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Coagulopathy

SANDRO RIZOLI | WILLIAM C. AIRD

Hemostasis is a dynamic and highly complex process typically divided into two components: primary and secondary. *Primary hemostasis* refers to the blood vessel and platelet response, whereas *secondary hemostasis* refers to the protein response (clotting cascade). In reality, both primary and secondary hemostasis are tightly interconnected, feed back on each other, and operate in unison. Nevertheless, from a conceptual standpoint, it is helpful to consider each limb of hemostasis separately. In this chapter, we review the clotting mechanism. The reader is referred to Chapter 20 for a discussion of the most common coagulation disorder in the ICU: thrombocytopenia.

General Principles

The blood clotting cascade is highly complex, consisting of a series of linked reactions. In each reaction, a serine protease, once activated, is capable of activating its downstream substrate. For the purposes of this chapter, the scheme will be simplified according to the following themes: (1) the final step in the clotting cascade is the conversion of fibrinogen to fibrin, a process mediated by thrombin; (2) fibrin is the "glue" that holds platelet plugs together and contributes to the host defense against pathogens; (3) there are two pathways—extrinsic and intrinsic—that converge to induce thrombin generation and fibrin formation; (4) blood coagulation is always initiated by the extrinsic pathway (via tissue factor) and amplified by the intrinsic pathway; (5) the prothrombin time (PT) measures the integrity of the extrinsic (and common) pathways, and the activated partial thromboplastin time (APTT) measures the integrity of the intrinsic (and common) pathways; and (6) every procoagulant step is balanced by a natural anticoagulant (antithrombin, protein C system, tissue factor pathway inhibitor). In the final analysis, hemostasis represents a balance between anticoagulant and procoagulant forces.[1-5]

Disorders in hemostasis occur when the hemostatic balance shifts toward one side or the other, resulting in one of two clinical phenotypes: bleeding or thrombosis. The myriad causes, diagnostic workup, and treatment of coagulation disorders are beyond the scope of this chapter. In the sections that follow, we consider the coagulopathy that occurs in patients with sepsis. The reasons for choosing sepsis as the case study are several-fold: (1) sepsis is common in the ICU and is responsible for most coagulation disorders; (2) a consideration of the mechanisms, diagnosis, and therapy of coagulopathy in this setting may be widely applicable to other conditions also associated with activation of the innate immune response (e.g., trauma, burns, postoperative systemic inflammatory response syndrome) and (3) recent therapeutic breakthroughs emphasize the importance of targeting the host response rather than the clotting cascade per se. In sepsis, hemostasis derangement is characterized by enhanced fibrin formation and dysfunction of the physiologic anticoagulant response, with depression of fibrinolysis and impaired fibrin removal.[2,4]

Incidence

Previous studies demonstrated that the coagulation system is activated in virtually all patients with severe sepsis.[2-4] In most such patients, activation may be minimal and detected only by test findings such as elevated circulating D-dimer levels,[6] low protein C levels, or antithrombin deficiency.[4,6] The activation also may be pronounced and characterized by the presence of thrombocytopenia or even

disseminated intravascular coagulation (DIC), with evidence of both thrombosis and bleeding. It is estimated that DIC occurs in 15% to 30% of patients with severe sepsis or septic shock.[2,4,7,8]

Mechanisms

In sepsis, the clotting cascade is initiated by tissue factor (TF). When TF is exposed to blood, it binds to factor VII. The complex TF-FVIIa activates factor X, which in turn forms a prothrombinase complex, leading to the generation of thrombin. Finally, thrombin converts fibrinogen into fibrin. TF is exposed to blood through either endothelial disruption or expression on the surface of circulating monocytes, tissue macrophages, and even endothelial cells.[4,9,10]

At the same time, sepsis attenuates all three physiologic anticoagulant mechanisms: activated protein C (APC), antithrombin (AT) and tissue factor pathway inhibitor (TFPI). APC has a key role in sepsis; along with protein S and thrombomodulin, it degrades factors V and VIII by a process accelerated by endothelial protein C receptors (EPCR). In sepsis, APC, protein S, thrombomodulin, and EPCR are down-regulated, rendering the system ineffective.[11,12] AT is the main inhibitor of thrombin and factor Xa, whereas TFPI inhibits the TF-FVIIa complex. Levels of both AT and TFPI are markedly reduced in patients with sepsis.[4,13,14] Sepsis also inhibits fibrinolysis.[2,4] Together, these changes tilt the balance toward the procoagulant side, resulting in thrombin generation, fibrin deposition, and consumption of clotting factors and platelets. DIC represents the extreme case in this pathophysiologic continuum.[2-4]

Local activation of the coagulation system in sepsis is an integral component of the innate immune response and may play a protective role in walling off infection. However, in patients with severe sepsis, systemic activation of coagulation is harmful to the patient and associated with increased mortality.[15] Other common forms of coagulopathy in the ICU are associated with severe trauma, massive blood losses, and shock. Recent studies suggest that early trauma-associated coagulopathy is triggered mainly by shock, mediated by activated protein C, and exacerbated by dilution of plasma and hypothermia.[16,17] Interestingly, the early trauma-associated hypercoagulable state converts to a hypercoagulable one by 24 hours after trauma, carrying a higher risk of thrombotic complications.[18] Other common coagulopathies in the ICU are caused by liver dysfunction, heparin and other anticoagulant medications, and vitamin K deficiency (Figures 21-1 and 21-2).

Clinical Manifestations and Diagnosis

Severe sepsis is usually associated with a net procoagulant state, as evidenced by local or diffuse microvascular thrombi. These changes occasionally manifest as skin lesions, as occurs in purpura fulminans. More commonly, the coagulation cascade interacts with the inflammatory pathway to induce endothelial cell activation and secondary dysfunction of internal organs, including the liver, kidneys, lungs, and brain. Patients are at risk for bleeding when the consumption of clotting factors outstrips the production. Bleeding is more common when the coagulopathy is exacerbated by concomitant thrombocytopenia, liver disease, heparin use, and invasive procedures. In large prospective studies, the incidence of serious bleeding in patients with severe sepsis varies between 2% and 6%.[19] The most sensitive laboratory markers of sepsis-associated coagulopathy include reduced circulating protein C
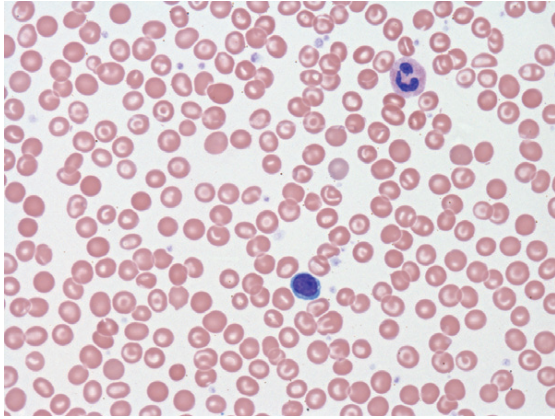
Figure 21-1 Normal peripheral blood film revealing normochromic normocytic red cells, morphologically unremarkable white cells, and adequate numbers of platelets. *(Courtesy Drs. David Good and Marciano Reis, Sunnybrook Health Sciences Centre, University of Toronto.)*

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Box 21-1

CAUSES OF INCREASED PROTHROMBIN TIME (PT) AND/OR ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

Increased PT—Defect in Extrinsic Pathway
Deficiency or inhibitor of factor VII
Early warfarin (Coumadin) therapy
Early liver disease

Increased APTT—Defect in Intrinsic Pathway
Deficiency or inhibitor of factors XII, XI, IX, or VIII
Heparin (though usually affects PT as well)
Liver disease (though usually affects PT as well)
Lupus anticoagulant (may affect PT as well)

Increased PT and APTT—Defect in Common Pathway or Combined Defect in Extrinsic and Intrinsic Pathways
Heparin (all serine proteases affected, especially II and X)
Disseminated intravascular coagulation (all factors, including pro- and anticoagulants, affected)
Liver disease (all factors except VIII affected)
Warfarin (factors II, VII, IX, and X affected)
Vitamin K deficiency (factors II, VII, IX, and X affected)
Direct thrombin inhibitors
Lupus anticoagulant

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levels and increased circulating D-dimer levels. However, protein C levels are not routinely measured, and an elevated level of D-dimers is a nonspecific finding. In general, coagulation factor levels are inversely correlated with the severity of sepsis,[2] except for factor VIII, an acute-phase protein. Fibrinogen, another acute-phase protein, may be elevated in the early stages of sepsis but is reduced in up to 50% of patients with severe sepsis.[20]

Marked activation of coagulation and secondary consumption of clotting factors may lead to DIC. No single test is sufficiently sensitive or specific to make the diagnosis of DIC. Recently a scoring system was proposed that employs simple laboratory tests, including platelet count, elevated fibrin-related marker (e.g., soluble fibrin monomers, fibrin degradation products), prolonged PT, and fibrinogen level.[20,21] Other markers of coagulation activation such as thrombin-antithrombin complexes, fibrinopeptides, and prothrombin fragment 1.2 are considered investigational in this setting.

The PT or APTT may be elevated for reasons other than sepsis-associated consumption of clotting factors (Box 21-1). As a general rule, increased clotting times are caused by inhibitors against one or more clotting factors or a congenital or acquired deficiency state. In
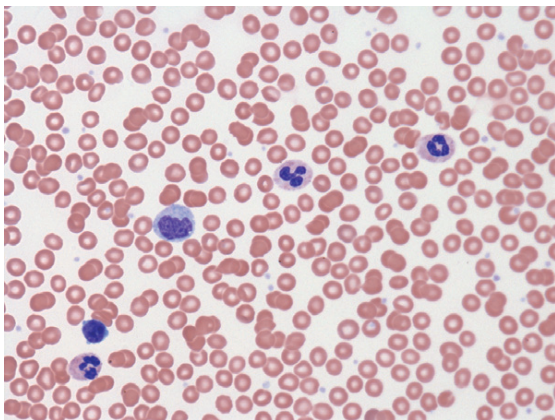
Figure 21-2 Peripheral blood film showing macrocytic red cells, numerous target cells, and slightly decreased platelets, indicative of liver failure. Thrombocytopenia is often accompanied by a coagulopathy, owing to dysfunctional platelets and decreased production of coagulation factors in the liver. *(Courtesy Drs. David Good and Marciano Reis, Sunnybrook Health Sciences Centre, University of Toronto.)*

the ICU, prolongation of the PT or APTT is almost always related to an acquired deficiency state. An isolated increase in PT indicates factor VII (extrinsic pathway) deficiency and may be seen in early liver failure or during the initial stages of warfarin (Coumadin) therapy. An isolated increase in the APTT points to a defect in the intrinsic pathway—namely, factors XII, XI, IX, or VIII. An increase in both PT and APTT reflects an abnormality in the common pathway (factors X or V, prothrombin, or fibrinogen) or a combined deficiency in the extrinsic and intrinsic pathways. The latter occurs with heparin therapy, long-term warfarin treatment, vitamin K deficiency, advanced liver disease, DIC, or dilutional coagulopathy.[3,4]

Prognosis

Certain markers of coagulation activation have been correlated with negative outcome in patients with sepsis. For example, low antithrombin levels in patients with sepsis are predictive of poor survival.[7] Decreased protein C levels in severe sepsis have been shown to correlate with mortality, presence of shock, length of ICU stay, and ventilator dependence.[2,4] In clinical studies of multiple organ dysfunction, maximum PT and APTT were shown to be longer in nonsurvivors than in survivors.[15] DIC is an independent predictor for mortality in patients with sepsis.[22]

Treatment

The most important treatment for coagulopathy in septic patients in the ICU is to treat the underlying infection. Many patients, however, still require additional treatments directed at correcting either the hemostatic defect or the deficit of physiologic anticoagulants.

The consumption of clotting factors and platelets, with or without DIC, may result in bleeding diathesis in patients with sepsis. For such patients, transfusion therapy with platelets, fresh frozen plasma, or plasma components may be indicated if the patient is actively bleeding or if there is a high risk of bleeding (e.g., due to other types of coagulopathy, trauma, need for surgery, invasive procedures).[2,4,16]

In view of recent advances in our understanding of the underlying pathophysiology of sepsis, emphasis has shifted from procoagulant replacement to anticoagulant therapy. A variety of thrombin inhibitors have been tested in patients with sepsis, including antithrombin (AT), tissue factor pathway inhibitor (TFPI) and activated protein C (APC).

These drugs inhibit thrombin generation and fibrin formation and demonstrated promising results in animal and early-phase clinical studies.[23,24] One possible explanation for these results is that the natural anticoagulants have a dual function: inhibition of coagulation and suppression of inflammation. AT, TFI and APC each have been shown to modulate the inflammatory response under in vitro and in vivo conditions.[25]

However, in subsequent large, randomized controlled trials, infusions with AT and TFPI (tifacogin) failed to improve 28-day all-cause mortality in patients with severe sepsis.[7,26,27] In contrast, the PROWESS study, which was stopped ahead of time, demonstrated that recombinant human activated protein C had both anticoagulant and antiinflammatory properties and improved survival of patients with severe sepsis.[6] Recombinant APC is approved for use in the United States and most of the world; its use is an integral part of many guidelines for the treatment of sepsis.[28] Recombinant APC's role in sepsis, however, continues to be debated following publication of negative trials.[29,30] Furthermore, we do not know at present whether the different outcomes in the phase 3 trials of AT, TFPI, and APC can be explained by differ- ences in study design or whether they reflect differences at the mechanistic level.

Conclusions

Most patients in the ICU have coagulation abnormalities and marked activation of the clotting cascade, which could be more apparent if these patients were routinely tested with assays such as protein C levels, markers of thrombin activation, or D-dimers. While the unrelenting coagulation activation leads to a prothrombotic state, it may also result in clotting factor consumption and bleeding diathesis. Important challenges for the intensivist are to (1) delineate and track a patient's position on the hemostatic scale (prothrombotic versus hemorrhagic), (2) understand that both phenotypes may occur concomitantly (e.g., microthrombi within internal organs and mucosal bleeding), and (3) target each component separately—that is, replenish the clotting factors in the face of bleeding (e.g., plasma products) while attenuating the underlying host response (e.g., low-tidal-volume ventilation, activated protein C, and early goal-directed therapy).

ANNOTATED REFERENCES

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