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Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients

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Anemia, thrombocytopenia, and coagulopathy are commonly encountered when caring for critically ill patients [1–3]. Pursuing structured evaluations of these hematologic problems is essential to their successful management. Certain clinical circumstances warrant blood product administration, but clinicians must balance potential benefits of transfusions against the risks. For example, red blood cell (RBC) transfusion increases red cell mass; this may be indicated to expand intravascular volume in bleeding or to enhance oxygen delivery in unstable angina or myocardial infarction, but it may offer uncertain benefits, or even harm, in other clinical scenarios [4,5]. Platelet transfusion can diminish bleeding in patients who have thrombocytopenia or impaired platelet function, but it is contraindicated in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) or type II heparin-induced thrombocytopenia (HIT). In these settings, platelet transfusion can fuel thrombosis and worsen clinical signs and symptoms [6,7]. Fresh frozen plasma (FFP) infusion in coagulopathy provides portions of all clotting factors that are required for adequate hemostasis [8]. Prothrombin complex concentrates (PCC) [9] or recombinant activated factor VII (rFVIIa) [10], that are administered in small volumes, may prove better than FFP when coagulopathies require quick intervention (as in life-threatening bleeding) without risk of volume overload (as in heart failure).

Evaluating anemia

Given the 120-day life span of a normal RBC, acquired anemias that are due to RBC underproduction generally develop and progress slowly over weeks to months. In contrast, anemias that are due to bleeding or hemolysis generally occur rapidly over days to weeks; the tempo of anemia development depends on the pace of bleeding or hemolysis in relation to RBC production. Knowing patients' histories of anemia throughout their lives is useful when considering congenital versus acquired causes of anemia, as well as acquired contributors to worsened RBC parameters in individuals who have congenital anemia (eg, thalassemia).

Anemia that develops quickly over days strongly supports bleeding or hemolysis as the cause of RBC mass decline. Kinetic changes in RBC mass, even due to these mechanisms, are often more subtle. Hence, clinical histories may not clearly distinguish bleeding or hemolysis from underproduction causes of anemia. Further, although physical examinations can offer important clues to the etiology of the patient's anemia (eg, bloody stool), they are often nonspecific (eg, pallor). Clinicians should supplement clinical histories and physical examination findings with consideration of anemia etiologies that are categorized by RBC size (mean cell volume [MCV]) and morphology. These categories include the microcytic (MCVs <80 fL),

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normocytic (MCVs 80 to 100 fL), and macrocytic (MCVs >100 fL) anemias (Table 1).

In all cases, clinicians should evaluate RBC measurements alongside white blood cell (WBC) counts, platelet counts, and WBC differentials. Although abnormalities in these other bloodlines may suggest a disorder of trilineage hematopoiesis, multiple competing factors may coexist; certain factors affect RBCs independent of those that affect WBCs or platelets. Reticulocyte counts suggest whether a patient's bone marrow is responding adequately to anemia. Appropriately increased reticulocyte counts almost always reflect RBC loss (eg, bleeding or hemolysis) or response to therapy (eg, iron, folate, or cobalamin replacement in patients who have these deficiencies). Variations in RBC size are reported as the red cell distribution width (RDW); increased RDWs may signify aberrant red cell morphologies. Nevertheless, the

Table 1
Anemia etiologies categorized by RBC size (MCV) and morphology

Etiologies	RBC morphologies
MCV < 80 fL (microcytic)	
Reduced iron availability	Hypochromia
Severe iron deficiency	Elliptocytes
Anemia of inflammation (chronic disease)	
Copper deficiency (copper plays a role in iron absorption)	
Reduced or abnormal globin chain production	Tear drops
Thalassemias (α and β)	Target cells (small)
Other hemoglobinopathies (Hgb E)	Basophilic stippling (generally fine)
Reduced heme synthesis	Basophilic stippling (often coarse)
Congenital sideroblastic anemia	
Acquired sideroblastic anemia	
Toxins and drugs (alcohol, lead, chloramphenicol, isoniazid)	
Idiopathic (myelodysplastic syndromes)	
MCV > 100 fL (macrocytic)	
Stress erythropoiesis, with increased reticulocytes	Large, polychromatophilic cells
Liver disease (MCVs generally no higher than 105 to 110 fL)	Target cells (large) Echinocytes (spur and burr cells with multiple undulating smooth or spiny RBC membrane projections)
Hyposplenism; asplenia (MCVs generally no higher than 105 to 110 fL)	Acanthocytes (RBCs with only several rather than multiple spiny RBC membrane projections) Howell-Jolly bodies Variable numbers of NRBCs
Megaloblastic maturation of RBCs (due to factors that affect nuclear to cytoplasmic maturation; MCVs greater than 115 fL are almost always due to megaloblastic causes)	Macro-ovalocytes Hypersegmented polys
Folate or cobalamin deficiencies	
Drugs that affect folate metabolism or DNA synthesis	
Acquired idiopathic causes (as in myelodysplastic syndromes)	
MCVs = 80 to 100 fL (normocytic)	
Evolving microcytic or macrocytic pathologies (assess MCVs that are either decreasing or increasing over time)	See findings associated with various microcytic and macrocytic pathologies (as noted above)
Underproduction erythropoietin (as in renal failure)	Normal
Inflammation (as in anemia of chronic disease)	Hypochromia Elliptocytes
Other deficient growth factors	Normal
Thyroid hormone	Target cells (in hypothyroidism)
Testosterone	
Infiltrative myelopathies (with leukoerythroblastosis from pathologies that disrupt normal bone marrow architecture)	Tear drops NRBCs Immature WBCs

Abbreviations: Hgb, hemoglobin; NRBC, nucleated RBC; WBC, white blood cell.

RDW is a poor surrogate for reviewing the peripheral blood smear, because it lacks specific information about aberrant RBC morphologies (eg, spherocytes, schistocytes, bite cells, spur cells). Ideally, clinicians should examine the peripheral blood smear for morphologic features of RBCs, WBCs, and platelets that may provide important clues to the cause of the patient's hematologic disorder.

Various blood chemistries help to refine or confirm diagnostic possibilities suggested by the complete blood count, reticulocyte count, and peripheral blood smear. Ferritin, folate, and cobalamin levels indicate the adequacy of body stores of iron and vitamins that are required for hematopoiesis. Serum iron levels and total iron binding capacity (TIBC) supplement interpretation of ferritin levels that might be confounded by inflammatory cytokines in acute and chronic disease [11,12]. In inflammatory states, cytokines increase serum ferritin levels by as much as threefold. Hence, if serum ferritin levels divided by 3 are 20 or less, clinicians should suspect concomitant iron deficiency in patients who have inflammatory states [13]. Interpretations of serum iron must also consider that levels increase within 1 hour of ingesting dietary and supplemental sources of iron (assuming absence of malabsorption). Pregnancy and supplemental estrogen increase TIBC levels and yield iron: TIBC ratios that are in the range of iron deficiency (ie, $< 10\%$ to 15%) in up to 20% of cases, thus decreasing the predictive value of iron: TIBC ratios in these clinical settings [14].

Inflammation can contribute to anemia. An increased erythrocyte sedimentation rate and increased levels of acute phase reactants (eg, fibrinogen, haptoglobin, and C-reactive protein) suggest inflammatory states. Inflammatory cytokines have protean effects which cause underproduction of erythropoietin (EPO), despite adequate renal function, decreased responsiveness of erythroid progenitor cells to EPO, and blocked iron transport from macrophage storage pools to maturing erythroid cells [11].

Increased creatinine levels signify possible underproduction of EPO, which is manufactured primarily by the kidneys. Creatinine levels vary by sex, age, race, and ethnicity, however, and they do not account for true glomerular filtration rate or lean body mass. Therefore, using single cut-off points (eg, 1.2 mg/dL in women and 1.5 mg/dL in men) to define elevated serum creatinine values may be misleading [15]. Other growth factor deficiency states, including hypotestosteronemia in men and hypothyroidism may cause anemia and require evaluation.

Elevated lactate dehydrogenase (LDH) and total bilirubin (indirect greater than direct bilirubin) levels with decreased haptoglobin levels suggests hemolysis; haptoglobin levels that are lower than 25 mg/dL support hemolytic anemia with sensitivity and specificity of 83% and 96%, respectively [16]. In inflammatory states, higher haptoglobin levels can occur despite hemolysis; cytokines increase haptoglobin as an acute phase reactant. Although LDH and total bilirubin levels are generally elevated in hemolysis, particularly in relation to prehemolysis levels, they may be in the high normal range. Detection of urinary hemosiderin supports intravascular hemolysis.

If laboratory assessments suggest hemolysis, then clinicians should consider the cause by type (spherocytic versus nonspherocytic), site (intramedullary versus extramedullary; intravascular versus extravascular), and mechanism (immune-mediated versus nonimmune-mediated; intrinsic versus extrinsic to the RBC). Coombs testing, both direct and indirect, can identify antibodies that target RBC antigens, particularly soon after RBC transfusions. Examining the peripheral blood smear can identify RBC morphologies that implicate certain hemolysis mechanisms. For example, finding spherocytes (Fig. 1A) implies loss of membrane, either by inherited (eg, hereditary spherocytosis) or acquired (eg, antibody-mediated) mechanisms. Schistocytes (Fig. 1B) suggest fragmentation hemolysis, as in micro- or macroangiopathic hemolytic anemias. In addition to microangiopathic hemolysis from disseminated intravascular coagulation (DIC), parasites (eg, malaria, babesia) and bacteria (eg, clostridium) cause hemolysis by way of intracellular and extracellular mechanisms, respectively (bacterial phospholipases digest RBC membranes).

Bite cells (Fig. 1C) imply oxidant stress hemolysis and they arise when macrophages latch onto, and ingest, bits of oxidized RBC membrane. Heinz body preparation can detect oxidized RBC proteins. RBC oxidant stress produces methemoglobin (containing ferric ions), which has altered spectrophotometric properties from hemoglobin (containing ferrous ions). As a consequence, arterial blood gas testing yields discordant pO_2 and O_2 oxygen saturation values. Although inherited deficiencies of glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase increase RBC susceptibility to oxidant stress, potent oxidants can produce oxidant hemolysis without defects in hexose monophosphate shunt enzymes (eg, dapsone, lidocaine). Treatment includes stopping all offending agents and considering the administration of either methylene blue (in individuals who do not have G6PD deficiency) or ascorbic acid.

Schistocytes (see Fig. 1B) occur in micro- or macroangiopathic hemolytic anemia and represent fragmented RBCs that are produced, for example, as RBCs traverse intravascular fibrin strands that are deposited

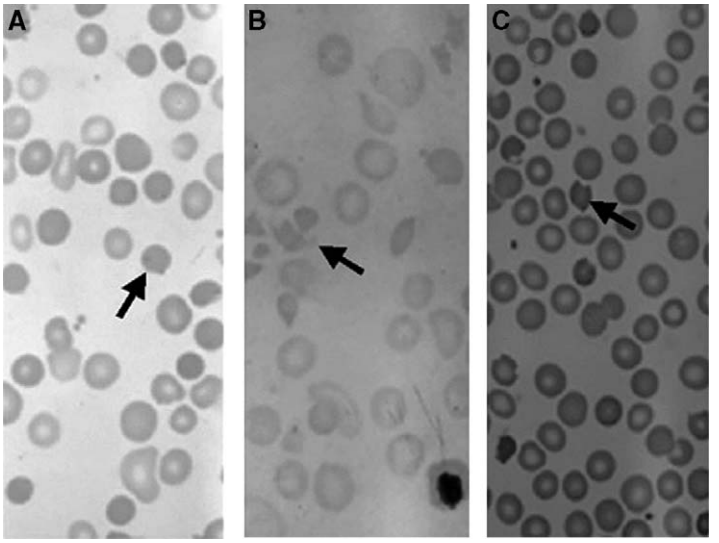

Fig. 1. Examples of peripheral blood smear RBC morphologies (*arrows*) that implicate certain hemolysis mechanisms. (*A*) spherocytes in warm autoimmune hemolytic anemia; (*B*) schistocytes in microangiopathic hemolytic anemia from thrombotic thrombocytopenic purpura; and (*C*) bite cells in oxidant stress hemolysis from intravenous lidocaine.

in disorders, such as DIC and TTP-HUS. Finding thrombocytopenia with elevated prothrombin time (PT), elevated activated partial thromboplastin time (aPTT), elevated thrombin time (TT), and decreased fibrinogen levels supports DIC rather than TTP-HUS, because the latter is not associated with consumptive coagulopathy [17]. Low-grade fevers and neurologic symptoms and signs (including headaches) are also features of TTP-HUS that can develop in various clinical settings. In TTP-HUS, plasmapheresis with plasma infusions saves lives [17]. Additional causes of microangiopathic hemolytic anemia include malignant hypertension, disseminated carcinoma, giant hemangioma, and immunologic vasculitis. Valvular heart disease can cause macroangiopathic hemolytic anemia, with schistocytes resulting from turbulent blood flow across a diseased native or prosthetic valve.

Assessing thrombocytopenia

In contrast to RBCs, platelets have a short life span of 10 days. Therefore, signs of thrombocytopenia occur quickly, including mucosal or cutaneous bleeding with epistaxis, gingival bleeding, large bullous buccal mucosal hemorrhages, petechiae, or superficial ecchymoses. These manifestations arise from one or more of three general mechanisms: decreased platelet production, increased platelet destruction, or dilutional or distributional causes. Examining the peripheral blood smear allows clinicians to dismiss spurious thrombocytopenia that arises from platelet clumping in vitro that is due to insufficient anticoagulation of the collected blood sample (excess ethylenediaminetetraacetic acid, [EDTA]) or EDTA-dependent agglutinins.

Causes of decreased platelet production include thrombopoietin underproduction in liver disease; suppression or damage of the bone marrow by viral infections (eg, rubella, mumps, varicella, parvovirus, Epstein Barr virus, human immunodeficiency virus, live-attenuated measles vaccine), drugs, or toxins (eg, alcohol, chemotherapy, radiation therapy); nutritional deficiencies (folate, cobalamin); and congenital or acquired disorders of hematopoiesis (bone marrow aplasia or hypoplasia, myelodysplastic or myeloproliferative syndromes).

Immune or nonimmune processes can increase platelet destruction (Table 2). In critically ill patients, sepsis syndrome is a leading cause of thrombocytopenia [18]; likely mechanisms include immune-mediated platelet destruction and hemophagocytic histiocytosis, as well as DIC. Because drug-induced thrombocytopenias represent a minority of cases in patients in the intensive care unit (ICU) [18], clinicians should regard evolving thrombocytopenia in critically ill patients as an early warning sign of sepsis.

Table 2
Increased platelet destruction because of immune or non-immune causes

Disorder	Mechanism of platelet destruction
Idiopathic ITP	Immune
Alloimmune destruction (posttransfusion, neonatal, posttransplantation)	Immune
Drug-induced thrombocytopenia	Immune and nonimmune
Infection-associated thrombocytopenia	Immune and nonimmune
HELLP syndrome	Immune and nonimmune
Disseminated intravascular coagulation	Nonimmune
TTP-HUS	Nonimmune
Antiphospholipid antibody syndrome	Nonimmune
Physical destruction (cardiopulmonary bypass, giant cavernous hemangiomas)	Nonimmune

Abbreviations: HELLP, hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets in pregnancy; ITP, immune thrombocytopenic purpura.

Transfusion for massive blood loss can cause dilutional thrombocytopenia. In one study, 75% of patients who were transfused with 20 or more red cell units in 24 hours developed platelet counts that were less than 50,000/μL, whereas no patient who received fewer than 20 RBC units developed platelet counts that were lower than this level [19]. Dilutional thrombocytopenia is distinguishable from posttransfusion purpura (PTP), which is an uncommon immune-mediated transfusion reaction that occurs primarily in women who have been sensitized to a foreign platelet antigen by pregnancy. Patients who are sensitized by previous platelet or platelet-containing RBC transfusions are also at risk. Human platelet antigen 1a, formerly named PlA1, is the most common antigen that is implicated in PTP. In PTP, severe thrombocytopenia arises 5 to 10 days after transfusion of platelets or platelet-containing RBCs and lasts days to weeks [20].

"Distributional" thrombocytopenia is commonly attributed to increased splenic sequestration in patients who have splenomegaly. Patients who have hepatic cirrhosis and splenomegaly from portal venous hypertension can develop thrombocytopenia, less from splenic sequestration than from reduced levels of thrombopoietin, which is produced by the liver [21].

Besides a careful history, physical examination, and review of all medications, initial evaluation of the patient who has thrombocytopenia should include peripheral blood smear examination. Schistocytes (see Fig. 1B) support micro- or macroangiopathy. Tear drops, nucleated RBCs, and immature granulocyte precursors, which are findings of leukoerythroblastosis (Fig. 2), suggest replacement of hematopoietic tissue in the bone marrow by abnormal tissue (myelophthisis) from fibrosis, granulomatous inflammation, infection, cancer metastatic to the marrow, or primary hematopoietic disorders, such as leukemia. Findings of dyspoiesis include coarse basophilic stippling of red cells, pelgeroid cells, Döhle bodies, hypogranulation of neutrophils, and giant platelets (Fig. 3); this suggests myelodysplasia.

Diagnosing drug-induced thrombocytopenias can prove challenging, because many medicines contribute to thrombocytopenia, and patients, particularly when critically ill, often receive multiple medications. Heparin (in particular, unfractionated heparin), quinine, quinidine, trimethoprim-sulfamethoxazole, gold, and valproic acid are commonly implicated drugs [22]. H_2 antagonists, which are routinely used to prevent stress ulcers in critically ill patients, rarely cause thrombocytopenia in this patient population [23]. Isolated megakaryocytic hypoplasia or aplasia is rare, but does occur in patients who use thiazide diuretics, alcohol, or estrogens. Unless clinicians suspect specific drug-associated or allo-specific antiplatelet antibodies, antiplatelet antibody testing is not recommended because it lacks sufficient sensitivity and specificity (eg, in idiopathic thrombocytopenic purpura) [24].

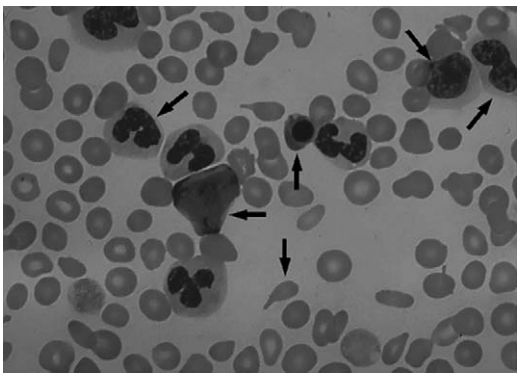

Fig. 2. Tear drops (↓), a nucleated red blood cell (↑), and immature granulocyte precursors, including band (*P*), metamyelocyte (↗), myelocyte (↘), and blast (←), are findings of leukoerythroblastosis from myelophthisis, as in this case of agnogenic myeloid metaplasia with idiopathic myelofibrosis.

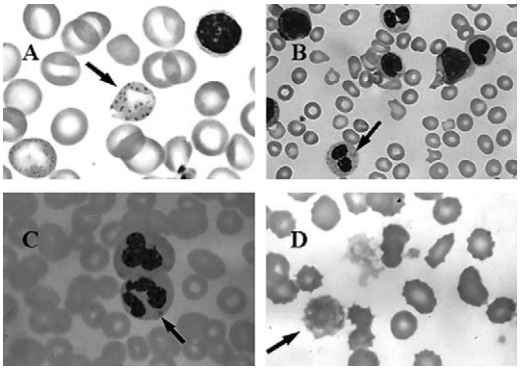

Fig. 3. Findings (*arrows*) that taken together suggest myelodysplasia. (*A*) Coarse basophilic stippling of RBCs; (*B*) pelgeroid cells, which in this case are also hypogranular; (*C*) a Döhle body; and (*D*) a giant platelet that rivals the size of adjacent red cells. Pelgeroid cells, Döhle bodies, and hypogranulated neutrophils can also be seen with sepsis.

There are two types of HIT. In the more common type I form, which occurs in 10% to 20% of patients who receive unfractionated heparin, nonimmune mechanisms result in platelet counts that decease 1 to 4 days after onset of heparin administration from normal levels to a nadir that is not less than 100,000/μL. Type I HIT is not associated with hemorrhagic or thrombotic sequelae, and management involves observation with normalization of platelet counts in most patients, despite heparin continuation [25].

In contrast, in type II HIT, 30% to 80% of patients experience thrombotic sequelae. Venous thromboses outnumber arterial thromboses by 4:1 and life-threatening pulmonary embolism occurs in 25% of patients who have thrombosis [25]. Type II HIT occurs in 1% to 3% of patients who receive unfractionated heparin; induced by an antibody-mediated mechanism, thrombocytopenia generally arises 5 to 10 days after onset of heparin administration [25]. If clinicians suspect type II HIT, they must promptly discontinue all heparin sources, including low molecular weight heparins (LMWHs), without awaiting laboratory confirmation, to avoid thrombotic sequelae. Although median nadir platelet counts are 50,000 to 60,000/μL in patients who have type II HIT, platelet counts decline within the normal range in 10% to 15% of patients and never decrease to less than 150,000/μL, despite the development of thrombosis [25]. Given this worrisome observation, clinicians must suspect type II HIT in any patient who has begun heparin therapy and whose platelet count declines 50% or more below pretreatment values. Decreases in platelet counts earlier than the fifth day of heparin administration are unlikely to represent type II HIT; however, more rapid-onset type II HIT can arise in patients who receive heparin within 3 to 4 months of previous heparin administration. In addition, thrombosis can arise even after discontinuing heparin promptly. A retrospective series of 62 patients who had discontinued heparin because of isolated thrombocytopenia that was attributed to heparin found a 53% 30-day risk of thrombosis [25].

Type II HIT begins with heparin-induced platelet activation and release of platelet factor 4 (PF4) from platelet α granules, and it is associated with formation of heparin-PF4 complexes and induction of IgG anti-heparin-PF4 antibodies. Tests for heparin-platelet–associated antibodies include the serotonin release assay, the heparin-induced platelet aggregation assay, and the ELISA. Although the serotonin release assay is the ‘‘gold standard,’’ the heparin-induced platelet aggregation assay and ELISA are used more commonly because they are easier to deploy and are more widely available than the serotonin release assay, which is generally performed at regional reference laboratories. The heparin-induced platelet aggregation assay, although specific (>90%), lacks sensitivity; the solid-phase immunoassay, although sensitive, lacks specificity. As with any test, positive and negative predictive values depend on the clinical context [26]. If the heparin-induced platelet aggregation or ELISA are negative and type II HIT remains a concern based on clinical judgment, then patients who require intravenous anticoagulation should receive anticoagulant alternatives (eg, lepirudin, argatroban) pending results of a serotonin release assay.

LMWH is less likely to cause type II HIT when used as a first-line anticoagulant, but its cross-reactivity with unfractionated heparin-induced antibodies is nearly 100%. Thus, using LMWH after development of type II HIT can perpetuate the condition and LMWH is not recommended after type II HIT is suspected [25]. Options for anticoagulation after heparin discontinuation include lepirudin and argatroban, direct thrombin inhibitors that are renally or hepatically cleared, respectively. Hence, the choice of one agent over the other may depend on the patient’s renal and hepatic function. The aPTT assesses therapeutic endpoints for both agents. Danaparoid, a heparanoid that cross-reacts weakly with heparin-induced antibodies in 10% to 40% of HIT sera and is monitored by measuring antifactor Xa levels, is no longer available commercially. Because warfarin anticoagulation induces acquired protein C deficiency, its use can exacerbate the prothrombotic state of type II HIT. Therefore, clinicians should withhold warfarin administration until the platelet count increases to more than 100,000/μL and type II HIT is clearly resolving [25].

Assessing coagulopathies

The presence of a consumptive coagulopathy in the setting of thrombocytopenia supports a diagnosis of DIC, not TTP-HUS, and is demonstrated by decreasing serum fibrinogen levels and increasing TTs, PTs, aPTTs, and fibrin degradation products. Increasing D-dimer levels are the most specific DIC parameter and reflect fibrinolysis of cross-linked fibrin, whereas increasing PTs and decreasing levels of fibrinogen and platelet counts are most sensitive in detecting early DIC development. Measuring levels of factor V (a vitamin K–independent clotting factor that is produced by liver) and factor VIII (a clotting factor not produced by liver) can help distinguish DIC (which consumes both clotting factors) from bleeding that is associated with liver disease, but this is generally unnecessary.

Bleeding in coagulation disorders typically manifests as large, palpable ecchymoses and large, spreading, deep soft tissue hematomas. Hemorrhage into synovial joints (hemarthrosis) most often indicates a severe inherited coagulation disorder, such as hemophilia. In patients who have a coagulation disorder, the onset of bleeding after trauma often is delayed; patients who have coagulation disorders can have extensive postsurgical bleeding. For example, bleeding after a tooth extraction may stop only to recur within hours. The preservation of normal platelet function causes this phenomenon, with absence of petechiae or bleeding from small cuts or scratches as is seen in patients who have platelet disorders.

The production of fibrin by way of the extrinsic pathway and the final common pathway (common to extrinsic and intrinsic cascades) requires tissue thromboplastin (tissue factor), factor VII (extrinsic pathway), and factors X, V, prothrombin, and fibrinogen. The plasma PT measures the functioning of these pathways by bypassing the intrinsic pathway and using thromboplastins to substitute for platelets. Prothrombin and factors VII and X are vitamin-K dependent, and thus are altered by warfarin. For this reason, the PT provides a measure of warfarin anticoagulant activity.

The aPTT measures the intrinsic and common pathways of coagulation. The test is called "partial" because the assay uses platelet substitutes that are only partial thromboplastins and are incapable of activating the extrinsic pathway, which requires complete tissue thromboplastin (tissue factor). In the original method, a glass test tube provided contact activation. Adding activators, such as ellagic acid or particulate silicates, provides better and more standardized activation. This activated version of the PTT (aPTT) is now routinely used to evaluate intrinsic coagulation and the degree of anticoagulation, for example, by heparin, lepirudin, and argatroban. The aPTT is sensitive to deficiencies of factors XII, XI, IX, and VIII and to inhibitors, such as heparin. It is less sensitive than the PT to deficiencies of the common pathway (factors X and V, prothrombin, and fibrinogen) and is unaffected by factor VII.

The absence of factors or the presence of inhibitors can cause elevated PTs or aPTTs (Table 3). Normal plasma should correct a factor deficiency. This is typically done by performing a PT or aPTT on a 1:1 mix of patient and normal plasma, also known as an inhibitor screen. Laboratories then determine specific factor deficiencies by assessing the PT or aPTT in mixes of test and commercially available plasmas that are deficient in known factors. Analysts functionally assess factor levels by comparing test results to stan-

Table 3
Cause of a prolonged prothrombin time (PT) or a prolonged activated partial thromboplastin time (aPTT)

Test results		
PT	aPTT	Causes of test result pattern
Prolonged	Normal	Inherited
		Factor VII deficiency
		Acquired
		Vitamin K deficiency
		Liver disease
		Coumadin administration
		Inhibitor of factor VII
Normal	Prolonged	Inherited
		Deficiency of vWF or factors VIII, IX, XI, or XII
		Acquired
		Heparin administration
		Inhibitor of vWF or factors VIII, IX, XI, or XII (PT may be slightly prolonged)
		Antiphospholipid antibody[a]
Prolonged	Prolonged	Inherited
		Deficiency of prothrombin, fibrinogen, or factors V or X
		Combined factor deficiencies
		Acquired
		Liver disease
		Disseminated intravascular anticoagulation
		Supratherapeutic coumadin administration
		Supratherapeutic heparin administration
		Combined coumadin and heparin administration
		Inhibitor of prothrombin, fibrinogen, or factors V or X

[a] Associated with thrombosis, rather than bleeding.

dard curves that are generated by mixtures of serially diluted normal plasma and factor-deficient plasma. Immunologic assays can also measure factor levels. Immunologic and functional assays should give equivalent results when a factor deficiency exists. A low functional assay but normal immunologic assay indicates a functionally abnormal factor.

Factor inhibitors are suspected when the prolonged PT or aPTT does not correct, or only partially corrects, following an immediate assay of a 1:1 mix of patient and normal plasma. In some cases, such as acquired factor VIII antibodies, the aPTT may correct immediately after mixing but becomes prolonged after 60 to 120 minutes of incubation. Hence, inhibitor screens routinely perform aPTT assays after incubation to these time points.

In addition to factor inhibitors, antiphospholipid antibodies (eg, lupus anticoagulant) can produce a prolonged aPTT that is not correctable with normal plasma. Adding excess phospholipid or platelets that have been frozen and then thawed can overcome the effect of these antibodies on the aPTT. These patients also have antibodies that are directed against β2-glycoprotein I and often cardiolipin. Paradoxically, lupus anticoagulants and the antiphospholipid antibody syndrome are associated with a tendency to thrombosis not bleeding; the prolonged aPTT is an artifact of the test [27,28].

The TT and reptilase time (RT) measure conversion of fibrinogen to fibrin monomers and the formation of initial clot by thrombin and reptilase, respectively. Reptilase, a thrombin-like snake enzyme, differs from thrombin by generating fibrinopeptide A but not fibrinopeptide B from fibrinogen and by resisting inhibition by heparin by way of antithrombin III. Hypofibrinogenemia, structurally abnormal fibrinogens (dysfibrinogens), or increased fibrin-fibrinogen degradation products (FDPs) can cause prolonged TTs and RTs. TTs are generally obtained to assess fibrinogen function, particularly in bleeding patients who have normal fibrinogen levels, but may have acquired dysfunctional fibrinogen that are due to such causes as impaired hepatic function. Because heparin prolongs the TT but not the RT, the RT helps in determining if heparin is causing a prolonged TT. As with hemostatic disorders that are due to hypofibrinogenemia, bleeding that is caused by dysfibrinogenemia is an indication for cryoprecipitate transfusion.

FDPs are protein fragments that result from the action of plasmin on fibrin or fibrinogen. States of fibrinolysis, such as DIC, produce elevated FDP levels. Because assays do not differentiate between degradation products of fibrin and fibrinogen, measurement of the concentration of fibrin D-dimers provides more specific information reflecting fibrinolysis of cross-linked fibrin [29]. When fibrinolysis exceeds thrombin generation, thereby increasing the risk of hemorrhage rather than thrombosis (as in DIC associated with acute promyelocytic leukemia), quantitative FDP levels may be more sensitive than D-dimer levels as an indication of the degree of fibrinolytic activity. Because D-dimers specifically reflect fibrinolysis of cross-linked fibrin (ie, clot), assessment of D-dimer levels suggests thrombosis more reliably. In patients who have a low pretest probability of pulmonary embolism, the negative predictive value of D-dimers is high [30].

Red blood cell transfusions

In critically ill patients, decreased cardiac output, decreased red cell mass, and lactic acidosis can impair oxygen delivery and tissue use of oxygen. Administering RBCs can enhance oxygen delivery to tissues. Historically, clinicians generally aimed to maintain henatocrit (HCT) and hemoglobin (HGB) levels that were higher than 30% and 10 g/dL, respectively, by RBC transfusion. The risks of transmitting blood-borne pathogens and efforts to reduce costs raised questions about this practice. In 1988, members of a National Institutes of Health consensus panel concluded that no single criterion could serve as an indication for red cell component therapy and that clinicians should consider multiple factors related to the patient's clinical status and oxygen delivery needs [31]. These and subsequent guidelines [32–34] recommend that, among patients who have no known risk factors, the threshold for transfusion should be HGB levels from 6.0 to 8.0 g/dL; patients who have HGB levels that are higher than 10.0 g/dL are unlikely to benefit from blood transfusion. As a consequence, bleeding and improving oxygen delivery became the most frequent reasons for administering RBCs, rather than low HGB levels [35].

In a multicenter, prospective, randomized study, Hébert and colleagues [36] tested the effects of restricted versus liberal RBC transfusion policies on 30-day all cause mortality and severity of organ dysfunction in critically ill patients. At 22 tertiary-level and three community ICUs in Canada between November 1994 and November 1997, Hébert and colleagues enrolled 838 critically ill patients who had euvolemia after initial treatment and HGB levels that were less than 9.0 g/dL within 72 hours after admission to the ICU. They randomly assigned 418 patients to a restrictive transfusion strategy (RBCs were transfused if the HGB level decreased to less than 7.0 g/dL and HGB concentrations were maintained

at 7.0 to 9.0 g/dL) and 420 patients to a liberal strategy (transfusions were given when the HGB level decreased to less than 10.0 g/dL and HGB concentrations were maintained at 10.0 to 12.0 g/dL). Baseline characteristics of the study patients were balanced with respect to sex, age, Acute Physiology and Chronic Health Evaluation (APACHE)-II score, multiple-organ dysfunction score, number of organs failing, primary diagnosis (respiratory, cardiovascular and gastrointestinal diseases, trauma, sepsis, and neurologic abnormality), serious coexisting illness, infection, location before admission to the ICU, interventions in the ICU (mechanical ventilation, pulmonary-artery catheter, and dialysis), and oxygen-delivery variables (HGB, RBC transfusion, total fluid intake, vasoactive drugs, and lactate levels). Subgroup analyses of patients who were at potential risk for the adverse effects of anemia included those who were 55 years of age or older, patients who had cardiac disease, and patients who had APACHE II scores that indicated more severe illness [36].

Overall, 30-day mortality was similar in the groups that received restrictive and liberal transfusions (18.7% and 23.3%, respectively; P = 0.11). Subgroup analyses demonstrated significantly lower death rates with the restrictive transfusion strategy among patients who were less acutely ill (as assessed by an APACHE II score of 20 or less; 8.7% in the group who had restrictive strategy, 16.1% in the group who had liberal strategy; P = 0.03) and among patients who were younger than 55 years of age (5.7% and 13.0%, respectively; P = 0.02) [36]. In contrast, patients who had clinically significant cardiac disease had 30-day mortality rates that were not significantly different (20.5% and 22.9%, respectively for restrictive versus liberal strategies; P = 0.69). This finding contrasted with results from two large cohort studies that reported a disproportionate increase in mortality rates among patients who had ischemic heart disease that was associated with increasing severity of anemia [37,38]. Hébert and colleagues [39] suggested that referral bias affected their study; attending physicians refused to enroll patients who had severe cardiac disease [36]. A follow-up analysis found that the more restrictive strategy of RBC transfusion seemed safe in most patients who had cardiovascular disease. Nevertheless, a subgroup of 257 patients who had ischemic heart disease demonstrated a nonsignificant (P = 0.30) decrease in overall survival among the patients who were treated according to the restrictive transfusion strategy.

To examine the effects of RBC transfusion in elderly patients who had ischemic heart disease, Wu and colleagues [40] retrospectively examined data on 78,974 Medicare beneficiaries who were 65 years of age or older who were hospitalized with confirmed acute myocardial infarction (AMI) [40]. They categorized patients according to admission HCT (5.0% to 24.0%, 24.1% to 27.0%, 27.1% to 30.0%, 30.1% to 33.0%, 33.1% to 36.0%, 36.1% to 39.0%, or 39.1% to 48.0%) and evaluated whether an association occurred between the use of RBC transfusion and 30-day mortality. They drew their study population from the 234,769 patients in the Cooperative Cardiovascular Project (CCP), a sample of fee-for-service Medicare beneficiaries who were discharged from nongovernmental acute care hospitals with a principal discharge diagnosis of AMI between January 1994 and February 1995, excluding patients who were readmitted for a previous AMI [40].

A total of 3680 patients (4.7%) received RBC transfusion during hospitalization [40]; 10.4% of all patients had admission HCTs that were at least 33% and only 24.1% of these patients received RBC transfusion. RBC transfusion rates were highest (71.3%) among patients who had the lowest admission HCTs (5.0% to 24.0%) and decreased steadily with higher HCTs. Crude 30-day mortality rates were highest among patients who had the lowest admission HCTs and steadily declined with increasing HCT values. Patients who had an HCT that was at least 27% and who did not receive a transfusion, had a mortality rate of almost 50%, nearly three times that among patients who had normal HCTs (ie, HCTs >39%). RBC transfusion was associated with a reduction in 30-day mortality among patients whose admission HCT fell between 5.0% and 24.0% (adjusted odds ratio [OR], 0.22; 95% confidence interval [CI], 0.11–0.45) and 30.1% to 33.0% (adjusted OR, 0.69; 95% CI, 0.53–0.89). Transfusion was not associated with reduced 30-day mortality among those whose HCT values fell in the higher ranges. Among patients who survived more than 2 days, RBC transfusion was not associated with a reduction in mortality for patients who had HCTs that were 30.1% or higher [40].

Although this study suggests that RBC transfusions lower short-term mortality rates among elderly patients who have AMI whose admission HCT is at least 30% (and perhaps as high as 33%), several caveats apply [4]. First, this retrospective study excluded 66.4% of the CCP cohort from analysis. Although the investigators justified these exclusions with various criteria, eliminating so many subjects may have introduced unrecognized bias. Second, unlike the study by Hébert and colleagues [36], this study is an observational retrospective analysis, not prospective with randomization, and criteria for transfusion thresholds were not defined. Lastly, findings cannot be gen-

eralized to younger patients and patients who have undergone successful revascularization following AMI. For example, one trial randomized 428 patients who were undergoing coronary artery bypass grafting to receive RBC transfusion postoperatively at a HGB of less than 8 g/dL, versus transfusion based on clinical judgment and institutional guidelines (HGB <9 g/dL). No differences occurred in morbidity, mortality, or selfassessment for fatigue or anemia between the two groups [41].

Other investigators found a significant association between RBC transfusions and increased mortality; transfused patients had longer ICU stays, more severe organ failure, and higher mortality rates than non-transfused patients [1]. Although these associations may be explained by different underlying clinical conditions and altered or blunted erythropoietic responses that are characteristic of anemia of inflammation (chronic disease) [1,42], attendant risks of RBC transfusion include febrile, nonhemolytic transfusion reactions, immunosuppression, and alloimmunization [43]. Nucleic acid amplification testing has markedly reduced the risks of transfusion-transmitted infections (1 per 1.935 million for hepatitis C and 1 per 2.135 million for HIV) [44]. Using newer, rather than older, RBCs (ie, RBCs stored for fewer than 15 days) [45] and leukocyte-depleted, rather than nonleukocyte-depleted, RBC products [46] may provide important benefits. Nevertheless, a tremendous impetus exists to limit RBC transfusion.

Using recombinant human erythropoietin (rHuEPO) offers an alternative to RBC transfusion [47]. rHuEPO can increase erythropoiesis, assuming normal, responsive progenitor cells and adequate iron, folate, and cobalamin stores. In a prospective, randomized, double-blinded, placebo-controlled, multicenter trial that was conducted between December 1998 and June 2001, 1302 patients who were admitted to the ICU for longer than 3 days received iron with either weekly injections of 40,000 units of rHuEPO or placebo [48]. The primary outcome was transfusion avoidance within 28 days. In contrast to the study of Hébert and colleagues [36], the transfusion trigger was an HGB of about 8.5 g/dL. The investigators approached only 19% of patients for consent, and the final sample included only 13% of those who were eligible which raised questions about the generalizability of the study [49].

Weekly injections of rHuEPO reduced exposure to any allogeneic blood by about 10%, from 60.4% with placebo to 50.5% with rHuEPO [48]. Among enrolled patients who stayed in the ICU for 3 days or longer, 10 patients required rHuEPO to prevent one patient from receiving a transfusion during the 28-day study period. Although admittedly underpowered to assess mortality, morbidity, length of stay, number of days receiving mechanical ventilation, or readmission to the ICU, these outcomes were not significantly different between the two groups of patients [48]. Furthermore, the relative costs are uncertain [49]. Additional studies are needed to assess rHuEPO administration and transfusions.

In summary, these studies support restricting transfusions (ie, transfusing RBCs when HGB levels decrease to less than 7.0 g/dL to maintain HGB levels between 7.0 and 9.0 g/dL) in critically ill patients who are euvolemic and do not have ischemic heart disease, particularly patients who are younger than 55 years of age with APACHE II scores that are 20 or less. In euvolemic patients who have ischemic heart disease, particularly patients who are 65 years of age or older or have not had successful revascularization, a liberal RBC transfusion policy (ie, RBC transfusion when HGB levels decrease to less than 10.0 g/dL) is appropriate. Future studies that examine the value of rHuEPO as an alternative to RBC transfusion should adopt these transfusion guidelines. Until such results are available, the use of rHuEPO in patients in the ICU cannot be widely endorsed.

Platelet transfusions

Because platelets play an instrumental role in primary hemostasis, platelet transfusions are often important in managing patients who are bleeding or at risk of bleeding with thrombocytopenia or impaired platelet function. Because transfusions carry risks [6], decisions to transfuse platelets must consider clinical circumstances. For example, surgical bleeding that is due solely to thrombocytopenia does not generally occur until platelet counts decrease to less than 50,000/μL, whereas spontaneous bleeding does not generally occur until platelet counts decrease to less than 10,000/μL. Other factors, including concomitant coagulopathy, fever, renal failure, and use of nonsteroidal anti-inflammatory drugs, may enhance spontaneous bleeding risk from severe thrombocytopenia. Most important, platelet transfusions are generally contraindicated if the underlying disorder is either TTP or type II HIT, because platelet transfusion in these settings may fuel thrombosis and worsen clinical signs and symptoms.

Recommended threshold platelet counts for triggering prophylactic platelet transfusion take into account the aforementioned clinical considerations, as well as recent advances in platelet collection and storage [50]. Thus, a threshold platelet count of 5000 to

10,000/μL can apply to patients who have no bleeding or only petechiae and ecchymoses, whereas higher threshold platelet counts of 15,000 to 20,000/μL are recommended in patients who have concomitant fever or infection. Assuming the absence of factors that affect platelet function (eg, renal failure, drugs that inhibit platelet function, accompanying coagulopathy, fever, infection), these prophylactic platelet transfusion guidelines apply to patients who have hypoproliferative thrombocytopenia that is due to a wide variety of causes, including acute and chronic leukemias, lymphomas, myeloma, myelodysplasia, and nonhematologic malignancies that are undergoing chemotherapy.

To avoid significant hemorrhage, extensive mucous membrane bleeding dictates platelet transfusion irrespective of platelet count. In patients who have active bleeding or are in need of invasive procedures, the threshold platelet count should be 50,000/μL. In patients who have severe, life-threatening bleeding from idiopathic thrombocytopenic purpura and platelet counts that are less than 50,000/μL, intravenous immune globulin may enhance platelet transfusion response, in addition to being therapeutic [24]. In patients who are at risk for dilutional thrombocytopenia, the platelet count should guide the decision to transfuse platelets. Because assessments of bleeding times are subject to considerable variation as a result of technical factors in executing the test, they play no role in determining hemorrhagic risk or need for platelet transfusion.

With advances in apheresis technology, a single donor in one pheresis sitting can produce 6 to 10 units of leukocyte-reduced platelets (3 to 8 $\times$ 10^{11} platelets). As a consequence, single-donor infusions can be used in place of platelets pooled from multiple donors. Commercial centers with expertise in maximizing platelet yields from single-donor apheresis supply single-donor concentrates that are used by many hospital blood banks. The advantages of this practice are reduced donor exposure, lower incidence of alloimmunization, and lower refractoriness to platelet transfusions [6]. HLA-matched platelet transfusions are useful in patients who have alloimmunization to non-HLA–matched platelet products. In general, transfusion of 6 to 10 units of platelets will increase patient platelet counts by 17,000 to 31,000/μL, respectively [51].

Plasma product transfusions

Plasma products are indicated to correct hemostasis when bleeding arises from malfunction, consumption, or underproduction of plasma coagulation proteins. Causes of coagulopathy may be congenital or acquired (Table 3). In the critical care setting, prophylactic administration of plasma products is indicated to correct coagulopathies before invasive or surgical procedures [8,52]. In active bleeding that is associated with coagulopathy, clinicians should administer plasma products until bleeding stops or the coagulopathy ceases. Vitamin K administration is indicated for suspected vitamin K deficiency, to improve hemostatic competency of the vitamin K-dependent clotting factors, namely factors II (prothrombin), VII, IX, and X.

Choice of plasma product for transfusion depends on clinical circumstances. As a general rule, hemostasis can be achieved when the activity of coagulation factors is at least 25% to 30% of normal, assuming the absence of inhibitors (including heparin) and the presence of adequate fibrinogen levels (>100 mg/dL). FFP contains all plasma clotting factors. Presuming tolerance of volume loads (250 mL per single unit), FFP is the most commonly used plasma product to correct clotting factor deficiencies, particularly coagulopathies that are attributable to multiple clotting factor deficiency states as in liver disease, DIC, or warfarin anticoagulation. In warfarin anticoagulation, for example, supratherapeutic PTs and international normalized ratios (INRs) represent reduced levels of factors II (half-life 60 hours), factor X (half-life 48 hours), factor IX (half-life 24 hours), and factor VII (half-life 6 hours), which are all required for adequate hemostasis. Thus, replacement of all these factors, as provided by FFP, is ideal therapy when INRs are supratherapeutic. Indications for FFP transfusion include patients who have factor XI deficiency; patients who are actively bleeding or facing hemostatic challenge and have INRs that are 2.0 or greater; patients who are undergoing massive blood transfusion (one blood volume exchange within 12 hours) and with INRs that are at least 2.0; and patients who have DIC, when cryoprecipitate does not correct factor V, factor VIII, and fibrinogen consumption defects that are associated with this disorder. FFP transfusion is not appropriate to treat hypovolemia or to correct INRs in the absence of active bleeding or hemostatic challenge. An important exception involves patients who have a major warfarin overdose (eg, INR >20.0) who require FFP administration in conjunction with intravenous vitamin K administration to prevent spontaneous life-threatening bleeding [53].

PCC is a pooled plasma product that contains chiefly factor IX and smaller amounts of factors II, VII, and X. Historically, PCC was used for factor IX replacement in patients who had hemophilia B, a practice that has largely been supplanted by the use

of recombinant factor IX. Because PCC contains varying amounts of factor X (a critical protein in the common pathway of the coagulation cascade), PCC has also been used to bypass the intrinsic coagulation pathway when patients have inhibitors of factor VIII. It is dosed according to the level of factor IX, but the presence of some activated factor components in PCC (eg, activated factor X) poses thrombogenic risks, particularly in patients who receive high or multiple PCC doses or have decreased clearance of activated factors from liver disease [9]. As a consequence, rFVIIa (NovoSeven) now serves as a bypassing agent in patients who have inhibitors to factors VIII or IX. Because PCC contains small amounts of factors II, VII, and X (alongside factor IX) and can be administered in small volumes of diluent (eg, 25 mL), it can potentially substitute for FFP (250 mL per single unit) when coagulopathies that are attributable to multiple clotting factor deficiency states, such as warfarin anticoagulation, require quick intervention (as in life-threatening bleeding) without risk of volume overload (as in heart failure). It remains unclear whether rFVIIa, also administered in small diluent volumes (eg, 10 to 15 mL), is equally effective for this purpose.

Cryoprecipitate is rich in von Willebrand factor (vWF), factor VIII, factor XIII, and fibrinogen; it contains about 200 mg of fibrinogen and 100 units of factor VIII per 10 to 15 mL bag. As a consequence, replacement of these factors requires smaller volumes of cryoprecipitate than with FFP; 10 bags of cryoprecipitate (obtained from 10 units of plasma) contain about 2 gm of fibrinogen and increase the fibrinogen level by about 70 mg/dL in a 70 kg patient. Cryoprecipitate is used to treat congenital and acquired deficiencies of fibrinogen and factor XIII; however, because of the risk of viral transmission, clinicians no longer use it to treat hemophilia A. Alternate replacement therapies for hemophilia A include recombinant factor VIII or pasteurized factor VIII concentrate. Because the latter also contains vWF, it is a preferred source of vWF when vWF replacement therapy is required to manage von Willebrand disease, although certain patients may need cryoprecipitate that contains large multimers of vWF.

Factor concentrates, either produced with recombinant technology or pooled and concentrated from thousands of donors, contain large amounts of specific clotting factors in small volumes. These products can replace specific factor deficiencies, as in hemophilia A or B. Human plasma products may offer limited usefulness in managing bleeding because of clotting factor inhibitors, a subject that is beyond the scope of this article. rFVIIa may bypass inhibitors to factors VIII and IX in patients who have hemophilia A and B, respectively, and treat patients who have severe vWF deficiency from type 3 von Willebrand disease who have developed antibodies to vWF [10].

Additional uses of rFVIIa include treatment of: congenital or acquired factor VII deficiency; congenital factor XI or factor V deficiency; coagulopathy of severe liver dysfunction; hemostatic changes that arise from extensive surgery, trauma, and bleeding; reversal of warfarin-induced excessive anticoagulation; certain inherited disorders of platelet function (eg, Glanzmann and Bernard-Soulier thrombasthenias, Hermansky-Pudlak syndrome); and bleeding from thrombocytopenia that is due to antiplatelet glycoprotein antibodies that thwart the effects of platelet transfusion [10]. In all instances, rFVIIa seems to enhance platelet-surface thrombin generation, acting independently of its usual cofactor, tissue factor [54]. A platelet dependent mechanism explains why rFVIIa does not cause systemic activation of coagulation, because the activated platelets on which activated factor VII acts localize to sites of endothelial injury [55]. Potentially related to predisposing factors, hypercoagulable complications that are associated with rFVIIa seem to be rare [54].

Minimum effective rFVIIa dosing in managing these hemorrhagic disorders is uncertain; rFVIIa doses ranged from 3 to 320 μg/kg in various studies and depended on the specific hemorrhagic disorder. Although single rFVIIa doses as low as 15 to 20 μg/kg have effectively achieved adequate hemostasis in patients who have excessive anticoagulation from warfarin [56], patients who have hemophilia may require doses in the range of 90 to 120 μg/kg to produce adequate hemostasis [54]. Determining the optimal and cost-effective dosing regimens, as well as the safety of rFVIIa administration under specific clinical circumstances, requires prospective studies.

Activated protein C, which reduces thrombin and clot generation by inactivating activated factors V and VIII, is available as a recombinant product (drotrecogin alfa; Xigris). In patients who have severe sepsis, levels of protein C decrease, as do levels of fibrinogen and platelets. Because fibrinogen and platelet levels may also increase as acute phase reactants, decreases in protein C levels may be a better marker of severe sepsis [57]. Additionally, sepsis impairs activation of protein C, at least in part by inhibiting thrombin-thrombomodulin. In patients who have severe sepsis, low levels of protein C correlate with higher mortality and higher occurrence of shock; survivors of sepsis exhibit a progressive normalization of protein C levels [57]. Hence, investigators sought to examine outcomes in severe sepsis following administration of recombinant activated protein C [58].

Recombinant activated protein C reduces mortality from severe sepsis that is associated with organ dysfunction in adults who are at high risk for death (APACHE II scores that are at least 25) [58]. Because of its anticoagulant effects, however, drotrecogin alfa may induce bleeding [58–61]. Such bleeding is most likely when DIC accompanies sepsis and fibrinolysis exceeds thrombin generation, which favors hemorrhage over thrombosis. Alternatively, sepsis may actively suppress antithrombotic mechanisms, which downregulates fibrinolysis and the protein C-thrombomodulin antithrombotic pathway. In meningococcemia, for example, protein C levels decrease substantially, which puts patients at risk for purpura fulminans. In this extreme circumstance, drotrecogin alfa administration may save lives [62]. Absolute contraindications for its use include: active internal bleeding; recent hemorrhagic stroke; recent intracranial or intraspinal surgery, or severe head trauma; trauma patients who have increased risk of life-threatening bleeding; patients who have epidural catheters; and patients who have intracranial neoplasm or mass lesion. Relative contraindications for its use include: INR that is greater than 3.0; concurrent use of platelet inhibitors, anticoagulants, or thrombolytic therapy; and platelet counts that are less than 30,000/μL [58–61].

Summary

Systematic evaluations of anemia, thrombocytopenia, and coagulopathy are essential to identifying and managing their causes successfully. In all cases, clinicians should evaluate RBC measurements alongside WBC and platelet counts and WBC differentials. Multiple competing factors may coexist; certain factors affect RBCs independent of those that affect WBCs or platelets. Ideally, clinicians should examine the peripheral blood smear for morphologic features of RBCs, WBCs, and platelets that provide important clues to the cause of the patient's hematologic disorder.

Thrombocytopenia arises from decreased platelet production, increased platelet destruction, or dilutional or distributional causes. Drug-induced thrombocytopenias present diagnostic challenges, because many medicines can cause thrombocytopenia and critically ill patients often receive multiple medications. If they suspect type II HIT, clinicians must promptly discontinue all heparin sources, including LMWHs, without awaiting laboratory confirmation, to avoid thrombotic sequelae. Because warfarin anticoagulation induces acquired protein C deficiency, thereby exacerbating the prothrombotic state of type II HIT, warfarin should be withheld until platelet counts increase to more than 100,000/μL and type II HIT is clearly resolving.

The presence of a consumptive coagulopathy in the setting of thrombocytopenia supports a diagnosis of DIC, not TTP-HUS, and is demonstrated by decreasing serum fibrinogen levels, and increasing TTs, PTs, aPTTs, and fibrin degradation products. Increasing D-dimer levels are the most specific DIC parameter and reflect fibrinolysis of cross-linked fibrin. Elevated PTs or aPTTs can result from the absence of factors or the presence of inhibitors. Clinicians should suspect factor inhibitors when the prolonged PT or aPTT does not correct or only partially corrects following an immediate assay of a 1:1 mix of patient and normal plasma. In addition to factor inhibitors, antiphospholipid antibodies (eg, lupus anticoagulant) can produce a prolonged aPTT that does not correct with normal plasma but is overcome by adding excess phospholipid or platelets. Paradoxically, a tendency to thrombosis, not bleeding, accompanies lupus anticoagulants and the antiphospholipid antibody syndrome.

Transfusion of red blood cells, platelets, or plasma products is sometimes warranted, but clinicians must carefully weigh potential benefits against known risks. In critically ill patients, administering RBCs can enhance oxygen delivery to tissues. Among euvolemic patients who do not have ischemic heart disease, guidelines recommend a transfusion threshold of HGB levels in the range of 6.0 to 8.0 g/dL; patients who have HGB that is at least 10.0 g/dL are unlikely to benefit from blood transfusion. The use of rHuEPO to increase erythropoiesis offers an alternative to RBC transfusion, assuming normal, responsive progenitor cells and adequate iron, folate, and cobalamin stores. Future research should examine whether clinical outcomes from rHuEPO use in critically ill patients are important and cost-effective.

Because platelets play an instrumental role in primary hemostasis, platelet transfusions are often important in managing patients who are bleeding or at risk of bleeding with thrombocytopenia or impaired platelet function. Platelet transfusions carry risks, and decisions to transfuse platelets must consider clinical circumstances. Most important, platelet transfusions are generally contraindicated if the underlying disorder is TTP or type II HIT, because platelet transfusion in these settings may fuel thrombosis and worsen clinical signs and symptoms.

Plasma products can correct hemostasis when bleeding arises from malfunction, consumption, or underproduction of plasma coagulation proteins. Choice of plasma product for transfusion depends on clinical circumstances. FFP is the most commonly used plasma product to correct clotting factor deficiencies,

particularly coagulopathies that are attributable to multiple clotting factor deficiency states as in liver disease, DIC, or warfarin anticoagulation. PCC or rFVIIa that is administered in small volumes may provide advantages over FFP when coagulopathies require quick reversal without risk of volume overload. Factor concentrates can replace specific factor deficiencies. Recombinant FVIIa bypasses inhibitors to factors VIII and IX and vWF. Use of rFVIIa in managing hemostatic abnormalities from severe liver dysfunction; extensive surgery, trauma, or bleeding; excessive warfarin anticoagulation; and certain platelet disorders requires further study to determine optimal and cost-effective dosing regimens. Recombinant activated protein C reduces mortality from severe sepsis that is associated with organ dysfunction in adults who are at high risk for death (APACHE scores of at least 25). In severe sepsis, levels of protein C decrease, as do fibrinogen and platelet levels. Because of its anticoagulant effect, however, drotrecogin alfa may induce bleeding. Guidelines for drotrecogin alfa use must take into account bleeding risks.

References

[1] Vincent JL, Baron J-F, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499–507.

[2] Stéphan F, Hollande J, Richard O, Cheffi A, Maier-Redelsperger M, Flahault A. Thrombocytopenia in a surgical ICU. Chest 1999;115:1363–70.

[3] Chakraverty R, Davidson S, Peggs K, Stross P, Garrard C, Littlewood TJ. The incidence and cause of coagulopathies in an intensive care population. Br J Haematol 1996;93:460–3.

[4] Goodnough LT, Bach RG. Anemia, transfusion, and mortality. N Engl J Med 2001;345:1272–4.

[5] Hébert PC, Fergusson DA. Red blood cell transfusions in critically ill patients. JAMA 2002;288:1525–6.

[6] Kruskall MS. The perils of platelet transfusions. N Engl J Med 1997;337:1914–5.

[7] Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. Am J Respir Crit Care Med 2000;162:347–51.

[8] Medical Directors Advisory Committee, National Blood Transfusion Council. Guideline for the use of fresh-frozen plasma. S Afr Med J 1998;88:1344–7.

[9] Pindur G, Mörsdorf S. The use of prothrombin complex concentrates in the treatment of hemorrhages induced by oral anticoagulation. Thromb Res 1999;95:S57–61.

[10] Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. Transfusion 2002;42:114–24.

[11] Means Jr RT, Krantz SB. Progress in understanding the pathogenesis of the anemia of chronic disease. Blood 1992;80:1639–47.

[12] Guyatt GH, Patterson C, Ali M, Singer J, Levine M, Turpie I, et al. Diagnosis of iron-deficiency anemia in the elderly. Am J Med 1990;88:205–9.

[13] Cook JD. Clinical evaluation of iron deficiency. Semin Hematol 1982;19:6–18.

[14] van den Broek NR, Letsky EA, White SA, Shenkin A. Iron status in pregnant women: which measurements are valid? Br J Haematol 1998;103:817–24.

[15] Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH, Coresh J, et al. Serum creatinine levels in the US population: third national health and nutrition examination survey. Am J Kidney Dis 1998;32:992–9.

[16] Marchand A, Galen RS, Van Lente F. The predictive value of serum haptoglobin in hemolytic disease. JAMA 1980;243:1909–11.

[17] George JN, Gilcher RO, Smith JW, Chandler L, Duvall D, Ellis C. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: diagnosis and management. J Clin Apheresis 1998;13:120–5.

[18] Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000; 28:1871–6.

[19] Leslie SD, Toy PTCY. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol 1991;96:770–3.

[20] McKrae KR, Herman JH. Posttransfusion purpura: two unusual cases and a literature review. Am J Hematol 1996;52:205–11.

[21] Peck-Radosavljevic M, Wichlas M, Zacherl J, Stiegler G, Stohlawetz P, Fuchsjäger N, et al. Thrombopoietin induces rapid resolution of thrombocytopenia after orthotopic liver transplantation through increased platelet production. Blood 2000;95:795–801.

[22] George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, et al. Drug-induced thrombocytopenia: a systematic review of published reports. Ann Intern Med 1998;129:886–90.

[23] Wade EE, Rebuck JA, Healey MA, Rogers FB. H_2 antagonist-induced thrombocytopenia: is this a real phenomenon? Intensive Care Med 2002;28:459–65.

[24] George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods of the American Society of Hematology. Blood 1996; 88:3–40.

[25] Warkentin TE. Heparin-induced thrombocytopenia: a ten-year retrospective. Annu Rev Med 1999;50: 129–47.

[26] Eichler P, Budde U, Hass S, Kroll H, Loreth RM, Meyer O, et al. First workshop for detection of heparin-induced antibodies: validation of the heparin-induced platelet-activation test (HIPA) in comparison with PF4/heparin ELISA. Thromb Haemost 1999;81:625–9.

[27] Levine JS, Branch W, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346:752–63.

[28] Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syn-

drome: a systematic review of the literature. Blood 2003; 101:1827–32.
[29] Greenberg CD, Devine DV, McCrae KM. Measurement of plasma fibrin D-dimer levels with the use of a monoclonal antibody coupled to latex beads. Am J Clin Pathol 1987;87:94–100.
[30] Ginsberg JS, Well PS, Kearon C, Anderson D, Crowther M, Weitz JI, et al. Sensitivity and specificity of a whole blood assay for D-dimer in the diagnosis of pulmonary embolism. Ann Intern Med 1998;129:1006–11.
[31] Consensus conference. Perioperative red blood cell transfusion. JAMA 1988;260:2700–3.
[32] American College of Physicians. Practice strategies for elective red blood cell transfusion. Ann Intern Med 1992;116:403–6.
[33] Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 1996;84:732–47.
[34] Expert Working Group. Guidelines for red blood cell and plasma transfusions of adults and children. Can Med Assoc J 1997;156(Suppl 11):S1–25.
[35] Hébert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, et al. Transfusion requirements in critical care: a pilot study. JAMA 1995;273:1439–44 [Erratum appears in JAMA 1995;274:944].
[36] Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–17.
[37] Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996; 348:1055–60.
[38] Hébert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, et al. Does transfusion practice affect mortality in critically ill patients? Am J Respir Crit Care Med 1997;155:1618–23.
[39] Hébert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med 2001;29:227–34.
[40] Wu W-C, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;345:1230–6.
[41] Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion 1999;39: 1070–7.
[42] von Ahsen N, Muller C, Serke S, Frei U, Eckardt KU. Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. Crit Care Med 1999;27:2630–9.
[43] Heddle NM, Klama LN, Griffith L, Roberts R, Shukla G, Kelton JG. A prospective study to identify the risk factors associated with acute reactions to platelet and red cell transfusions. Transfusion 1993;33:794–7.
[44] Dodd RY, Notari IV EP, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. Transfusion 2002;42:975–9.
[45] Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993;269:3024–9.
[46] van de Watering LM, Hermans J, Houbiers JG, van den Broek PJ, Bouter H, Boer F, et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 1998; 97:562–8.
[47] Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized double-blind placebo-controlled trial. Crit Care Med 1999;27:2346–50.
[48] Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. JAMA 2002;288:2827–35.
[49] Carson JL. Should patients in intensive care units receive erythropoietin? JAMA 2002;288:2884–6.
[50] Contreras M. Final statement from the consensus conference on platelet transfusion. Transfusion 1998;38: 796–7.
[51] Klumpp TR, Herman JH, Gaughan JP, Russo RR, Christman RA, Goldberg SL, et al. Clinical consequences of alterations in platelet transfusion dose: a prospective, randomized, double-blind trial. Transfusion 1999; 39:674–81.
[52] Consensus conference. Fresh-frozen plasma: indications and risks. JAMA 1985;253:551–3.
[53] Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1998;114(Suppl 5):445S–69S.
[54] Lisman T, Moschatsis S, Adelmeijer J, Nieuwenhuis HK, De Groot PG. Recombinant factor VIIa enhances deposition of platelets with congenital or acquired $\alpha_{IIb}\beta_3$ deficiency to endothelial cell matrix and collagen under conditions of flow via tissue factor-independent thrombin generation. Blood 2003;101:1864–70.
[55] Hoffman M, Monroe DM. The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. Semin Hematol 2001;38:6–9.
[56] Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. Ann Intern Med 2002; 137:884–8.
[57] Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR. Low levels of protein C are associated with poor outcome in severe sepsis. Chest 2001;120: 915–22.
[58] Bernard GR, Vincent J-L, Laterre P-F, LaRosa SP, Dhainaut J-F, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.
[59] Ely EW, Laterre P-F, Angus DC, Helterbrand JD, Levy

H, Dhainaut J-F, et al. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. Crit Care Med 2003;31: 12–9.

[60] Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med 2002;347:1027–30.

[61] Siegel JP. Assessing the use of activated protein C in the treatment of severe sepsis. N Engl J Med 2002;347: 1030–4.

[62] Rintala E, Seppala OP, Kotilainen P, Pettila V, Rasi V. Protein C in the treatment of coagulopathy in meningococcal disease. Crit Care Med 1998;26:965–8.