CHEST®

Official publication of the American College of Chest Physicians

Coagulopathy in Critically Ill Patients : Part 1: Platelet Disorders

Todd W. Rice and Arthur P. Wheeler

Chest 2009;136;1622-1630
DOI 10.1378/chest.08-2534

ISSN:0012-3692

CHEST Recent Advances in Chest Medicine

Coagulopathy in Critically Ill Patients

Part 1: Platelet Disorders

Todd W. Rice, MD, MSc; and Arthur P. Wheeler, MD, FCCP

Abnormalities of platelet number and function are the most common coagulation disorders seen among ICU patients. This article reviews the most frequent causes of thrombocytopenia by providing an overview of the following most common mechanisms: impaired production; sequestration; dilution; and destruction. Guidelines for treating thrombocytopenia and platelet dysfunction are also provided. ***(CHEST 2009; 136:1622–1630)***

Abbreviations: aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, and low platelets; HIT = heparin-induced thrombocytopenia; HUS = hemolytic uremic syndrome; PF4 = platelet factor 4; PT = prothrombin time; TTP = thrombotic thrombocytopenic purpura; vWD = von Willebrand disease; vWF = von Willebrand factor

Even though coronary, cerebrovascular, and venous thromboses are the leading killers of adults in ICUs, clinicians often have greater apprehension about bleeding than clotting. These concerns may stem from a sense of responsibility for bleeding following procedures or anticoagulant therapy, or perhaps it is the mere fact that hemorrhage is often visible externally, whereas thrombosis is more clandestine. Fortunately, humans are largely protected from clinically significant bleeding by the following three hemostatic systems: intact vasculature; platelets; and soluble clotting factors. Significant bleeding is rare until two of the three systems malfunction, and then the magnitude of each failure often must be significant. This article, the initial one in a two-part series on coagulation disorders in the ICU, focuses on the causes and treatment of the most common coagulation disorder in critically ill patients, namely thrombocytopenia, and it also briefly discusses disorders of platelet function despite normal platelet counts.

Manuscript received October 21, 2008; revision accepted February 5, 2009.
Affiliations: From the Medical Intensive Care Unit (Drs. Rice and Wheeler), and the Division of Allergy, Pulmonary, and Critical Care Medicine (Dr. Wheeler), Vanderbilt University Medical Center, Nashville, TN.
Correspondence to: Arthur Wheeler, MD, FCCP, T-1210 MCN, Vanderbilt Medical Center, Nashville, TN 37232-2650; e-mail: art.wheeler@vanderbilt.edu

DOI: 10.1378/chest.08-2534

Platelet Disorders

Platelets form the first line of defense when endothelial surfaces are breached. Exposure of the subendothelial layer of vessels results in exposure of tissue factor, collagen, and von Willebrand factor (vWF), which promote fibrinogen and vWF-mediated platelet aggregation. In rapid succession, platelets change shape, degranulate, and expose surface phospholipids that generate small amounts of thrombin, triggering clotting amplification. Hence, the deficiency or dysfunction of platelets represents a serious hemostatic problem.

Thrombocytopenia

Thrombocytopenia is the most common coagulation problem in the ICU with an incidence of 15 to 60% depending on the definition used, population evaluated, and period of ICU stay studied.[1–8] About half of all ICU patients with thrombocytopenia present with the condition[6,9]; the remainder acquire it promptly.[9] The highest incidence is seen in patients with severe sepsis.[1,9–12] Surgical and trauma patients reportedly have a higher frequency than medical patients.[7,8] Patients receiving dialysis support also frequently exhibit thrombocytopenia.[6]

Definition and Implications: Traditionally, thrombocytopenia has been defined as a platelet count of $< 150 \times 10^9$ /L, but in critically ill patients a threshold of $< 100 \times 10^9$ /L has been suggested,[13,14] due to the relatively high incidence and lack of significant bleeding with counts between 100 and 150×10^9 /L. A category of severe thrombocytopenia ($< 50 \times 10^9$ /L) has also been designated but fortunately is uncommon, occurring in just 2 to 15% of ICU patients.[1–6,8,13]

Thrombocytopenia is important because it increases the risk of bleeding, alters plans for care, and serves as a marker of morbidity and mortality. Thrombocytopenia may also be a manifestation of a disease that promotes clotting, such as heparin-induced thrombocytopenia (HIT) or disseminated intravascular coagulation (DIC). The threshold at which bleeding risk increases significantly is debated but probably lies below, maybe even well below, 100×10^9 /L. In the ICU, counts $< 100 \times 10^9$ /L have been associated with a 10-fold increased risk of bleeding compared to those between 100 and 150×10^9 /L.[1] Lower platelet counts are associated with an even higher risk of hemorrhage, especially counts below 50×10^9 /L,[1,2,13] and although rare, spontaneous intracerebral hemorrhage is usually a complication only when platelet counts fall below 10×10^9 /L.[15]

Tradition largely drives practice with regard to care of the thrombocytopenic patient. Invasive procedures are commonly avoided when the counts are below 50×10^9 /L and sometimes even when 50 to 100×10^9 /L, especially if the procedure involves the neuraxis or other critical or difficult-to-access sites.[16–18] For patients with intact soluble clotting factors not undergoing invasive procedures, this practice may be overly conservative. Surgical bleeding is uncommon with platelet counts $> 50 \times 10^9$ /L,[19,20] and oncology data indicate that the risk of spontaneous bleeding does not increase until counts fall below 20×10^9 /L and perhaps even 10×10^9 /L.[21–23] In patients with aplastic anemia, this threshold may even be as low as 5×10^9 /L.[23] Surprisingly, even among patients with severe sepsis receiving the anticoagulant activated protein C, significantly higher bleeding rates are not seen until platelet counts decline below 30×10^9 /L unless invasive procedures are performed.[24,25]

Even though concern for bleeding in thrombocytopenic patients is understandable, oftentimes such patients are unnecessarily exposed to risks of platelet transfusions.[26] Ironically, platelet transfusions decrease endogenous platelet production because the c-Mpl receptor on the surface of transfused platelets binds and inactivates thrombopoietin produced by the liver.[27] Furthermore, platelet transfusions place the patient at risk for other complications.[17,18] Platelets are obtained from blood donors, and, as such, they carry a risk, although very small, of transmitting infections such as HIV or hepatitis viruses. In addition, transfusion-related acute lung injury can also occur after platelet transfusions. Finally, platelets increase the propensity to clot, which is why they are given to bleeding patients or those at risk for bleeding. However, platelet transfusions may actually cause excessive clotting or deep vein thromboses in some patients.

Although platelet transfusions are often used to increase the absolute platelet count in many critically ill patients, they may be unnecessary, ineffective, or contraindicated in certain patients. In addition to the complications just listed, platelet transfusions also can exacerbate clotting in many of the prothrombotic thrombocytopenic conditions, such as thrombotic thrombocytopenic purpura (TTP) and HIT. In fact, in DIC, where the thrombocytopenia is a result of excessive formation and degradation of clots, treatment of the underlying cause is indicated over platelet transfusion. Likewise, anticoagulation to prevent clots from forming, concurrently with discontinuation of the heparin, is also part of the treatment for HIT.

Independent of bleeding, studies have consistently demonstrated an association between thrombocytopenia and poor clinical outcomes. For example, low platelet counts have been associated with longer ICU and hospital lengths of stay[3,6,7,28] and are an independent predictor of ICU mortality and lower rates of long-term survival.[1,2,6,7,12,29] In fact, data suggest that the severity of thrombocytopenia is inversely related to survival in critically ill patients, and that sustained thrombocytopenia over 4 days is associated with a fourfold to sixfold increase in mortality.[1,9] The relationship between thrombocytopenia and poor outcomes is particularly prominent for patients meeting the formal DIC criteria.[24,30] Although the reasons for the association between thrombocytopenia and poor outcomes are speculative, they likely relate to the seriousness of conditions causing the thrombocytopenia (*eg*, severe sepsis and neoplasia).

Etiology

The cause of thrombocytopenia in most ICU patients is multifactorial, involving some combination of the following four mechanisms: increased destruction or consumption; decreased production; dilution; and sequestration (Table 1).[31]

Spurious Thrombocytopenia: The initial step in evaluating thrombocytopenia should always be to make sure the laboratory result really reflects a low

Table 1—*Categories of Thrombocytopenia*

Category	Pathophysiology	Diseases	Degree of Thrombocytopenia	Other Cytopenias	Treatment
Spurious thrombocytopenia	Pseudothrombocytopenia caused by clumping of platelets in collection tubes	Laboratory error	Variable	Unlikely	Redraw specimen in heparin or citrate tube; repeat automated count or manual count
Increased platelet destruction	Non–immune-mediated	DIC	Variable but usually severe	Anemia	Treat underlying cause; anticoagulation
		TTP			Plasma exchange
		HELLP			Delivery of infant
	Immune-mediated (drug)	Drugs (see Table 3)	Variable	Unlikely	Stop offending drug
		Type 2 HIT	Mild to moderate	None	Stop heparin therapy; direct thrombin inhibitor
	Immune-mediated (nondrug)	ITP	Mild to moderate	Unlikely	Steroids; IV Ig; splenectomy
Dilutional thrombocytopenia	Platelet count diluted by administration of massive amounts of non-platelet-containing blood products and IV fluids	Trauma after massive transfusions	Variable, can be severe	With or without anemia; leukopenia	Platelet transfusion; supportive care
Distributional thrombocytopenia	Platelets sequestered in spleen and not in circulation	Splenomegaly; portal hypertension	Mild to moderate	Unlikely	Supportive care; splenectomy
Decreased platelet production	Bone marrow suppression	Nutritional deficiencies	Variable, but can be severe	With or without anemia; with or without leukopenia	Replete deficiencies
		Drugs (see Table 3); toxins			Stop offending agent
		Viral infections			Supportive care
		Metastases			Chemotherapy; radiation therapy

ITP = idiopathic thrombocytopenic purpura.

platelet count. Spurious thrombocytopenia, or pseudothrombocytopenia, arises from platelets clumping in the collection tubes due to either ethylenediaminetetraacetic acid-dependent antibodies or insufficient anticoagulant. The reasons for the development of antibodies are in question. The process, however, seems to be most common among patients with severe sepsis, or autoimmune, neoplastic, or liver diseases.[32] As a result, automated counters fail to recognize clumped platelets as such due to their abnormally large size, resulting in a falsely decreased reported platelet count. If spurious thrombocytopenia is suspected because the laboratory finding does not fit the clinical picture or clumped platelets are seen on the peripheral smear, blood should be redrawn in heparin or citrate-containing collection tubes and assayed again for platelet count using the automated counter and/or examined microscopically. The examination of platelet size may also provide clues to the etiology of thrombocytopenia. Larger platelets are usually associated with diseases of increased platelet turnover and adequate marrow production (*eg*, idiopathic thrombocytopenic purpura), whereas small platelets are more likely to be associated with production disorders.[33]

Increased Platelet Destruction or Consumption

Increased platelet destruction is the most common mechanism for thrombocytopenia and may occur through immune-mediated and non–immune-mediated mechanisms.[34] Nonimmune causes include DIC as seen with some malignancies, severe sepsis, trauma, or obstetrical catastrophes, and physical destruction as seen with cardiopulmonary bypass or giant hemangiomas.[35,36] The physical destruction is thought not to be mediated by specific antibodies, but some of the conditions may indeed occur via an unknown immune-mediated process. In addition, some of the thrombocytopenia in these conditions may simply reflect the consumption of platelets in the overexuberant formation of clots.

DIC, TTP, and Hemolysis, Elevated Liver Enzymes, Low Platelets Syndrome: DIC is usually associated

with other signs of accelerated clot formation and dissolution, such as reduced fibrinogen levels, elevated levels of d-dimer or other fibrin split products, and possibly an increased activated partial thromboplastin time (aPTT) or prothrombin time (PT) [see following]. Although rare to develop in the ICU, patients may also present with other thrombotic microangiopathies, such as TTP-hemolytic uremic syndrome (HUS). In these cases, thrombocytopenia results from platelets aggregating with abnormally large vWF multimers that result from a deficiency in a vWF-cleaving protease.[37] The often profound thrombocytopenia is accompanied by elevated serum lactate dehydrogenase levels and the presence of schistocytes on the peripheral smear representing mechanical destruction of erythrocytes.[38] Only microangiopathic hemolytic anemia and thrombocytopenia are required for the diagnosis, despite the description of a "classic pentad" of TTP-HUS, which also includes renal dysfunction, neurologic abnormalities, and low-grade fever.[39] Numerous conditions, including cancer, pregnancy, autoimmune conditions such as antiphospholipid antibody syndrome, and pneumococcal infection can be associated with "TTP-like" syndromes. Likewise, medications, such as cyclosporine, clopidogrel, and some chemotherapeutic agents, can produce a similar syndrome.[14] The absence of an increased aPTT or PT in patients with TTP-HUS can sometimes help differentiate it from DIC, which also can have schistocytes on the peripheral smear. Unfortunately, increased coagulation parameters are not universally present in DIC, making the distinction difficult at times. Low fibrinogen levels and prolonged thrombin times are also commonly present in patients with DIC but rarely occur with TTP-HUS (Table 2). A temperature $>$ 39°C (102°F) may also help to distinguish DIC from TTP-HUS because fever, when present in the latter condition, is almost always low grade.[40] Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome of pregnancy represents another condition with hemolysis and thrombocytopenia that may be difficult to discriminate from TTP-HUS[14] (Table 2). Elevated liver enzymes may be helpful in differentiating the two, but the pregnant state itself is less helpful because it is also a risk factor for TTP. However, HELLP primarily occurs during the third trimester, so thrombocytopenia prior to 20 weeks of gestation is almost never HELLP syndrome. Because HELLP syndrome usually resolves within 72 h of delivery, continued worsening of thrombocytopenia beyond this time should prompt the strong consideration of TTP.

Table 2—*Comparison of DIC, TTP-HUS, and HELLP Syndromes*

Variables	DIC	TTP-HUS	HELLP
Platelets	Low	Extremely low	Low to extremely low
Anemia	MAHA	MAHA	MAHA
Schistocytes	Usually	Always	Always
INR/PT	Normal or prolonged	Normal	Normal
aPTT	Normal or prolonged	Normal	Normal
Thrombin time	Prolonged	Normal	Normal
Fibrinogen	Low	Normal	Normal
FDP	Elevated	Normal	Normal
Liver enzymes	Normal or slightly elevated	Normal	Elevated
Underlying disorders	Sepsis	Usually idiopathic	Always pregnancy or postpartum
	Malignancy	Rarely pregnancy	
	Obstetric complications	Medication	
LDH	Elevated	Markedly elevated	Elevated
Fever	Present; may be high	If present, low grade	Variable
Associated features*		Diarrhea, renal failure, neurologic symptoms	Proteinuria hypertension

FDP = fibrin degradation products; INR = international normalized ratio; LDH = lactate dehydrogenase; MAHA = microangiopathic hemolytic anemia.
*Not universally present.

Immune-Mediated Damage

Drug-Induced, Immune-Mediated Thrombocytopenia: Immune-mediated thrombocytopenia occurs via the production of platelet antibodies with subsequent destruction. The antibodies can be idiopathic or induced by drugs,[41–43] infections (*eg*, cytomegalovirus, HIV, Epstein-Barr virus, or parvovirus), or alloimmune disease following transfusion or transplantation. Many drugs have been implicated as causes of thrombocytopenia. Table 3 presents a partial list of nonchemotherapeutic agents (a more extensive list can be found at http://moon.ouhsc.edu/jgeorge/DITP.html). In the ICU, drug-induced thrombocytopenia can be overlooked because its onset often occurs a week or more after beginning therapy with the medication,[42] there are no distinguishing clinical features, and numerous other possible etiologies for thrombocytopenia exist. Nonetheless, recognition is important because the problem may sometimes be reversed by simply discontinuing the

Table 3—*Nonchemotherapeutic Drugs Commonly Used in the ICU Associated With Thrombocytopenia*

Drugs	Mechanism (If Known)
Antibiotics	
Penicillins	Hapten-dependent antibody
Vancomycin	Drug-dependent antibody
Linezolid	Myelosuppression
Daptomycin	Unknown
Meropenem	Interference with folate metabolism by inhibition of dihydrofolate reductase and/or drug-specific antibody
Trimethoprim/sulfamethoxazole	
Nitrofurantoin	Unknown
Ganciclovir	Unknown
Valganciclovir	Unknown
Fluconazole	Unknown
Rifampin	Drug-dependent antibody
Heparins and low-molecular-weight heparins	
Unfractionated heparin	Forms immune complex with platelet factor 4
Enoxaparin	
Histamine 2 receptor blockers	
Cimetidine	Drug-specific antibody
Ranitidine	Drug-specific antibody
Salicylates/nonsteroidal antiinflammatory drugs	
Aspirin	Drug-dependent antibody
Diclofenac	Drug-dependent antibody
Ibuprofen	Drug-dependent antibody
Glycoprotein IIb/IIIa inhibitors	
Abciximab	Preexisting antibodies specific for murine structural elements of abciximab
Tirofiban	Reacts with glycoprotein IIb/IIIa to induce neoepitope
Eptifibatide	
Ticlopidine	Thrombotic microangiopathy
Clopidogrel	
Antiarrhythmics	
Procainamide	Induction of autoantibodies
Amiodarone	Drug-dependent antibody/bone marrow granulomas
Antiepileptics	
Valproate	Drug-dependent antibody
Carbamazepine	Drug-dependent antibody
Phenytoin	Drug-dependent antibody
Miscellaneous	
Digoxin	Unknown
Furosemide	Drug-dependent antibody
Thiazides	Drug-dependent antibody
Haloperidol	Unknown
Morphine	Drug-dependent antibody

offending agent. The drug-induced destruction of platelets usually occurs via the formation of antiplatelet antibodies, which bind normal platelets in the presence of the sensitizing drug.[42,44] Only a few drugs, such as procainamide, induce autoantibodies that react with platelets even in the absence of the drug.[45] Although specific drug platelet-associated antibodies have been demonstrated for numerous compounds, *in vitro* testing is usually not helpful because it lacks sensitivity and specificity.[46] A third mechanism of drug-induced thrombocytopenia involves a direct interaction between drug and platelets, resulting in immune destruction. Tirofiban, for example, interacts with the glycoprotein IIb/IIIa receptor on platelets, changing their shape and thereby facilitating antibody recognition.[47]

HIT: Heparin is thought to be the most common noncytotoxic drug associated with thrombocytopenia. Although it is fairly common for platelet counts to reversibly decline modestly in the first few days after starting therapy with heparin (sometimes called *type 1 HIT*), the term *HIT* describes a specific syndrome of antibody formation, low platelets, and thrombosis.[48,49] Occasionally referred to as *type 2 HIT*, the incidence of this syndrome varies widely by population studied with the highest rates seen among patients given high doses of unfractionated heparin on multiple occasions. Although well known for its devastating thrombotic complications, type 2 HIT occurs in $< 5\%$ of patients treated with unfractionated heparin for up to 7 days.[48] Any exposure to any amount or form of heparin can cause, or exac-

erbate, HIT, including flushes for IV or arterial lines, use in dialysis machines, or subcutaneous dosing for deep venous thrombosis prophylaxis. Low-molecular-weight heparins can also incite HIT, although much less frequently,[50] and now there is even a case report[51] of HIT resulting from the factor Xa inhibitor fondaparinux.

In patients with no, or distant, previous heparin exposure, the fall in platelet counts can take 5 to 10 days. However, in patients with a history of recent exposure, the process can occur within hours. Platelet counts below 10×10^9 /L and bleeding are both exceedingly rare in patients with HIT.[48] In fact, the biggest risk for patients with HIT is thrombosis, which is 30 times more likely than in the general population.[52] The clots that result from HIT do not have to be unusual; in fact, the most common presentation of HIT is deep venous thrombosis.

The pathophysiology of HIT is complex and has been well reviewed elsewhere.[48] Briefly, heparin binds platelet factor 4 (PF4) forming a heparin-PF4 immune complex. Antibodies then bind to this immune complex and destroy platelets. An enzyme-linked immunosorbent assay is available for the detection of heparin-PF4 antibodies, and although highly sensitive, the assay has low specificity. Most patients with PF4-heparin antibodies do not have HIT.[53] Functional assays, which measure platelet degranulation in response to PF4-heparin complexes, have higher specificity but are not widely available.[53] Treatment recommendations, largely stemming from expert advice because randomized large-scale trials are lacking, consist of the discontinuation of all forms of heparin and the initiation of therapy with a direct thrombin inhibitor at least until improvement of the platelet count. Once the platelet count has demonstrated at least partial recovery (*eg*, $> 100 \times 10^9$ /L), warfarin therapy can be started and should be continued for at least 3 months.[48] Treatment with a direct thrombin inhibitor should be continued until therapeutic anticoagulation from the warfarin has been achieved. Controversy exists regarding the safety of reexposure of HIT victims to heparin, but it is safe to say that reexposure should not occur for several months, and then only after heparin-PF4 antibodies are undetectable.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia and concurrent soluble clotting factor deficiencies occur following massive blood product administration through the following two mechanisms: simple loss; and consumption without adequate replacement. There are no absolute rules for the volume of transfusion required for this problem to emerge, but replacement of the entire blood volume within a day, or half within 3 to 4 h, is often sufficient to precipitate a dilutional coagulopathy. The occurrence of dilutional coagulopathy is so variable that a strategy advocating a fixed recipe of blood product replacement probably does not make sense. Although one might suspect mild thrombocytopenia would result from dilution, surprisingly in cases where ≥ 20 units of blood products are transfused, platelet counts below 50×10^9 /L are not uncommon.[2] Dilutional coagulopathy is also commonly compounded by hypothermia resulting from patient exposure and the infusion of large volumes of cool fluids,[54] by acidosis resulting from underperfusion and the transfusion of acidic fluids, and by the presence of DIC in some patients. The contribution of hypothermia to coagulopathy can be significant because hypothermia impairs platelet activation, adhesion, and aggregation,[55] as well as the enzymatic activity of soluble clotting factors.[54]

Distributional Thrombocytopenia: Sequestration in patients with marked splenomegaly resulting from portal hypertension or splenomegaly from other causes can result in distributional thrombocytopenia. The mechanism for the thrombocytopenia is likely multifactorial, including "pooling in the spleen," decreased production, and immune platelet destruction (especially in idiopathic thrombocytopenic purpura).[56] Patients with cirrhosis-induced portal hypertension may also have decreased platelet production because of reduced levels of thrombopoietin, normally produced by the liver[57] or from the toxic effects of ethanol on the marrow.[58]

Decreased Platelet Production

Bone marrow suppression results in a reduction in all cell lines, but it often manifests as thrombocytopenia because of the relatively short lifespan of platelets, especially if consumption is increased. Because drugs are the main culprit causing bone marrow suppression (Table 3), all medicines, including nonprescription drugs, should be thoroughly reviewed and potential offenders discontinued, if possible. Clinicians recognize chemotherapeutic or immunosuppressive agents as causing dose-dependent hematosuppression. However, nonchemotherapeutic agents, like the antibiotic linezolid, may also result in decreased platelet production.[59–61] Some medications often mentioned as potential agents of thrombocytopenia (*eg*, proton pump inhibitors), actually have little evidence to support such a claim. Other etiologies, such as viral infections (*eg*, HIV, parvovirus, Epstein-Barr virus, or varicella), toxins (*eg*, alcohol or radiation

therapy), metastases, and nutritional deficiencies (*eg*, vitamin B_{12}, folic acid, or iron) can also result in bone marrow suppression.[13]

Disorders of Platelet Function

Disorders of platelet function occur when platelet numbers are normal but activity is impaired by medications; the platelet environment, as in renal failure; or intrinsic platelet defects. These disorders are not readily apparent via simple examination of the platelet count from the CBC. Clinically, patients with dysfunctional platelets characteristically demonstrate abnormal mucosal or cutaneous bleeding, manifested as epistaxis, gingival bleeding, cutaneous petechiae, superficial ecchymoses, or menorrhagia.[31] If platelet dysfunction is suspected, specialized platelet function studies, which test the ability of platelets to aggregate and form a clot, should be ordered. The simplest of these is bleeding time, where the interaction between platelets and the blood vessel wall is measured by the time needed to stop bleeding after a cut in the skin. Unfortunately, bleeding time is poorly reproducible, insensitive, and time consuming. Newer studies of platelet function have been developed that measure the ability of platelets to aggregate in response to the addition of an external stimulus. Many of these tests are performed only in specialized laboratories and are not available clinically. A complete discussion of platelet aggregation testing is beyond the scope of this review and has been detailed elsewhere.[62–64]

Medications that cause platelet dysfunction include aspirin, which irreversibly inhibits platelet aggregation, and a host of cyclooxygenase inhibitors that reversibly inhibit platelet function. The glycoprotein IIb/IIIa inhibitors, abciximab, tirofiban, and eptifibatide alone, or in combination with aspirin, are commonly used to deter rethrombosis after percutaneous coronary interventions.[42] Although all of these agents significantly impair platelet function, the effects of abciximab persist until new platelets are produced. Clopidogrel, a functionally related compound, inhibits adenosine diphosphate-induced platelet aggregation, preventing activation of the IIb/IIIa mechanism. In bleeding patients exposed to these medications, discontinuation of the drug may not be sufficient to return platelet function to normal, and transfusion of platelets may be needed to restore hemostasis.

Although patients with end-stage renal disease may have mild thrombocytopenia, more often they have a number of normal, but dysfunctional, platelets.[65] The pathophysiology behind this "uremic coagulopathy" has yet to be fully elucidated but is likely multifactorial.[65] Some speculate that decreased circulating RBCs resulting from reduced erythropoietin production cause platelets to travel in a more midstream position within vessels, rendering them further away and less likely to react to endothelial damage.[66] In addition, uremic toxins result in dysfunctional vWF and vWF-factor VIII complex, and impaired platelet aggregation. The treatment of long-term dialysis patients who are bleeding may require a multifaceted approach, including short-term dialysis to remove uremic toxins,[66] IV desmopressin to release factor VIII from endothelial storage sites and minimize the effect of dysfunctional vWF,[67,68] IV conjugated estrogens (in men and women) to promote coagulation,[69] and in some cases, the administration of cryoprecipitate to increase the proportion of functional factor VIII, vWF, and fibrinogen.[70] Obviously, if the patient is significantly thrombocytopenic, platelet transfusions are also indicated.

A triad of very rare intrinsic platelet disorders can also result in functional thrombocytopenia, as follows: Bernard-Soulier syndrome, in which the glycoprotein Ib portion of the receptor is absent; Glanzmann thrombasthenia, in which the entire glycoprotein IIb/IIIa receptor is absent; and Hermansky-Pudlak syndrome, which is a platelet storage pool disease. In contrast to these rare conditions, von Willebrand disease (vWD) is a relatively common disorder that pathophysiologically bridges platelet and soluble clotting factor disorders. Fortunately, clinically significant bleeding is rare in almost all types of vWD, and when bleeding occurs it is usually confined to mucosal surfaces. vWD has several major types, and multiple subtypes are classified according to the quantity or functionality of vWF or its binding to platelet glycoprotein Ib receptors. A complete discussion of vWD is beyond the scope of this review and has been done nicely by others.[71] Suffice it to say that clinicians entertaining a diagnosis of vWD in a patient with easy bruising, skin bleeding, and prolonged bleeding from mucosal surfaces should consult a specialist in coagulation.

Conclusion

Thrombocytopenia is commonly seen in critically ill patients. In addition, some patients, such as those with uremia or vWD, may have dysfunctional platelets despite normal counts. When mild, thrombocytopenia may not increase the bleeding risk substantially, but severe thrombocytopenia is associated with both increased bleeding risk and higher mortality. As the most common coagulopathy in the ICU, the etiology of low platelet counts is often multifactorial

resulting from the underlying disease state, medications, or as a result of consumption of thrombi. Although thrombocytopenia often improves with treatment of the underlying illness, an in-depth understanding of the causes of thrombocytopenia and subsequent action may raise platelet counts and prevent unnecessary deferment of invasive procedures or exposure to platelet transfusion risks in critically ill patients.

Acknowledgments

Financial/nonfinancial disclosures: Dr. Rice has reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Dr. Wheeler has received research support from Novo Nordisk and Eli Lilly, and honoraria from Sanofi-Aventis.

References

1 Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000; 28:1871–1876
2 Strauss R, Wehler M, Mehler K, et al. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002; 30:1765–1771
3 Baughman RP, Lower EE, Flessa HC, et al. Thrombocytopenia in the intensive care unit. Chest 1993; 104:1243–1247
4 Bonfiglio MF, Traeger SM, Kier KL, et al. Thrombocytopenia in intensive care patients: a comprehensive analysis of risk factors in 314 patients. Ann Pharmacother 1995; 29:835–842
5 Chakraverty R, Davidson S, Peggs K, et al. The incidence and cause of coagulopathies in an intensive care population. Br J Haematol 1996; 93:460–463
6 Crowther MA, Cook DJ, Meade MO, et al. Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. J Crit Care 2005; 20:348–353
7 Stephan F, Hollande J, Richard O, et al. Thrombocytopenia in a surgical ICU. Chest 1999; 115:1363–1370
8 Hanes SD, Quarles DA, Boucher BA. Incidence and risk factors for thrombocytopenia in critically ill trauma patients. Ann Pharmacother 1997; 31:285–289
9 Akca S, Haji-Michael P, De MA, et al. Time course of platelet counts in critically ill patients. Crit Care Med 2002; 30:753–756
10 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699–709
11 Mavrommatis AC, Theodoridis T, Orfanidou A, et al. Coagulation system and platelets are fully activated in uncomplicated sepsis. Crit Care Med 2000; 28:451–457
12 Sharma B, Sharma M, Majumder M, et al. Thrombocytopenia in septic shock patients: a prospective observational study of incidence, risk factors, and correlation with clinical outcome. Anaesth Intensive Care 2007; 35:874–880
13 Mercer KW, Macik B, Williams ME. Hematologic disorders in critically ill patients. Semin Respir Crit Care Med 2006; 27:286–296
14 Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. Am J Respir Crit Care Med 2000; 162:347–351
15 Oppenheim-Eden A, Glantz L, Eidelman LA, et al. Spontaneous intracerebral hemorrhage in critically ill patients: incidence over six years and associated factors. Intensive Care Med 1999; 25:63–67
16 Contreras M. Consensus conference on platelet transfusion: final statement. Vox Sang 1998; 75:173–174
17 British Society for Haematology. Guidelines for use of platelet transfusions. Br J Haematol 2003; 122:10–23
18 Arnold DM, Crowther MA, Cook RJ, et al. Utilization of platelet transfusions in the intensive care unit: indications, transfusions triggers, and platelet count responses. Transfusion 2006; 46:1286–1291
19 Slichter SJ, Harker LA. Thrombocytopenia: mechanisms and management. Clin Haematol 1978; 7:523–539
20 Rebulla P. Revisitation of the clinical indications for the transfusion of platelet concentrates. Rev Clin Exp Hematol 2001; 5:288–310
21 Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med 1962; 266:905–909
22 Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. N Engl J Med 1997; 337:1870–1875
23 Sagmeister M, Oec L, Gmür J. A restrictive platelet transfusion policy allowing long-term support of outpatients with severe aplastic anemia. Blood 1999; 93:3124–3126
24 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699–709
25 Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. Crit Care Med 2003; 31(suppl):S85–S93
26 Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? Crit Care Med 2006; 34(suppl):S170–S173
27 de Sauvage FJ, Hass PE, Spencer SD, et al. Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. Nature 1994; 369:533–538
28 Shalansky SJ, Verma AK, Levine M, et al. Risk markers for thrombocytopenia in critically ill patients: a prospective analysis. Pharmacotherapy 2002; 22:803–813
29 Stephan F, de Montblanc J, Cheffi A, et al. Thrombocytopenia in critically ill surgical patients: a case-control study evaluating attributable mortality and transfusion requirements. Crit Care 1999; 3:151–158
30 Ely EW, Laterre PF, Angus DC, et al. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. Crit Care Med 2003; 31:12–19
31 Drews RE. Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. Clin Chest Med 2003; 24:607–622
32 Berkman N, Michaeli Y, Or R, et al. EDTA-dependent pseudothrombocytopenia: a clinical study of 18 patients and a review of the literature. Am J Hematol 1991; 36:195–201
33 George JN, Raskob GE. Idiopathic thrombocytopenic purpura: diagnosis and management. Am J Med Sci 1998; 316:87–93
34 Bogdonoff DL, Williams ME, Stone DJ. Thrombocytopenia in the critically ill patient. J Crit Care 1990; 5:186–205
35 Martin JF, Daniel TD, Towbridge EA. Acute and chronic changes in platelet volume and count after cardiopulmonary bypass induced thrombocytopenia in man. Thromb Haemost 1987; 57:55–58
36 Hall GW. Kasabach-Merritt syndrome: pathogenesis and management. Br J Haematol 2001; 112:851–862

37 Tsai HM, Lian ECY. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998; 339:1585–1594
38 Moake JL. Thrombotic microangiopathies. N Engl J Med 2002; 347:589–600
39 George JN. Thrombotic thrombocytopenic purpura. N Engl J Med 2006; 354:1927–1935
40 Singer K. Thrombotic thrombocytopenic purpura. Adv Intern Med 1954; 6:195–234
41 Von Drygalski A, Curtis BR, Bougie DW, et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med 2007; 356:904–910
42 Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med 2007; 357:580–587
43 George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998; 129:886–890
44 Visentin GP, Liu CY. Drug-induced thrombocytopenia. Hematol Oncol Clin North Am 2007; 21:685–696
45 Aster RH. Can drugs cause autoimmune thrombocytopenic purpura? Semin Hematol 2000; 37:229–238
46 George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the Society of Hematology. Blood 1996; 88:3–40
47 Aster RH. Immune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors. Chest 2005; 127(suppl):53S–59S
48 Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. N Engl J Med 2006; 355:809–817
49 Greinacher A, Farner B, Kroll H, et al. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis: a retrospective analysis of 408 patients. Thromb Haemost 2005; 94:132–135
50 Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005; 106:2710–2715
51 Rota E, Bazzan M, Fantino G. Fondaparinux-related thrombocytopenia in a previous low-molecular-weight heparin (LMWH)-induced heparin-induced thrombocytopenia (HIT). Thromb Haemost 2008; 99:779–781
52 Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. Blood 2003; 101:2955–2959
53 Warkentin TE, Sheppard JAI, Moore JC, et al. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? J Lab Clin Med 2005; 146:341–346
54 Levy JH. Massive transfusion coagulopathy. Semin Hematol 2006; 43(suppl):S59–S63
55 Wolberg AS, Meng ZH, Monroe DM, et al. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004; 56:1221–1228
56 Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest 1966; 45:645–657
57 Peck-Radosavljevic M, Wichlas M, Azcherl J, et al. Thrombopoietin induces rapid resolution of thrombocytopenia after orthotopic liver transplantation through increased platelet production. Blood 2000; 95:795–801
58 Clark DA, Krantz SB. Effects of ethanol on cultured human megakaryocytic progenitors. Exp Hematol 1986; 14:951–954
59 Attassi K, Hershberger E, Alam R, et al. Thrombocytopenia associated with linezolid therapy. Clin Infect Dis 2002; 34:695–698
60 Gerson S, Kaplan S, Bruss S, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother 2002; 46:2723–2726
61 French G. Safety and tolerability of linezolid. J Antimicrob Chemother 2003; 51(suppl):ii45–ii53
62 Dempfle CE, Borggrefe M. Point of care coagulation tests in critically ill patients. Semin Thromb Hemost 2008; 34:445–450
63 Dickinson KJ, Troxler M, Homer-Vanniasinkam S. The surgical application of point-of-care haemostasis and platelet function testing. Br J Surg 2008; 95:1317–1330
64 Ingerselv J, Sorensen B, Castaman G, et al. New approaches in the measurement of coagulation. Haemophilia 2008; 14(suppl):104–112
65 Hedges SJ, Dehoney SB, Hooper JS, et al. Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol 2007; 3:138–153
66 Stewart JH, Castaldi PA. Uraemic bleeding: a reversible platelet defect corrected by dialysis. Q J Med 1967; 36:409–423
67 Watson AJ, Keogh JA. Effect of 1-deamino-8-D-arginine vasopressin on the prolonged bleeding time in chronic renal failure. Nephron 1982; 32:49–52
68 Mannucci PM, Remuzzi G, Pusineri F, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. N Engl J Med 1983; 308:8–12
69 Livio M, Mannucci PM, Vigano G, et al. Conjugated estrogens for the management of bleeding associated with renal failure. N Engl J Med 1986; 315:731–735
70 Janson PA, Jubelirer SJ, Weinstein MJ, et al. Treatment of the bleeding tendency in uremia with cryoprecipitate. N Engl J Med 1980; 303:1318–1322
71 Robertson J, Lillicrap D, James PD. Von Willebrand disease. Pediatr Clin North Am 2008; 55:377–392

CHEST

Official publication of the American College of Chest Physicians

Coagulopathy in Critically Ill Patients : Part 2 –Soluble Clotting Factors and Hemostatic Testing

Arthur P. Wheeler and Todd W. Rice

Chest 2010;137;185-194
DOI 10.1378/chest.08-2535

ISSN:0012-3692

CHEST Recent Advances in Chest Medicine

Coagulopathy in Critically Ill Patients

Part 2—Soluble Clotting Factors and Hemostatic Testing

Arthur P. Wheeler, MD, FCCP; and Todd W. Rice, MD, MSc

This manuscript provides an overview of how to interpret *in vitro* clotting studies and how to select studies to evaluate patients with bleeding disorders in the ICU. It provides a practical approach to understanding the complex subject of clotting factor abnormalities, including the most common problems of preanalytical error and anticoagulation therapy. Limitations and pitfalls of diagnostic testing are highlighted. ***CHEST 2010; 137(1):185–194***

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; FDP = fibrin degradation product; HMWK = high-molecular-weight kininogen; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PT = prothrombin time; rhAPC = human recombinant activated protein C; TT = thrombin time; UFH = unfractionated heparin

Concerns about the risk of bleeding in critically ill patients are common. This apprehension may stem from a sense of responsibility for bleeding following procedures or anticoagulant therapy, or perhaps the fact that hemorrhage is often visible externally. In addition, the clinical laboratory may raise awareness by offering tests that clinicians think provide information about impaired clotting. Unfortunately, many intensivists are not skilled or trained in carrying out assessments of coagulation testing or disorders. As the second of a two-part series on coagulopathy in critically ill patients, this article reviews soluble clotting factors and the most frequent coagulation disorders seen among adults in the ICU. Although this article does not discuss thrombophilia in detail, it does provide a framework for understanding hemostatic testing and interpreting common coagulation tests.

Manuscript received October 21, 2008; revision accepted October 21, 2008.

Affiliations: From the Medical Intensive Care Unit, Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN.

Correspondence to: Arthur P. Wheeler, MD, FCCP, T-1210 MCN Vanderbilt Medical Center, Nashville, TN 37232-2650; e-mail: art.wheeler@vanderbilt.edu

DOI: 10.1378/chest.08-2535

Evaluating Classic Clotting Pathways

Many critical care physicians have little more than superficial knowledge of clotting pathways because they are hard to remember, with confusing nomenclature and redundant terminology (Table 1). In addition, in-depth knowledge is usually not necessary on a daily basis. Clotting factors were numbered in the order of their discovery, adding to the seemingly nonsensical sequence of activation. Furthermore, the historically taught concept that there are *two* distinct pathways by which blood clots is an artificial and misleading construct. In the body, physiologic clotting is the result of the activation of the tissue factor pathway (formerly called the extrinsic pathway), a process that is amplified by the contact activation pathway (formerly called the intrinsic pathway). Two separate, merging pathways were popularized predominately for purposes of understanding the sequence of clotting events in the laboratory. Nonetheless, comprehending these pathways is necessary to accurately interpret laboratory values, avoid acting on spurious results, and forgo unnecessary testing. For example, the activated partial thromboplastin time (aPTT) and the prothrombin time (PT) are habitually linked in some clinicians' minds, resulting in unnecessary testing and confusing results.

Common Laboratory Assays

The PT monitors the tissue factor pathway and common portions of the clotting pathway (Fig 1). The

Table 1—*Clotting Pathway Nomenclature and Terminology*

Factor	Alternative Name
I	Fibrinogen
Ia	Fibrin
II	Prothrombin
IIa	Thrombin
III	Tissue factor, CD142
IV	Not used
V	Proaccelerin, labile factor
VI	Not used
VII	Proconvertin
VIII	Antihemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Hemophilia C factor
XII	Hageman factor
XIII	Fibrin-stabilizing factor
HMWK	Fitzgerald factor
Prekallikrein	Fletcher factor

HMWK = high-molecular-weight kininogen.

PT is relatively easy to understand: citrate anticoagulated plasma is centrifuged to remove platelets (centrifugation removes the effect of platelets on clotting, isolating the role of soluble clotting factors), then tissue factor (a *complete* thromboplastin) and calcium are added to activate clotting. This procedure preferentially activates factor VII, which in turn activates factors X, V, and II (prothrombin), which converts fibrinogen (factor I) to fibrin, which is detected using optical or electrical methods and reported in seconds. Perhaps because there are fewer steps in the sequence or because factor VII circulates in the highest concentration of any factor, the PT is relatively resistant to change, typically requiring single-factor levels to fall to 10% of normal or less before becoming prolonged. As seen in Figure 1, there is only a single factor unique to this pathway, and selective factor VII deficiency is the only way the PT can be prolonged without impacting the aPTT. Because the sensitivity of reagents varies between laboratories and sometimes even within a hospital over time, PT is referenced to an international standard (the international normalized ratio [INR]).[1] Use of the INR allows patients who are therapeutically anticoagulated with warfarin to have their anticoagulation intensity interpreted in a standardized fashion. Because the INR calibration was developed using patients with stable warfarin anticoagulation, its applicability to other causes of an elevated PT, like liver failure, is uncertain.[2]

The aPTT is more complex, but hints to understanding this test, which monitors the contact activation and common pathways, are apparent from its name. A particulate contact activator (eg, ellagic acid, kaolin, celite, or silica), is added to platelet-poor, citrated plasma substrate, hence the designation "activated." A "partial thromboplastin" (lacking tissue

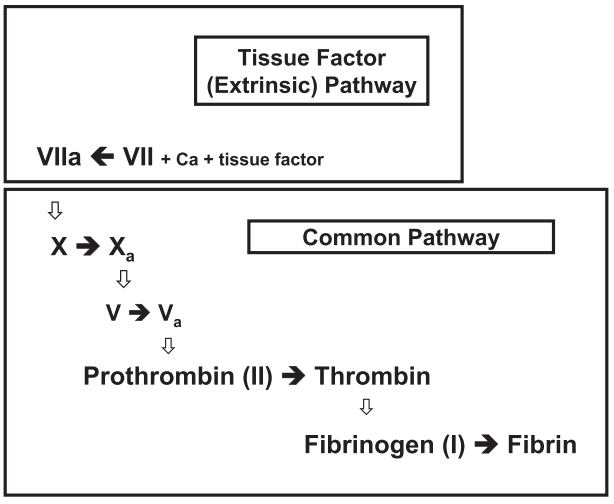

FIGURE 1. Overview of the tissue factor and common clotting pathways.

factor) is added, followed by reversal of the citrate effect with calcium. As shown in Figure 2, the particulate activates factor XII, which activates factor XI, then IX, and VIII, which then activates the common sequence of factor X through fibrin formation. As with the PT, the result is reported in seconds. Maybe because the sequence is lengthier or the concentration of each factor is lower, single factors unique to the contact activation pathway must decline to only 15% to 30% of normal before the aPTT is prolonged. Milder deficiencies of multiple factors can also prolong the aPTT, and as a result it is usually a more sensitive measure of factor changes, especially factors VIII and IX. Prekallikrein, high-molecular-weight kininogen (HMWK), antiphospholipid antibodies, and factor XII deficiencies will also prolong the aPTT, but the former two are rare, and none of the four increases the risk of bleeding, despite altering the aPTT. In fact, patients with antiphospholipid antibodies

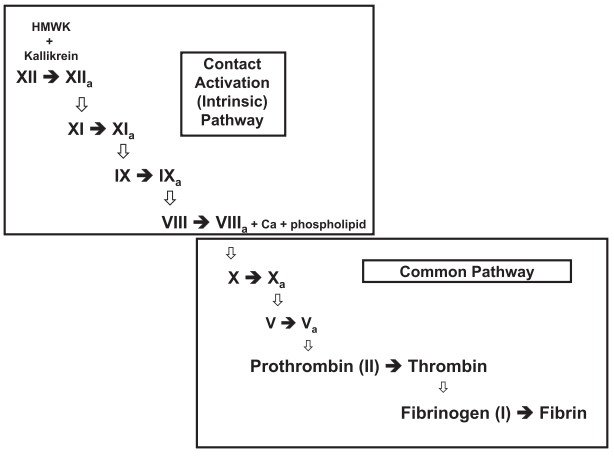

FIGURE 2. Overview of the contact activation and common clotting pathways. HMWK = high-molecular-weight kininogen.

are prone to thrombotic events despite having an elevated aPTT.

One test being used with increasing frequency because of the popularity of low-molecular-weight heparin (LMWH) therapy is the anti-Xa activity assay. The anti-Xa assay may have another advantage in that it is also less susceptible to influence by acute phase reactants, especially factor VIII, than the aPTT. The methodology is straightforward but unfamiliar to most physicians: an excess of factor Xa and antithrombin are added to platelet-poor, citrated patient plasma. If there is any heparinoid in the patient sample, it binds to the exogenous antithrombin and inhibits the activity of the added Xa. This inhibition of Xa is detected as a decrease in the cleavage of an added chromogenic substrate relative to the amount cleaved without the patient plasma. The primary reason the anti-Xa assay exists is because LMWHs and direct Xa inhibitors such as fondaparinux bind to antithrombin through a 5-oligosaccharide sequence, but do not have sufficient length to bind to thrombin (factor IIa). For this reason, the aPTT is less sensitive to LMWH than to unfractionated heparin (UFH). Contrary to common belief, anti-Xa inhibitors do prolong the aPTT and PT minimally (on average 1-4 s), but because these drugs cannot efficiently bind thrombin, clotting times are not altered as much as with UFH. Because of the predictability of anticoagulation using weight-based LMWH therapy, monitoring is rarely necessary. Potential candidates for whom anti-Xa monitoring might be considered are patients at the extremes of weight, those with a glomerular filtration rate $<$ 30-50 mL/min, and patients with higher renal clearance than expected as a result of increased cardiac output (eg, pregnant women and neonates).[3,4]

Specialized Assays

In locations like the cardiac catheterization laboratory, where a real-time estimate of clotting is necessary, the activated clotting time (ACT) is often used, especially to monitor UFH or bivalirudin activity. The ACT is a nonspecific test that reports the time for an activating agent (eg, celite, kaolin, glass particles) to produce a clot in whole blood, thereby evaluating soluble factor and platelet function *in toto*. Because neither the reagents nor the clot detection method (eg, resistance to mechanical deformation of a clot or changes in the electrical or mechanical properties of the blood) are standardized, results of different assay systems are not equivalent, and the ACT correlates poorly with aPTT, PT, and anti-Xa assays.

As shown in Figure 2, abnormalities of factors X, V, II, and fibrinogen alter both the PT and aPTT by impairing the shared common pathway. If clinically important, a specific common factor pathway abnormality can be detected using additional tests: the Russell's viper venom assay, and the thrombin time (TT) or Reptilase time assays. The viper venom assay directly activates factor X, testing the complete common pathway. The TT and Reptilase time determine the speed with which fibrinogen is converted to fibrin in response to exogenous thrombin; hence, they test only the sufficiency and functionality of fibrinogen and help distinguish patients with hypofibrinogenemia or dysfibrinogenemia.[5] The main difference between the TT and the Reptilase time is that the latter is not altered by the presence of heparin. Alternatively, the quantity of fibrinogen can also be evaluated by direct assay. Such tests can sometimes be useful following massive transfusion when hypofibrinogenemia is suspected.

The bleeding time is a relatively crude test in which a standardized skin wound is made with a lancet and the time for blood to clot is recorded as the lesion is gently dabbed with gauze. It is alleged to measure the combined effects of tissue integrity, platelet function, and soluble clotting factor adequacy, with an emphasis on adequacy of platelet function. This test is highly subject to variations in technique, and correlates poorly with other *in vitro* tests, except that it can be guaranteed to be prolonged when platelet counts decline below 50×10^9/L.[6] Bleeding time testing has largely been abandoned in the ICU because it is difficult to perform, labor intensive, and a poor predictor of bleeding in the clinical setting.

Tests of Fibrinolysis

The term "fibrin degradation product" (FDP) is a general one that describes the breakdown products of fibrin *and* fibrinogen generated by the enzymatic action of plasmin. The D-dimer is a more specific FDP resulting only from degradation of fibrin from an intact clot, whereas a nonspecific FDP or fibrin split-product assay could be positive without a clot. Unfortunately, both assays lack specificity and are positive not only in patients with thrombotic diseases (eg, venous thromboembolism, myocardial infarction, and disseminated intravascular coagulation [DIC]), but can also be elevated in surgical, cancer, and pregnant patients. Because of impaired hepatic clearance, chronic liver disease can also result in elevated FDPs. Given this list of conditions, FDP assays are usually not very helpful in ICU patients. Commercially available assay methods differ significantly (ie, latex or red blood cell agglutination or enzyme-linked immunosorbant assays), resulting in widely divergent sensitivities. If using a D-dimer assay as an adjunctive test for ruling out thromboembolic disease, it is imperative to use an ultrasensitive assay to avoid false-negative results. Tests using latex agglutination methods tend to be the least sensitive, with enzyme-linked immunosorbant

assay methods being more sensitive but also more time consuming and expensive.

Causes of Abnormal Clotting Assays

Surprisingly, the most common cause of an abnormal clotting assay is not a physiologic problem, or even a laboratory mistake, but rather an improperly obtained sample. There are several common causes of this so-called "preanalytical error" (Table 2). Accurate results from aPTT and PT tests require a specific ratio (9:1) of plasma to an anticoagulant, typically sodium citrate, in a "blue-stoppered" tube. If the tube is underfilled, both results will be prolonged. Conversely, if the tube is forcefully overfilled, clotting times will be shortened.[7] In addition, if polycythemia is present, the amount of plasma in the sample will be reduced compared with that of a patient with a normal hematocrit. This will result in a relative excess of the citrated anticoagulant solution and artificial prolongation of the clotting times.[8] Another potential source of error is blood contaminated with another anticoagulant during collection. This error occurs in one of two ways: the blood is drawn from a heparin-containing catheter without removal of sufficient volume to clear the dead space,[9-11] or blood is placed into the wrong tube and then transferred to the correct tube. For example, blood initially drawn into a "purple-top" ethylenediaminetetraacetic acid-containing tube or a "green-top" heparin-containing tube and then transferred to a citrate tube will yield prolonged PT and aPTT values. Another problem results when blood is not *promptly and gently* mixed with citrate. For example, initial collection of blood into a tube not containing anticoagulant, delay in transferring blood from a syringe to an anticoagulant-containing tube, or failure to mix blood in with the anticoagulant all will artificially prolong the PT and aPTT. Conversely, hemolysis or excessively vigorous agitation of blood with citrate will artificially shorten the PT and aPTT.[12] Excessive tourniquet time will elevate von Willebrand Factor and factor VIII levels, resulting in falsely shortened PT and aPTT assay results. Because factor VII is temperature sensitive, cooling will also falsely shorten the PT, but will leave the aPTT unaffected, unless the patient is receiving heparin.[13] Since both the aPTT and PT are performed on platelet-depleted plasma, thrombocytopenia does not alter their *in vitro* value.

Table 2—*Preanalytical Coagulation Abnormalities*

Error	Effect
Inadequate plasma in sodium citrate tube Incompletely filled tube Polycythemia resulting in relative plasma deficiency	Prolonged aPTT and PT
Contamination with exogenous anticoagulant Indwelling line Initial collection in heparin- or EDTA-containing tubes.	Prolonged aPTT > PT
Delayed assay, > 3 h Platelet factor 4 release in heparinized samples Factor VIII degradation	Unpredictable effects, shortened aPTT and PT, prolonged aPTT and PT
Clotting activation Hemolysis Excessive sample agitation Prolonged tourniquet application Failure to mix blood with citrate Factor VIII level elevations	Shortened aPTT and PT
Chilled sample Factor VII activation	Shortened PT

aPTT = activated partial thromboplastin time; PT = prothrombin time; EDTA = ethylenediaminetetraacetic acid.

Soluble Clotting Factor Disorders

Introduction

The prevalence of inherited deficiencies of single clotting factors ranges from 0.5 to 2 per million persons.[14,15] Many of these congenital disorders are diagnosed in childhood following a major bleeding episode. However, patients with von Willebrand disease may not present with a bleeding diathesis until adulthood. In addition, some clotting factor deficiencies resulting in thrombophilia, such as protein C or protein S deficiencies, in addition to factor V leiden, may not become apparent until adulthood.

Most soluble clotting disorders in the adult ICU are acquired and involve multiple clotting factor abnormalities. As a result, the majority of these acquired conditions, including those caused by the use of exogenous anticoagulants, will alter both the PT and the aPTT. All clotting test abnormalities must be evaluated in the clinical context as there is no unique interpretation of a laboratory result. The hemostatic laboratory values seen in some of the more common critical illnesses are compared in Table 3. In addition, there are numerous situations in which prolongation of an *in vitro* clotting test either has no influence on clinical bleeding or actually may increase the tendency for thrombosis. For example, the rare deficiency of the cofactor HMWK dramatically prolongs the aPTT but has no effect on bleeding predilection, while antiphospholipid antibody syndrome also prolongs the aPTT but predisposes patients to thromboses. Thus, not all PT and aPTT prolongations *in vitro* equate to an increased bleeding tendency. On the other hand, deficiencies in other soluble factors, such as protein C or protein S, may predispose patients to abnormal clot formation. The prevalence of a hereditary propensity for clotting is substantial but often not evaluated. A discussion of inherited thrombophilia is beyond the scope of this article and can be found elsewhere.[16,17]

Table 3—*Comparison of Hemostatic Testing Found With Common Medications and Disease States in Critically Ill Patients*

Condition	PT	aPTT	Fibrinogen	FDP	Platelets	BT	TT
UFH	Normal or prolonged[a]	Prolonged	Normal	Normal	Normal	Normal	Prolonged
LMWHs	Normal or prolonged[a]	Normal or minimally prolonged	Normal	Normal	Normal	Normal	Normal or minimally prolonged
Direct factor Xa inhibitors	Normal or prolonged[a]	Normal or minimally prolonged	Normal	Normal	Normal	Normal	Normal
Direct thrombin inhibitors	Prolonged	Prolonged	Normal	Normal	Normal	Normal	Prolonged
Coumadin	Prolonged	Normal or prolonged[b]	Normal	Normal	Normal	Normal	Normal
Vitamin K deficiency	Prolonged	Prolonged	Normal	Normal	Normal	Normal	Normal
Hepatic Insufficiency	Prolonged	Normal or prolonged	Low or normal	Normal or elevated	Low	Normal or prolonged	Prolonged
DIC	Normal or prolonged	Normal or prolonged	Normal or low	Elevated	Low	Prolonged	Prolonged
Dilution	Prolonged	Prolonged	Low or normal	Normal	Low	Normal or prolonged	Normal or prolonged
von Willebrand Disease	Normal	Prolonged	Normal	Normal	Normal	Prolonged	Normal
Lupus anticoagulant	Normal or prolonged	Prolonged	Normal	Normal	Normal	Normal	Normal
Thrombocytopenia	Normal	Normal	Normal	Normal	Low	Normal or prolonged	Normal

BT = bleeding time; DIC = disseminated intravascular coagulation; FDP = fibrin degradation product; LMWH = low-molecular-weight heparin; TT = thrombin time; UFH = unfractionated heparin. See Table 2 for expansion of other abbreviations.

[a]At supratherapeutic dosages.

[b]Early in coumadin treatment.

Isolated PT Abnormalities

As shown in Figure 1, an isolated abnormality of the tissue factor (extrinsic) pathway, measured by the PT assay, can only result from a factor VII abnormality. Although an autosomal recessive factor VII deficiency has been reported, it is exceedingly rare.[18] Since factor VII is synthesized in the liver and has a half-life of just 4 to 6 h, incipient liver failure or the initial stages of warfarin anticoagulation can cause a transient isolated PT abnormality. However, within days of liver failure onset or warfarin use, both the aPTT and PT will be prolonged as other hepatically produced factors IX, X, and II will also be depleted, despite having longer half lives. Since the production of factor VII is highly dependant on vitamin K, mild vitamin K deficiency, secondary to poor nutrition or prolonged use of broad spectrum antibiotics, may prolong only the PT and not the aPTT. However, in more severe vitamin K deficiency, both the PT and aPTT will be prolonged as a result of the effect on the other vitamin K-dependent clotting factors.

Isolated aPTT Abnormalities

Currently, aPTT methods are not standardized in a manner similar to the INR. As such, differences in local instrument calibrations and reagents result in variations in testing results, and clinicians should be familiar with the normal values for their local laboratories. In a properly collected sample, the most common cause of an isolated aPTT prolongation (contact activation pathway) is the presence of UFH, hirudin, argatroban, or human recombinant activated protein C (rhAPC). Heparin is the prototypical example as it binds to antithrombin and thereby inhibits the actions of factors XII, XI, IX, X, and II. Because three of these factors (IX, XI, XII) are exclusive to the contact activation pathway and are more sensitive to heparin effects than the two factors in the common pathway (X and II), heparin alters the aPTT to a greater degree than the PT. In the event one suspects inadvertent contamination of a specimen with heparin (or LMWH), it is possible to add heparinase as an *in vitro* reversing agent. Heparin as a cause for a prolonged aPTT can also be effectively ruled out with a normal TT; since the TT is very sensitive to heparin, a normal result is exclusionary. Very high heparin levels, as might occur shortly after an UFH bolus or with an accidental overdose, will inhibit factors II and X, resulting in a prolongation of both the PT and aPTT. Endogenous clotting disorders rarely result in an aPTT greater than 100 s; hence, when aPTT of that magnitude is encountered, the cause is almost always heparin. When approved for the treatment of severe sepsis with high risk of death, rhAPC represents a special case in that it has a half-life of between 10 and 15 min, so that aPTT testing performed quickly after the specimen is obtained is substantially more prolonged than when the same specimen is tested as little as 15 to 30 min later.[19]

Although common experience suggests an association between bleeding risk and degree of aPTT prolongation, scant data are available confirming this correlation. An excessive amount of any anticoagulant may cause bleeding, and the treatment is intuitive;

stopping the medication in most cases reverses anticoagulation in minutes to hours. If there is urgency to reverse the effects of UFH or to a lesser extent LMWH, protamine sulfate can be used as an antidote. Typically, doses of 1 mg of protamine for each 100 units of residual heparin are recommended, but practically, it is difficult to determine how much heparin activity remains. Protamine does not reverse the effects of fondaparinux.

The aPTT will also be prolonged by inhibitors to contact activation pathway components. Such inhibitors are usually antibodies directed against phospholipid (ie, lupus anticoagulant, anticardiolipin) or, less commonly, specific clotting factors. Inhibitors can be detected by performing a mixing study in which the patient sample is mixed with an equal volume of normal plasma. However, since the presence of an anticoagulant mimics the presence of an inhibitor, care should be taken to ensure samples sent for mixing studies are not contaminated with anticoagulants. If the sample contains inhibiting antibodies, the aPTT of the mixture will remain abnormal, whereas the aPTT will normalize if a simple deficiency exists. (A deficiency state is corrected because the mixing study produces at least a 50% concentration of each factor, a quantity sufficient for a normal aPTT). The one exception to this rule is that mixing studies typically result in an initially normal aPTT in the presence of antifactor VIII antibodies, but with prolonged incubation, the aPTT becomes prolonged. If clinically beneficial, specific-factor assays can be performed to identify the deficiency. It is sometimes a clinical challenge to monitor heparin anticoagulation in patients with antiphospholipid antibodies because the aPTT may be prolonged at baseline or may demonstrate an exaggerated prolongation when heparin is started. In either case an anti-Xa activity assay can be used for UFH monitoring.

As can be seen from Figure 2, an inhibitor or deficiency of factors VIII (hemophilia A), IX (hemophilia B), XI, or XII may also produce an isolated aPTT abnormality, but probably only if levels are sufficiently low. In theory, such deficiencies can be corrected using fresh-frozen plasma, but doing so is inefficient and exposes recipients to risks of infection, volume overload, and transfusion reaction. Although cryoprecipitate is a more concentrated source of factor VIII and von Willebrand's factor, recombinant factors VIII or IX are commercially available and free of human plasma, and thus free from infection transmission risks. In addition, since these can be given in a small volume, they have become the preferred therapies. For patients who have acquired antibodies to factor VIII, bypassing agents or human recombinant activated factor VII can overcome the functional deficiency of factor VIII. In addition, prothrombin complex, available in 15 or more brands worldwide, can be used to treat factor IX deficiency. Outside the United States, factor XI and XIII concentrates are also available options.[20] Any clinician caring for a patient with a suspected or proven single-factor deficiency should consult a coagulation specialist because the treatment is complex, expensive, and potentially dangerous.

Combined PT and aPTT Abnormalities

Most clotting disorders will affect both the PT and aPTT because components of the common pathway will either be inadequately produced or consumed in excess of their production. The easiest disorders to understand are those in which there is simple underproduction. Since all clotting proteins except factor VIII are produced by the liver, logically, hepatic failure is a common cause of dual assay abnormalities. Likewise, dietary deficiency or warfarin exposure will impair hepatic production of vitamin K-dependent proteins (II, VII, IX, X), three of which are in the common pathway. Simply replacing the missing factors with fresh-frozen plasma will correct the clotting test of either condition. However, if established liver failure is the cause, correction will be transient, lasting only about one day, as the clotting factors are consumed without the production of new ones. In contrast, nutritional deficiency or warfarin effect is promptly reversed by replacing vitamin K. Differentiating warfarin use from hepatic insufficiency is usually easily done with a clinical history. However, the two conditions can also be distinguished by measuring clot degradation products (eg, fibrin split products, D-dimer) or fibrinogen levels or activity (see Table 3). All should be normal with warfarin use. In distinction, severe hepatic disease often results in the inability to clear clot degradation products, raising D-dimer levels. Even when synthetic deficits are corrected, this impaired clearance activity can produce *in vitro* clotting study prolongations. Elevated bilirubin and transaminase levels with reduced albumin concentrations also support a diagnosis of liver disease.

As mentioned in the "Isolated aPTT Abnormalities" section, heparin, in low doses, has the greatest effect on factors XII, XI, and IX. Hence, the aPTT is preferentially affected over the PT. Large heparin doses, however, also inhibit both factor Xa and thrombin-mediated conversion of fibrinogen to fibrin. Both of these inhibitions disrupt the common pathway of the coagulation cascade, resulting in prolongation of both the PT and aPTT. In some laboratories, heparinase is routinely added to blood undergoing PT testing to neutralize any heparin effects. A clinical history alone is almost always sufficient to distinguish heparin exposure from that of warfarin or liver disease, but if laboratory confirmation is needed, heparin exposure is associated with normal

fibrinogen levels and FDPs (unlike liver disease), and warfarin exposure is associated with a normal TT (unlike heparin). In addition, the effects of heparin can be neutralized *in vitro* with heparinase, if needed to help make the differentiation.

In the ICU, DIC is probably the single most common cause of dual pathway abnormalities. It is a condition in which clotting factors and platelets are consumed, clot degradation products are released, and eventually even anticlotting proteins are exhausted.[21] Regardless whether triggered by severe sepsis, trauma, or tumor, the initial stimulus to clot results in the progressive depletion of all clotting factors through consumption. FDPs also interfere with platelet function and fibrin formation, and in this way, further aggravate the accelerated clotting process. As platelets are destroyed, platelet factor 4 can be released, and in some settings, this can lead to diagnostic confusion between DIC and heparin-induced thrombocytopenia.[21] Although DIC is typically viewed as a bleeding problem, it is the formation of microvascular thrombi that can damage red blood cells, forming schistocytes, and insidiously lead to tissue ischemia. Thrombosis in DIC is initially offset by key anticlotting protein systems: tissue factor pathway inhibitor counteracts effects of activated factor IX and X, the protein C-S complex inhibits activity of activated factors V and VIII, and general proteinase inhibition is accomplished by antithrombin and other lesser proteins. Simultaneously, activation of endogenous thrombolytic pathways, including plasminogen, occurs in an attempt to dissolve these thrombi. However, unless the stimulus is corrected, progressive clotting factor consumption occurs, eventually leading to a severe deficiency state.

By depleting all clotting factors, DIC can increase both the PT and aPTT values, reduce fibrinogen levels, and elevate levels of clot degradation products. It has been empirically observed that the PT is prolonged more than the aPTT,[22] possibly as the result of the short half-life of factor VII. In a substantial percentage of DIC cases, however, the process is sufficiently tame that neither the PT nor the aPTT is prolonged and fibrinogen levels can remain in the normal range. FDPs and/or D-dimer levels should be elevated in all cases of DIC. A vast array of other markers of accelerated coagulation are available, including prothrombin fragment 1.2, fibrinopeptide A, fibrin monomers, and thrombin-antithrombin complexes, but it is not clear whether any of these tests augment clinical care. The same can be said for tests of fibrinolysis such as plasminogen and antiplasmin levels.

Although the age-old maxim that the best treatment of DIC is to reverse the underlying cause is true, it is often not feasible. Nonetheless, specific treatments exist for DIC arising from certain etiologies. For severe sepsis, use of rhAPC has been shown to decrease markers of inflammation and accelerated coagulation, and that action is associated with improved clinical outcomes.[23] Acute promyelocytic leukemia is the most common cancer associated with DIC and is another example in which specific therapy is available. In acute promyelocytic leukemia, promyelocytes bear a surface tissue factor-like molecule that activates the tissue factor pathway and also express a receptor for plasminogen, resulting in primary fibrinolysis.[24,25] In addition to supportive therapy with platelet and clotting factor transfusions (either using cryoprecipitate or fresh-frozen plasma), all-*trans*-retinoic acid therapy has been shown to shorten the duration of the coagulopathy. All-*trans*-retinoic acid therapy accelerates the differentiation of the malignant cells, resulting in a downregulation of the expression of the tissue factor and other procoagulant surface antigens.[26-28]

Dilutional coagulopathy also can result in prolongation of both the PT and aPTT since all clotting factors are diluted. Although commonly reported in trauma patients, dilution of the clotting factors can result from any major bleed that requires massive transfusions. Correction of the PT and aPTT can be accomplished by replacing the clotting factors through the use of fresh-frozen plasma or fresh whole blood.

Monitoring Acute Therapeutic Anticoagulation

Monitoring Warfarin

Although warfarin depletes factor VII within 24 h, thereby prolonging the PT, the patient remains at risk for clot propagation or recurrence until all vitamin K-dependent clotting proteins are depleted, including factor IX (t 1/2 of 24 h), factor X (t 1/2 of 48 h), and factor II (t 1/2 of nearly 60 h). For this reason, some form of heparin or factor Xa inhibitor is necessary for at least a few days.[29] The PT is indexed to a worldwide standard and reported as the INR to allow direct comparisons between laboratories.[30] The risks of bleeding and PT prolongation are reasonably correlated, but the correlation does not appear to be linear. For example, the risk is relatively low until the INR exceeds 3 but increases exponentially when the INR exceeds 10.[31] Numerous other factors come into play: deficiencies of platelet numbers or function, advanced age, alcoholism, heart failure, and hypertension all appear to significantly increase the risk of bleeding with a prolonged PT.[32-36]

Monitoring Heparinoid Therapy

In addition to its diagnostic value, the aPTT is also commonly used to monitor the effects of several anticoagulants, including heparin, hirudin, lepirudin, bivalirudin, and argatroban. The aPTT is monitored during UFH infusions because a UFH-antithrombin complex inhibits the actions of factors II, IX, X, XI, and XII. Clinicians are sometimes puzzled that heparin does not prolong the PT, even though it inhibits the actions of factors X and II, which are both part of the tissue factor pathway; the explanation is not simple, some PT assay systems contain a heparin-neutralizing compound, and in assays that do not remove heparin, heparin interacts with more components of the contact activation pathway than the tissue factor pathway. The aPTT is not an ideal monitoring tool for heparinoids because it is subject to numerous non-heparin influences. For example, many acute phase reactants, including fibrinogen, can bind and neutralize UFH. In addition, factor VIII is not only an acute phase reactant, but also shortens the aPTT *in vitro*, occasionally leading clinicians to conclude that patients are resistant to the effects of UFH. In these cases, an anti-Xa assay or heparin level assay reveals whether the patient is adequately anticoagulated. Heparin resistance can occur in patients with antithrombin deficiency. However, the appearance of heparin resistance is much more likely to be the result of inadequate dosing or nonspecific acute phase reactants than from antithrombin deficiency.[37] Although there is some variation by laboratory, the typical aPTT target is 1.5 to 2.5 times the average normal aPTT and roughly corresponds to an anti-Xa level of 0.3 to 0.7 units/mL. Checking an initial aPTT roughly 6 h after initiating therapy is important to ensure prompt adequate anticoagulation. The use of a heparin dosing protocol, especially if administered by a dedicated anticoagulation service, is a key to rapid, safe, effective anticoagulation.[38,39] All forms of heparin are subject to at least partial renal clearance; hence, dose reductions are necessary when glomerular filtration rates fall below 30 to 50 mL/min. For the LMWHs, dose reductions should follow the manufacturer's recommendations, and an anti-Xa assay must be performed if monitoring is desired.[40] Since LMWHs inactivate factor Xa with little effect on thrombin, they will not prolong (much) the aPTT, which is prone to variability due to alterations to non-thrombin components. However, laboratory monitoring is usually not required because the anticoagulant response to a fixed-dose LMWH is highly correlated with the patient's body weight. Following the aPTT is usually sufficient for UFH, but when seemingly high heparin doses are required, checking either an anti-Xa activity assay or directly measuring heparin levels may better reflect the actual level of anticoagulation. The pharmacokinetic profile of LMWH in critically ill patients is uncertain, with some reports indicating impaired bioavailability[41,42] and others reporting that renal insufficiency does not lead to drug accumulation.[43]

Hirudin, lepirudin, bivalirudin, and argatroban inhibit activated factor II (thrombin) and can thus be monitored using the aPTT. Although it can be monitored using the aPTT, bivalirudin is used predominately in cardiac and vascular interventions, and as such is more commonly monitored using the ACT. Furthermore, in the absence of renal insufficiency, monitoring of anticoagulation with bivalirudin is rarely necessary. Data suggest an imperfect relationship between drug concentrations and the aPTT, with the test becoming less responsive at high drug concentrations. The clinician must become familiar with the drug specifics before using any of these compounds, but as a general rule an aPTT similar to that of UFH (1.5-3 times the mean baseline) is the goal. Monitoring is usually started approximately 3 to 4 h after initiating dosing and performed less frequently as the aPTT enters the goal range and stability is demonstrated. Once stabilized, daily monitoring is sufficient, provided renal function is unchanging. Like heparins, hirudin and lepirudin doses need to be reduced in the presence of renal insufficiency. Bivalirudin is predominately cleared by plasma peptidases with an additional renal component, allowing more freedom of dosing in renal insufficiency. In contrast, argatroban is cleared largely by the liver and needs dose reductions for patients with hepatic insufficiency.

Coagulation Tests and Procedures

One of the common uses of hemostatic testing is to evaluate the adequacy of coagulation and appropriateness of a patient for either surgery or invasive procedures. This is especially true for patients taking anticoagulant medicines and those with conditions known to produce abnormalities in these laboratory tests, such as hepatic insufficiency. The "acceptable" level of coagulation (or anticoagulation) for a procedure is dependent on both the nature of the procedure (ie, elective operation vs emergent bedside procedure) and the ease and safety in which the coagulation abnormality can be corrected. Since patients hardly ever undergo elective surgical procedures while they are critically ill, the following discussion will focus on urgent and emergent procedures. The safety of correcting the abnormality must include an evaluation of both the risk of bleeding from anticoagulation during the procedure as well as the risk of clotting while off anticoagulation for the procedure in

patients receiving treatment of thrombotic disorders.[44] The risk of bleeding is dependent on a number of factors, including age, comorbidities, intensity of anticoagulant therapy, and type of surgery or procedure.[45] Patients undergoing prolonged, complex, or emergent procedures are at increased risk of significant bleeding compared with those undergoing short, minor, or bedside procedures. Likewise, patients undergoing endoscopy may be at low risk for bleeding if only inspection and simple biopsy are undertaken, as opposed to a higher risk of bleeding for placement of percutaneous tubes, dilations, sphincterotomies, and fine needle aspirations.[46] In cases where the exact procedures required will not be known until endoscopy allows visualization, coagulation parameters should be managed to accommodate the most invasive procedure possible. Patients with significant thrombotic disorders or dispositions may require reversal of therapeutic anticoagulation and bridging with short-lived anticoagulation during the periprocedure period.[47-49] Monitoring during this periprocedure period requires frequent hemostatic testing.

Because of the complexity of the issue, the values of PT, INR, and aPTT for which procedures are considered safe are largely driven by clinical opinion. Usually, an INR of 1.5 or lower is desired for surgery and many invasive bedside procedures. Some bedside procedures, such as paracenteses, thoracenteses, and nonsubclavian central venous catheter may be undertaken with higher INR levels, especially if required emergently. However, performance of even these procedures should be avoided if at all possible in patients with INR levels above 2. The INR can be lowered by administration of exogenous clotting factors, such as fresh-frozen plasma, administration of vitamin K, or a combination of the two. Administration of vitamin K can be especially useful if the elevated INR is the result of receiving vitamin K antagonists (like coumadin) or nutritional deficiencies. Despite the common practice of administering 10 mg, a smaller dose of vitamin K (1 or 2 mg) is often adequate to correct most PT and INR levels. Since heparin administration is the most common cause for an elevated aPTT, discontinuing the heparin is the most frequent therapy for correction. UFH infusions should be discontinued at least 1 h prior to the procedure, and LMWH should be held for 12 h prior to the procedure. Both UFH and LMWH can be restarted postprocedure once hemostasis is certain. If the effects of UFH, or to a lesser extent LMWH, must be reversed urgently, protamine sulfate, at a dose of 1 mg per 100 units of residual heparin, can be used as an antidote. Protamine does not, however, reverse the effects of fondaparinux.

Conclusion

Tests of coagulation are often abnormal in critically ill patients. Unfortunately, many of these abnormal results are artifactual. When true, clotting test abnormalities can be associated with bleeding or clotting complications and are associated with worse patient outcomes. Abnormalities in soluble clotting factors are less common than thrombocytopenia, but also occur in this population. Low platelet counts and/or prolonged clotting times predispose critically ill patients to bleeding and may result in avoidance of diagnostic and therapeutic procedures. An in-depth understanding of the causes, limitations, and results of clotting time assays will help the clinician better identify and treat coagulopathy in critically ill patients.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Wheeler has received research support from Novo-Nordisc and Eli Lilly, and honoraria from Sanofi-Aventis. Dr Rice has reported no potential conflicts with any companies/organizations whose products or services may be discussed in this article.

References

1. Horsti J, Uppa H, Vilpo JA. Poor agreement among prothrombin time international normalized ratio methods: comparison of seven commercial reagents. *Clin Chem*. 2005;51(3):553-560.
2. Deitcher SR. Interpretation of the international normalised atio in patients with liver disease. *Lancet*. 2002;359(9300):47-48.
3. Ma JM, Jackevicius CA, Yeo E. Anti-Xa monitoring of enoxaparin for acute coronary syndromes in patients with renal disease. *Ann Pharmacother*. 2004;38(10):1576-1581.
4. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. *Thromb Res*. 2005;116(1):41-50.
5. Jim RT. A study of the plasma thrombin time. *J Lab Clin Med*. 1957;50(1):45-60.
6. Rodgers RPC, Levin J. A critical reappraisal of the bleeding time. *Semin Thromb Hemost*. 1990;16(1):1-20.
7. Adcock DM, Kressin DC, Marlar RA. Minimum specimen volume requirements for routine coagulation testing: dependence on citrate concentration. *Am J Clin Pathol*. 1998;109(5):595-599.
8. Spaet TH. Case 20-1979: false prolongation of prothrombin time in polycythemia. *N Engl J Med*. 1979;301(9):503.
9. Konopad E, Grace M, Johnston R, Noseworthy T, Shustack A. Comparison of PT and aPTT values drawn by venipuncture and arterial line using three discard volumes. *Am J Crit Care*. 1992;1(3):94-101.
10. Lew JK, Hutchinson R, Lin ES. Intra-arterial blood sampling for clotting studies. Effects of heparin contamination. *Anaesthesia*. 1991;46(9):719-721.
11. Laxson CJ, Titler MG. Drawing coagulation studies from arterial lines: an integrative literature review. *Am J Crit Care*. 1994;3(1):16-22.

12. Lippi G, Montagnana M, Salvagno GL, Guidi GC. Interference of blood cell lysis on routine coagulation testing. *Arch Pathol Lab Med*. 2006;130(2):181-184.
13. Adcock D, Kressin D, Marlar RA. The effect of time and temperature variables on routine coagulation tests. *Blood Coagul Fibrinolysis*. 1998;9(6):463-470.
14. Pevvandi F, Kaufman RJ, Seligsohn U, et al. Rare bleeding disorders. *Haemophilia*. 2006;12(Suppl 3):137-142.
15. Acharya SS, Coughlin A, Dimichele DM; North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost*. 2004;2(2):248-256.
16. Whitlatch NL, Ortel TL. Thrombophilias: when should we test and how does it help? *Semin Respir Crit Care Med*. 2008;29(1):25-39.
17. Khan S, Dickerman JD. Hereditary thrombophilia. *Thromb J*. 2006;4:15.
18. McVey JH, Boswell E, Mumford AD, Kemball-Cook G, Tuddenham EG. Factor VII deficiency and the FVII mutation database. *Hum Mutat*. 2001;17(1):3-17.
19. Bernard GR, Ely EW, Wright TJ, et al. Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis. *Crit Care Med*. 2001;29(11):2051-2059.
20. Drews RE. Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. *Clin Chest Med*. 2003;24(4):607-622.
21. Toh CH, Dennis M. Disseminated intravascular coagulation: old disease, new hope. *BMJ*. 2003;327(7421):974-977.
22. Spero JA, Lewis JH, Hasiba U. Disseminated intravascular coagulation. Findings in 346 patients. *Thromb Haemost*. 1980;43(1):28-33.
23. Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost*. 2004;2(11):1924-1933.
24. Gralnick HR, Abrell E. Studies of the procoagulant and firinolytic activity of promyelocytes in acute promyelocytic leukemia. *Br J Haematol*. 1973;24(1):88-89.
25. Falanga A, Marchetti M, Giovanelli S, Barbui T. All-trans-retinoic acid counteracts endothelial cell procoagulant activity induced by a human promyelocytic leukemia-derived cell line (NB4). *Blood*. 1996;87(2):613-617.
26. Barbui T, Finazzi G, Falanga A. The impact of all-trans-retinoic acid on the coagulopathy of acute promyelocytic leukemia. *Blood*. 1998;91(9):3093-3102.
27. Fenaux P, Le Deley MC, Castaigne S, et al. Effect of all transretinoic acid in newly diagnosed acute promyelocytic leukemia. Results of a multicenter randomized trial. European APL 91 group. *Blood*. 1993;82(11):3241-3249.
28. Falanga A, Iacoviello L, Evangelista V, et al. Loss of blast cell procoagulant activity and improvement of hemostatic variables in patients with acute promyelocytic leukemia administered all-trans-retinoic acid. *Blood*. 1995;86(3):1072-1081.
29. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):204S-233S.
30. Hirsh J, Poller L. The international normalized ratio. A guide to understanding and correcting its problems. *Arch Intern Med*. 1994;154(3):282-288.
31. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost*. 2006;4(9):1853-1863.
32. Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. *Arch Intern Med*. 2005;165(13):1527-1532.
33. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briët E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. *Arch Intern Med*. 1993;153(13):1557-1562.
34. Abdelhafiz AH, Wheeldon NM. Risk factors for bleeding during anticoagulation of atrial fibrillation in older and younger patients in clinical practice. *Am J Geriatr Pharmacother*. 2008;6(1):1-11.
35. Hylek EM. Complications of oral anticoagulant therapy: bleeding and nonbleeding, rates and risk factors. *Semin Vasc Med*. 2003;3(3):271-278.
36. Visser LE, Bleumink GS, Trienekens PH, Vulto AG, Hofman A, Stricker BH. The risk of overanticoagulation in patients with heart failure on coumarin anticoagulants. *Br J Haematol*. 2004;127(1):85-89.
37. Levine MN, Hirsh J, Gent M, et al. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med*. 1994;154(1):49-56.
38. Kershaw B, White RH, Mungall D, Van Houten J, Brettfeld S. Computer-assisted dosing of heparin. Management with a pharmacy-based anticoagulation service. *Arch Intern Med*. 1994;154(9):1005-1011.
39. Wheeler AP, Jaquiss RD, Newman JH. Physician practices in the treatment of pulmonary embolism and deep venous thrombosis. *Arch Intern Med*. 1988;148(6):1321-1325.
40. Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. *Chest*. 2004;125(3):856-863.
41. Priglinger U, Delle Karth G, Geppert A, et al. Prophylactic anticoagulation with enoxaparin: is the subcutaneous route appropriate in the critically ill? *Crit Care Med*. 2003;31(5):1405-1409.
42. Dörffler-Melly J, de Jonge E, Pont AC, et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet*. 2002;359(9309):849-850.
43. Douketis J, Cook D, Meade M, et al; Canadian Critical Care Trials Group. Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study. *Arch Intern Med*. 2008;168(16):1805-1812.
44. Larson BJ, Zumberg MS, Kitchens CS. A feasibility study of continuing dose-reduced warfarin for invasive procedures in patients with high thromboembolic risk. *Chest*. 2005;127(3):922-927.
45. Otley CC. Continuation of medically necessary aspirin and warfarin during cutaneous surgery. *Mayo Clin Proc*. 2003;78(11):1392-1396.
46. Eisen GM, Baron TH, Dominitz JA, et al; American Society for Gastrointestinal Endoscopy. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastrointest Endosc*. 2002;55(7):775-779.
47. Spandorfer JM, Lynch S, Weitz HH, Fertel S, Merli GJ. Use of enoxaparin for the chronically anticoagulated patient before and after procedures. *Am J Cardiol*. 1999;84(4):478-480., A10.
48. Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med*. 2008;168(1):63-69.
49. Wysokinski WE, McBane RD, Daniels PR, et al. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. *Mayo Clin Proc*. 2008;83(6):639-645.