CHAPTER 170  COAGULATION DISORDERS
IN THE INTENSIVE CARE UNIT
ROBERT I. PARKER

This chapter focuses on various pathophysiologic conditions associated with abnormal hemostasis or abnormal laboratory measurements of hemostasis. However, to understand how to approach a patient with a bleeding problem, one must first have a basic understanding of the processes involved in regulating blood coagulation. Consequently, we will start with a brief overview of our current understanding of coagulation, including 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: (i) those associated with serious bleeding or a high probability of bleeding, (ii) thrombotic syndromes or conditions associated with a higher probability of thrombosis, and (iii) 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 not associated with an increased bleeding risk. A topical listing of these conditions is included for review in Table 170.1. The order in which these categories are listed suggests their relative importance to the critical care practitioner. This chapter will end by noting future directions in research and care of the critically ill patient with hematologic and oncologic disease and dysfunction.

OVERVIEW OF COAGULATION

For years, medical students have been taught that the process of blood clotting is divided into the intrinsic, extrinsic, and common pathways (Fig. 170.1), and students have come away with the thought that clotting occurs as the result of an orderly sequential process. Although 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 that 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.

Whereas previously it was thought that the intrinsic pathway, beginning with the activation of factor XII (fXII) to activated factor XII (fXIIa) 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 fX to fXa through the action of the fVIIa/tissue factor (fXII) 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, "cross talk," to describe the action of fVIIa/fXII complex along with the fIXa/fVIIIa 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 Ia). In addition, we now know that there is cross talk between the two arms of the clotting cascade, with fVIIa being able to enhance the activation of IX (to fIXa) and XIX (to fXla), further pointing out the central role that fVIIa and TF play in vivo (Fig. 170.2). Furthermore, there are various positive feedback loops principally involving thrombin that enhance the upstream activation of the clotting process.

Tissue factor for the activation of coagulation is present not only in the subendothelial matrix, but is also found circulating freely in plasma as soluble tissue factor and contained 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—for example, catheters, grafts, stents, and so on—can provide these surfaces for clot formation, and all play a critical role in clot formation.

Platelets not only initiate clot formation through the formation of a platelet plug, but, more significantly, they bring specialized proteins that regulate the clotting response—for example, fVIII, inhibitors of fibrinolysis, and so on—to the area of bleeding, and provide a surface for the localization of clotting factors for efficient clot formation (Fig. 170.3). 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 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 platelet adherence and aggregation, vascular contraction, clot formation, and wound healing (3).

The endothelium is a specialized organ that plays a central role in the regulation of clot formation (i.e., hemostasis) by presenting a nonsignificant surface to flowing blood and by enhancing clot formation when the endothelium is disrupted by trauma or injured by infection or inflammation (4,5) (Fig. 170.4). The normal endothelium produces...
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**Table 170.1**

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<thead>
<tr>
<th>OVERVIEW OF COAGULATION DISORDERS SEEN IN THE ICU</th>
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<td>CONDITIONS ASSOCIATED WITH SERIOUS BLEEDING OR A HIGH PROBABILITY OF BLEEDING</td>
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<td>Disseminated intravascular coagulation (DIC)</td>
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<td>Liver disease/hepatic insufficiency</td>
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<td>Vitamin K deficiency/depletion</td>
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<td>Massive transfusion syndrome</td>
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<td>Anticoagulant overdose (heparin, warfarin)</td>
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<tr>
<td>Thrombocytopenia (drug-induced, immunologic)</td>
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<td>Acquired platelet defects (drug-induced, uremia)</td>
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<tr>
<th>THROMBOTIC CLINICAL SYNDROMES</th>
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<td>Thrombotic thrombocytopenia purpura/hemolytic uremic syndrome</td>
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<tr>
<td>Deep venous thrombosis</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Coronary thrombosis/acute myocardial infarction</td>
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<tr>
<th>LABORATORY ABNORMALITIES NOT ASSOCIATED WITH CLINICAL BLEEDING</th>
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<tr>
<td>Lupus anticoagulant</td>
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<th>OTHER SELECTED CLINICAL SYNDROMES</th>
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<tr>
<td>Hemophilia (A and B)</td>
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<td>Specific factor deficiencies associated with specific diseases</td>
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<tr>
<td>Amyloidosis, factor X</td>
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<td>Gaucher, factor IX</td>
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<tr>
<td>Nephrotic syndrome, factor IX, antithrombin III</td>
</tr>
<tr>
<td>Cyanotic congenital heart disease (polycythemia, qualitative platelet defect)</td>
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<tr>
<td>Depressed clotting factor levels (newborns)</td>
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Inhibitors of 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, thrombocytin, and vWF. When the endothelium is disrupted, bleeding occurs. However, when injured, the endothelium often becomes a prothrombotic rather than an antithrombotic organ, and unwanted clot formation may occur.

**INTERACTION OF COAGULATION AND INFLAMMATION**

There are multiple points of intersection between the biochemical events of inflammation and those of coagulation (6). Although 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 (6) (Fig. 170.5). While many different inflammatory cytokines have been identified as promoters of a procoagulant milieu, the interconnection of tissue factor (TF) and tissue necrosis factor-α (TNF-α) may potentially be the most important of these. During sepsis, tissue factor expression is up-regulated in activated monocytes and endothelial cells as a response to endotoxin, with the consequence being both the secretion of proinflammatory cytokines, such as interleukin-6 (IL-6) and TNF-α, 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 (7). Thrombin...
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Extrinsic Pathway

surface contact

PK

Intrinsic Pathway

XIa

XI

Ca2+

Ca2+

PL

IXa

IX

Xa

X

Ca2+

Ca2+

PL

Prothrombin

Thrombin

Fibrinogen

Fibrin monomer

Fibrin polymer

Cross-linked fibrin polymer

FIGURE 170.2. Modified clotting cascade indicating cross talk between the intrinsic and extrinsic pathways by the action of VIIa/thrombin factor (TF) enhancing the conversion of factor XI to activated factor XI (XIa) (dotted lines). Ca2+, calcium; HK, high-molecular-weight kininogen; PK, prekallikrein; PL, phospholipids.

results in the activation, aggregation, and lysis of leukocytes and platelets, and activation of endothelial cells, with resultant increase in proinflammatory cytokines IL-6 and TNF-α expression. The net result of thrombin generation is to produce a proinflammatory and procoagulant state, leading to the formation of fibrin and microvascular thrombosis. However, these proinflammatory effects of thrombin are counterbalanced by the anti-inflammatory effects of activated protein C (Fig. 170.4) (7).

A second important point of connection of coagulation and inflammation is through the protein C system (8–10). Although the anticoagulant effects of activated protein C (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 complement factor C4b bound protein S (9,10).

In vitro, aPC inhibits TNF-α elaboration from monocytes and blocks leukocyte adhesion to selectins, as well as having an influence on apoptosis (7). The protein C pathway is engaged when thrombin binds to thrombomodulin on the vascular injury.

Platelet adhering to endothelial cell layer surface

Platelet aggregation formation

Platelet plug with fibrin clot formation

Hemostasis

FIGURE 170.3. 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.
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Protein C Pathway

Coagulation
Inhibition of FVa and FVIIa

Inflammation
• Cytokine production
• Leucocyte adherence
• Apoptosis, etc.

Fibrinolysis
Inhibition of PAI-1

Inflammation
• ↓ Cytokine production
• ↓ Leucocyte adherence
• ↓ Apoptosis, etc.

Protein C

Endothelial Cell Membrane

Surface of the endothelial cell. Binding of PC to the endothelial cell protein C receptor (EPCR) augments protein C activation by the thrombin-TM complex more than tenfold in vitro. 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. Activated PC is capable of neutralizing the fibrinolytic inhibitors, plasminogen activator inhibitor type-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI). Consequently, depressed levels of aPC not only promote clot formation by reducing the inactivation of the procoagulant molecule-activated factors V (FVa) and VIII (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 that lead to differences in PAI-1 production have been demonstrated to affect the prognosis.

Bacterial Sepsis
• LPS
• Lipoteichoic acid
• Peptidoglycan

Activated Monocyte

Cytokines
• IL-1
• IL-6
• TNF

Gene Transcription

Activated Neutrophil

TF (Tissue Factor)

Fibrin Clot

TF (Tissue Factor)

Gene

Endothelial Cell Membrane

FIGURE 170.5. Inflammation enhances coagulation through the induction of proinflammatory cytokines, which induce tissue factor (TF) formation, which in turn decreases activated protein C (aPC) formation, leading to enhanced thrombin and fibrin generation. In addition, the decrease in aPC allows for greater inhibition of fibrinolysis through the action of plasminogen activator inhibitor type-1 (PAI-1). ICAM, intercellular adhesion molecule; IL, interleukin; LPS, lipopolysaccharide; TNF, tissue necrosis factor.
in meningococcal sepsis and multiple trauma, highlighting the important role of this regulatory system (11). This finding illustrates the significance of developing our knowledge of how common polymorphisms of genes that encode important molecules affect our response to infection and injury. A recent report, which demonstrated increased mortality and organ dysfunction and increased inflammation in patients who exhibited a specific polymorphism (1641AA) of the protein C gene (12), further reinforced the importance of the interactions between coagulation and inflammation and the central role of protein C, as well as the significant role that gene polymorphisms play in host responses and clinical outcomes.

**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 (13,14). A prior history of prolonged or excessive bleeding, or of recurrent thrombosis, is a significant finding and should be ruled out. 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 hemorrhage
- 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
- 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 are also associated with bleeding abnormalities and are discussed below. In situations involving trauma (either surgical or accidental), it is imperative to determine the severity of injury relative to the magnitude of bleeding that followed. A prior history of significant thrombosis, such as deep venous thrombosis, pulmonary embolus, or stroke, also suggests the possibility that a hypercoagulable condition may be present. Given that 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 the patient. These include deficiencies of antithrombin III, protein C or protein S, the presence of the factor V Leiden R506Q mutation, the prothrombin G20210A (or the newly described A19911G) (15,16) polymorphism/mutation, and the C677T methionine/polymorphism of the MTHFR (methylenetetrahydrofolate reductase) gene. 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 essential 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 hemoctytic defects tend to manifest platelet or capillary type bleeding—oozing from cuts or incisions, mucous membrane bleeding, or excessive bruising. In women, this may manifest as menorrhagia. This type of bleeding is seen in patients with quantitative or qualitative platelet defects or von Willebrand disease. In contrast, patients with dysfunction of 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 and, 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, such as oliguria or anuria, respiratory failure, or hypotension, often are readily apparent. With the exception of massive transfusion syndrome (see below), generalized bleeding in critically ill patients is often caused by sepsis-related disseminated intravascular coagulation (DIC) (17,18). 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 (17–19).

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 mucosal bleeding? And finally, when appropriate, are there signs of either arterial or venous thrombosis? These answers may give clues to the cause of the problem as being a primary versus secondary hemostatic dysfunction, or anatomic bleeding versus 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 cause 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. Furthermore, evidence of liver disease, such as portal hypertension and ascites, points to decreased factor synthesis as a possible cause 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 tanglecrosis 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 peripheral access is no longer available. Heparin-containing solution is, therefore, commonly present, either in the cannula flush medium 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 prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) can be spuriously prolonged. A minimum of 20 mL of blood in adolescents and adults, and 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 (20). 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 will also be prolonged, but will normalize if the contaminating heparin is neutralized (e.g., with toluidine blue or Hepasorb).

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 fibrin degradation products 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. 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—for example, 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 170.2 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

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<th>TABLE 170.2</th>
<th>HEMORRHAGIC SYNDROMES AND ASSOCIATED LABORATORY FINDINGS</th>
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<td><strong>Clinical syndrome</strong></td>
<td><strong>Screening tests</strong></td>
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<tr>
<td>DIC</td>
<td>Prolonged PT, aPTT, TT; decreased fibrinogen, platelets; microangiopathy</td>
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<td>Massive transfusion</td>
<td>Prolonged PT, aPTT; decreased fibrinogen, platelets</td>
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<tr>
<td>Anticoagulant overdose</td>
<td>Heparin</td>
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<tr>
<td>Warfarin (same as vitamin K deficiency)</td>
<td>Prolonged PT; ± prolonged aPTT (severe); normal TT, fibrinogen, platelets</td>
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<tr>
<td>Liver disease</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td>Late</td>
</tr>
<tr>
<td>Primary fibrinolysis</td>
<td>Prolonged PT, aPTT, TT; decreased fibrinogen; ± platelets decreased</td>
</tr>
<tr>
<td>TTP</td>
<td>Thrombocytopenia, microangiopathy with mild anemia; PT, aPTT, fibrinogen generally WNL/mildly abnormal</td>
</tr>
<tr>
<td>HUS</td>
<td>Microangiopathic hemolytic anemia; ± thrombocytopenia; PT, aPTT generally WNL</td>
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DIC, disseminated intravascular coagulation; PT, prothrombin time; aPTT, activated partial thromboplastin time; TT, thrombin time; FDPs, fibrin degradation products; TTP, thrombotic thrombocytopenic purpura; WNL, within normal limits; vWF, von Willebrand factor; HUS, hemolytic-uremic syndrome.
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.

**Evaluation of Thrombosis**

Patients who present with a thrombotic event will generally not display abnormalities of usual clotting studies—that is, there will be no elevation of PT, TT, and aPTT. Acute thrombosis will usually be within normal ranges. Whereas 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 generally not helpful in the evaluation of a thrombotic event in an acutely ill individual. 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 the 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[Glu]), prothrombin ([Gly]G20210A[Ala] and [Ala]A1935G[Gly]) and methylenetetrahydrofolate reductase (MTHFR; [Cys]C677T[Thr]) genes should be performed. In addition, a baseline serum homocysteine may be obtained given that the thrombosis risk of the MTHFR mutation may be related to elevations of homocysteine caused by alterations in the metabolism of folate acid rather than the mutation per se. Acquired thrombotic 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 intensive care unit 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), and so forth, 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 due to the rate of consumption outpacing the rate at which the clotting factors and platelets are produced (21). Table 170.3 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 can generally be considered in two categories: those intrinsically processes that enzymatically activate procoagulant proteins, and 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 (21). Thrombin generation or release of tissue plasminogen activator usually initiates this process. Plasmin is generated, which in turn digests fibrinogen and fibrin clots as they form. Plasmin also inactivates several activated coagulation factors and impairs platelet aggregation. DIC represents an imbalance between the activity of thrombin, which leads to microvascular thrombs 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 thrombus 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 thrombs. The fibrinopeptides A and B, resulting from enzymatic cleavage of fibrinogen, lead to pulmonary and systemic 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 50% of patients with DIC, however, the presentation is exclusively thrombotic—for example, pulmonary emboli with pulmonary hypertension, renal insufficiency, altered mental status, acrocyanosis—without

<table>
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<td><strong>Underlying Diseases Associated With Disseminated Intravascular Coagulation</strong></td>
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<td>Sepsis</td>
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<td>Liver disease</td>
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<tr>
<td>Shock</td>
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<td>Penetrating brain injury</td>
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<td>Necrotizing pneumonia</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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<td>Acute promyelocytic leukemia</td>
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hemorrhage. Whether the presentation of DIC is thrombotic, hemorrhagic, or compensated (that is, laboratory results consistent with DIC without overt bleeding), macrothrombosis probably contributes to the development and progression of multorgan failure.

Clinical Presentation and Diagnosis

The suspicion that DIC is present usually stems from one of two situations: unexplained generalized ooze or bleeding, or unexplained abnormal laboratory parameters of hemostasis. This usually occurs in the context of a suggestive clinical scenario or associated disease (Table 170.3). Although infection and multiple trauma are the most common underlying conditions associated with the development of DIC, several other organ system dysfunctions predispose to DIC, including hepatic insufficiency and splenectomy (17,18). Both of these conditions are associated with impaired reticuloendothelial system function and consequent impaired clearance of activated coagulation proteins and fibrin/fibrin 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 using 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 the prognosis and direct initial therapy at the time of diagnosis. A list is found in Table 170.4. 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 (22–24). The systems suggested by Leclerc et al. (25) and Taylor et al. (26) are two of the more commonly used scoring systems and may serve as a template for the diagnosis of DIC; a qualitative score (3 out of tests positive) (Leclerc) or a quantitative score (Taylor) 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 clot formation.

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

- Massel transfusion
- Primary fibrinolysis
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
- 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 170.2. To confirm a diagnosis of suspected DIC, confirmatory tests indicating an increased fibrinogen turnover, such as 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 used 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 will correct 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.

### Table 170.4

<table>
<thead>
<tr>
<th>Test</th>
<th>Discriminator value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>&lt;80–100,000 cells/dl or a decrease of &gt;50% from baseline</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&lt;100 mg/dL or a decrease of &gt;50% from baseline</td>
</tr>
<tr>
<td>PT</td>
<td>&gt;1 sec prolongation above ULN</td>
</tr>
<tr>
<td>FDPs</td>
<td>&gt;80 μg/dL</td>
</tr>
<tr>
<td>d-Dimer</td>
<td>Moderate increase</td>
</tr>
</tbody>
</table>

### Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

Specific mention of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) should be made. Although neither generally produces a coagulopathic state, both are characterized by marked microangiopathy and microvascular thrombosis. Presently, these two diseases are felt to represent different ends of the spectrum of end organ dysfunction possible in microangiopathic states. HUS is more commonly seen in children, and is characterized by a prodomme of fever and diffuse, often bloody, diarrhea. Endemic cases of HUS are generally caused by verotoxin expressing enteropathic strains of *E. coli* (O157:H7) or Shiga toxin expressing strains of *Shigella*. Sporadic cases are generally not associated with diarrhea, and may represent variant TTP or familial defects in complement factor H. Therapy, including renal replacement measures, is supportive. Neither plasma infusion nor plasma exchange appears to be beneficial in the treatment of HUS. TTP is characterized by the pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurologic symptoms of fever, and renal dysfunction. Whereas only 40% of patients will display the full pentad, up to 75% will manifest a triad of MAHA, neurologic symptoms, and thrombocytopenia. This
ensuing ischemic injury. Two new recombinant blood products:

- **Management**

  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 (a) the patient has significant bleeding or organ dysfunction secondary to DIC, (b) significant thrombosis has occurred, or (c) if treatment of the underlying disorder—for example, acute promyelocytic leukemia—is likely to increase the severity of DIC.

  Supportive therapy for DIC includes the use of several component blood products (27). Packed red blood cells are given according to accepted guidelines in the face of active bleeding. Fresh whole blood—that is, 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. Cryoprecipitate contains a much higher concentration of fibrinogen than does whole blood or fresh frozen plasma (FFP), and therefore is more likely to provide the quantity of fibrinogen needed to replete fibrinogen consumed during DIC. In this regard, 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. 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 or FFP in the treatment of DIC has, in the past, been open to debate because of concern that these products merely provide further substrate for ongoing DIC and thus increase the amount of fibrin thrombi formed. However, clinical (autopsy) studies have failed to confirm this concern.

  The goal of blood component therapy is not to produce normal numbers but rather to produce clinical stability. If the serum fibrinogen level is less than 75 to 50 mg/dL, repletion with cryoprecipitate to raise plasma levels to 100 mg/dL or higher is the goal. A reasonable starting dose is one bag of cryoprecipitate for every 10 kg body weight every 8 to 12 hours. As cryoprecipitate is not a standardized component (i.e., its content varies from bag to bag), one should recheck the fibrinogen level after an infusion to document the increase in fibrinogen level. The amount and timing of the next infusion is then adjusted according to the results. Platelet transfusions also may be used when thrombocytopenia is thought to contribute to ongoing bleeding. Many of the fibrin/fibrinogen fragments produced in DIC have the potential to impair platelet function by inhibiting fibrinogen binding to platelets. This may be clinically significant at the concentration of FDPs achieved with DIC. Platelet transfusions in patients with DIC should be considered to maintain platelet counts up to 40,000 to 80,000 cells/μL, depending on the clinical specifics of the patient. Pharmacologic therapy for DIC has two primary aims: to “turn off” ongoing coagulation so that repletion of coagulation factors may begin, and to impede thrombus formation and ensuing ischemic injury. Two new recombinant blood products have been recently developed that have some usefulness in the treatment of DIC. The first is recombinant-activated protein C. This product has been shown to result in a 67% reduction in sepsis mortality in adults and possibly a reduction in the incidence of DIC (28). However, in older adults, its use was associated with an increase in intracranial bleeding. The second new agent for the treatment of severe bleeding, including DIC, is recombinant-activated factor VII (rhfVIIa). Although there are limited controlled trials of its use and none in the pediatric age range, with the exception of those patients with acquired inhibitors to VIII, it has been proven to be a potent agent for the control of bleeding from several medical and surgical causes, including DIC and other consumptive coagulopathies (29–31). This agent has also been shown to correct the hemostatic defect caused by the antiplatelet agents aspirin and clopidogrel (32). There have been reports that use of rhfVIIa may result in an increase in thrombosis and thromboembolic events, although the incidence appears to be small and the severity of most events mild (33). In addition to activated protein C, other anticoagulant molecules such as heparin and antithrombin III and thrombolytic agents continue to be studied as therapy for DIC and sepsis (34,35).

**Liver Disease and Hepatic Insufficiency**

### Abnormal Hemostasis in Liver Disease

Liver disease is a common cause of abnormal hemostasis in ICU patients, with abnormal coagulation studies or overt bleeding occurring in approximately 50% of patients with severe liver disease (36). The hemostatic defect associated with liver disease is multifactorial, with multiple aspects of hemostasis affected (36,37).

- **Liver disease**, the synthesis of several plasma coagulation proteins is impaired. These include factors II, V, VII, IX, and X. Fibrinogen synthesis by the liver is usually maintained at levels that prevent bleeding until terminal liver failure supervenes. However, the function of fibrinogen synthesized by a diseased liver may not be normal, owing to an increased sialic acid content in its structure, which may result in a diminished ability to form clots (i.e., a dysfibrinogen). Factor 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 normal fibrin clot stabilization. Although it is apparently synthesized by the liver, factor VIII (i.e., factor VIII coagulant protein [VIII:C]), antithrombin factor A ([AHF]) synthesis seems to be independent of the state of hepatic function. Indeed, factor VIII levels may be decreased 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 defects 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 concurrent DIC, as patients with cirrhosis are...
at increased risk for the development of DIC. 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. 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.

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 hematologic 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 disease may also exhibit decreased synthesis of the vitamin K–dependent anticoagulant proteins, protein C and protein S, as well as antithrombin-III (37). 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—4 to 6 hours—and increased turnover. This results in a prolonged PT, and can be noted even when usual markers of hepatic cellular injury or hepatic insufficiency remain relatively normal (36,37). A prolonged thrombin time 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 does 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, the synthetic hypofibrinogenemia of liver disease 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. Differentiating between concomitant DIC and fibrinolysis attributable to liver disease alone may be difficult. The d-dimer assay result should be negative in the patient with liver disease and elevated FDPs, but no active bleeding. Further clinical distinction usually is not possible.

Management

If the patient is not actively bleeding, with certain provisos, no specific therapy is required. In patients with a prolonged PT who are in a postoperative state or are scheduled for an invasive procedure, correction of the PT may be attempted. FFP provides the most immediate source of specific coagulation factors (i.e., factor VII), and usually corrects an isolated mild PT prolongation. Cryoprecipitate is required only if fibrinogen levels are less than 50 to 100 mg/dL, or if there is documentation of a significant dysfibrinogenemia. Vitamin K deficiency also is relatively common in this patient population, and replacement may be needed. In contrast to patients with 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. The immediate use of FFP is therefore appropriate when rapid correction is necessary. Recombinant human-activated factor VII (rhfVIIa) infusions have been shown to control the bleeding in severe liver disease, although this does not necessarily result in reduced mortality (38,39).

When the synthetic capability of the liver becomes more profoundly impaired, and the aPTT is also prolonged, greater volumes of FFP or more specific therapy may be needed. The use of factor IX concentrates (prothrombin complex concentrates) or rFVIIa has been advocated, particularly if bleeding is present; however, their use remains controversial. Those products produced from plasma pooled from multiple donors carry a significant risk of both hepatitis B and C. In addition, they may provoke DIC and actually worsen hemostasis. The use of prothrombin complex concentrates or rhFVIIa should be reserved for patients with poorly controlled bleeding that is unresponsive to other more established therapeutic modalities such as infusion of FFP. Guidelines for the use of rFVIIa are under development.

A comprehensive therapeutic approach is needed in the patient with active bleeding as a result of liver disease. Initially, FFP, 10 to 15 mL/kg body weight, may be given every 6 to 8 hours until bleeding slows significantly, and should then be continued at maintenance levels as dictated by clinical status and coagulation studies. Recombinant human-activated factor VII or prothrombin complex concentrates may be used in those patients unresponsive to FFP infusions (39). Cryoprecipitate should be infused for fibrinogen levels less than 50 to 100 mg/dL. Platelet transfusions also may be required if the platelet count is less than 40,000 to 80,000 cells/µL, depending 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 vitamin K deficiency. Vitamin K is necessary for the gamma-carboxylation 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
In addition to a prolonged PT, include a normal fibrinogen and 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 deficiency, 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 reversal, usually by intravenous or subcutaneous routes in critically ill patients. Therapy should not await the development 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 absorption from the soft tissues. The possibility of anaphylactoid reactions with the intravenous use of vitamin K is of concern. This risk is markedly reduced 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 (40); this is the preferred method of drug administration in hemodynamically unstable patients. However, incidences of anaphylaxis are still reported with this mode of infusion (41,42). The usual dose of vitamin K in adults is 10 to 15 mg intravenously or subcutaneously, 1 to 5 mg in young children, and 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 used, 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 additional benefit in this setting.

When the patient is actively bleeding, it is not sufficient to only provide vitamin K. A more immediate restoration of coagulation is required. FFP has traditionally been used in this setting. To restore hemostasis to an acceptable level, 30% to 50% of normal factor activity, 10 to 20 mL/kg body weight of FFP is typically required. A similar approach is used in patients previously given warfarin. Recombinant human-activated factor VII (rFVIIa) has been used with success to reverse the bleeding noted in vitamin K deficiency and in warfarin overdose (39,43).

**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 (44).

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 red blood cells (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 qualita-
tive platelet defect can be demonstrated in whole blood within hours of its storage, especially if an acid-citrate-dextrose so-
lation is used. Consequently, transfusion of large quantities of stored whole blood may produce limited improvement of the bleeding resulting from decreased clotting factors and platelets. The development of a washout coagulopathy is directly depen-
dent on the volume of blood transfused relative to the blood volume of the patient. As a general rule, residual plasma clot-
ting 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 clini-
cal settings, including some associated with major hemorrhage or massive transfusion. In the presence of hypotension associ-
ated with hypovolemia or hemorrhagic shock, DIC is a com-
mon sequela. Major trauma itself, especially with the release of tissue factors into the plasma, also can result in the develop-
ment 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 life-
saving 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 incompatibil-
ity can produce severe hemolysis and be lethal. Finally, mi-
croaggregates 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 administra-
tion, 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 oozing and bleed-
ing from all surgical wounds and puncture sites. Laboratory
abnormalities include prolonged PT, aPTT, and TT. Fibri
ogen levels and platelet counts are typically decreased; FDPs
are not usually increased unless concurrent DIC is present (Table 170.2). The likelihood that the clinico-laboratory picture is a direct result of the massive transfusion can be estimated from the amount of bleeding that has occurred and the blood vol-
ume 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 coagu-
lopathy from massive transfusion is supportive. Platelets and
FFP are given to replete the components of coagulation that are typically lacking (43). 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 cells/μL of blood. Because of the com-
plex nature of bleeding seen with massive transfusion, patients may benefit from platelet transfusion at counts even as high as 80,000 to 100,000 cells/μL. FFP is preferred over cryoprecipit-
tate because it has a more complete coagulation protein compo-
sition. However, cryoprecipitate may be specifically given when fibrinogen depletion is thought to be a major contributor to the observed bleeding.

The prospective identification of those at risk of developing a coagulopathy from massive transfusion is critical. When the magnitude of the insult and the anticipated need for blood are large, both platelets and FFP should be given before a coag-
ulopathy develops. In most patients (e.g., weight greater than or equal to 30 to 40 kg or body surface area [BSA] greater than or equal to 1.0 m², four units of platelets (or ¼ unit of apheresis-collected platelets) and one unit of FFP should be given for each five units of whole blood or packed cells trans-
fused. This should prevent washout and its attendant bleeding. If the patient continues to bleed despite what should be ade-
quate therapy for massive transfusion syndrome, other causes should be considered. Specifically, anatomic bleeding and the possibility of DIC should be investigated. Therapy in this set-
ing may include rhVIIa infusion (31).

### Anticoagulant Overdose

Anticoagulant therapy is not unusual in the ICU, and the pos-
sibility of errors in administration exists. Methods of prophyl-
actic anticoagulant use, systemic anticoagulation, and throm-
boLytic therapy are sometimes poorly standardized and can lead to overdose.

#### Heparin

Heparin is a repeating polymer of two disaccharide gly-
cosaminoglycans, 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 un-
derstand the differences between these two forms of the drug, as they have different mechanisms of action and associated pre-
cautions. 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 ef-
flect of inhibiting activated factor X (Xa). This anticoagulant effect of UH is relatively minor. Consequently, achieving a ther-
apneu aPTT with UH is very difficult in the face of low levels of AT-III. The degree of anticoagulation produced by heparin is 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 Xa. This produces a more stable degree of anticoagulation and, due to its longer half-life (approximately 3 to 5 hours) and biologic activity (approxi-
mately 24 hours), allows for intermittent bolus therapy every 12 or 24 hours while still maintaining a steady-state effect. However, LMWH does not produce consistent prolongation of the aPTT, and requires assay of anti-Xa activity for moni-
toring, if monitoring is desired.

Heparin is metabolized in the liver by the “heparinase” enzy-
m in a dose-dependent fashion, with excess heparin then being excreted through the kidneys. As the rate of heparin ad-
mistration is increased, the half-life of the drug is prolonged due to the increase in the percentage of the drug being excreted
3 days. Factor VII has a half-life of only 4 to 6 hours, and the ac-
tio (INR) calculated from the PT, is an accurate indicator of
sufficient plasma concentrations, there is depletion of the active
into its enzymatically active form. When warfarin is present in
K–dependent coagulation proteins—factors II, VII, IX, and X–
mechanism of action of warfarin is through competi-
tive 4-hydroxycoumarin nucleus and naphthoquinone ring.
Warfarin and vitamin K are structurally similar in their respec-
tively has anticoagulant activity. As a general rule, 1 mg of protamine
neutralizes approximately 100 units 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 sys-
tem. 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 poten-
tially has anticoagulant effects, and precautions necessary
during its administration. The drug should be given by slow in-
travenous push over 8 to 10 minutes. A single dose should not
exceed 1 mg/kg, with a 50-mg maximum dose. This dose may
be repeated, but no more than 2 mg/kg, to a 100-mg maximum
dose, should be given as a cumulative dose without recheck-
ing 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 adminis-
tration, and include hypotension and anaphylactoid-like reac-
tions. 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 rhFVIIa.

**Warfarin**

Warfarin and vitamin K are structurally similar in their respec-
tive 4-hydroxycoumarin nucleus and naphthoquinone ring.
The mechanism of action of warfarin is through competi-
tive binding at the vitamin K receptor site, where postrib-
osomal modification, through γ-carboxylation of the vitamin K–
dependent coagulation proteins—factors II, VII, IX, and X–
occur. This posttranslational 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 the active
forms of vitamin K–dependent factors.

The PT, or more precisely the international normalized ra-
tio (INR) calculated from the PT, is an accurate indicator of
the effects of 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 ac-
tive 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 vi-
tamin 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 depletion of the
active forms of factors II, IX, and X.

Several drugs and pathophysiologic conditions are associ-
ted with potentiation of warfarin's effects on coagulation.
Table 170.5 lists many of the drugs known to prolong the
effects of warfarin. These drugs have various mechanisms,
which generally include either inhibition of function or com-
petitive binding of the enzymes responsible for active warfarin
metabolism. Aspirin does not seem to have any direct effect on
warfarin metabolism, but can so profoundly influence quali-
lative platelet function that it must be considered as a poten-
tiator of warfarin's anticoagulant effects. The same is true for
clofibrate. Ingestion of large quantities of aspirin may also im-
pair prothrombin (factor II) synthesis, further increasing the
effects of warfarin administration. As warfarin is metabolized
by the liver, conditions of acute and chronic hepatic dysfunc-
tion can alter warfarin metabolism and vitamin K–mediated
γ-carboxylation of the vitamin K–dependent coagulation pro-
teins. 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 fac-
tors 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 anticoagu-
lation with a vitamin K antagonist. It is characterized chiefly
by the development of skin and subcutaneous necrosis, partic-
ularly in areas of subcutaneous fat, and pathologically by the
thrombosis of small blood vessels in the fat and subcutaneous

**TABLE 170.5**

**DRUGS THAT POTENTIATE THE ANTICOAGULANT EFFECTS OF WARFARIN**

**ANTIBIOTICS**

- Broad-spectrum antibiotics (especially cephalosporins)
- Griseofulvin (oral)
- Metronidazole
- Sulfonamides
- Trimethoprim-sulfamethoxazole

**ANTI-INFLAMMATORY DRUGS**

- Steroids (anabolic, in particular)
- Axitrated salicylates
- Phenylbutazone (oxyphenbutazone)
- Sulfinpyrazone

**OTHER DRUGS**

- Cimetidine
- Clofibrate
- Diclofenac
- Phenytoin (both D- and L-isomers)
- Tolbutamide
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. Whereas 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% of normal 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 overanticoagulation with warfarin presents with bleeding, immediate reversal is usually mandated (43). The treatment of choice is FFP, which provides prompt restoration of the deficient vitamin K–dependent coagulation proteins, along with restoration of hemostatic function. Ten to 15 mL/kg of FFP are 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 (43). Vitamin K also may be administered, particularly in situations that are less acute (see above 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 FFP infusions, rhVIIa has been used successfully.

**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 (Fig. 170.3). Quantitative and qualitative platelet disorders are a common cause of clinical bleeding

### TABLE 170.6

**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><strong>DRUGS</strong></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., cefalothin)</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>
<tr>
<td><strong>DECREASED PRODUCTION</strong></td>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Marrow suppression</td>
<td>Methylxanthines (e.g., theophylline)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Other drugs</td>
</tr>
<tr>
<td>Viral illness (e.g., cytomegalovirus, Epstein-Barr virus, herpes simplex, parvovirus)</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Drugs (thiazides, ethanol, cimetidine)</td>
<td>Alpha-blockers (e.g., phentolamine)</td>
</tr>
<tr>
<td>Marrow replacement</td>
<td>Beta-blockers (e.g., propranolol)</td>
</tr>
<tr>
<td>Tumor</td>
<td>Dextrans</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Other conditions</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>Heparin</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation syndrome</td>
<td>Local anesthetics (e.g., lidocaine)</td>
</tr>
<tr>
<td><strong>METABOLIC CAUSES</strong></td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Uremia</td>
<td>Tri cyclic antidepressants</td>
</tr>
<tr>
<td>Stored whole blood</td>
<td>Nitrites (e.g., sodium nitroprusside, nitroglycerin)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (i.e., FDP-mediated inhibition)</td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; FDP, fibrin degradation product.
in the ICU. Table 170.6 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), SLA, 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 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, at a dose of 2 to 4 mg/kg/day of prednisone or its equivalent, may be given. High doses of intravenous gamma globulin at 1 to 2 g/kg and given over 2 to 5 days, and infusions of anti-RhD antibody (Win-Rho) at 25 to 60 μg/kg, are equally efficacious in producing at least transient elevations in platelet counts. Agents such as vincristine/vinblastine, cyclophosphamide, and, most recently, rituximab (Rituxan; anti-CD20 monoclonal antibody) also have been used as immunosuppressants, with variable success, although responses are generally not immediate. Splenectomy 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 noted when thrombocytopenia results from decreased production. In general, severe bleeding is not noted until the platelet count is less than 10,000 cells/μL, although levels below 40,000 to 50,000 cells/μL may increase the risk of bleeding with an invasive procedure.

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, drug–drug complex, or both, of a specific antibody. The resulting platelet–drug–antibody complexes then are cleaved 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 anti-convulsant valproic acid (Depakote, Depakene) frequently produces a dose-dependent thrombocytopenia that, at least in part, is immunologic in nature.

Various 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 are also 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, and the thrombocytopenia seen with its use 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 generally mild and usually resolves despite continued use of the drug (type I HIT, or heparin-associated thrombocytopenia). The thrombocytopenia that develops has no clinical significance, and 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 being 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, stroke, pulmonary embolism, or renal infarction. The mechanism of thrombosis is thought to be a consequence of the deposition of platelet aggregates in the microcirculation (46). Thrombocytopenia, like other immune-mediated drug reactions, seems to involve the formation of platelet aggregates mediated by the binding of specific antibody, directed against a heparin–platelet factor 4 complex, to platelets in the presence of heparin. 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 (enzyme-linked immunosorbent 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. Although heparin-induced thrombocytopenia is 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 low-molecular-weight heparin. When type II HIT is suspected or confirmed, all exposure to heparin—including heparin flushes, heparin in total parenteral nutrition (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 removal of heparin exposure (46). Patients with type II HIT should receive continued anticoagulation with direct thrombin inhibitors (argatroban, lepirudin) or with the heparinoid, Danaparoid. The direct thrombin inhibitors are preferred, as they carry no risk of cross-reacting with the heparin-dependent antibodies already present (47). 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 adequate therapy for suspected type II HIT because of the risk of thrombosis from depression of protein C levels before the other factors are inhibited. However, warfarin can be used 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 (46).

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 or 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 170.6 provides an abbreviated list of the drugs that can affect at least one in vitro platelet function.

Unnecessary drugs should always be viewed as a jaundiced eye and discontinued. These agents, as well as necessary drugs are, of course, suspect 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 cyclooxygenase, resulting in a defect that lasts for the duration of the platelet life span—about 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 cyclooxygenase. 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 clopidogrel (Plavix) or dipyridamole (Persantine), can produce platelet inhibition that remains evident for several days after discontinuing the drug. The β-lactam antibiotics can sterically hinder the binding of the platelet aggregation agonist adenosine diphosphate (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 few 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 may have an inherited disorder of platelet function. Although rare, these disorders are encountered from time to time and include Glanzmann thrombasthenia (abnormal platelet GP IIb/IIIa), Bernard-Soulier syndrome (abnormal GP IIb/IIIa), Wiskott-Aldrich syndrome, platelet storage pool deficiency (abnormal platelet dense bodies), and the Gray platelet disorder (abnormal platelet granules).

Management. Because many of the adverse drug-related platelet effects are reversible, unnecessary medications should always be discontinued promptly when platelet function seems impaired. In fact, as a general rule, it is never acceptable to leave a nonessential agent on the patient’s medication list simply because it is benign; any drug in this category must be discontinued.

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, and patients at clotting risk are transfused with platelets at counts as low as 80,000 or even 100,000 platelets/µL, although bleeding in the presence of a platelet count of 80,000 cells/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 10,000 to 20,000 cells/µL. As previously stated, rHuVIIIa has also been used to reverse the hemostatic defect caused by aspirin or clopidogrel (32).

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 cells/µL. The empirical administration of platelets to those 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 the 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 (48,49). 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 von Willebrand factor. 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 cause but, in part, reflect the increased renal loss of antithrombin III and protein S in nephrotic-range proteinuria (50).

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 mg), and conjugated estrogens (10 mg/day 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 von Willebrand factor, thus greatly improving platelet adhesion. The duration of action of these agents, however, is 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 the following:

1. Deep venous thrombosis (DVT) (specifically in association with a central venous catheter)
2. Heparin-induced thrombocytopenia
3. Pulmonary embolism syndrome
4. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
5. Thrombotic DIC
6. Stroke
7. 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 candidates for some sort of thromboprophylaxis (51). Approximately 10% of ICU patients will develop DVT while in the ICU in spite of receiving a form of thromboprophylaxis, and up to 15% of these patients will experience a symptomatic pulmonary embolus (52,53). 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 is critical for the care of these patients.

**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 (54). 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 units/kg, followed by a continuous infusion of 10 units/kg/hour; 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). Dosing of LMWH is weight related. 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 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 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 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 remits 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 the associated laboratory abnormalities. As an isolated hemostatic defect, thrombosis is the more likely problem (25% incidence rate), with bleeding in one series occurring in only 1 of 219 patients with the lupus anticoagulant (55,56).

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 antiphospholipid 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 greatest when the lupus anticoagulant has specificity for β2-glycoprotein I or 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 whereas arterial thrombosis is more common in the central nervous system. 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 laboratory, fibrinogen is measured using a functional assay in which time to fibrin clot formation is the end point. 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 are formed that inhibit further fibrin clot formation. Other hematologic parameters, such as the aPTT, PT, and the TT, are consequently prolonged, suggesting a potential, although artifactual, risk 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 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

Currently, much attention is being given to better understanding the interplay of coagulation and inflammation, and how the inflammatory state sets off a chain reaction resulting in microvascular thrombosis and multisystem dysfunction/failure. Improving our grasp of these interactions requires that we increase our knowledge of the normal function of the endothelium, and how this function is disrupted in sepsis and severe acute illness. Other areas that need further research are the specific host factors that regulate the balance between too little and too much thrombosis, including how the numerous genetic polymorphisms of important regulatory protein genes affect the overall regulation of hemostasis. As our ability improves in treating the initial acute event that brings a patient to the ICU, we will gain a better understanding of all the processes and mechanisms that increase the risk of end-organ failure, which will allow us to treat them proactively. Newer, and old, drugs are being tested in the setting of sepsis to prevent DIC and microvascular thrombosis and, if successful, they may result in improved survival with decreased morbidity. Some of these strategies will involve ways to better regulate the coagulation process, but we also need to develop means by which to protect the endothelium. While waiting for these scientific and therapeutic advances, we, as clinicians, must also work to recognize disease processes earlier (e.g., DIC) so we can determine how to best use those treatments already available to us (e.g., activated protein C, thrombolytics, anticoagulants, and so on) more precisely, cost effectively, and safely.

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