

Coagulation Disorders in the ICU

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KEYWORDS

- Coagulation • Hemorrhage • Thrombocytopenia
- Thrombosis • Transfusion

Hemostasis results from the interplay among the vessel wall, the platelets, and the soluble coagulation factors.¹ Coagulation is initiated when von Willebrand factor is activated by substances such as exposed collagen in a blood vessel wall. Activated von Willebrand factor serves to recruit and activate platelets to the area of injury. In addition to serving as a physical barrier to blood loss from the vessel, platelets provide the phospholipid scaffold for activating the soluble coagulation cascade. The soluble factors include various proteolytic enzymes, including the vitamin K-dependent factors II, VII, IX, and X; the cofactors V and VIII; and the structural protein fibrinogen. Because the proteases involved in coagulation are potent, several different regulatory mechanisms exist to prevent excessive clot formation. These mechanisms include tissue factor pathway inhibitor, activated protein C, and antithrombin (**Fig. 1**).²

Although various coagulation tests are available, much diagnostic information can be obtained from thoughtful review of tests that are routinely available: the complete blood count, peripheral blood smear, prothrombin time (PT), and activated partial thromboplastin time (PTT). Some additional tests that are useful in specific circumstances include functional fibrinogen and d-dimer assays, inhibitor screen (mixing study), and specific factor assays.³ When abnormalities in the PT or PTT are detected, these additional laboratory studies may be guided by consideration of the appropriate differential diagnosis (**Table 1**).

CAUSES OF THROMBOCYTOPENIA

Low platelet counts are commonly encountered in the ICU setting and may be associated with diverse conditions (**Box 1**). Determining whether or not

a potentially life-threatening cause of thrombocytopenia is present is absolutely essential. A platelet count of 35,000/ μ L may require emergent intervention, or may require nothing more than observation. Such a low platelet count resulting from thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT, see later discussion) may result in severe morbidity or mortality if immediate intervention is not undertaken. Alternatively, if a similarly low platelet count is the result of immune thrombocytopenic purpura, the risk for adverse consequences without immediate intervention is minimal.

Discussion of all the causes of thrombocytopenia is beyond the scope of this article; however, one general cause of thrombocytopenia is highly relevant in the ICU. Microangiopathic hemolytic anemia (MAHA) is manifest as fragmented red blood cells and thrombocytopenia. MAHA may be associated with various causes, including malignant hypertension and scleroderma renal crisis.⁴ Malfunctioning prosthetic valves and prostheses with perivalvular leaks may present similarly, though the pathogenesis (a mechanical cause or turbulent blood flow) is different.⁵ Other specific types of MAHA are determined by additional associated abnormalities.

TTP is manifest as thrombocytopenia and microangiopathic changes on blood smear, often, but not invariably, in association with fever, acute kidney injury, and neurologic abnormalities.⁶ TTP is caused by deficiency in the ADAMTS13 protease that is involved in the regulation of von Willebrand multimer size. In its acquired form, TTP may be associated with the presence of an antibody inhibitor to ADAMTS13. The most common presentation is of an otherwise healthy individual who suddenly, over the course of hours to days, becomes ill. Pregnancy, HIV infection, and certain

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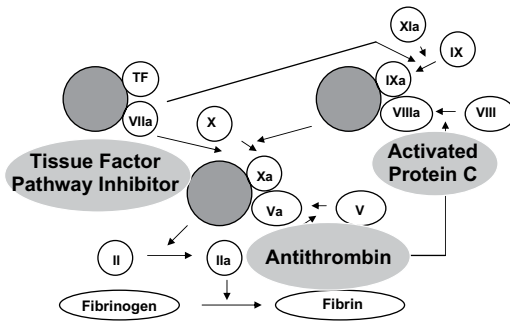


Fig. 1. Coagulation is the result of the interplay among the vessel wall, the platelets, and the soluble coagulation factors. Coagulation is initiated *in vivo* through binding of factor VIIa to tissue factor (TF). Several of the soluble coagulation factors with enzymatic activity then form complexes with cofactors and are coordinated through calcium at phospholipid surfaces, ultimately leading to production of fibrin strands, the structural polymer that is critical in achieving effective hemostasis. The prothrombin time assesses the activity of factor VII and the common pathway factors (I, II, V, X), and the activated partial thromboplastin time assesses the activity of factors VIII, IX, XI and the common pathway. Abnormalities in factor XII, high-molecular-weight kininogen, and prekallikrein are also detected by the PTT, but these are not associated with bleeding. Light-gray shading represents the natural anticoagulant pathways, and darker gray shading represents phospholipid surfaces.

medications, such as clopidogrel, have also been associated with the development of TTP.⁷ Rapid intervention with plasma exchange, or at the least, plasma administration, is indicated for this disorder, which otherwise can be rapidly fatal.

Hemolytic uremic syndrome (HUS) presents with many features in common with TTP, except that renal manifestations are more prominent, and fever and neurologic symptoms are not commonly observed.⁸ HUS appears to result from vascular injury, and deficiencies in complement regulatory proteins have been identified in some cases.⁹ Although some cases appear to be idiopathic in nature, many are associated with a prior diarrheal illness with Shiga toxin-producing bacteria, such as *Escherichia coli* H:0157. Other associations include treatment with medications such as the calcineurin inhibitors (cyclosporin A, tacrolimus) and mitomycin C, among others. The treatment of HUS in children is mainly supportive. However, plasma exchange is sometimes used in adults, although its efficacy has not been documented by well-controlled randomized trials.¹⁰ A trial of this therapy may be warranted in adults who have severe or progressive HUS, although this is an area of controversy.

Disseminated intravascular coagulation (DIC) represents a consumptive coagulopathy that may develop in any number of settings, such as infection, malignancy, trauma, or amniotic fluid

Table 1

Differential diagnosis of coagulation disorders based on the prothrombin time/partial thromboplastin time

PT	PTT	Differential Diagnosis
Normal	Normal	von Willebrand disease Platelet function abnormality Factor XIII deficiency
Normal	Prolonged	Factor VIII, IX, XI, or XII deficiency Lupus anticoagulants Heparin/direct thrombin inhibitor treatment Spurious (improperly drawn or heparin contamination)
Prolonged	Normal	Factor VII deficiency Lupus anticoagulant Warfarin treatment Spurious (improperly drawn)
Prolonged	Prolonged	Factor II, V, X deficiency Abnormalities in fibrinogen Disseminated intravascular coagulation Lupus anticoagulant Excessive warfarin or heparin treatment Direct thrombin inhibitor treatment Spurious (improperly drawn or heparin contamination)

Box 1**Some of the more common causes of thrombocytopenia in the ICU setting****MAHA**

DIC (due to infection, malignancy)

TTP

HUS

Malignant hypertension

Prosthetic valve malfunction

Immune-mediated thrombocytopenia

Idiopathic

Associated with rheumatologic disorders

Associated with lymphoproliferative disorders (ie, chronic lymphoid leukemia)

HIV-related

Hepatitis C-related

Medication-related (ie, penicillins, vancomycin, many others)

Drugs/toxins

Alcohol-induced marrow suppression

HIT

Intra-aortic balloon pump/intravascular device use

Hypersplenism

embolism.¹¹ In most cases, DIC presents with hemorrhage, although occasionally, thrombotic complications such as peripheral embolic phenomena may be observed. The pathogenesis in the different settings likely has in common the presence or release of phospholipid surfaces that serve to activate coagulation. Although a decreased platelet count, decreased fibrinogen, and elevated PT or PTT often accompany the microangiopathic change in DIC, in some cases only some of these abnormalities are present. The treatment of DIC consists of treatment of the underlying disorder in conjunction with replacement of coagulation factors, as appropriate.

In some cases when DIC is present, replacement may not be necessary. An example is the stable, nonbleeding patient who has an adequate platelet count and fibrinogen accompanied by modestly elevated PT or PTT. Patients who are bleeding, who have low fibrinogen levels (<80–100 mg/dL), or who require invasive procedures may require treatment. Fresh frozen plasma

(FFP) provides all the clotting factors, including fibrinogen. Repeated administration may be required because the efficacy of FFP is potentially limited by the half-life of the shortest-lived component, factor VII (4–6 hours). Cryoprecipitate mainly is a source of fibrinogen, factor VIII, and von Willebrand factor. Because other more purified concentrates exist for factor VIII and von Willebrand factor, its use is essentially restricted to the replacement of fibrinogen. The advantage of cryoprecipitate is that a 10-unit pool contains approximately the same amount of fibrinogen as 4 units of FFP in a volume of only about 50 to 100 mL of volume, which allows for rapid administration. Use of cryoprecipitate can be of great advantage in some circumstances. For example, in amniotic fluid embolism, often the blood is rapidly defibrinated, leading to bleeding accompanied by a marked rise in the PT and PTT. These two tests will be elevated when fibrinogen is depleted, even when the amount of the other soluble clotting factors is adequate.¹² Administration of cryoprecipitate may facilitate the rapid correction of a large portion of the coagulation defect. In some cases, the administration of platelets, FFP, and cryoprecipitate may be ineffective in DIC, and then consideration may be given to use of recombinant factor VIIa (see later discussion).

MANAGEMENT OF THROMBOCYTOPENIA

Thrombocytopenia may accompany the MAHAs. In addition, it may be an isolated finding, as in the case of marrow suppression due to sepsis, immune mediated thrombocytopenia, use of intra-aortic balloon pumps and other devices, and thrombocytopenia due to drugs commonly administered in the ICU setting (see **Box 1**).^{13,14} Although determination of the definitive cause of thrombocytopenia may not be possible in the ICU setting, potential causes that would be a contraindication to platelet administration, such as TTP and HIT, should be eliminated from consideration based on clinical and laboratory evaluation.

Although no absolute threshold exists for platelet transfusion, the risk for complications such as intracranial hemorrhage increases as the count decreases, such that transfusion is reasonable even in the stable, nonbleeding patient when the platelet count declines below 10,000 to 20,000/ μ L.¹⁵ Obviously, a lower threshold is required in patients who are bleeding or who require surgical procedures. In the absence of platelet dysfunction, line placement and most general surgical procedures can be performed safely with platelet count above the range of

30,000 to 50,000/ μ L. Neurosurgical procedures generally require a higher platelet count of 70,000 to 100,000/ μ L.

Patients may be refractory to platelet transfusion because of prior alloimmunization or increased consumption. Alternatively, platelet function may be impaired by the concomitant presence of uremia or by previously administered drugs. In such cases, use of desmopressin (DDAVP) or ϵ -aminocaproic acid may be considered. DDAVP may enhance the function of the existing platelets through improved signal transduction. It may be administered at a dose of 0.3 μ g/kg every 12 to 24 hours for several doses, although care must be taken to watch for hypotension and hyponatremia.¹⁶ ϵ -aminocaproic acid is an antifibrinolytic agent that has been associated with reduction or cessation in bleeding, particularly from mucosal sources, when thrombocytopenia is present.¹⁷ Its use is contraindicated if DIC or upper urinary tract bleeding is present. Doses of ϵ -aminocaproic acid, 1 g every 6 hours by mouth or intravenously, are often effective in this setting. When uremia is present and continued bleeding is occurring despite more conservative measures, consideration may be given to the use of high-dose conjugated estrogens.¹⁸

MANAGEMENT OF AN ELEVATED PROTHROMBIN TIME/INTERNATIONAL NORMALIZED RATIO

An issue that often arises in the ICU is management of an elevated PT/international normalized ratio (INR). Two commonly encountered situations are the patient who presents with an elevated PT/INR in the setting of anticoagulation with vitamin K antagonists (ie, warfarin) and the patient who has an elevated PT/INR and requires an invasive diagnostic or therapeutic intervention.

Guidelines for the management of patients who have an elevated PT/INR have been published.¹⁹ In the absence of bleeding or other complications, patients who have an INR less than 20 do not invariably require the emergent administration of FFP. Vitamin K should be administered at doses between 2 mg and 5 mg. In this regard, use of oral vitamin K is the preferred route for correction when urgent correction is not required (correction in about 24 hours). The slow intravenous route may be used when rapid correction is desirable (correction in 4–8 hours). Subcutaneous vitamin K is less reproducibly absorbed, particularly in the ICU setting.²⁰ Patients who are bleeding or who have high INR values do require the administration of FFP. In this case, the administration of 15 to 30 mL/kg of FFP will generally normalize the INR.²¹ The FFP needs to be administered rapidly over

the course of 1 to 2 hours, and repeated administration may be required, particularly if vitamin K is not also given. In the case of patients who cannot tolerate the volume of FFP required, prothrombin complex concentrate may be used to correct the INR.²² Although available concentrates in the United States are not yet labeled for this indication, they facilitate correction of the INR in a rapid manner (10–15 minutes) with a small volume load (about 50 mL). Use of these agents may be preferable to the use of recombinant factor VIIa, which has also been used off-label for this purpose.²³

The other issue often encountered in the ICU, correction of the PT/INR before invasive diagnostic procedures, is an area of some controversy. No definitive recommendations can be made. However, data suggest that in the absence of other hemostatic defects, most invasive procedures that do not involve the central nervous system can be performed safely at an INR less than 2, and certainly at an INR less than 1.5.^{24,25} Unnecessary correction of the INR with FFP can be associated with a delay in required treatment and with transfusion-associated complications.

MANAGEMENT OF REFRACTORY HEMORRHAGE

Refractory hemorrhage may result from surgical or medical causes. Correction of surgical defects associated with blood loss is critical because even the most effective hemostatic agents cannot replace appropriately placed sutures when a vessel wall has a defect. In particular, refractory bleeding in a patient who has normal or only mildly abnormal coagulation parameters and a recent surgical history requires thorough evaluation for this possibility.

In some cases, no surgical cause will be found, or coagulation defects will be impossible to correct using conservative measures. In these cases, off-label use of recombinant factor VIIa may be entertained after a consideration of the potential benefits versus risks (thrombosis).²⁶ Optimally, documentation of an adequate platelet count ($\geq 30,000$ – $50,000$ / μ L) and fibrinogen level (>100 mg/dL) should be made before administration. Doses of 70 to 100 μ g/kg have been used, and may be repeated if necessary. However, if hemostasis is not achieved after two to three doses, it is unlikely that this agent will be effective. As an alternative, or for patients who continue to bleed after the administration of recombinant factor VIIa, provided that DIC or upper urinary tract bleeding is not present, consideration may also be given to a trial of ϵ -aminocaproic acid, 1 g/hour by intravenous continuous infusion.

PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

A detailed discussion of venous thromboembolism is beyond the scope of this article and excellent reviews have been published elsewhere recently.^{27,28} However, it is worthwhile mentioning the importance of appropriate prophylaxis against venous thromboembolism in the ICU setting, which has been associated with improvements in morbidity and mortality.²⁹ Unfractionated heparin, low-molecular-weight heparins (LMWH), and fondaparinux are all options (Table 2). The choice of which agent to use depends on whether or not rapid correction of anticoagulation is required. Unfractionated heparin is completely reversible with protamine sulfate, whereas LMWH is partially reversible and fondaparinux is not.

Use of thrombolysis or thrombectomy may be considered in cases of massive pulmonary embolism. However, to date, thrombolysis has not been associated with a clear survival advantage.³⁰ Use of vena caval interruption devices (inferior vena cava filters) may be indicated under certain circumstances, such as in the setting of neurosurgical procedures within the recent past. However, few data are available (only one randomized trial) documenting their safety and efficacy.³¹ Although the one randomized trial of permanent filters demonstrated a reduction in pulmonary embolism, it revealed an increase in deep venous thrombosis, with no effect on survival. In general, use of conventional anticoagulation is preferable whenever possible.

HEPARIN-INDUCED THROMBOCYTOPENIA AND ALTERNATIVE ANTICOAGULANTS

Appropriate management of HIT is an issue that frequently arises in the ICU setting. In a patient receiving unfractionated or LMWH, a reduction in the platelet count of 50%, or a platelet count that

drops below 100,000/ μ L should trigger consideration of this diagnosis.³² Prompt institution of appropriate management is critical because between 10% and 25% of cases of HIT are associated with arterial or venous thromboembolic complications, which may be limb or life threatening.

Once a diagnosis of HIT is clinically suspected, before the return of any confirmatory laboratory tests, administration of heparin in any form should be discontinued (including small amounts used to flush intravenous lines). An effective anticoagulant appropriate for this setting should be administered at least until the platelet count has returned to above 150,000/ μ L or to baseline. In the absence of thrombosis, which would require transition to warfarin or an alternative agent, the choice of duration of anticoagulation after normalization of the platelet count is controversial. Durations between 1 week and 1 month have been proposed; however, few data currently support these recommendations.

Effective anticoagulants available today for use in the management of HIT include several direct thrombin inhibitors (see Table 2).³¹ Lepirudin is a recombinant hirudin that is approved for use in the management of HIT. It is administered by continuous infusion at a rate of 0.15 mg/kg/h with adjustment to bring the PTT to about 1.5 to 2.5 times the baseline value after an initial bolus dose of 0.4 mg/kg. Administration of an initial bolus dose may not be required, however, and has been associated with an increased risk for bleeding complications. Lepirudin has a half-life of 1.3 hours in individuals who have normal renal function. Because it is mainly metabolized by the renal route, the half-life is markedly increased in the setting of renal insufficiency. In addition, re-treatment with lepirudin has sometimes been associated with allergic reactions caused by antibody formation against the protein. Bivalirudin is a hirudin derivative that has a shorter half-life of about 25 minutes. It has not been associated

Table 2
Properties of available parenteral anticoagulants

Anticoagulant	Half-Life	Metabolism	Monitoring
UFH	30 min	Endothelial uptake	PTT
LMWH	3–7 h	Renal	Anti-Xa level (only when indicated)
Fondaparinux	13–30 h	Renal	Anti-Xa level (only when indicated)
Argatroban	40 min	Hepatic	PTT (also increases PT/INR)
Lepirudin	80 min	Renal	PTT (may also increase PT/INR)
Bivalirudin	25 min	Renal and proteolytic cleavage	PTT

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

with allergic reactions on patient re-treatment. Although potentially effective in the management of HIT, it is not labeled for this use. Argatroban is a small-molecule, direct thrombin inhibitor that is also approved for use in the management of HIT. The recommended administration rate is 2 $\mu\text{g}/\text{kg}/\text{min}$ with adjustment to bring the PTT to about 1.5 to 3.0 times the baseline value. In clinical practice, starting at administration rates of 1.0 to 1.5 $\mu\text{g}/\text{kg}/\text{min}$ in critically ill patients often produces PTT values of 1.5 to 2.0 times the baseline value. Argatroban undergoes hepatic metabolism and has a half-life of 39 to 51 minutes in patients who have normal liver function. Its clearance in liver disease is significantly decreased, so dose adjustment is required. Argatroban increases the INR to a noticeable extent (INR values of 2 to 4 are not uncommon when the PTT is in the therapeutic range), which is also true of lepirudin, to a somewhat lesser extent. The use of the pentasaccharide fondaparinux as a parenteral agent administered subcutaneously for the treatment of HIT is under investigation. Its use for HIT outside of the clinical research setting has been limited, given that one case of HIT related to fondaparinux has been reported in the literature. Additional orally bioavailable anticoagulants besides coumarin derivatives are likely to become available soon.^{33,34} These anticoagulants include dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban, an inhibitor of factor Xa. These agents have been shown to be effective anticoagulants and may simplify the management of HIT in specific settings and transform the approach to the prophylaxis and management of thromboembolic disease.

Two practical considerations often arise when using the currently available direct thrombin inhibitors in critically ill patients. The first consideration is deciding whether to use lepirudin or argatroban. The former is reasonable to use in patients who have normal renal function, and the latter in patients who have normal hepatic function. In the not uncommonly encountered setting of the individual who has renal and hepatic impairment, a decision needs to be made regarding the driving factor. In the presence of moderate renal impairment and moderate hepatic impairment, initial use of low doses of argatroban (0.5 $\mu\text{g}/\text{kg}/\text{min}$ to 1 $\mu\text{g}/\text{kg}/\text{min}$) followed by titration to a PTT of 1.5 to 2.0 times the baseline value (aiming for the lower part of the range) is recommended. The second consideration is transitioning to warfarin in patients on direct thrombin inhibitors, and argatroban in particular. In this case, the following procedure is recommended. After warfarin is initiated, at least 4 to 5 days have elapsed, the platelet count

has normalized, and the INR has increased by about 1.5 to 2 over the value observed while on a steady infusion, argatroban infusion can be held for about 3 hours. At that point, the INR can be determined and if in the therapeutic range, argatroban can be discontinued; otherwise, it can be restarted.

SUMMARY

Hematologic issues commonly complicate the management of patients in the ICU. Thoughtful clinical and laboratory evaluation of such patients allows appropriate administration of agents that promote hemostasis or prevent thrombosis. Use of FFP, cryoprecipitate, and other hemostatic agents should generally be reserved for those who have active bleeding, those undergoing invasive procedures, and those at high risk for bleeding because of their underlying diagnoses or because of associated hematologic derangements. Appropriate mechanical or pharmacologic prophylaxis should be provided to all ICU patients to prevent thromboembolic complications. When such complications do occur, the choice of therapy should take into consideration the patient's underlying clinical status and the potential need for invasive diagnostic procedures. HIT is a complication of anticoagulation with heparin and LMWH that should be managed aggressively to prevent associated morbidity and mortality.

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