Review

The Hematologic System as a Marker of Organ Dysfunction in Sepsis

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Sepsis with acute organ dysfunction (severe sepsis) results from a systemic proinflammatory and procoagulant response to infection. Organ dysfunction in the patient with sepsis is associated with increased mortality. Although most organs have discrete anatomical boundaries and carry out unified functions, the hematologic system is poorly circumscribed and serves several unrelated functions. This review addresses the hematologic changes associated with sepsis and provides a framework for prompt diagnosis and rational drug therapy. Data sources used include published research and review articles in the English language related to hematologic alterations in animal models of sepsis and in critically ill patients. Hematologic changes are present in virtually every patient with severe sepsis. Leukocytosis, anemia, thrombocytopenia, and activation of the coagulation cascade are the most common abnormalities. Despite theoretical advantages of using granulocyte colony-stimulating factor to enhance leukocyte function and/or circulating numbers, large clinical trials with these growth factors are lacking. Recent studies support a reduction in the red blood cell transfusion threshold and the use of erythropoietin treatment to reduce transfusion requirements. Treatment of thrombocytopenia depends on the cause and clinical context but may include platelet transfusions and discontinuation of heparin or other inciting drugs. The use of activated protein C may provide a survival benefit in subsets of patients with severe sepsis. The hematologic system should not be overlooked when assessing a patient with severe sepsis. A thorough clinical evaluation and panel of laboratory tests that relate to this organ system should be as much a part of the work-up as taking the patient's blood pressure, monitoring renal function, or measuring liver enzymes.

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ATIII = antithrombin III; DIC = disseminated intravascular coagulation; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICU = intensive care unit; MCV = mean corpuscular volume; TFPI = tissue factor pathway inhibitor

Sepsis and its sequelae represent a continuum of clinical and pathological severity. The sepsis continuum has definable phases that characterize populations at risk for morbidity and mortality. The most important determinant of mortality is not the pathogen but rather the degree and nature of the host response. The development of the multiple organ dysfunction syndrome in sepsis represents the extreme in the spectrum and is associated with a high risk of death.[1,2] Therefore, health care providers treating patients with sepsis must be aware of the signs of organ dysfunction and specifically look for the development of this complication.

Most organs have discrete anatomical boundaries and carry out unified functions, but the hematologic system is poorly circumscribed and serves several unrelated functions. Cellular elements, including white blood cells, red blood cells, and platelets, originate in the bone marrow and are distributed systemically, in some cases taking up residence in local tissues, lymph nodes, or the spleen. Anticoagulant and procoagulant proteins are synthesized and released from the liver, endothelium, and circulating cells. The hematologic system plays a critical role in oxygen delivery, carbon dioxide disposal, hemostasis, and defense against pathogens. As a result of its widespread distribution and disparate functions, the hematologic system is often overlooked as an organ in the work-up of the patient with sepsis. This is a critical oversight for several reasons. First, hematologic changes are present in virtually every patient with severe sepsis. Second, patients with hematologic dysfunction have increased morbidity and mortality. Third, rapid identification and treatment of hematologic dysfunction may lead to improved survival. This is particularly true with the advent of novel sepsis-modifying therapies. This review addresses sepsis-associated hematologic changes and provides a framework for prompt diagnosis and rational drug therapy.

HEMATOLOGIC CHANGES IN SEPSIS—ADAPTATION VS DYSFUNCTION

There are 2 components to the host response, a nonspecific innate immune response and a specific or acquired immune response. The innate immune response (or acute phase

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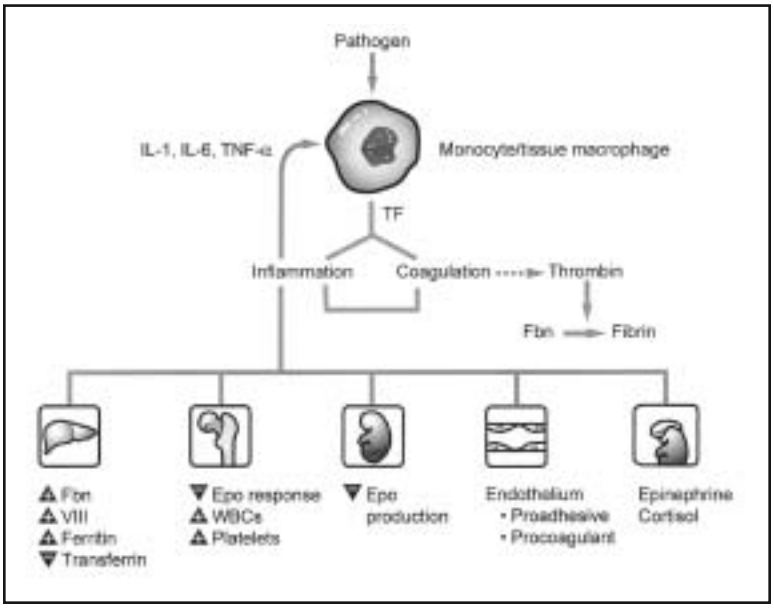

Figure 1. The acute phase response (innate immunity) is associated with several changes in the hematologic system, including effects on the monocyte (activation of coagulation and inflammation, sequestration of iron), liver (release of acute phase proteins), bone marrow (release and production of platelets and white blood cells [WBCs]), kidney (reduced erythropoietin [Epo] production), endothelium (proadhesive and procoagulant phenotype), and neuroendocrine axis (epinephrine and glucocorticoid [cortisol] release). Fbn = fibrinogen; IL = interleukin; TF = tissue factor; TNF-α = tumor necrosis factor α.

response) is a highly evolutionarily conserved mechanism that serves to combat pathogens, minimize tissue injury, promote host recovery, and set the stage for the acquired immune response.[3,4] Innate immunity involves the coordinated activity of both cells and proteins (Figure 1). The principal cellular and soluble effectors are monocytes/macrophages and activated complement, respectively; the primary communicators are cytokines interleukin 1, interleukin 6, and tumor necrosis factor α. Normally, the innate immune response defends the host against pathogen and leads to full recovery. However, the innate immune response may turn on its host, leading to pronounced morbidity and mortality. A debated issue is the extent to which the physiological alterations of the innate immune response are, at any given time in the sepsis continuum, adaptive or harmful to patients with sepsis. This issue is important because the therapeutic modulation of an adaptive response may have deleterious effects on patients. The theoretical advantages and disadvantages of the hematologic changes in sepsis are addressed subsequently (Table 1).

WHITE BLOOD CELL ALTERATIONS IN SEPSIS

Incidence

In patients with sepsis, the white blood cell count is normally elevated (leukocytosis). This observation is supported in animal models of sepsis in which administration of endotoxin results in pronounced leukocytosis.[5] The leukocyte differential count typically reveals increased numbers of neutrophils (neutrophilia).[6] Occasionally, the degree of leukocytosis is extreme, with white blood cell counts of more than 50×10^9/L (leukemoid reaction). In some cases, sepsis is associated with a decreased neutrophil count (neutropenia), especially in the pediatric population. Funke et al[7] found that 38% of neonates with sepsis had neutropenia and that the duration of neutropenia was less than 24 hours in 75% of these patients.

Mechanisms

Several mechanisms contribute to neutrophilia, including demargination, increased release from the bone marrow, and increased production of neutrophils (Figure 2). Mobilization of bone marrow reserves may also result in the release of an increased number of bands and/or earlier myeloid forms in the peripheral blood (left shift). Neutropenia may arise from an exhaustion of bone marrow progenitors, a maturation arrest in the committed granulocytic lineage, or an imbalance between extravasation and production.[8,9] The development of neutropenia has been associated with a poor prognosis.[10] Sepsis is also associated with activation of circulating monocytes and neutrophils.[11-14]

Table 1. **Hematologic Changes in Sepsis***

	Adaptation†	Dysfunction†	Laboratory tests available	
			Widely	Rarely
WBC	Increased number and function Antimicrobial	Excessive increased number (leukemoid reaction) Hyperviscosity Neutropenia	WBC count Differential Left shift Peripheral smear Döhle bodies Toxic granulations	WBC functional assays
RBC	Anemia Reduced viscosity Decreased PLT-endothelial interactions	Anemia Decreased oxygen-carrying capacity Decreased PLT function Decreased deformability Increased viscosity	Hematocrit, hemoglobin Reticulocytes Peripheral smear Ferritin Iron Total iron-binding capacity	RBC viscosity Erythropoietin levels
PLT	Thrombocytosis Increased membrane surface area PLT activation Proinflammatory/coagulant Microparticle formation Proinflammatory/coagulant	Thrombocytopenia Bleeding Excessive PLT activation Proinflammatory/coagulant Microparticle formation Proinflammatory/coagulant	PLT count Peripheral smear Clumping (pseudo) Schistocytes (disseminated intravascular coagulation)	Antigen-specific autoantibodies Cell surface activation markers
Activation of coagulation	Thrombin generation Fibrin formation Proinflammatory PLT activation Fibrin generation Walling off infection Wound healing	Decreased protein C Proinflammatory/coagulant Consumptive coagulopathy Bleeding Excessive thrombin and fibrin generation	D-dimer Prothrombin time Activated partial thromboplastin time Fibrinogen	Protein C levels Antithrombin III levels Activation markers (ie, thrombin/antithrombin, prothrombin fragment F1+2)

*PLT = platelet; RBC = red blood cell; WBC = white blood cell.
†The distinction between adaptation and dysfunction is hypothetical. An important challenge is to develop diagnostic tools for defining the threshold at which the host response becomes dysfunctional.

Activation of 1 or both of these cell types results in the release of a large number of inflammatory mediators, increased expression of tissue factor, enhanced interactions with the endothelium, and/or changes in biomechanical properties.[15] Various neutrophil functions may actually be reduced in sepsis, including chemotaxis, phagocytosis, and production of reactive oxygen species.[16]

The increased production and activation of circulating neutrophils and/or monocytes are important components of host response to infection. However, excessive or sustained changes in the number or function of white blood cells may be deleterious to the patient. For example, neutropenia increases the risk of septic death, and leukemoid reactions can increase blood viscosity. Furthermore, excessive release of cytokines from circulating monocytes or reactive oxygen species from neutrophils may also contribute to the pathophysiology of severe sepsis.[17-20]

Diagnosis

Leukocytosis or leukopenia is diagnosed on the basis of the complete blood cell count. Modern-day automated cell counters also provide an accurate white blood cell differential count. Inspection of the peripheral blood smear may show toxic granulations, vacuolization, and/or the presence of Döhle bodies in polymorphonuclear cells. The leukocytosis and left shift associated with the leukemoid reaction may mimic the changes of chronic myelogenous leukemia. The diagnosis is usually obvious based on the clinical context. However, in difficult cases, a leukocyte alkaline phosphatase score is helpful in differentiating the 2 syndromes. The leukocyte alkaline phosphatase measurement is a simple laboratory test with scores that are elevated in patients with sepsis and decreased in patients with chronic myelogenous leukemia.

Treatment

During the past several years, the therapeutic potential of recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) has been explored in animal models of sepsis and in patients who have sepsis with or without neutropenia.[21] Of these 2 growth factors, G-CSF appears to have the most favorable risk-benefit profile.[21] Indeed, G-CSF has been shown not only to selectively stimulate the production and function of neutrophils (hence, more effective clearance of pathogens) but also to potentially dampen deleterious aspects of the proinflammatory response in sepsis.[21-26] Generally, G-CSF is well tolerated; the most com-

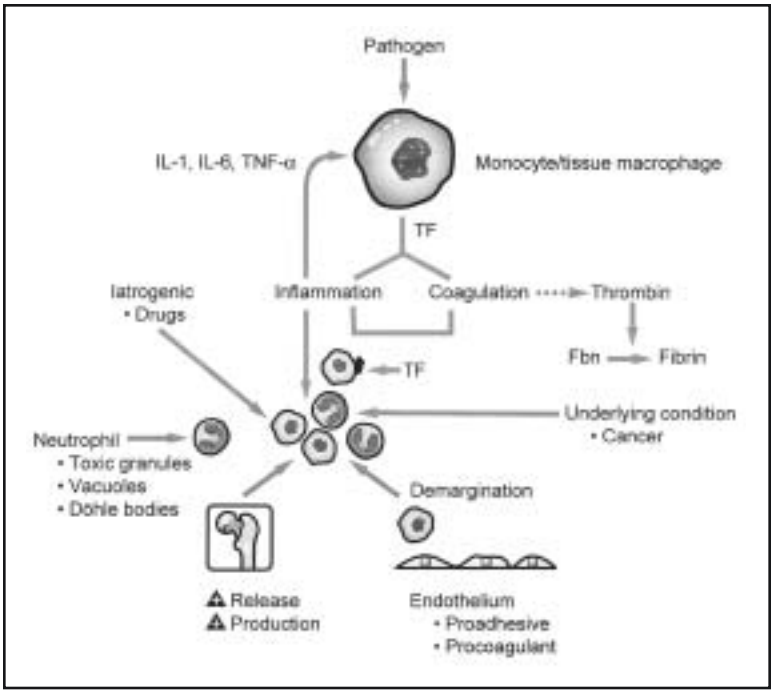

Figure 2. Sepsis and the acute phase response result in demargination of neutrophils from the endothelial surface, release and increased production of neutrophils and/or monocytes from the bone marrow, and activation of circulating leukocytes. Rarely, sepsis may result in neutropenia or in a leukemoid reaction. The white blood cell count may be increased or decreased because of an underlying medical condition such as cancer and/or associated treatment with chemotherapy and corticosteroids. Neutrophil morphology may reveal toxic granulations, vacuolization, and/or the presence of Döhle bodies. Fbn = fibrinogen; IL = interleukin; TF = tissue factor; TNF-α = tumor necrosis factor α.

monly reported toxicity is musculoskeletal pain.[21] Although it seems reasonable to consider the use of G-CSF in patients with severe sepsis complicated by neutropenia, there is no evidence at present that this therapy improves patient outcomes.[27] Moreover, the role of GM-CSF or G-CSF in treating the nonneutropenic adult patient with sepsis remains to be established.[28]

RED BLOOD CELL ALTERATIONS IN SEPSIS

Red Blood Cell Deformability

Sepsis-induced changes in the mechanical and membrane properties of red blood cells lead to decreased deformability.[29-31] The mechanism is unclear but may involve membrane damage from reactive oxygen species derived from circulating leukocytes and ischemic tissues.[32,33] Red blood cell deformability is an important determinant of blood flow, particularly in the microcirculation.[34,35] Indeed, decreased deformability results in increased transit time and reduced flow. These changes may negatively impact tissue oxygen delivery and contribute to organ dysfunction.

Red Blood Cell Aggregation

Sepsis has also been associated with aggregation of red blood cells.[36] The importance of this phenomenon in mediating the sepsis phenotype is unknown. One manifestation of this process can be an elevated erythrocyte sedimentation rate.

Free Hemoglobin

When sepsis is associated with increased destruction of red blood cells, free hemoglobin may be released into the circulation. In experimental models, free hemoglobin has been shown to increase lethality during endotoxemia by a mechanism that involves sensitization of tumor necrosis factor α–producing monocytes and macrophages.[37] As part of the acute phase response, levels of haptoglobin are increased. Haptoglobin binds free hemoglobin, protecting the host from the deleterious effects of free hemoglobin.

Anemia

Incidence.—Anemia is commonplace in critically ill patients with or without sepsis. In a study of intensive care

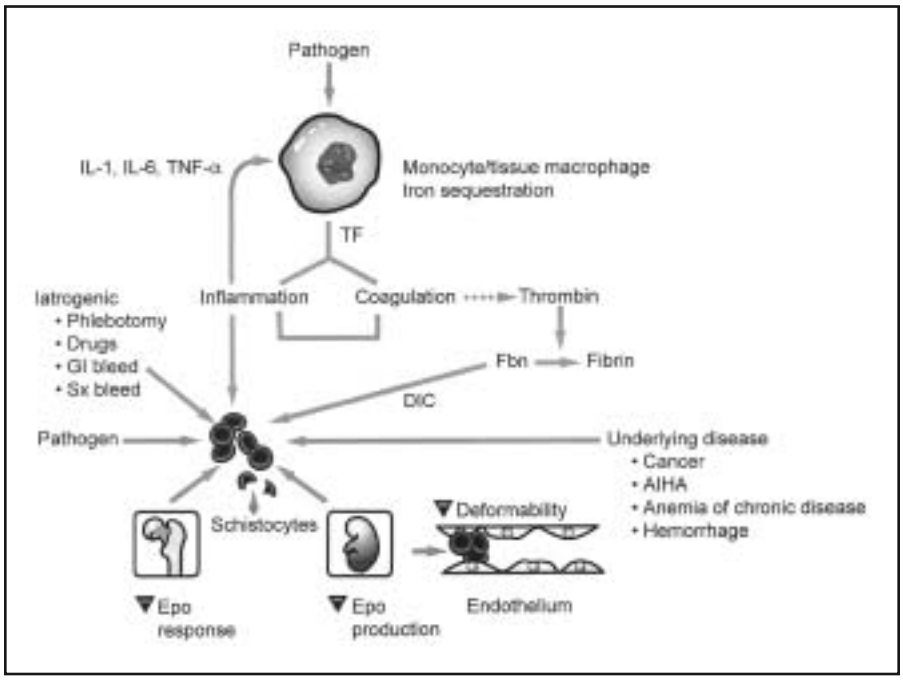

Figure 3. Sepsis and the acute phase response result in anemia of inflammation, characterized by iron sequestration in monocytes/macrophages, decreased erythropoietin (Epo) production, and blunted bone marrow response to Epo. When sepsis is complicated by disseminated intravascular coagulation (DIC), hemolysis may contribute to the anemia. Rarely, pathogens (eg, *Clostridium perfringens*) interact directly with red blood cells to induce a hemolytic anemia. Patients may present to the intensive care unit with preexisting anemia. Examples shown are cancer, autoimmune hemolytic anemia (AIHA), anemia of chronic disease, and hemorrhage. Iatrogenic causes of anemia include repeated phlebotomy, drugs that cause immune hemolytic anemia or bone marrow suppression, and gastrointestinal (GI) and/or surgical (Sx) blood loss. Sepsis results in reduced deformability of red blood cells, which may lead to increased viscosity and decreased tissue perfusion. Fbn = fibrinogen; IL = interleukin; TF = tissue factor; TNF-α = tumor necrosis factor α.

unit (ICU) admissions in which patients with end-stage renal failure and primary hematologic disease were excluded, the median hemoglobin level at the time of admission to the ICU was 12.1 g/dL, and 77% of patients had anemia during their stay.[38] In another survey of ICU admissions, the mean hemoglobin level of patients admitted to the ICU was 11.3 g/dL, with 29% having a hemoglobin level lower than 10 g/dL.[39] The impact of anemia is reflected by the high transfusion requirements in this patient population. Previous studies have reported that critically ill patients receive a mean of 1 U of packed red blood cells per patient-day,[40] that 16% of patients in the medical ICU and 27% of patients in the surgical ICU receive blood transfusions on any given day,[41] and that between 37% and 60% of all patients admitted to the ICU receive at least 1 transfusion.[39,42]

Mechanisms.—There are many causes of anemia in the patient with severe sepsis (Figure 3). Blood loss occurs through repeated phlebotomy, via the gastrointestinal tract, or from surgical procedures. Withdrawal of blood has been estimated to result in a mean daily loss of 24 to 41 mL of blood.[39,43,44] Smoller and Kruskall[45] reported that patients in the ICU who had arterial lines had a mean of 944 mL of blood withdrawn during their stay. Patients with severe sepsis also develop anemia of inflammation. Once known by the misnomer "anemia of chronic disease," this syndrome may occur within days of the initial insult.[46] The pathophysiology of anemia of inflammation is complex and includes reduced production of erythropoietin, impaired bone marrow response to erythropoietin, and decreased red blood cell survival.[43,47-55] Anemia of inflammation is typically mild, with hemoglobin levels rarely decreasing lower than 8 g/dL. Patients may also have chronic anemia secondary to disorders such as cancer, liver disease, or renal impairment. In addition to preexisting medical conditions, new-onset multiple organ dysfunction, particularly of hepatic and renal systems, may contribute to a worsening of anemia while the patient is in the ICU. Other contributing factors include disseminated intravascular coagulation (DIC), pathogen-associated hemolysis, hypoadrenalism, and nutritional deficiency.[56-58]

Bacteria require iron for their growth. Several studies have shown a link between iron and infection.[49,59] The human host sequesters iron as a component of nonspecific immunity. In addition, sepsis-associated low serum iron levels may protect against iron-catalyzed oxidant cell damage.[60,61] Red blood cells also require iron for growth and maturation. Therefore, anemia of acute infection may represent collateral damage during the host's bid to starve the pathogen of iron.

The most important risk associated with anemia is reduction in the oxygen-carrying capacity of blood. Although these changes are usually compensated for by an increase in cardiac index and oxygen extraction, they may profoundly affect patients with coronary heart disease.

Another potential adverse effect of anemia is its effect on platelet function.[62-64] In general, the hematocrit level is inversely correlated with the bleeding time. However, most studies have been performed in patients with renal failure, and the extent to which anemia in the patient with severe sepsis affects bleeding tendency is less clear.[65] It is tempting to speculate that anemia of inflammation may actually serve an adaptive role by limiting the interaction between platelets and the blood vessel wall, thereby attenuating platelet-endothelial cell interactions and offsetting the tendency to develop platelet activation and thrombocytopenia. Moreover, a reduced hemoglobin level would be expected to offset the deleterious effect of altered red blood cell deformability, red blood cell aggregation, and increased plasma fibrinogen on blood viscosity.

Clinical Manifestations and Diagnosis.—Anemia is diagnosed when the hematocrit or hemogloblin level decreases 2 SD below the mean. Of these 2 values, hemoglobin is the preferred marker because it correlates directly with the oxygen-carrying capacity of blood. In patients with preexisting anemia, red blood cell indices may be helpful in narrowing the diagnosis. An increased mean corpuscular volume (MCV) may reflect increased reticulocytes (from bleeding or hemolysis), liver disease, alcohol toxicity, chemotherapy, human immunodeficiency virus infection, or vitamin B_{12}/folate deficiency. A decreased MCV indicates an underlying diagnosis of iron deficiency, thalassemia, sideroblastic anemia, or chronic inflammatory disease. Red blood cell indices are rarely helpful in the diagnosis of patients who develop de novo anemia in the ICU. For example, as a result of bone marrow suppression, the reticulocytosis and increased MCV characteristic of acute bleeding or hemolysis are often absent in patients with severe sepsis. Patients with severe sepsis often develop markers of anemia of inflammation, including decreased serum iron and transferrin saturation, normal or reduced iron-binding capacity, and increased ferritin.[38] Erythropoietin levels, while inappropriately low for the level of hemoglobin, are not routinely measured in these patients.

Prognosis.—The contribution of anemia to the morbidity and mortality of patients with severe sepsis is presently unknown. Although healthy individuals have been shown to tolerate severe isovolemic anemia, these observations cannot be readily extrapolated to patients with severe sepsis. The ability of patients to tolerate anemia is likely due to the capacity to compensate with an increased cardiac index, an increased oxygen extraction, and perhaps a shift of the oxygen dissociation curve to the right. Any disease process that interferes with these compensatory mechanisms (eg, congestive heart failure) is likely to reduce the level of tolerance to any degree of anemia.

Treatment.—There is no defined optimal hemoglobin concentration in the patient with sepsis. As a general rule, patients should receive transfusions when the benefits associated with the incremental oxygen-carrying capacity outweigh the adverse effects of transfusions.[66-69] Use of transfusions in patients in the ICU has been associated with increased morbidity and mortality. For example, in one study, administration of packed red blood cells resulted in an increased risk of nosocomial infection and a longer ICU and hospital stay.[70] In a recent multicenter randomized controlled clinical trial, a restrictive strategy of red blood cell transfusions to maintain a hemoglobin level between 7.0 and 9.0 g/dL was shown to be equal if not superior to a liberal transfusion strategy to maintain a hemoglobin level higher than 10.0 to 12.0 g/dL in critically ill patients without acute coronary syndromes.[71] Indeed, the trial documented a trend toward reduced 30-day mortality in the group treated with the lower transfusion trigger.[71] Consistent with these results, other studies have reported an association between red blood cell transfusions and increased mortality in critically ill patients.[39,70] Although these mortality data remain to be confirmed in large randomized trials, they provide additional incentive (over and above the standard risks associated with transfusion) to explore alternative approaches to blood transfusion. One such strategy is to administer recombinant erythropoietin as a means of boosting the patient's endogenous erythropoiesis.[43,72,73] This treatment is based on the premise that exogenous erythropoietin will replenish the inappropriately low erythropoietin levels and at least partially overcome the blunted bone marrow response. Indeed, erythropoietin treatment has been shown to induce a reticulocyte response in critically ill patients.[43] In a phase 3 prospective randomized placebo-controlled trial, weekly administration of recombinant human erythropoietin to patients in the ICU was well tolerated and resulted in a 19% reduction in the total number of red blood cell units transfused, without a difference in mortality.[42] A cost-benefit analysis is necessary before routine use of erythropoietin in the ICU setting can be recommended. The potential benefit of other transfusion

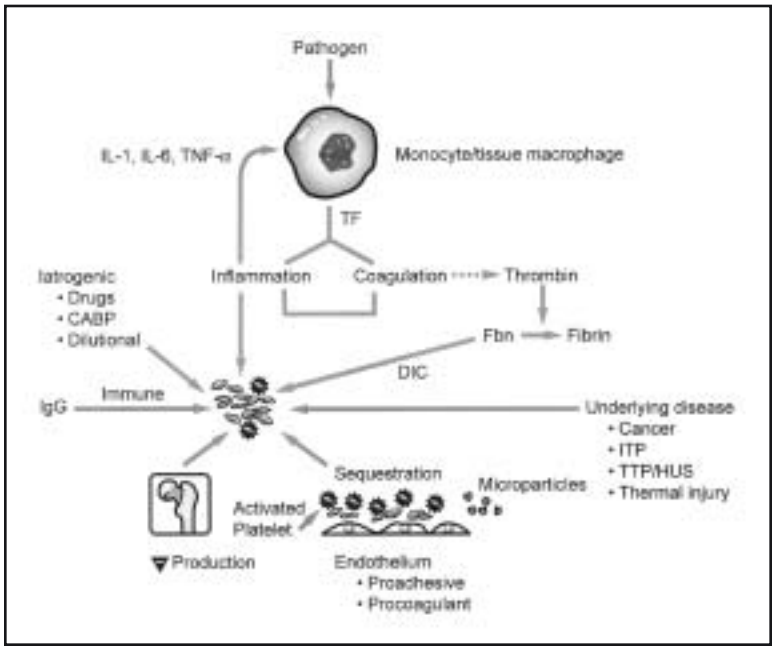

Figure 4. Initially, the acute phase response normally results in an increased platelet count. However, severe sepsis is more commonly associated with thrombocytopenia. Several mechanisms have been implicated in the development of thrombocytopenia. Most importantly, sepsis induces the binding of platelets to activated endothelium, resulting in sequestration and destruction within microvessels. Platelets may be consumed when sepsis is complicated by disseminated intravascular coagulation (DIC). Rarely, platelet-specific autoantibodies (IgG) may play a role in immune-mediated destruction of platelets. Patients may have an established diagnosis of thrombocytopenia secondary to an underlying disease. Examples include cancer, immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (TTP/HUS), and thermal injury. Iatrogenic causes of thrombocytopenia include drugs (particularly heparin), coronary artery bypass procedure (CABP), and trauma or surgery with massive red blood cell transfusion (dilutional). Sepsis results in activation of platelets and formation of prothrombotic microparticles. Fbn = fibrinogen; IL = interleukin; TF = tissue factor; TNF-α = tumor necrosis factor α.

alternatives, including hemoglobin-derived blood substitutes or perfluorocarbon, warrants further investigation.[74]

PLATELET ALTERATIONS IN SEPSIS

Platelet Function

Platelets are activated during sepsis.[75,76] Activated platelets aggregate, provide a phospholipid-rich surface for coagulation complexes, release proinflammatory mediators, and interact with leukocytes and endothelial cells.[75] In addition, platelets may generate procoagulant-rich microparticles, which contribute to a prothrombotic state.[77,78] At the present time, platelet function assays provide little diagnostic or therapeutic value and are not routinely performed in these patients.

Thrombocytopenia

Incidence.—The acute phase response is often characterized by increased platelet counts (thrombocytosis).[79,80] However, patients who are admitted to the ICU with or without underlying sepsis are more commonly diagnosed as having reduced platelet counts (thrombocytopenia). Thrombocytopenia occurs in up to 20% of medical ICU and 35% of surgical ICU admissions.[81-84] Sepsis is a clear risk factor for thrombocytopenia, with an estimated incidence of 35% to 59%.[85,86] In addition, there is an inverse relationship between the severity of sepsis and the platelet count.[87]

Mechanisms.—Patients with sepsis may develop de novo EDTA-dependent antibodies that cause platelet clumping in the test tube, with resultant pseudothrombocytopenia.[88] As a general rule, true thrombocytopenia arises from decreased production, increased destruction, and/or sequestration of platelets.[89] In sepsis, the primary cause of thrombocytopenia is nonimmune destruction of platelets (Figure 4). In animal models of sepsis, platelets have been shown to adhere to activated endothelium in organs and sites such as the lung, liver, and retina.[90-96] Once

activated, platelets may be destroyed and/or prevented from returning to the circulating pool. In addition, platelets aggregate in response to bacterial lipopolysaccharide and inflammatory mediators, an effect that is enhanced by platelet-leukocyte interactions.[97] In a prospective study of critically ill patients with thrombocytopenia (primed lymphocyte typing $<100 \times 10^9$/L), only 34% had a diagnosis of DIC.[81] Secondary consumptive thrombocytopenia and DIC represent an extreme in the continuum of hemostatic abnormalities in patients with sepsis.

Immune mechanisms may contribute to sepsis-induced thrombocytopenia. Nonspecific platelet-associated antibodies can be detected in up to 30% of ICU patients.[81] In these patients, nonpathogenic IgG presumably binds to bacterial products on the surface of platelets, to an altered platelet surface, or as immune complexes. A subset of patients with platelet-associated antibodies have autoantibodies directed against glycoprotein IIb/IIIa.[81] These antibodies have been implicated in the pathogenesis of immune thrombocytopenic purpura and, although not proved, may play a role in mediating sepsis-induced thrombocytopenia.

Hematophagocytosis in the bone marrow is a common finding in patients with sepsis and thrombocytopenia.[98,99] The degree to which this pathological process is a cause or simply a marker of sepsis-related thrombocytopenia is unclear. The bone marrow of patients with sepsis who have thrombocytopenia infrequently shows hypocellularity with reduced numbers of megakaryocytes.[83]

In addition to sepsis-related mechanisms, other causes of thrombocytopenia should be considered in the critically ill patient. For example, thrombocytopenia may occur as a complication of heparin therapy.[89,100] Other types of drug-induced thrombocytopenia are rare in the ICU setting. Dilutional thrombocytopenia may occur in patients with trauma or those who have undergone complicated surgery.[101] Acute folate deficiency has been described in patients admitted to the ICU.[102] Preexisting underlying disease, including cancer and immune thrombocytopenic purpura, may also contribute to a low platelet count.

Given the inverse correlation between platelet count and mortality and the proposed association of platelet activation with tissue injury and organ dysfunction, the development of thrombocytopenia in the patient with sepsis is best regarded as maladaptive.[75]

Clinical Manifestations and Diagnosis.—Thrombocytopenia is a common cause of bleeding in the ICU setting.[103] Patients with thrombocytopenia may have petechiae, purpura, bruising, or bleeding. Thrombocytopenia is diagnosed on the basis of the complete blood cell count. A peripheral smear may show evidence of platelet clumping. If that is the case, the platelet count should be remeasured in blood withdrawn into a non-EDTA containing tube. If the thrombocytopenia is associated with consumptive coagulopathy, the DIC screen may be abnormal, and the peripheral smear may show schistocytes. Although patients with sepsis may have increased platelet-associated IgG, testing for this gives nonspecific results and does not help to guide therapy.

Prognosis.—Thrombocytopenia is a predictor of mortality in patients in the ICU and in patients with severe sepsis.[86,103] The degree and duration of thrombocytopenia, as well as the net change in the platelet count, are important determinants of survival.[84,103,104] Interestingly, once the platelet count decreases lower than 100×10^9/L, mortality continues to increase, whereas the risk of bleeding does not increase.

Treatment.—Patients with severe thrombocytopenia should be treated with platelet transfusions. Although guidelines for prophylactic transfusions in patients with chemotherapy-induced thrombocytopenia have been established, the threshold for transfusions for the thrombocytopenic patient with sepsis is not as clear. In the absence of confounding factors, patients should probably receive transfusions when the platelet count is less than 10 to 15×10^9/L.[105] If the patient has concomitant coagulopathy (eg, liver disease), active bleeding, or platelet dysfunction (eg, uremia), the transfusion threshold should be increased.

Coagulation Alterations in Sepsis

Incidence.—Previous studies have shown that the coagulation system is activated in the vast majority of patients with severe sepsis. For example, D-dimers are elevated in virtually all patients with severe sepsis, whereas protein C levels are decreased in up to 90% of such patients.[85,106] Acquired antithrombin III (ATIII) deficiency is also common in the setting of sepsis, with levels lower than 60% in more than one half of patients.[107,108] Although the operational definition varies among studies, DIC is estimated to occur in 15% to 30% of patients with severe sepsis, including those with septic shock.[109-114]

Mechanisms.—Hemostasis represents a balance between anticoagulant and procoagulant forces.[115,116] In sepsis, the clotting cascade is initiated through the up-regulation of tissue factor on circulating monocytes,[117] tissue macrophages, and possibly subsets of endothelial cells (Figure 5). At the same time, sepsis attenuates many of the natural anticoagulant mechanisms. For example, circulating levels of protein C and ATIII are reduced, and the fibrinolytic pathway is suppressed.[118,119] Moreover, sepsis-mediated down-regulation of thrombomodulin on the endothelial cell surface may impair activation of protein C.[120] Together, these changes further tilt the balance toward the procoagulant side, resulting in thrombin generation, fibrin deposition, and clotting factor consumption. DIC represents the extreme in the pathophysiological continuum. In

addition to these systemic effects, sepsis also results in local activation of the endothelium through the release of several inflammatory mediators. Once activated, the endothelium expresses a procoagulant phenotype. The nature and degree of this response vary among different sites of the vascular tree.[116,121,122] Other factors that may contribute to sepsis-associated bleeding include vitamin K deficiency, liver dysfunction, and heparin treatment.[123]

Local activation of the coagulation system in patients with sepsis is an integral component of the innate immune response and may play a protective role in walling off the infection.[3] However, in patients with severe sepsis, systemic activation of coagulation is harmful and is associated with increased mortality.

Clinical Manifestations and Diagnosis.—Severe sepsis is usually associated with a net procoagulant state, as evidenced by local or diffuse microvascular thrombi. These changes are occasionally manifested by 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, kidney, lungs, and brain. Patients are at risk of bleeding when the consumption of clotting factors is greater than production.[124,125] Bleeding is more common when coagulopathy is exacerbated by concomitant thrombocytopenia, liver disease, heparin use, and invasive procedures. In large prospective studies, the prevalence of serious bleeding in patients with severe sepsis varies between 2% and 6%.[106,108] The most sensitive laboratory markers of sepsis-associated coagulopathy include reduced protein C levels and increased D-dimers. However, protein C levels are not routinely measured, and elevated D-dimers are nonspecific. In general, coagulation factor levels are inversely correlated with the severity of sepsis.[76] One exception is 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.[85,87,104]

Marked activation of coagulation and secondary consumption of clotting factors may ultimately lead to the clinical syndrome of DIC. No single test is sufficiently sensitive or specific for diagnosing DIC. Recently, a scoring system was proposed that uses simple laboratory tests, including platelet count, elevated fibrin-related marker (eg, soluble fibrin monomers, fibrin degradation products), prolonged prothrombin time (or international normalized ratio), and fibrinogen level.[126,127] Other markers of coagulation activation, such as thrombin-antithrombin complexes, fibrinopeptides, and prothrombin fragment F1+2, are considered investigational in this setting.

Prognosis.—Certain markers of coagulation activation have been correlated with negative outcome in patients with sepsis.[128] For example, low ATIII levels in patients with sepsis are predictive of poor survival.[104] Decreased protein C levels in patients with severe sepsis have been shown to correlate with mortality, presence of shock, length of ICU stay, and ventilator dependence.[85] In clinical studies of multiple organ dysfunction, maximum prothrombin time and partial thromboplastin time were shown to be longer in nonsurvivors than in survivors.[129] DIC has been shown to be an independent predictor of mortality in patients with sepsis.[130]

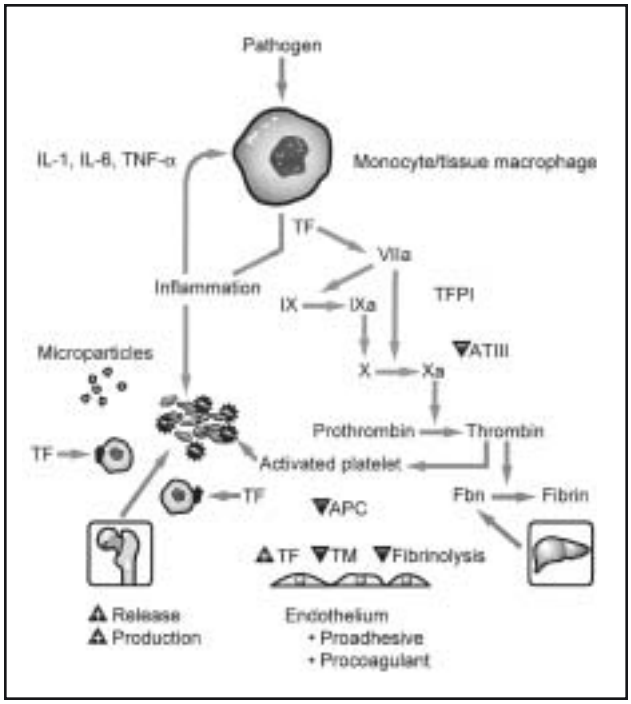

Figure 5. Sepsis results in the induction of tissue factor (TF) on the surface of monocytes and possibly some subsets of endothelial cells. Tissue factor initiates the clotting cascade, ultimately resulting in thrombin generation and fibrin formation. The clotting cascade is normally inhibited by several natural anticoagulant mechanisms, including tissue factor pathway inhibitor (TFPI), antithrombin III (ATIII), thrombomodulin/protein C/protein S, and fibrinolysis. In sepsis, circulating levels of activated protein C (APC) and ATIII are decreased. In addition, there is an attenuation of thrombomodulin (TM) expression on the endothelial cell surface. Finally, the fibrinolytic pathway is inhibited. In sepsis, the activated endothelium may express a procoagulant phenotype, with increased expression of TF, plasminogen activator inhibitor, and von Willebrand factor and decreased expression of TM. The activation of endothelial cell and platelet membranes, as well as the formation of microparticles, results in the acceleration of clotting reactions. Finally, the clotting factors, once they become activated, may interact with protease-activated receptors present on the surface of endothelial cells, monocytes, and/or platelets, resulting in amplification of the proinflammatory response. Fbn = fibrinogen; IL = interleukin; TNF-α = tumor necrosis factor α.

Treatment.—The consumption of clotting factors with or without secondary DIC is rarely associated with a bleeding diathesis. Rather, the underlying coagulopathy reflects a procoagulant state and is associated with increased fibrin deposition in the microvasculature. Thus, transfusion therapy with platelets, fresh frozen plasma, or plasma components is indicated only in patients with active bleeding or in those with a high risk for this complication (eg, other types of coagulopathy, invasive procedures).[126,127]

Based on an understanding of the underlying pathophysiology, there has been a shift in emphasis from procoagulant replacement to anticoagulant therapy. Initial studies with thrombin inhibitors were disappointing. Although these drugs clearly inhibit thrombin generation and fibrin formation, they do not appear to affect organ dysfunction and survival.[131] In contrast, preclinical and early phase clinical studies using protein C, ATIII, and tissue factor pathway inhibitor (TFPI) not only resulted in decreased thrombin generation but also in improved survival.[109,132-135] One possible explanation for these findings is that the natural anticoagulants have a dual function: inhibition of coagulation and suppression of inflammation. Activated protein C, ATIII, and TFPI have each been shown to modulate the inflammatory response under in vitro and in vivo conditions.[136-138]

Unfortunately, recent phase 3 studies of infusions with ATIII or TFPI failed to improve 28-day all-cause mortality in patients with severe sepsis.[108] In contrast, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, a large phase 3 study, confirmed the anticoagulant and anti-inflammatory properties of recombinant human activated protein C (drotrecogin alfa [activated]).[106] Most importantly, these effects translated into a survival advantage for patients with high-risk severe sepsis.

CONCLUSION

Patients with sepsis who develop organ failure have an increased mortality rate. Prompt diagnosis of organ dysfunction is critical in identifying patients who may benefit from therapeutic intervention. In assessing patients for organ dysfunction, the hematologic system should not be overlooked. A thorough clinical evaluation and panel of laboratory tests that relate to this organ system should be as much a part of the work-up as taking the blood pressure, monitoring renal function, or measuring liver enzymes.

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