Thrombocytopenia, often defined as a platelet count below 100,000/μl, is a relatively common hematologic problem seen in a wide variety of critically ill patients. Studies conducted in medical and surgical intensive care units (ICUs) have found platelet counts less than 100,000/μl in 20 to 40% of patients at some point during their stay in the unit, whereas severe thrombocytopenia (platelet counts < 50,000/μl) occurred in 10 to 20% of patients (1, 2). Although the cause was often not identified (1), thrombocytopenia was commonly associated with sepsis, disseminated intravascular coagulation (DIC), massive blood transfusion (dilutional thrombocytopenia), and chemotherapy (1, 2). Intensivists caring for patients with thrombocytopenia must establish the cause of the thrombocytopenia, monitor and manage the clinical consequences of thrombocytopenia and/or its underlying cause, and decide whether or not to support the platelet count by platelet transfusion.

An abnormally low platelet count arises from one or more of four general mechanisms (see Table 1): (1) decreased platelet production, (2) increased platelet destruction, (3) dilutional or distributional causes, and (4) spurious thrombocytopenia. Dilutional thrombocytopenia may arise during transfusion for massive blood loss. In one study, 75% of patients transfused with 20 or more red blood cell units in 24 h developed platelet counts less than 50,000/μl, while no patients receiving fewer than 20 red blood cell units developed platelet counts below this level (3). "Dilutional" thrombocytopenia is commonly attributed to increased splenic sequestration in patients with splenomegaly. However, in patients with hepatic cirrhosis and splenomegaly from portal venous hypertension, thrombocytopenia may derive less from splenic sequestration than from reduced levels of thrombopoietin, which is produced by the liver (4). Spurious thrombocytopenia, diagnosed by examining the peripheral blood smear, arises from platelet clumping in vitro due to either insufficient anticoagulation of the collected blood sample or EDTA -dependent agglutinins.

Besides a careful history, physical examination, and review of all medications, initial evaluation of the patient with thrombocytopenia should include review of other blood cell counts and examination of the peripheral blood smear. The presence of schistocytes (red blood cell fragments) is diagnostic of a microangiopathy. The presence of tear drops, nucleated red cells, and immature granulocyte precursors suggests 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. A myelodysplastic syndrome is suggested by dyspoiesis including coarse basophilic stippling of red cells, pelgeroid cells, Döhle bodies, hypogranulation of neutrophils, and giant platelets.

Drug-induced thrombocytopenias can be challenging to diagnose, since many medicines may be associated with thrombocytopenia and patients, particularly when critically ill, are often receiving more than one medicine. Heparin (in particular unfractionated heparin), quinine, quinidine, trimethoprim-sulfamethoxazole, gold, and valproic acid are commonly implicated drugs (5). If heparin-induced thrombocytopenia (HIT) is suspected, all heparin sources, including low molecular weight heparins (LMWHs), must be discontinued promptly. Isolated megakaryocytic hypoplasia or aplasia is rare, but should be considered in patients using thiazide diuretics, alcohol, or estrogens. Unless specific drug-platelet-associated antibodies are suspected, anti-platelet antibody testing is not recommended since it lacks sufficient sensitivity and specificity to be useful (6).

Blood chemistries are useful for evidence of hemolysis, including increased serum lactate dehydrogenase (LDH) and indirect bilirubin accompanied by decreased haptoglobin levels. The presence of a consumptive coagulopathy, which supports a diagnosis of DIC (and is not a component of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome [TTP–HUS]), is demonstrated by decreasing serum fibrinogen levels; increasing thrombin, prothrombin, and activated partial thromboplastin times (TT, PT, and aPTT, respectively); and increasing fibrin degradation products. Increasing D-dimer levels are the most specific DIC parameter, reflecting fibrinolysis of cross-linked fibrin, while increasing PTs and decreasing levels of fibrinogen and platelet counts are most sensitive in detecting early DIC development. While measuring levels of factor V (a vitamin K–dependent clotting factor produced by liver) and factor VIII (a clotting factor not produced by liver) may help to distinguish a role for DIC (which consumes both factors) in bleeding associated with liver disease, this is generally not necessary.

**DISSEMINATED INTRAVASCULAR COAGULATION**

DIC is a systemic disorder of thrombosis and bleeding, triggered by exposure of blood to procoagulants. The chief inciting procoagulant is tissue factor, whose expression by vascular endothelium and monocytes rises in response to endotoxin and various cytokines, and whose circulating blood level increases with extensive vascular endothelial injury. Increased tissue factor levels generate excessive thrombin, which overwhelms antithrombotic pathways such as antithrombin III (ATIII) and tissue factor pathway inhibitor (7).

A's thrombin generates fibrin from fibrinogen and widespread intravascular fibrin deposition ensues, platelets, fibrinogen, prothrombin, and factors V and VIII are consumed, increasing bleeding risk. In some instances, bleeding risk is further compounded by secondary fibrinolysis, mediated by plasmin (derived from plasminogen on release of tissue plasminogen activator) and accentuated by fibrin degradation...
products (which inhibit platelet aggregation and formation of fibrin oligomers). In other instances, antithrombotic mechanisms are actively suppressed with downregulation of fibrinolysis and the protein C/thrombomodulin antithrombotic pathway. In meningococcemia, for example, protein C levels are substantially reduced, and patients are at risk for purpura fulminans (8). The balance of thrombin generation, clotting factor consumption, and thrombolysis determines whether the primary clinical manifestation of DIC is thrombosis or hemorrhage (7).

Clinical conditions causing DIC include sepsis, trauma, extensive surgery, cancer, and obstetric complications (7). Both gram-negative and gram-positive bacterial infections can cause DIC; rarely does DIC complicate viral infection. Decreased blood flow (hypotension or shock) and impaired hepatic function further exacerbate DIC by decreasing clearance of procoagulants. In addition, tissue damage from infection or hyperfibrinolysis, especially when complicated by systemic inflammatory response syndrome (9), exacerbates DIC by providing an added source of thrombin. In trauma, extensive surgery, or obstetric complications such as amniotic fluid embolism and abruptio placentae, DIC is triggered by release of tissue enzymes and thromboplastins (7).

The onset of DIC in malignancy may be more insidious than acute, allowing liver and bone marrow to replenish consumed clotting factors and platelets. As a result, patients with malignancy-associated DIC, especially those with solid tumors, may be at greater risk for thrombosis than hemorrhage (10). In contrast, patients with DIC from acute leukemia (primarily acute promyelocytic leukemia [APL]) have more of a hyperfibrinolytic state and are therefore at greater risk for bleeding (11).

Managing DIC requires identifying and treating the inciting disorder; all other measures are supportive. Transfusions of platelets and/or clotting factors (fresh frozen plasma and cryoprecipitate) are not indicated unless patients have serious bleeding, are at high risk for bleeding (e.g., following surgery, with platelet counts < 20,000/\mu l or fibrinogen levels < 50 mg/dl), or require invasive procedures (7). Heparin administration is not indicated unless thrombotic complications are the primary manifestation of DIC (as in chronic, compensated DIC associated with solid tumors (7). Heparin probably does not benefit all patients with DIC because levels of ATIII, the target substrate of heparin, are reduced and vary considerably across patients, particularly those with acute, as opposed to chronic, DIC (7). This finding forms the basis of ATIII replacement therapy, which may benefit patients with DIC, particularly from sepsis complicated by shock (12). A large randomized, controlled multicenter trial of ATIII replacement therapy is ongoing to examine this intervention (7).

Other supportive measures target certain coagulation abnormalities associated with specific causes of DIC. For example, protein C concentrate infusions appear to benefit patients with meningococcemia-induced DIC complicated by acquired protein C deficiency and purpura fulminans (8). A II-trans-retinoic acid, which induces leukemia cell differentiation in patients with A PL, reduces the incidence of severe DIC in this disorder by altering the expression of a number of leukemia cell factors that contribute to the A PL-associated coagulopathy (11, 13).

### PREECLAMPSIA AND HELLP

A bout 15% of pregnant women with preeclampsia (hypertension, proteinuria, and edema in pregnancy) develop thrombocytopenia; up to one-third of these women experience severe thrombocytopenia with platelet counts < 50,000/\mu l (12). HELLP syndrome (hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets in pregnancy) was defined in a large series as the presence of microangiopathic hemolysis with platelet counts < 150,000/\mu l, serum LDH > 600 IU/l, and serum aspartate aminotransferase (AST) > 40 IU/l (14). The majority of patients present with midzegastic or right upper quadrant abdominal pain and nausea and/or vom-

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**TABLE 1**

**CAUSES OF THROMBOCYTOPENIA**

| Decreased platelet production due to marrow suppression or damage or thrombopoietin underproduction |
| Viral infections (rubella, mumps, varicella, parvovirus, EBV, HIV, live-attenuated measles vaccination) |
| Drugs or toxins (alcohol, chemotherapy, radiation therapy) |
| Nutritional deficiencies (vitamin B12, folic acid) |
| Congenital or acquired disorders of hematopoiesis (bone marrow aplasia or hypoplasia, myelodysplastic or myeloproliferative syndromes) |
| Liver disease |
| Increased platelet destruction due to immune or nonimmune causes |
| Idiopathic ITP |
| Drug-induced ITP (heparin, quinine, quinidine, valproic acid) |
| Infection-associated ITP (EBV, CMV, HIV) |
| Alloimmune destruction (posttransfusion, neonatal, posttransplantation) |
| Disseminated intravascular coagulation |
| Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome |
| Antiphospholipid antibody syndrome |
| HELLP syndrome |
| Physical destruction (cardiopulmonary bypass, giant cavernous hemangiomas) |
| Dilutional or distributional causes |
| Massive blood loss and transfusional support |
| Splenic sequestration |
| Spurious thrombocytopenia |
| EDTA-dependent agglutinins |
| Insufficient anticoagulation of collected blood samples |

*Definition of abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; EDTA = ethylenediaminetetraacetic acid; HELLP = hemolysis, elevated liver enzymes, and low platelets in pregnancy; HIV = human immunodeficiency virus; ITP = immune thrombocytopenic purpura.*
iting. A small number of patients are asymptomatic (14). The frequency and severity of thrombocytopenia tend to be worse than in patients with preeclampsia, and signs of DIC occur in nearly 20% of patients (14). While HELLP syndrome can complicate preeclampsia, 15 to 20% of patients with the findings of HELLP do not have hypertension or proteinuria (14). Hence, HELLP syndrome and preeclampsia may have separate etiologies (15).

Hematologic manifestations of preeclampsia and HELLP syndrome usually develop in the third trimester of pregnancy. In most patients, delivering the fetus is effective treatment. The hematologic abnormalities usually resolve within 3 d of delivery. However, as many as 30% of women with HELLP syndrome develop hematologic abnormalities postpartum, usually within 48 h of delivery, although sometimes as long as 7 d after delivery. In both antepartum and postpartum HELLP, parenteral corticosteroids (betamethasone or dexamethasone) achieve more rapid improvement in clinical and laboratory parameters (16). When given antepartum, corticosteroid therapy can help to delay parturition. In some patients, however, clinical and laboratory manifestations of HELLP worsen or do not improve after 3 d. In these patients, HELLP syndrome is indistinguishable from TTP–HUS (see below), and plasma exchange should be initiated promptly, particularly if neurologic symptoms or signs and/or renal failure are evident (17).

As platelet counts decline below 20,000/μL, patients are at significant risk of hepatic hematoma. While platelet transfusions may be advisable, there is no evidence that prophylactic platelet transfusions prevent development of this complication. Computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive than ultrasonography in detecting hepatic hematomas (18). When hematomas are contained, treatment is supportive; with rupture, surgical intervention may require orthotopic liver transplantation (19).

THROMBOTIC THROMBOCYTOPENIC PURPURA–HEMOLYTIC UREMIC SYNDROME

TTP–HUS exhibits increased turnover of platelets; unlike DIC, fibrin turnover is not increased, and coagulation parameters are generally normal. Schistocyte numbers and LDH levels are generally higher in TTP–HUS than in DIC. The source of extremely high LDH levels in TTP is tissue ischemia rather than hemolysis (20).

The classic pentad of TTP–HUS includes microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms and signs, renal disease, and fever. Microangiopathic hemolytic anemia and thrombocytopenia are invariably present, whereas neurologic symptoms and signs (most commonly confusion and headaches) and renal disease are variable in their manifestations. Fever is the least frequent of the five TTP–HUS features (21). Whether acute renal failure is marked versus minimal or absent determines whether patients are classified as having HUS versus TTP, respectively.

Conditions associated with TTP–HUS development are numerous and varied (21), including enterohemorrhagic infections (Escherichia coli O157:H7), cancer (mucinous adenocarcinomas of the gastrointestinal tract, pancreas, and prostate), drug toxicity, pregnancy and the postpartum state, autoimmune diseases (systemic lupus erythematosus [SLE] and antiphospholipid antibody syndrome), AIDS and early symptomatic HIV infection, and pneumococcal infection. A mong drug therapies commonly triggering TTP–HUS are cancer chemotherapy (mitomycin, combination bleomycin and cisplatin, conditioning for bone marrow transplantation), oral contraceptives, cyclosporine, tacrolimus, OKT3, quinine, and ticlopi-
ber arterial thromboses by 4:1, and life-threatening pulmonary embolism occurs in 25% of patients with thrombosis (28). Type II HIT occurs in 1 to 3% of patients who receive unfractionated heparin, generally rises 5 to 10 d after onset of heparin administration, and induces by an antibody-mediated mechanism median nadir platelet counts of 50,000 to 60,000/μl (28). However, in 10 to 15% of patients diagnosed with type II HIT, platelet counts decline within the normal range, never falling below 150,000/μl despite development of thrombosis (28). This worrisome observation dictates that type II HIT should be suspected in any patient who has begun heparin therapy within the preceding 5 to 10 d and has developed a decline in platelet count of 50% or more below pretreatment values.

While falls in platelet counts earlier than the fifth day of heparin administration are unlikely to represent Type II HIT, more rapid-onset Type II HIT can arise in patients who receive heparin within 3 to 4 mo of previous heparin administration. In addition, thrombosis can arise even after discontinuing heparin promptly. In a retrospective series of 62 patients who had heparin discontinued due to isolated thrombocytopenia attributed to heparin, the 30-d risk of thrombosis was 53% (28).

The development of Type II HIT, which begins with heparin-induced platelet activation and release of platelet factor 4 (PF4) from platelet α granules, 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 enzyme-linked immunosorbent assay (ELISA). A (though the serotonin release assay is the “gold standard,” the heparin-induced platelet aggregation assay and ELISA are used more commonly, since, in contrast to the serotonin release assay, they are easier to deploy and more widely available. However, the heparin-induced platelet aggregation assay, while specific (> 90%) lacks sensitivity; and the solid-phase immunoassay, while sensitive, lacks specificity. A s with any test, positive and negative predictive values depend on the clinical context in which these tests are used (29).

Once Type II HIT is clinically suspected, all sources of heparin, including LMWH, must be discontinued promptly without waiting for laboratory confirmation. While LMWH is less likely to cause HIT when used as a first-line anticoagulant, its cross-reactivity with unfractionated heparin-induced antibodies is nearly 100%, and use of LMWH after development of Type II HIT can perpetuate the condition (28). Thus, LMWH is not recommended.

There are two options for anticoagulation after heparin discontinuation: lepirudin (a direct thrombin inhibitor) and danaparoid (a heparanoid). Lepirudin demonstrates no cross-reactivity with heparin-induced antibodies and requires measuring aPTTs for monitoring anticoagulation (28). In contrast, danaparoid cross-reacts weakly with heparin-induced antibodies in 10 to 40% of HIT sera and requires measuring anti-factor Xa levels for anticoagulation monitoring (28). While the weak association of danaparoid with heparin-induced antibodies is of uncertain clinical significance (28), the more cumbersome aspects of measuring anti-factor Xa levels may favor use of lepirudin. Because warfarin anticoagulation induces acquired protein C deficiency, its use can exacerbate the prothrombotic state of Type II HIT. A s a consequence, warfarin administration should be withheld until the platelet count rises above 100,000/μl and Type II HIT is clearly resolving (28).

**PLATELET TRANSFUSIONS**

Since 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. However, since transfusions carry risks (30), decisions to transfuse platelets must consider clinical circumstances. For example, surgical bleeding due solely to thrombocytopenia does not generally occur until platelet counts fall below 50,000/μl, while spontaneous bleeding does not generally occur until platelet counts fall below 10,000/μl. Other factors, including concomitant coagulopathy and fever, 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, since 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 preceding clinical considerations as well as advances in platelet collection and storage (31). Thus, a threshold platelet count of 5,000 to 10,000/μl can be used in patients with no bleeding or only petechiae and ecchymoses, while somewhat higher threshold platelet counts of 15,000 to 20,000/μl are recommended in patients with concomitant fever or infection.

Extensive mucous membrane bleeding dictates platelet transfusion irrespective of platelet count, to avoid significant hemorrhage. In patients with active bleeding or in need of invasive procedures, the threshold platelet count should be 50,000/μl. In patients with severe, life-threatening bleeding from immune thrombocytopenic purpura and platelet counts below 50,000/μl, intravenous immune globulin may enhance platelet transfusion response in addition to being therapeutic (6). In patients at risk for dilutional thrombocytopenia, the decision to transfuse platelets should be guided by the platelet count. Because assessments of bleeding times are subject to considerable variation due to technical factors in executing the test, they play no role in determining hemorrhagic risk or need for platelet transfusion.

With advances in apheresis technology, 6 to 10 units of leukocyte-reduced platelets (3 to 8 × 10^11 platelets) can be collected from a single donor in one pheresis sitting. As a consequence, single-donor infusions can be used in place of platelets pooled from multiple donors. The advantages of this practice are reduced donor exposure, lower incidence of alloimmunization, and lower refractoriness to platelet transfusions (30). Human leukocyte antigen (H LA-)matched platelet transfusions are useful in patients with 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 (32).

**References**


