction also may occur in conjunction with lymphocytic leukemia or lymphoma. The prototypic example of immune thrombocytopenia is ITP, in which immunoglobulin (generally

**TABLE 143.5 Drugs That Potentiate the Anticoagulant Effects of Warfarin**

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<thead>
<tr>
<th>Antibiotics</th>
<th>Anti-inflammatory drugs</th>
<th>Other drugs</th>
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<tbody>
<tr>
<td>Broad-spectrum antibiotics (especially cephalosporins)</td>
<td>Steroids (anabolic, in particular)</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Griseofulvin (oral)</td>
<td>Acetylated salicylates</td>
<td>Clofibrate</td>
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<td>Metronidazole</td>
<td>Phenytoin</td>
<td>Disulfiram</td>
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<tr>
<td>Sulfoxonamide</td>
<td>Sulfonamides</td>
<td>Phenytoin</td>
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<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Sulfapyridine</td>
<td>Thyroxine (both D- and L-isomers)</td>
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<tr>
<td>Tolbutamide</td>
<td>Acetylated salicylates</td>
<td>Tolbutamide</td>
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<tr>
<td>Thyroxine (both D- and L-isomers)</td>
<td>Acetylated salicylates</td>
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</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Sulfonamides</td>
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</table>

**Management**

When over-anticoagulation with warfarin presents with bleeding, immediate reversal is usually mandated (38). Infusion of FFP or 4PCCs, which provide prompt restoration of the deficient vitamin K–dependent coagulation proteins, is preferred over rhFVIIa infusions for the restoration of hemostatic function in patients on VKA therapy. The routine correction of prolonged PT/INR in patients who are to undergo minor invasive procedures has not been shown to affect procedural blood loss (59,73,74). A typical dose of 4PCC for correction of a prolonged INR secondary to VKA therapy in 15 IU FVII/kg body weight; for correction with FFP, 10 to 15 cc/kg is usually sufficient to produce significant correction of the PT although repeat infusions of FFP may be needed to effect continued correction of the PT due to the short half-life of factor VII (40). Vitamin K also may be administered, particularly in situations that are less acute (see section “Vitamin K Deficiency”) although this will make it more difficult to “re-coumadinize” the patient afterwards. For severe bleeding or bleeding not controlled by 4PCC or FFP infusions, an activated PCC or rhFVIIa may be given.

**Platelet Disorders**

Platelets are necessary for efficient clot formation. They not only produce a physical barrier at the site of vascular injury (the so-called “platelet plug”), they also serve to focus the clotting process at the point of bleeding by delivering vasoconstrictors, clotting factors, and a surface on which clot development occurs to the bleeding site (see Fig. 143.3). Quantitative and qualitative platelet disorders are a common cause of clinical bleeding in the ICU. Table 143.6 presents an overview of platelet disorders based on this classification scheme.

**Quantitative Platelet Disorders**

A decrease in the number of circulating platelets reflects the presence of increased peripheral destruction/sequestration, decreased marrow production, or a combination of these factors. Examples of increased peripheral destruction include immune-mediated processes (both autoimmune and drug-induced), abnormal consumption (as in DIC), and mechanical destruction (e.g., cardiopulmonary bypass, hyperthermia). Autoimmune processes such as idiopathic thrombocytopenic purpura (ITP), SLE, or acquired immunodeficiency syndrome (AIDS) can result in increased peripheral destruction and increased splenic sequestration of platelets. Autoimmune destruction also may occur in conjunction with lymphocytic leukemia or lymphoma. The prototypic example of immune thrombocytopenia is ITP, in which immunoglobulin (generally

**TABLE 143.5 Drugs That Potentiate the Anticoagulant Effects of Warfarin**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Anti-inflammatory drugs</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad-spectrum antibiotics (especially cephalosporins)</td>
<td>Steroids (anabolic, in particular)</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Griseofulvin (oral)</td>
<td>Acetylated salicylates</td>
<td>Clofibrate</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Phenytoin</td>
<td>Disulfiram</td>
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<td>Sulfoxonamide</td>
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<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Sulfonamides</td>
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</tr>
</tbody>
</table>
CHAPTER 143  Coagulation issues

Drug-induced immune-mediated platelet destruction is a cause of thrombocytopenia frequently considered in the thrombocytopenic ICU patient. Fortunately, when present it is usually reversible; withdrawal of the offending drug prevents further immune-mediated platelet destruction. The exact mechanism of platelet destruction seems to be related to the binding of a drug to the platelet membrane, with subsequent binding to the platelet, platelet–drug complex, or both, of a specific antibody. The resulting platelet–drug–antibody complexes then are cleared by the reticuloendothelial system (e.g., the spleen) and thrombocytopenia develops. Drugs used in the ICU that are most commonly associated with this clinical picture include quinidine, quinine, heparin, gold salts, various penicillin and cephalosporin antibiotics, and the sulfonamides. The anticonvulsant valproic acid (Depakote, Depakane) frequently produces a dose-dependent thrombocytopenia which, at least in part, is immunologic in nature. A variety of drugs are associated with a nonimmune mechanism of thrombocytopenia by bone marrow suppression. Most cancer chemotherapeutic agents produce thrombocytopenia as a consequence of marrow suppression. The thiazide diuretics, cimetidine, ethanol, and several of the cephalosporin and penicillin antibiotics may suppress platelet production. Generalized infection, such as bacterial sepsis, and many viral illnesses also are associated with bone marrow suppression and thrombocytopenia, even if there is an element of immune platelet destruction. Disorders such as Gaucher disease may produce a mild-to-moderate thrombocytopenia as a result of marrow replacement by nonhematopoietic cells.

Consumption of platelets also can cause thrombocytopenia. Mechanical destruction invariably occurs during the use of cardiopulmonary bypass machines and it is not uncommon to note a 50% drop in platelet count postbypass when compared to preoperative platelet levels. Platelet counts may continue to decrease for 48 to 72 hours after bypass before recovering toward preoperative levels. Platelets may also be destroyed by the high body temperatures seen in severe hyperthermic syndromes, and are consumed during microvascular coagulation in DIC. In many of these circumstances, the thrombocytopenia may be the sole or a contributing cause of significant bleeding.

Heparin-Induced Thrombocytopenia

The special problems associated with heparin merit emphasis. Heparin use is ubiquitous in the ICU. Heparin-induced thrombocytopenia may develop in one of two ways. Acute nonidiosyncratic heparin-induced thrombocytopenia is seen in approximately 10% to 15% of patients receiving heparin. The degree of thrombocytopenia is usually mild and usually remits despite the continued use of the drug (type I HIT). The thrombocytopenia that develops has no clinical significance. Heparin need not be stopped in these patients. Idiosyncratic heparin-induced thrombocytopenia is of much greater clinical consequence. Although it is a less frequent occurrence (typically seen in fewer than 5% of patients receiving heparin), it has a much greater potential for clinical morbidity. Arterial thrombosis is the most significant risk of this form of heparin-induced thrombocytopenia (type II HIT) and may be life-threatening causing myocardial infarction, cerebrovascular accident, pulmonary embolism, or renal infarction. The mechanism of thrombosis is thought to be a consequence of the deposition of platelet aggregates in the microcirculation (75). Thrombocytopenia, like other immune-mediated

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**Table 143.6 Platelet Disorders Seen in the ICU**

<table>
<thead>
<tr>
<th>Quantitative</th>
<th>Qualitative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased destruction</strong></td>
<td>Drugs</td>
</tr>
<tr>
<td>Immune</td>
<td>Anti-inflammatory agents</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Aspirin (Irreversible)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Drugs (gold salts, heparin, sulfonamides, quinidine, quinine)</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Penicillins (e.g., ampicillin, carbenicillin, ticarcillin, penicillin-G)</td>
</tr>
<tr>
<td>Nonimmune</td>
<td>Cephalosporins (e.g., cephalothin)</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Mechanical destruction (e.g., cardiopulmonary bypass, hyperthermia)</td>
<td>Chloroquine, hydroxychloroquine</td>
</tr>
<tr>
<td>Consumption (i.e., DIC)</td>
<td>Phosphodiesterase inhibitors</td>
</tr>
</tbody>
</table>

- Dipryridamole |
- Methylxanthines (e.g., theophylline) |

**Decreased production**

- Marrow suppression |
- Chemotherapy |
- Viral illness (e.g., cytomegalovirus, Epstein-Barr virus, herpes simplex, parvovirus) |
- Drugs (thiazides, ethanol, cimetidine) |

**Marrow replacement**

- Tumor |
- Myelodysplasia |

**Other conditions**

- Splenic sequestration |
- Dilution (see massive transfusion syndrome) |

**Metabolic causes**

- Uremia |
- Stored whole blood |
- Disseminated intravascular coagulation (i.e., FDP-mediated inhibition) |
- Hypothyroidism |

IgG directed against specific platelet antigens is thought to be responsible for platelet destruction. Acute ITP is usually self-limited, with life-threatening bleeding occurring only rarely. In contrast, chronic ITP generally requires some sort of immunosuppressive therapy. Steroids may be given (2 to 4 mg/kg day of prednisone or its equivalent). High doses of intravenous gamma globulin (1 to 2 g/kg given over 2 to 5 days), infusions of anti-RhD antigen antibody (WinRho; 25 mg/kg) are equally efficacious in producing at least transient elevations in platelet counts. Agents such as vincristine/ vinblastine, cyclophosphamide, and most recently rituximab (Rituxin; anti-CD20 monoclonal antibody) also have been used as immunosuppressants, with variable success, although responses are generally not immediate. Splenectomy also may be required to avert serious bleeding complications in patients who do not respond to medical management, although this approach is chosen much less often in children than in adults. In ITP, the degree of bleeding attributed to the thrombocytopenia is generally less than that which is noted when thrombocytopenia results from decreased production. In general, severe bleeding is not noted until the platelet count is <10,000/μL, although levels below 40,000 to 50,000/μL may increase the risk of bleeding with invasive procedure.
drug reactions, seems to involve the formation of heparin-dependent IgG antibodies directed against a heparin–platelet factor-4 complex expressed on the platelet membrane. Binding of this antibody–heparin complex results in platelet activation with aggregation leading to microvascular thrombus. This process requires minuscule amounts of heparin. Clinical bleeding is an infrequent problem in these patients in spite of the often marked thrombocytopenia observed.

From a practical perspective, the diagnosis of heparin-induced thrombocytopenia is usually one of exclusion. Diagnostic markers do exist (e.g., heparin-dependent platelet antibodies, aggregation, or serotonin release), but these tests are best considered confirmatory and not exclusionary. An ELISA assay for heparin-dependent platelet antibodies is the most common test obtained to investigate a possible diagnosis of HIT, but because of a relatively high “false-positive” rate, it is generally recommended that a more specific heparin-induced platelet injury assay, such as a serotonin release assay, be performed for confirmation. The diagnosis may be difficult to confirm because coexisting clinical illnesses with the potential to cause thrombocytopenia also may be present. While heparin-induced thrombocytopenia may be more likely to be associated with the use of bovine lung heparin, it can occur after exposure to porcine heparin or, much less commonly, to LMWH. When type II HIT is suspected or confirmed, all exposure to heparin, including heparin flushes, heparin in TPN, and heparin-coated catheters, must be removed and anticoagulation with an alternate agent must be initiated because of the risk of delayed thrombosis which can occur up to 30 days after the removal of heparin exposure (75). Patients with type II HIT should receive continued anticoagulation with direct thrombin inhibitors (argatroban, bivalirudin) (76, 77). While other agents have been employed to provide anticoagulation in the past, production of the direct thrombin inhibitor lepirudin was discontinued in 2012 and the heparinoid. Danaparoid is not available in the United States. The direct thrombin inhibitors are preferred as they carry no risk of cross-reacting with the heparin-dependent antibodies already present (78). Argatroban is cleared by the liver and lepirudin by the kidney. Consequently, the choice and dose of drug may be affected by the presence of hepatic or renal insufficiency. Warfarin alone is not an adequate therapy for suspected type II HIT because of the risk of thrombosis from depression of protein C levels. However, warfarin can be utilized in conjunction with a direct thrombin inhibitor and subsequently continued as a single agent once therapeutic suppression of vitamin K–dependent clotting factors has been achieved. Platelet transfusions are contraindicated in type II HIT due to the risk of inducing vascular thrombosis (75).

Qualitative Platelet Disorders

Many of the drugs frequently used in the ICU have the potential to impair platelet function. Frequently, the sicker the patient, the greater the likelihood that he/she will be exposed to one of these drugs. These patients often have other underlying pathophysiologic conditions that in and of themselves can predispose to bleeding. Table 143.6 provides an abbreviated list of the drugs that can affect at least in vitro platelet function.

All unnecessary drugs should be viewed as suspect and discontinued in patients with evidence or a strong suspicion of qualitative platelet dysfunction. In most cases, terminating the offending drugs usually results in a restoration of normal platelet functional activity. Aspirin is the notable exception as it irreversibly inhibits platelet cyclo-oxygenase, resulting in a defect that lasts for the duration of the platelet life span (8 to 9 days). The effect is profound: a single 325 mg aspirin tablet results in a qualitative platelet defect that remains in 50% of the circulating platelets 5 days after its ingestion. Ideally, one would like to avoid all aspirin ingestion for at least 7 days prior to an elective invasive procedure.

Nonsteroidal anti-inflammatory agents (NSAIDs) such as ibuprofen or naproxen sodium similarly inhibit platelet cyclo-oxygenase. However, their effects are reversible, and normal platelet function is usually restored within 24 hours of the last dose. Under most circumstances, the degree of platelet inhibition produced by NSAIDs is not clinically significant and patients can receive these drugs for analgesia and fever control. It is reasonable, however, to minimize the use of NSAIDs in the bleeding severely thrombocytopenic patient. Other antiplatelet agents such as the thienopyridines clopidogrel and prasugrel, ticlopidine and dipyridamole can produce platelet inhibition that remains evident for several days after discontinuing the drug. The β-lactam antibiotics can sterically hinder the binding of a platelet aggregation agonist (e.g., ADP) to its specific platelet receptor, thus resulting in impaired platelet aggregation under circumstances of normal physiologic stimulation. This, too, is reversed on removal of the drug. Fortunately, only a minority of patients exposed to these antibiotics will exhibit clinically significant platelet inhibition.

In the ICU, one must also always consider the possibility that a patient with bleeding suggestive of a platelet defect might have an inherited disorder of platelet function. While rare, these disorders are encountered from time to time and include Glanzmann’s thrombasthenia (abnormal platelet GP IIb/IIIa), Bernard–Soulier syndrome (abnormal GP Ib/IX), Wiskott–Aldrich syndrome, platelet storage pool deficiency (abnormal platelet dense bodies), and the Gray platelet disorder (abnormal platelet α-granules).

Management

Because many of the adverse drug-related platelet effects are reversible, all unnecessary medications should be discontinued promptly when platelet function seems impaired. The more controversial issue is deciding whether platelet transfusions are warranted in a particular patient. The relationship of thrombocytopenia to clinical bleeding is relative, that is, it is difficult to identify a specific, arbitrary platelet count (threshold) below which bleeding is likely to occur. Several conditions, such as massive transfusion syndrome and DIC, may respond to empirical platelet transfusion at counts as high as 80,000 or even 100,000 platelets/µL, although bleeding in the presence of a platelet count of 80,000/µL (or greater) is unlikely to be a result of the thrombocytopenia. With other causes, such as thrombocytopenia seen with cancer chemotherapy and bone marrow aplasia, therapy may not be required until counts fall below 10 to 20,000/µL. As previously stated, rhFVIIa has also been used to counteract the hemostatic defect caused by aspirin or clopidogrel (50).

The morbidity and mortality related to bleeding increase measurably in patients undergoing induction chemotherapy for acute leukemia when the platelet count falls below 10,000 to 20,000/µL. Empirical administration of platelets to these patients significantly limits both morbidity and mortality. This finding, however, has been generalized to virtually all patients with platelet counts in this range. The appropriateness of this
approach is unclear. A major concern that should temper the empirical use of platelet transfusion is the development of alloimmunization to transfused platelets, potentially negating any future benefit from platelet transfusion in a time of need. Patients with acute leukemia typically have self-limited marrow aplasia resulting from chemotherapy. Therefore, the need for platelet transfusion is also limited and the chances for development of antiplatelet antibodies are greatly decreased. Patients with aplastic anemia, however, have an ongoing need for platelet transfusion, so their risk of alloimmunization is high. Autoimmune disorders associated with increased peripheral platelet destruction, disorders of splenic sequestration, and drug-related thrombocytopenia are unlikely to benefit from platelet transfusion. An exception is related to a planned invasive procedure associated with an increased risk of bleeding. In this situation, empirical platelet transfusion immediately before the procedure may be reasonable. As previously noted, platelet transfusions in the presence of type II HIT are contraindicated.

Uremia

Uremia is commonly seen in the ICU and is associated with an increased risk of bleeding (79,80). Uremia has been shown to cause a reversible impairment of platelet function, although the “toxin” responsible for this defect is not well defined. Some studies have demonstrated an impairment of platelet-vessel wall interactions and suggest defects in vWF. The degree of platelet impairment appears to be related to the severity of uremia for a given patient. In addition, thrombotic events are also increased in patients with uremia. These, too, appear to be multifactorial in etiology but in part reflect the increase in renal loss of antithrombin III and protein S in nephrotic range proteinuria (81).

Several therapeutic approaches may modulate the qualitative platelet defect associated with uremia. The primary therapy in this setting is dialysis. Cryoprecipitate, 1-deamino-8-D-arginine vasopressin (DDAVP; 0.3 μg/kg maximum dose 21 μg), and conjugated estrogens (10 mg/d in adults) have been given to patients with severe uremia and an acquired defect in primary hemostasis with good results. The benefit derived by treatment with cryoprecipitate or DDAVP appears to be related to the consequent increase in the plasma concentration of the large multimeric forms of vWF, thus greatly improving platelet adhesion. The durations of action of these agents, however, are limited, reaching their zenith between 2 and 6 hours. Additional doses of DDAVP during the same 24-hour period may result in a diminished response to the drug (tachyphylaxis) with little or no further benefit. Patients who exhibit tachyphylaxis to DDAVP may require 48 to 72 hours before again responding to this agent. The mechanism of action of the conjugated estrogens is not known. In contrast to the first two therapies described, the effect of estrogen is more protracted and does not diminish with repeat dosing although a benefit is not noted for 3 to 5 days after starting therapy.

THROMBOTIC SYNDROMES

Thrombotic events may often be the cause of admission to an ICU, particularly if one includes acute coronary syndromes in this category. The noncardiac thrombotic syndromes frequently encountered in the ICU include:

Deep venous thrombosis (specifically in association with a central venous catheter)

Heparin-induced thrombocytopenia
Pulmonary embolism syndrome
TTP/hemolytic-uremic syndrome
Thrombotic DIC

Stroke and central nervous system (CNS) venous sinus thrombosis (most commonly seen in infants and the elderly in association with marked dehydration)

Many of these conditions, particularly venous thromboembolic events, often develop while the patient is in the ICU and may be preventable. The intensivist should assess risk of DVT and risks of thromboprophylaxis in all patients and institute appropriate therapy on a case-by-case basis based on the assessed risk of thrombosis. In general, postoperative patients and those who will be immobilized for long periods of time are considered at risk and should be considered candidates for some sort of thromboprophylaxis (82). Approximately 10% of ICU patients will develop DVT while in the ICU in spite of receiving some sort of thromboprophylaxis, and up to 15% of these patients will experience a symptomatic pulmonary embolus (83,84). However, not all patients are at the same risk and not all respond to prophylactic measures equally. Consequently, recognition of patient risk factors and initiation of effective prophylaxis measures are critical for the care of these patients. Patients with multiple genetic thrombosis risk factors have been shown to have a greater risk for DVT or pulmonary emboli than do patients without any or only one identified risk factor (85).

Management

The initial management approach for a patient with a documented (or highly suspected) thrombotic event is generally anticoagulation with either UH or LMWH. The efficacy of either appears to be equivalent although some studies suggest that the incidence of severe bleeding is less with LMWH (86). The use of LMWH may produce a more stable level of anticoagulation which may result in fewer laboratory tests and dose adjustments. The choice of which agent to use is at the discretion of the intensivist. However, if repeated invasive procedures are anticipated, UH may be the preferred agent owing to its shorter half-life. Most patients may be started on UH with a bolus dose of 50 unit/kg followed by a continuous infusion of 10 units/kg/hr, these doses may be reduced for the elderly or frail patient. Once initiated, anticoagulation is adjusted to keep the aPTT roughly 1.5 to 2.5 times baseline values (corresponding to a plasma heparin concentration of 0.2 to 0.4 units/ml or anti-Xa level of 0.4 to 0.7 units/mL). Dosing of LMWH is weight based generally starting at 1 mg/kg every 12 or 24 hours depending on the clinical presentation. Doses are titrated to achieve an anti-Xa activity level of between 0.4 and 1.0 units/mL (determined 3 to 4 hours after a dose) depending on the intensity of anticoagulation desired. The dose of warfarin is titrated to maintain an INR of the PT between 1.5 and 4.0 depending on the intensity of anticoagulation desired.

SELECTED DISORDERS

Systemic Diseases Associated with Factor Deficiencies

Amyloidosis, Gaucher’s disease, and the nephrotic syndrome are occasionally seen in the ICU. Each may have one or more
associated factor deficiencies that may complicate patient management and result in bleeding. Patients with either amyloidosis or Gaucher’s disease may develop factor IX deficiency. Factor X deficiency also has been associated with amyloidosis. These deficiencies generally result from the absorption of the specific clotting factor onto the abnormal proteins present with each disorder. In the nephrotic syndrome, factor IX deficiency also may develop. Although it was originally thought that proteinuria was responsible for the development of factor IX deficiency, this may not be the case. The deficiency typically occurs with corticosteroid therapy. Finally, antithrombin III deficiency can be seen along with the nephrotic syndrome and may lead to thrombosis. The loss of antithrombin III does appear to be related to proteinuria.

**Laboratory Disorders not Associated with Bleeding**

**Lupus Anticoagulants**

The lupus anticoagulant has received much attention as a potential cause of bleeding by virtue of its name and its associated laboratory abnormalities. As an isolated hemostatic defect, thrombosis is the most likely problem (25% incidence rate) with bleeding in one series occurring in only 1 of 219 patients with the lupus anticoagulant (87–89).

The PT and aPTT assays depend on the interaction of various coagulation factors with either a lipoprotein or phospholipid to activate coagulation efficiently. The lupus anticoagulant is an antiphospholipid antibody directed against these phospholipids or lipoproteins and produces prolongation of the PT, aPTT, or the measured recalcification time of platelet-rich plasma. Prolongation of the aPTT occurs more commonly than prolongation of the PT, although an isolated prolongation of the PT can be seen. Twenty-five percent of patients with active SLE and the lupus anticoagulant also have associated thrombocytopenia or hypoprothrombinemia and are therefore at risk for bleeding in contrast to those patients with the lupus anticoagulant alone who are not at increased risk for bleeding. Although the lupus anticoagulant was originally described in patients with SLE, it is not limited to this class of diseases. Indeed, lupus anticoagulants or anticardiolipin antibodies, or both, have been demonstrated in large percentages of patients with human immunodeficiency virus infection, hemophilia A, or both. Lupus anticoagulants also are observed in disorders accompanied by chronic and acute inflammation.

Thrombotic events in patients who exhibit a lupus anticoagulant may occur independent of the underlying disorder and can be directly related to the lupus anticoagulant itself. The likelihood of thrombosis associated with a lupus anticoagulant appears to be the greatest when the lupus anticoagulant has specificity for β2-glycoprotein I or for phosphatidylserine. Some forms of the disorder, such as that associated with pregnancy, do respond to anti-inflammatory drugs such as aspirin or prednisone. Thrombosis, when it occurs, is equally likely to be venous or arterial. Venous thrombosis is more common in the extremities while arterial thrombosis is more common in the CNS. Placental infarcts are frequently seen in placental specimens in those patients with repeated fetal wastage. Stroke, myocardial infarction, and pulmonary embolization are also well described in patients with the lupus anticoagulant.

**Reactive Hyperfibrinogenemia**

Hyperfibrinogenemia is defined as a plasma fibrinogen concentration greater than 800 mg/dL. In the clinical lab, fibrinogen is measured using a functional assay in which time to fibrin clot formation is the endpoint. Plasma from the patient is allowed to clot in the presence of excess thrombin. The time to clotting in this setting is proportional to the amount of fibrinogen present in the sample. When excessive amounts of fibrinogen are present, clotting is incomplete and fibrin fragments that inhibit further fibrin clot formation are formed. Other hematologic parameters, such as the aPTT, PT, and the TT, are consequently prolonged, suggesting a potential (artifactual) for bleeding despite a high fibrinogen level. This can be evaluated by diluting the plasma to a normal fibrinogen concentration using saline or defibrinated plasma. These same clotting studies will now be normal. Bleeding is not seen unless the fibrinogen also is a dysfibrinogen, although even in these patients, bleeding remains an uncommon problem. In patients with dysfibrinogenemia, clotting studies fail to correct when either saline or defibrinated plasma dilutions are undertaken, thus distinguishing them from patients with reactive hyperfibrinogenemia.

**Future Directions**

Current areas of active investigation include defining subsets of patients with acute illness-related coagulopathies to better identify appropriate therapeutic interventions that address specific pathophysiologic aberrations causing the coagulopathic state (e.g., complement activation, metabolic abnormalities, endothelial injury, etc.). Progress in this area will require continued investigation into endothelial function, the links between hemostasis (coagulation) and inflammation, and the various regulatory pathways involved in both hemostasis and inflammation. While we look for new drugs that address these issues, we must take care to not discard older drugs that may represent important therapies for some of these patient groups. While single-institution case series comparing new treatment strategies to historic outcomes may help identify potential treatments, large multi-institutional studies will be required to answer the questions. In a similar fashion, work to better define those patients most at risk for thrombosis in the ICU and prophylactic therapies to be employed continues. Thirdly, investigation into transfusion practices to maximize benefit and minimize risks and unnecessary transfusions need to continue. This, too, will require large, multi-institutional randomized studies.

**Key Points**

- Hemostasis is a dynamic process in which clot formation (coagulation) and clot lysis (thrombolysis) are active and balanced according to the needs of the patient.
- Bleeding may result from too little coagulation, too much fibrinolysis, or both.
- Localized bleeding generally indicates a local (anatomic) problem while a generalized hemostatic abnormality generally results in generalized bleeding.
• The routine tests of coagulation (APTT, PT/INR) only provide a measure of in vitro clot formation and do not provide information on platelet function or fibrinolysis. Consequently, they are of limited value in determining bleeding risk.

• If HIT is suspected, all heparin exposure must be eliminated and alternate anticoagulation provided until the diagnosis is confirmed (or excluded).

• Use of blood product support (e.g., FFP, platelet concentrates, factor concentrates) should be directed to correct a known hemostatic deficit. FFP should not be utilized to provide intravascular volume in the absence of a plasmatic hemostatic abnormality.

• While DIC is the 800-lb gorilla of bleeding, it is frequently not in the room.

References


