INTRODUCTION

Hematopoiesis is a polyclonal process responsible for the production and maintenance of blood and immune cells, thereby producing billions of new blood cells each day. Large numbers of blood and immune cells can be traced to a pool of hematopoietic stem cells (HSCs) from which these clones have originated (1). It is also known that these HSCs can mobilize out of the bone marrow into circulating blood and can undergo programmed cell death, called apoptosis—a process by which cells that are detrimental or unneeded self-destruct, all for the purpose of maintaining homeostasis. The most primitive stem cell, in the bone marrow, is responsible for the production of all peripheral blood cell lineages, while maintaining sufficient numbers of pluripotent stem cells to sustain hematopoiesis throughout adult life. These cells are characterized by the surface expression of CD34 molecule and by lack of markers of differentiation.

The HSC population supports a tremendous production of blood cells over an animal’s life span; for example, adult humans produce their body weight of red cells, white cells, and platelets every 7 years, whereas the mouse produces 60% of its body weight over a 2-year life span. Using DNA labeling data, investigators in the field have tried to characterize the HSC kinetics in the mouse. Based on such data, MacKey (2) was able to calculate that in the course of producing a mature, circulating blood cell, the original single HSC will undergo between 17 and 19.5 divisions, providing a net output between approximately 170,000 and 720,000 blood cells.

A wide array of environmental factors, both humoral and cellular, regulate the quantity and behavior of HSCs, including cytokines and chemokines, extracellular matrix components, as well as hematopoietic and nonhematopoietic cells such as natural killer (NK) cells, T cells, macrophages, fibroblasts, osteoblasts, adipocytes and, perhaps, even neurons. In addition to this wide array of microenvironmental factors, several intrinsic genetic events are critical to hematopoiesis and are currently the subject of intense research (3). This complex interplay determines whether HSCs, progenitors, and mature blood cells remain quiescent, proliferate, differentiate, self-renew, or undergo apoptosis (4–6).

Production of a specific type of differentiated blood cell from a stem cell is thought to occur randomly. Cytokines promote proliferation and survival of certain types of cells but do not affect which cell type is produced from a stem cell. Cytokines are made and secreted mainly by helper T lymphocytes and macrophages, but also by other stroma cells such as fibroblasts and endothelial cells. A few of these cytokines have been synthesized and are FDA approved for clinical use (7).

PATHOPHYSIOLOGY

In the event of stress, such as bleeding or infection, several processes occur. Stored pools of cells in the marrow or adherent to the endothelium are quickly released into the circulation to localize to the site of injury; additionally, fewer progenitors and mature cells undergo apoptosis. Furthermore, quiescent progenitors and HSCs are stimulated by various growth factors to proliferate and differentiate into mature white cells, red blood cells (RBCs), and platelets. Finally, when the bleeding, infection, or other underlying stress ceases, the kinetics of hematopoiesis return to baseline levels. This process repeats itself innumerable times during the life span of an individual, and is seen in an exaggerated form following chemotherapy or bone marrow transplantation.

Cytokines are very important in critical care medicine, especially those proinflammatory cytokines released by monocytes/macrophages in response to infectious and noninfectious inflammation. The release of these cytokines results in whole body inflammation such as that seen in the systemic inflammatory response syndrome (SIRS). These patients also undergo an anti-inflammatory phase, which includes the release of cytokines with opposing—anti-inflammatory—biologic effects or naturally occurring cytokine antagonists, such as interleukin-1 receptor antagonist and tumor necrosis factor-α (TNF-α) soluble receptors p55 and p75 (8,9). Clinical studies to intervene in the inflammatory response using these and other anticytokine therapy have been more than a little disappointing, but efforts continue with several FDA-approved cytokines antagonists.

Many acquired and inherited abnormalities that interfere with the normal mechanisms of hematopoiesis result in known diseases of decreased, or increased, production of one or more of the blood cell lineages; any one of these can be encountered in patients hospitalized in the ICU. The pathophysiology, diagnosis, and treatment of these diseases will be the main subject of this chapter.

DECREASED BLOOD COUNTS

Anemias

Diagnosis and Transfusions Guidelines

Anemia—hemoglobin concentration less than 12 g/dL—is present in 95% of patients in the intensive care unit, with
Anemia resulting from underproduction versus anemia due to

Anemia in Critical Illness

The physician in the ICU may be faced with the immediate decision of whether the patient requires transfusion with packed red blood cells (PRBC). For years, many physicians firmly believed that hemoglobin of 10 g/dL or hematocrit of 30% was desirable in anemic patients, especially those undergoing surgical procedures or with critical illness (14). This approach—of using fixed transfusion triggers—has been recognized as the main reason for high transfusion rates in ICU patients and is finally being replaced by a more physiologic approach in which the patient’s intravascular volume and tissue oxygen needs are considered. A restrictive transfusion policy, in which hemoglobin concentration is maintained between 7 and 9 g/dL, has proved to be effective and yields decreased death rates in comparison to the liberal strategy (14–17). More recent studies and a meta-analysis, as discussed below (18–20), concluded that there is no difference in outcomes of patients receiving restrictive versus liberal PRBC transfusion approaches. Indeed, in young traumatized patients, the hemoglobin is sometimes allowed to drift to as low as 5 g/dL, as long as there are no signs of oxygen delivery deficit, such as elevated lactate levels, an unacceptable heart rate, or other symptoms. These patients are most often started on recombinant erythropoietin and have iron stores repleted, if necessary, to keep from undergoing transfusion.

There are few specific questions regarding transfusions that pertain to specific conditions encountered in the ICU, which the American Association of Blood Banks (AABB) recent guidelines (based on the TRICC, TRIPICU, and FOCUS trials) has addressed (21):

• When to transfuse hospitalized hemodynamically stable patient? Consider transfusion when Hgb 7 g/dL or less for adult and pediatric patients in the ICU and 8 g/dL or less for postoperative surgical patients (based on studies done in surgical patients).

• When to transfuse hospitalized hemodynamically stable patient with pre-existing cardiovascular disease? Based on the FOCUS trial, transfuse for Hgb 8 g/dL or less, or if symptoms are present.

• When to transfuse in hospitalized hemodynamically stable patient with acute coronary syndrome? No definite recommendation was given because of lack of randomized trials.

• Should symptoms rather than Hgb levels guide transfusions in hospitalized hemodynamically stable patient? Again without significant evidence, it was recommended to consider both.

Recently published randomized studies address two other important questions, one regarding transfusions in patients with gastrointestinal bleeding (18) and another in patients with septic shock (19). Both studies support the use of 7 g/dL threshold in these situations. Finally, a meta-analysis of 31 trials comparing the benefit and harms of restrictive versus liberal transfusion strategies showed that liberal transfusion strategies have not been shown to convey any benefit to patients and, overall, there was no differences in mortality, morbidity, or myocardial infarction incidence (20). A key principle is that one should not give blood unless one can show benefit from its administration. Obviously, different transfusion approaches will be addressed under the specific types of anemia discussed in this chapter.

<table>
<thead>
<tr>
<th>TABLE 146.1 Anemia Classification</th>
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<tbody>
<tr>
<td>Anemias Secondary to Marrow Underproduction</td>
</tr>
<tr>
<td>Decreased erythropoietin production</td>
</tr>
<tr>
<td>• Renal disease</td>
</tr>
<tr>
<td>• Endocrine deficiency</td>
</tr>
<tr>
<td>• Starvation</td>
</tr>
<tr>
<td>Adequate response to erythropoietin</td>
</tr>
<tr>
<td>• Iron deficiency</td>
</tr>
<tr>
<td>• B12 deficiency</td>
</tr>
<tr>
<td>• Folic acid deficiency</td>
</tr>
<tr>
<td>• Anemia of chronic disease</td>
</tr>
<tr>
<td>• Marrow infiltration</td>
</tr>
<tr>
<td>• Sideroblastic anemia</td>
</tr>
<tr>
<td>• Myelodysplastic syndrome</td>
</tr>
<tr>
<td>Marrow failure</td>
</tr>
<tr>
<td>• Congenital dyserythropoietic anemia</td>
</tr>
<tr>
<td>• Aplastic anemia</td>
</tr>
<tr>
<td>• Pure red cell aplasia</td>
</tr>
<tr>
<td>• Toxic marrow damage</td>
</tr>
<tr>
<td>Anemias Secondary to Increased Destruction</td>
</tr>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>• Immune-mediated hemolytic anemia</td>
</tr>
<tr>
<td>• Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>• Hemolytic anemia due to red cell fragmentation (TPIDIC)</td>
</tr>
<tr>
<td>• Hemolytic anemia due to chemical or physical agents</td>
</tr>
<tr>
<td>• Infections</td>
</tr>
<tr>
<td>• Acquired hemoglobinopathies (methemoglobinemia)</td>
</tr>
<tr>
<td>Hereditary</td>
</tr>
<tr>
<td>• Congenital hemoglobinopathies (sickle cell disease)</td>
</tr>
<tr>
<td>• Enzyme deficiency (G6PD, pyruvate kinase)</td>
</tr>
<tr>
<td>• Red cell membrane defects (spherocytosis, elliptocytosis)</td>
</tr>
</tbody>
</table>

TTP: thrombotic thrombocytopenic purpura; DIC: disseminated intravascular coagulopathy.
revealed some similarities. First, the vast majority of critically ill patients have anemia on admission to the ICU. Second, the most common indication for RBC transfusion in the ICU was treatment of the anemia. Third, the transfusion trigger in all these studies was hemoglobin of about 8.5 g/dL. Finally, RBC transfusions were increased in patients with prolonged ICU length of stay and increased age.

**Pathophysiology**

Possible mechanisms involved in anemia of acute critically ill patients include a blunted erythropoietin (EPO) response to anemia, with blood concentrations being inappropriately low in these patients; suppression of erythropoiesis by pro-inflammatory cytokines; possible blood loss from frequent phlebotomies; and blood loss from gastrointestinal bleeding as a result of gastric tubes, stress-induced mucosal ulcerations, acute renal failure, and frequent coagulation problems in ICU patients. This anemia shares characteristics with anemia of chronic inflammation such as high ferritin concentrations and low-to-normal transferrin saturation with functional iron deficiency.

Until recently, we understood little about the pathogenesis of anemia of chronic inflammation. It now appears that the inflammatory cytokine interleukin-6 (IL-6) induces the production of hepcidin, an iron-regulatory hormone that may be responsible for the hypoferremia and suppressed erythropoiesis (24). This discovery has led to multiple studies focused on the role of hepcidin in the anemia of the critically ill patient, and exploring potential therapeutic applications.

**Treatment**

The approach to treatment of this type of anemia should include measures to reduce blood loss, a restrictive blood transfusion policy, and possibly the use of recombinant human EPO (rh-EPO). Multiple studies have shown that the subcutaneous administration of rh-EPO at 40,000 units weekly, starting between days 3 and 7 of the ICU stay, resulted in a significant reduction in RBC transfusions and a higher hemoglobin level (25,26). Because iron is locked up in the phagocytic system and hardly available, the administration of intravenous iron, together with rh-EPO, may result in an enhanced rh-EPO effect. As only about 10% of oral iron is bioavailable, this route may not be appropriate in ICU patients. Additionally, several intravenous formulations are available including iron dextran, iron gluconate, and iron sucrose. Typically, intravenous iron is administered at small doses over several sessions up to a total cumulative dose of 1,000 mg.

**Autoimmune Hemolytic Anemia**

**Pathophysiology and Diagnosis**

When a patient is critically ill from autoimmune hemolytic anemia (AIHA), the presenting signs and symptoms are those of normovolemic anemia, unless massive hemolysis is associated with hypotension, significant hemoglobinuria, and acute renal failure. Variable levels of jaundice may also be present in the nonmassive AIHA. Initial laboratory data may show an elevated reticulocyte index of more than 2, decreased haptoglobin, hemoglobinuria, and an elevated indirect bilirubinemia and lactate dehydrogenase (LDH); the blood smear shows increased numbers of diffusely basophilic red cells, reflecting the increased reticulocytes, and variable numbers of microspherocytes and fragmented cells, indicative of the hemolysis (Fig. 146.1). A positive result on direct antiglobulin (Coombs) test, indicating that immunoglobulin or complement is on the surface of the circulating red cells, identifies the immune etiology of the hemolysis. This information may first become available when the blood bank attempts to cross-match the patient’s blood for transfusion.

It is important to determine, by history and appropriate laboratory studies, whether the hemolysis could be related to a drug the patient is taking and whether it is caused by warm-reacting (usually IgG) or cold-reacting (usually IgM) antibodies. In some instances, the drug must be present for hemolysis to occur (e.g., quinidine, penicillin); in others, hemolysis occurs even in the absence of the drug (e.g., methyldopa). Underlying diseases that may be associated with AIHA include infections, such as infectious mononucleosis and pneumonia caused by Mycoplasma pneumoniae; collagen vascular diseases, especially systemic lupus erythematosus; and lymphoproliferative disorders such as chronic lymphocytic leukemia. In other instances,
the AIHA may be associated with idiopathic thrombocytopenic purpura (ITP) as part of Evans syndrome.

**Treatment**

The mainstay of treatment of AIHA caused by warm-reacting antibodies is the administration of corticosteroids, usually given in dosages equivalent to 60 to 80 mg/day of prednisone. In patients who do not respond to steroids, splenectomy, high-dose intravenous gamma globulin, rituximab, chimeric anti-CD20 antibody, or other immunosuppressive drugs may be useful.

Steroids are usually ineffective in AIHA caused by cold-reactive antibodies (cold agglutinin disease), but responses have been observed using larger doses. Patients with cold agglutinins may have symptoms related to impaired blood flow in acral parts where the blood temperature is low enough to permit agglutination of RBCs by antibodies. Warming usually prevents or alleviates such symptoms; however, in a small percentage of cases, plasmapheresis to reduce the concentration of the offending IgM antibodies may be required. In drug-induced immune hemolysis, discontinuing the drug is usually the only treatment needed.

In a patient with AIHA with a critical degree of anemia, transfusion must be considered (27). It may be impossible to find compatible RBCs by the usual cross-matching procedures, and transfused cells may be subject to rapid antibody-mediated destruction. On the other hand, the patient must not be allowed to die because of undue caution regarding the transfusion of incompatible red cells. The key to optimal care in this critical situation is close communication between the intensivist and the blood bank physician. When an AIHA patient is transfused, the patient must be observed closely for signs of accelerated hemolysis, such as visible hemoglobin in the plasma or urine.

Certain special considerations pertain to transfusion of patients with cold-reacting antibodies. Administered blood should be warmed to body temperature. Transfusion of plasma, which contains complement, should be avoided because hemolysis is complement mediated and may be limited by depletion of complement in vivo. In massive hemolysis, therapeutic efforts should be directed at maintenance of blood pressure, renal blood flow, and urinary output; intravenous fluids and diuretics such as furosemide should be used to maintain a urine flow of 100 mL/hr.

**Hemolytic Anemia from G6PD Deficiency**

**Pathophysiology**

RBC glucose-6-phosphate dehydrogenase (G6PD) deficiency is inherited as an X-linked recessive disorder, affecting various population groups around the world. In the United States, African Americans are the group most often affected, with a gene frequency of about 11%. They have the G6PD A variant of the enzyme and a mild-to-moderate deficiency. A recent study by the US army found that 2.5% of males and 1.6% of females were deficient. The highest rates of G6PD deficiency were in African American males (12.2%) and females (4.1%), along with Asian males (4.3%) (28). Among drugs producing hemolysis are some sulfonamides, nitrofurantoin, and antimalarials, such as primaquine. Illnesses most likely to trigger hemolysis are acute infections. Infectious hepatitis, in particular, has been associated with severe hemolytic episodes in G6PD-deficient patients.

**Diagnosis and Treatment**

Hemolysis in the G6PD-deficient patient may be sudden and massive, usually becoming apparent 1 to 3 days after the inciting stress, such as administration of an oxidant drug. Hemoglobinemia and hemoglobinuria may occur; the blood smear shows polychromatophilia within a few days, reflecting the developing reticulocytosis. Early in the course of the hemolytic episode, Heinz bodies may be identified in red cells by special staining methods. These precipitates of oxidatively denatured hemoglobin provide a useful diagnostic clue and should be sought if G6PD deficiency is suspected as a cause of acute hemolysis. However, the absence of Heinz bodies does not exclude this diagnosis. The red cell enzyme deficiency may be readily detected by laboratory assay when the patient is in a stable state but may be more difficult to demonstrate during a hemolytic episode. This is because the enzyme deficiency is greatest in the oldest red cells. These cells are the first destroyed in a hemolytic episode and, as they are replaced by newly produced young cells, the overall red cell enzyme level may rise to the normal range. This replacement of susceptible erythrocytes by more resistant cells also tends to ameliorate the hemolysis with time.

If the diagnosis is suspected, any potentially offending drugs should be stopped. Otherwise, supportive care is usually all that is necessary. Although the deficiency is an X-linked trait, female heterozygotes may have hemolytic episodes.

**Hemolytic Anemia from Red Cell Injury in the Circulation**

**Pathophysiology**

Fragmentation and destruction of red cells in the circulation may result from increased shear stresses caused by turbulent blood flow. The two major categories of disease in which this kind of hemolysis occurs are malfunctioning intravascular prosthetic devices (e.g., heart valves, vascular grafts, and shunts) and disorders affecting blood vessels that result in microangiopathic hemolytic disease, such as disseminated intravascular coagulopathy (DIC) or thrombotic microangiopathy (TMA).

TMA encompasses the spectrum of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). These forms of hemolytic disease are rarely of sufficient severity to require critical care. However, they can be seen in critically ill patients admitted to the ICU, and have been associated with various initiating factors such as severe infections, drug intake, malignancies, connective tissue diseases, and pregnancy (29). Characteristically, the blood smear shows red cell fragmentation producing micropoikilocytes (schistocytes, similar to that shown in Fig. 146.1). Typically, the TMA patients will also have thrombocytopenia (TP), fever, and possibly neurologic and renal involvement. TTP must be considered in the presence of TP and microangiopathic hemolytic anemia (29). ADAMTS13 assays help to confirm the diagnosis and monitor the course of the disease.

**Treatment**

The diagnosis of TMA/TTP should be treated as a medical emergency. The treatment of TMA with plasma administration, either infusion or plasmapheresis, is the only effective therapy
that has dramatically improved the prognosis of these patients, and should be initiated within 4 to 8 hours to prevent early deaths from TTP.

Specific treatment is directed at the underlying disorder. Supportive measures may be required for the effects of hemolysis itself and to minimize any adverse renal consequences of hypotension and hemoglobinuria. These may include blood transfusion and hydration to ensure good urine flow. Occasionally, a badly malfunctioning prosthesis, such as an artificial heart valve, may require replacement, but this is more often necessary to correct a life-threatening hemodynamic abnormality than to alleviate severe hemolysis.

### Sickle Cell Anemia

#### Pathophysiology and Clinical Symptoms

Sickle cell hemoglobin (hemoglobin S) is the result of a single nucleotide mutation in the sixth codon of the β-globin gene (β). Heterozygous inheritance of hemoglobin S does not usually cause disease or symptoms but is detectable as sickle cell trait (30). Homozygous inheritance or compound heterozygous inheritance with another β-globin gene results in disease. The discussion here is directed primarily toward homozygous sickle cell disease (SCD) which includes those genotypes associated with chronic hemolytic anemia and vaso-occlusive pain: homozygous SCD (hemoglobin SS), homozygous SC disease (hemoglobin SC), sickle-β(+) thalassemia (hemoglobin Sβ(+)β), and sickle-β thalassemia (hemoglobin Sββ(−)), and other less common hemoglobin mutants. The clinical manifestations are related to the degree of intracellular polymerization of deoxyhemoglobin S (Table 146.2), and it is different among the various genotypes.

The clinical symptoms of SCD affect multiple organs and may vary widely among patients. Chief among the clinical features are episodes of severe pain—namely, crises—in the chest, back, abdomen, or extremities. The acute chest syndrome (ACS), sometimes fatal complication, affects over 40% of all patients with SCD and can lead to acute and chronic respiratory insufficiency, including pulmonary hypertension. Its cardinal features are fever, pleuritic chest pain, referred abdominal pain, cough, lung infiltrates, and hypoxia. Other complications of SCD include recurrent strokes in young adults; parvovirus B19-induced aplastic crisis; hyperbilirubinemia from cholestatic syndrome or cholecystitis; liver disease; splenic infarctions; autosplenectomy with increased risk of fulminant septicemia caused by encapsulated organisms such as Streptococcus pneumoniae and Haemophilus influenzae; hematuria; priapism; bone infarctions with the risk of avascular necrosis; osteomyelitis and other musculoskeletal manifestations; leg ulcers; and spontaneous abortions (32). Despite the fact that some of these complications are fatal, many patients with SCD survive into their fifth and sixth decades in industrialized countries.

#### Treatment

The reasons for ICU admission may result from SCD-related or SCD-unrelated causes. ACS is the most frequent cause for ICU admission; it can be a life-threatening condition when it precipitates acute respiratory syndrome (ARDS) and multiorgan failure. Expanding on prior small studies, Cecchin et al. (33) showed that SC patients still face death in ICU with 7% mortality in 138 consecutive ICU admissions. About 20% of 119 SC patients required vital support including mechanical ventilation, vasopressors, and hemodialysis. This complicated outcome correlated to more rapid deterioration in the 48 hours prior to ICU transfer, rapidly declining hemoglobin, and progressive renal injury. Expert consensus holds that early recognition of deterioration and timely transfusion can abort an impending catastrophe (34). However, one should always remember the double-edged sword of transfusions. Because there is no clear evidence that transfusion therapy shortens a simple painful crisis, and because the crisis is unpredictable and self-limited, transfusion is not a treatment for the uncomplicated painful crisis. Urgent transfusions are needed when there is a severe sudden drop in hemoglobin, especially in children in whom splenic sequestration or aplastic crises present in this manner, and in severe ACS with hypoxia. Exchange transfusion is the most rapid method to reduce the hemoglobin S concentration to less than 30% in urgent situations that arise from complications of SCD, including stroke and cholestatic syndrome with signs of liver failure.

### TABLE 146.2 Clinical and Hematologic Findings in the Common Variants of Sickle Cell Disease after the Age of 5 Years

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Hemoglobin Electrophoresis</th>
<th>Hematologic Values&lt;br&gt;(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S (%)</td>
<td>F (%)</td>
</tr>
<tr>
<td>SS</td>
<td>Usually marked</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Sβ(+) Thal</td>
<td>Marked to moderate</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Sββ(−) Thal</td>
<td>Mild to moderate</td>
<td>&gt;60</td>
</tr>
<tr>
<td>SC</td>
<td>Mild to moderate</td>
<td>50</td>
</tr>
<tr>
<td>S HPFH</td>
<td>Asymptomatic</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

MCV, mean corpuscular volume; NRBCs, nucleated red blood cells.

*For findings in younger children, see Brown AK et al. (31).

**Hematologic values are approximate. There is tremendous variability between disease groups and between individual patients of the same group, particularly regarding clinical severity.

Adapted from NIH Publication No. 96–2117.
The goals of the SCD treatment are either to relieve symptoms of the complications or to prevent complications by using some of the new treatments targeting disease mechanisms. The treatment of the painful crisis is supportive. Dehydration, acidosis, infection, and hypoxemia all promote red cell sickling and should be prevented or corrected. Summary points regarding the treatment of SCD patients include:

- Sufficient analgesics should be used to relieve pain without worrying about addiction or side effects of opiates; patients can be given oral analgesics to take at home.
- Oxygen is often administered in sickle cell crisis, although its benefits are uncertain.
- Antibiotics that cover major pulmonary pathogens should be administered in patients with ACS.
- Chronic red cell transfusions have been shown to prevent strokes in patients with SCD.
- For patients undergoing general anesthesia, preoperative transfusion to a hematocrit above 30% reduced postoperative complications.
- Preventive treatments should include early vaccinations against S. pneumoniae and H. influenzae; prophylactic penicillin in children until the age of 5 years.
- Folic acid (1 mg daily) to all patients to prevent megaloblastic erythropoiesis.
- Hydroxyurea treatment should be reserved for patients with SCD who have severe complications.

Aplastic Crisis in Hemolytic Anemia

Pathophysiology

Sudden intensification of anemia in hemolytic disease resulting from a precipitous reduction in the rate of red cell production is known as aplastic crisis. It may occur in the course of any hemolytic disease but has been most commonly reported in congenital hemolytic disorders such as hereditary spherocytosis and sickle cell anemia. It is most common in children but also occurs in adults. Patients characteristically have fever, anorexia, nausea, and vomiting; abdominal pain and headache are common. Their anemia is usually severe and may be life-threatening; mild leukopenia and TP are often present. The episode is self-limited, and recovery usually begins by 2 weeks.

• Preventive treatments should include early vaccinations against S. pneumoniae and H. influenzae; prophylactic penicillin in children until the age of 5 years.
• Folic acid (1 mg daily) to all patients to prevent megaloblastic erythropoiesis.
• Hydroxyurea treatment should be reserved for patients with SCD who have severe complications.

Diagnosis and Treatment

Prompt recognition of this syndrome is important because of the suddenness and severity of the anemia. A low reticulocyte count in a patient with hemolytic disease is usually the main clue to the diagnosis. Treatment is via transfusion with RBCs. The volume given should be sufficient to alleviate signs or symptoms of inadequate tissue oxygenation; that amount need not be exceeded, as episodes are self-limited, and the patient’s hematocrit will return rapidly to its baseline level.

Leukopenias

The term leukopenia refers to a total white blood cell (WBC) count of less than 4,000 cells/μL, whereas granulocytopenia or neutropenia refers to a circulating granulocyte count below 1,500 cells/μL. WBC and granulocyte levels are lower in some ethnic groups, for example, Africans, African Americans, and Yemenite Jews, without any clinical significance. The clinical importance of granulocytopenia relates to the associated increased risk of bacterial infection. If the absolute neutrophil count is less than or equal to 500 cells/μL, bacterial infection becomes the rule. Agranulocytosis implies severe neutropenia or a complete absence of granulocytes. The pathophysiology of three patient groups is discussed below as most pertinent to critical care situations.

Primary Bone Marrow Diseases and Cytoxic Treatment

This is the largest and most frequent entity that causes neutropenia. Bone marrow diseases such as leukemias, myelodysplastic syndrome, and narrow fibrosis frequently present with neutropenia. Chemotherapy-induced neutropenia is a common complication of the treatment of cancer. The risk of life-threatening infections increases with the increased severity of neutropenia and its duration, increasing patient age, and the coexistence of other severe illnesses. Many of these patients, whether inpatient or outpatient, end up in the ICU due to a rapid onset of septic shock. In current practice, the occurrence of neutropenic fever is an indication for hospitalization and prompt institution of intravenous wide-spectrum antibiotics. Before starting antibiotics, cultures of blood, sputum, and urine should be obtained in all patients, and other sites should be cultured as indicated in individual patients. All patients should have chest radiographs taken as well. The common effects of bacterial infections—purulent sputum in pneumonia, pyuria in urinary tract infection, or abscess formation—are usually absent because of lack of granulocytes.

Bone Marrow Aplasia

Neutropenia is part of the pancytopenia commonly present in aplastic anemia. Some cases of aplastic anemia seem to have an autoimmune basis; in others, a drug or chemical exposure may be suspected as a cause; no tests are available to prove an association in individual cases. Benzene and its derivatives are potentially toxic to the bone marrow, and many other chemicals, such as dichlorodiphenyltrichloroethane (DDT) and other insecticides, are suspect. Toluene exposure in glue sniffers may be associated with aplastic anemia. Many medications have been linked with aplastic anemia, which occurs as an idiosyncratic reaction in a small percentage of patients exposed to a given drug. Drugs for which an etiologic role seems likely include chlorohemepnicol, phenylbutazone, indomethacin, diphenylhydantoin, sulfonamides, and gold preparations. In at least half the cases of aplastic anemia, no cause is found or suspected.

Immune and Drug-related Granulocytopenia

Neutropenia in adults often occurs as an isolated finding or in association with autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, and other similar conditions. The evaluation should include peripheral blood smear to seek

*When blood cultures are drawn, there should never be any less than two full sets—four bottles—drawn. This routine is needed to pre- vent the possibility of a contaminated specimen being overtreated, or worse, undertreated.
out large granular lymphocytes (LGL); measurement of antinuclear antibodies, rheumatoid factor, and other autoantibodies; and possibly a bone marrow examination. Patients with chronic neutropenia, either idiopathic or autoimmune, usually do not require treatment. Patients with an absolute neutrophil count less than 500 cells/μL are prone to develop recurrent fevers and infections. In addition to antibiotics, G-CSF administration may improve the neutrophil count during the infection. Patients with LGL syndrome may not respond well to G-CSF, and may require immunosuppressive therapy, such as methotrexate or cyclosporine, alone or with G-CSF. Chronic neutropenia in association with rheumatoid arthritis, or Felty syndrome, is usually seen in severe cases with elevated rheumatoid factor. These patients who have recurrent fevers and infection require treatment similar to patients with LGL syndrome; splenectomy should be considered in refractory cases.

Drug-induced agranulocytosis is a serious medical problem and occurs in 1% to 3% of patients treated with certain medications. The characteristic clinical syndrome includes high fever, chills, and severe sore throat (agranulocytic angina) caused by bacterial infection. Oral and pharyngeal ulcers, necrotizing tonsillitis, pharyngeal abscesses, and bacteremia may occur. The blood will demonstrate a virtual absence of granulocytes. The bone marrow may show absence of all granulocyte precursors or only the mature cells. The picture may superficially resemble acute leukemia, or a state of maturation arrest; the disease mechanism is often unclear. In some cases, it is an antibody against the drug acting as a hapten in association with endogenous antigen on neutrophil surface. Other drugs may impair production of neutrophils by direct toxic mechanism.

Serial blood counts are now recommended for patients on some drugs such as phenothiazines, clozapine, sulfasalazine, and antithyroid drugs because of the relatively high frequency of drug-induced neutropenia. Otherwise, management should include prompt withdrawal of all potentially offending drugs and the use of broad-spectrum antibiotics. Bone marrow examination is not usually indicated. The time to recovery may be proportional to the severity but is usually within about a week after withdrawal of the offending drug.

**Prophylactic Antibiotics and Treatment Approaches**

Many antibiotic regimens have been tested, and guidelines for a rational approach to therapy have been formulated (36). The choice of an antibiotic regimen should take into account any findings in the individual patient that suggest a specific site of infection and any knowledge of patterns of infection in a given institution. If cultures are positive, the antibiotic treatment should be adjusted accordingly. If cultures are negative, as is frequently the case, empirical therapy should be continued if the patient remains neutropenic and until counts recover. If, on the other hand, fever continues and the patient’s general condition deteriorates with persistent neutropenia, it is appropriate in selected patients to prescribe empirical treatment with an antifungal agent, such as amphotericin B, because of the frequency of fungal infections in patients with prolonged neutropenia. Patients should be screened by obtaining a CT scan of sinuses, chest, abdomen, and pelvis for possible foci of invasive fungal infections. The galactomannan antigen test for aspergillus should be done routinely on blood and sputum (usually bronchoalveolar lavage) of immunosuppressed patients with neutropenia. If patients have central venous catheter, fungal and bacterial blood cultures should be obtained1, and removal of catheters should be considered if blood cultures are positive for fungal infection or certain bacterial infections that are difficult to eradicate.

Various regimens of prophylactic antibiotics have been investigated for their efficacy in preventing infection in the neutropenic patient. The results have been too variable to justify blanket recommendations (37,38). The routine therapeutic use of colony-stimulating factors—such as G-CSF and GM-CSF—in febrile neutropenia to stimulate the proliferation and maturation of neutrophil progenitor cells was not recommended by the American Society of Clinical Oncology (ASCO). However, these factors should be considered in such patients at high risk for infection-related complications or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (>10 days) and profound (<0.1 × 10^3 cells/μL) neutropenia, age older than 65 years, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction, invasive fungal infection, or being hospitalized at the time of the development of the fever. On the other hand, colony-stimulating factors are recommended for primary and secondary prophylaxes used to prevent chemotherapy-induced neutropenia (39). I CU physicians should be aware of respiratory status deterioration or the development of ARDS during neutropenia recovery with or without the use of G-CSF (40,41). This could be related to the release of inflammatory cytokines by resident alveolar neutrophils and macrophages. Mortality can be as high as 62% in these patients, and therefore, immediate evaluation by bronchoscopy to rule out infection and early use of high-dose steroids could be critical for their survival.

The principles of treating infectious complications resulting from neutropenia in aplastic states are the same as those outlined earlier for neutropenia in malignant diseases. The treatment of aplastic anemia includes allogeneic bone marrow transplantation in suitable patients, immunosuppressive therapy including antithymocyte globulin, and other supportive care measures such as antibiotic prophylaxis and colony-stimulating factors.

**Thrombocytopenias**

TP is a common laboratory abnormality in ICU patients that has been associated with adverse outcomes. The incidence of TP—defined as a platelet count (PC) below 150 × 10^3 cells/μL—has been reported to be 23% to 41.3%, with mortality rates up to 54% (42). The incidence of more severe TP—less than 50 × 10^3 cells/μL—is lower, about 10% to 17%, but is associated with greater mortality (42,43). Two more recent studies showed hospital and ICU mortality were independently associated with moderate and severe TP (44,45). The relationship between the time course of platelet counts and mortality in 1,449 critically ill patients was examined in a prospective multicenter observational study in 40 ICUs from Europe, the United States, and Australia (42). There was a documented increase in mortality in patients who had TP on

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1The CDC recommends against the routine culturing of CVLs. However, in the neutropenic patient with difficult IV access, cultures could be obtained from the CVL as long as the preparation of the hub is acceptable.
The 4Ts score is the sum of the values for each of the four categories. Scores of 1–3, 4–5, and 6–8 are considered to correspond to a low, intermediate, and high probability of HIT due to immune mechanisms (47).

**Pathophysiology**

Systematic evaluation of TP is essential to the identification and management of the causes (43). There are numerous potential causes of TP in the ICU (Table 146.3). Although sepsis is the most common cause, accounting for more than 48% of TP cases in the ICU, more than 25% of ICU patients have more than one cause (46). Drug-induced thrombocytopenia (DIT) presents a diagnostic challenge inasmuch as many medications can cause TP, and critically ill patients often receive multiple drugs. One such drug is heparin, the most common cause of DIT due to immune mechanisms (47).

**Diagnosis**

A thorough history could elucidate the following: chronicity (familial thrombocytopenia), temporal relationship to a medication or travel history (tick-borne infection), past medical history of autoimmune disorders, infections, or malignancies; pregnancy status in premenopausal woman; recent medications and vaccinations (MMR); recent organ transplantation; ingestion of alcohol and quinine-containing beverages; viral hepatitis (hepatitis C) and other liver conditions associated with splenomegaly. Physical examination should focus on finding the cause and severity of the process. A hepatosplenomegaly could be the etiology of TP and bleeding in joints with findings the cause and severity of the process. A hepatosplenomegaly could be the etiology of TP and bleeding in joints with findings consistent with days 5–10 fall, but not clear (e.g., missing platelet counts); onset after day 10; or fall ≤1 day (prior heparin exposure 30–100 days ago) Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven) None

**TABLE 146.3 Potential Causes of Thrombocytopenia**

- Sepsis, infections
- Disseminated intravascular coagulopathy
- Perioperative and postresuscitation hemodilution
- Immune thrombocytopenias
- Drug-induced thrombocytopenias
- Liver disease/hypersplenism
- Massive transfusion
- Primary marrow disorder
- Antiphospholipid antibody syndrome/lupus anticoagulant
- Intravascular devices

over time—duration, speed of decrease or rise, etc.—should be considered to be associated with the prognosis. The following should be the rough guide to initiate a thorough workup (45,48):

- More than 30% decrease in PC
- Rapid decline in PC over 24 to 48 hours
- Failure to rebound after 5 to 7 days
- Decline in PC after initial recovery
- PC less than 100,000 cells/μL

Peripheral smear in the initial workup and in a specific clinical context can lead to the appropriate diagnosis (48):

- Platelet clumping is a common but a benign cause of TP and does not require any further diagnostics
- If the transfusion of blood products is associated with an abrupt PC fall within hours, TP can be caused by bacterial contamination or passive alloimmunization.
- Schistocytes in the context of TP and hemolytic anemia suggest potentially catastrophic conditions TTP/HUS and should obligate emergent workup.
- Blasts, nucleated RBCs and Pelger–Huet anomaly of neutrophils suggest underlying bone marrow process necessitating bone marrow aspirate (BMA) and biopsy.
- Macrospherocytes, RBC clumping or agglutination suggest autoimmune process.
- Lymphocytosis, atypical lymphocytes, neutrophilia, toxic granulation suggest underlying infection.
- Isolated TP requires astute clinical acumen and workup should be based on the clinical context with the differential diagnosis including the different entities mentioned in this section.

BMA is often not indicated in the initial workup and the information gathered often does not change the management. However in the context of severe sepsis if hemophagocytosis is suspected, BMA can be life-saving.

HIT, even though it is a rare cause of TP in ICU settings, should be suspected in the context of thrombosis and TP. The presence of anti-PF4/heparin antibodies alone cannot confirm the diagnosis given that the seroprevalence is high in ICU patients, being 10.8% on admission and increasing to 29.4% on day 7 (45,49). Therefore patients suspecting of having HIT after an initial antibody test need a confirmation with functional assays (e.g., serotonin release assay [SRA]). Given the low prevalence of HIT in ICU in comparison to incidence of TP, calculating 4Ts score is helpful and only patients scoring 4 or more should have heparin stopped and be tested further for HIT (Table 146.4) (50). A meta-analysis of 12 studies
applying 4Ts score reported a negative predictive value (NPV) of 99.8% (51). However, the addition of rapid particle gel immunoassay for PF4-H/PaGIA to the 4Ts score was better able to exclude HIT in patients with low or intermediate 4Ts score (52). This is on condition that the results of the immunoassay are available within 24 hrs.

**Treatment**

Multiple studies have shown TP to be associated with mortality, whether increasing PCs lead to decrease in mortality is yet to be established (44). Considering this, we suggest that the management of TP in the ICU is challenging and should address platelet transfusion, anticoagulation, and etiology-specific treatments (i.e., addressing the underlying cause). When TP is caused by destruction or sequestration of the patient’s own platelets, transfused platelets are subject to the same fate. Thus, platelet transfusions most often are of little benefit, and are reserved for the treatment of severe bleeding. Transfusion of one random donor platelet unit per 10 kg of recipient weight, or single-donor unit from apheresis, is usually used to achieve that goal, which can be confirmed by a repeat PC within an hour posttransfusion. The effectiveness of platelet transfusions is diminished in febrile, infected patients who may require larger and more frequent transfusions.

Platelet prophylaxis, as compared with a therapeutic transfusion strategy, has shown interval reduction in bleeding in hospitalized patients with therapy-induced hypo proliferative thrombocytopenia. Per the AABB 2015 guidelines, patients with less than 10,000 platelets/μL should be transfused (53). This recommendation is based on two trials in which prophylactic platelet transfusions to achieve counts greater than 10,000 cells/μL had reduction in severe bleeding (54,55). The evidence for platelet transfusion in the setting of instrumentation-placement of central venous catheter (CVC) and lumbar puncture (LP), is weak. Based on several observational studies, a CVC placement obligates a PC of greater than 20,000 cells/μL and for an LP, a PC of greater than 50,000 cells/μL is desired (53).

For patients undergoing invasive surgery, the recommendations are now based on the locations and type of surgery. Per AABB 2015 guidelines, nonbleeding patients can undergo major nonneuraxial surgery with PC more than 50,000 cells/μL; patients undergoing neuraxial surgery have a threshold set at a PC of greater than 100,000 cells/μL.

In patients with sepsis, there is not much evidence for the threshold for transfusion, but given the underlying consumption potentially causing acute drop in PC, maintaining higher PC could be considered (45). In the setting of severe hemorrhage, patients should be considered for transfusion if PC is less than 30,000 cells/μL (48). Following the transfusion, depending on the context, a posttransfusion PC could be checked within 1 hour; this would be helpful in conditions where transfusion refractoriness is suspected (spleenomegaly, sepsis, fever, medications, active bleeding, and alloimmunization).

Chemoprophylaxis, using unfractionated heparin (UFH) or low–molecular-weight heparin (LMWH), is usually prescribed routinely in all adult patients admitted to the ICU, except when the PC is less than 30,000 cells/μL or when there is a major risk of hemorrhage (48). In a retrospective multivariate analysis, LMWH was found to have a lower risk of bleeding in all patients with TP, and therefore should be the preferred agent unless contraindicated (44).

**Thrombocytopenia with Infection**

Mild and transient TP occurs with many systemic infections; the mechanism for this may be a combination of suppressed bone marrow production, increased destruction, and increased splenic sequestration. In bacteremia, platelets may be consumed because of DIC, whereas in viral infection, platelet production may be suppressed. TP is commonly associated with human immunodeficiency virus (HIV) infection, mainly due to decreased production, although sometimes an autoimmune mechanism is also involved. TTP or TMA may be associated with HIV as well as other infections, such as streptococcal and *Escherichia coli* (56–58). Treating the underlying infection in most cases is usually adequate to correct the TP.

**Drug-Induced Thrombocytopenia**

DIT presents a diagnostic challenge because many medications can cause TP, and patients in ICU are often on multiple medications (59). The most commonly reported drugs with probable or definite relation to TP were quinidine, quinine, rifampin, and trimethoprim-sulfamethoxazole. Many other drugs can cause TP, including heparin, which is discussed in detail below, intravenous antibiotics, anticonvulsants, diuretics, and the platelet GP IIb/IIIa antagonists used in acute coronary syndrome. The underlying mechanism of DIT is usually immune, and at least three different types of antibodies appear to play a role: hapten-dependent antibodies, drug-induced platelet-reactive autoantibodies, and drug-dependent antibodies. Targets for drug-dependent antibodies are glycoproteins (GP) on the cell membrane of platelets, such as GP IIb/IX and GPIIb/IIIa. The diagnosis of DIT is usually supported by recovery to a normal PC within 5 to 7 days.

Treatment of DIT may only require withdrawal of the offending drug. Prednisone may be given if the diagnosis of idiopathic autoimmune thrombocytopenia (ITP) cannot be ruled out. Patients with severe TP caused by GP IIb/IIIa antagonists may require platelet transfusions because they are typically also receiving heparin and aspirin for their acute coronary syndrome. Although platelet serology tests are available, the results may not be available in a time frame that allows such information to be used in the decision-making process for drug-induced immune thrombocytopenia.

**Heparin-Induced Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is an anticoagulant-induced prothrombotic disorder caused by platelet activation of heparin-dependent antibodies of the immunoglobulin G class. The diagnosis of HIT should be considered when the PC falls to less than 150 × 10^3 cells/μL, or more than 50% decrease of the PC from baseline, between days 5 and 14 from start of heparin therapy; a high index of suspicion on the physician’s part is key in making the diagnosis. The TP is usually moderate and resolves within a few days of discontinuing heparin. HIT without thrombosis is called isolated HIT, whereas HIT thrombotic syndrome (HITTS) denotes HIT complicated with thrombosis. The mortality rate associated with HIT ranges between 10% and 20%.
HIT is an immune-mediated hypersensitivity reaction to platelet factor 4 (PF4)/heparin complex. PF4 is a heparin-binding protein found naturally in platelet α granules, which undergoes conformational changes once bound to heparin. Anti-PF4/heparin antibodies are produced by many patients taking heparin, but only a few will develop TP. Anti-PF4/heparin antibodies are transient and usually become undetectable within a median of 50 to 85 days. If heparin is readministered to a patient with high levels of HIT antibodies, abrupt TP can occur. However, this likely will be more than 100 days after the last exposure to heparin. It is important to note that seroconversion can be found by ELISA (enzyme-linked immunosorbent assay) in up to 15% of patients on heparin; however, this does not constitute a diagnosis of HIT. In general, surgical patients, individuals exposed to higher doses of heparin for a longer time, and patients receiving UFH, as opposed to LMWH, are more likely to develop HIT.

The frequency of HIT in ICU patients was examined in two major studies (56,57). The results suggested that only a small minority of ICU patients with TP receiving UFH have HIT, and that the PF4/heparin-reactive antibodies are more likely to be detected by ELISA assay than SRA, suggesting a possible over diagnosis—due to a high false-positive rate by ELISA—of HIT. The Complications After Thrombocytopenia Caused by Heparin (CATCH) registry is a recent attempt to achieve better understanding of the prevalence, consequences, and temporal relationship of HIT and TP among patients treated with anticoagulants. The thrombotic sequelae of HIT carry significant morbidity and may even be lethal. Some of the morbidity events include deep venous thrombosis (DVT), pulmonary embolism, skin necrosis, limb ischemia, thrombotic stroke, and myocardial infarction. Venous thrombosis is the most common manifestation, with lower limb DVT predominating.

All strategies should be used to prevent HIT in ICU patients. Heparin locks for central venous catheters and hemodialysis catheters are commonly used in the ICU setting and may need to be reconsidered. Hemodialysis without heparin has been shown to be safe and effective. However, once the diagnosis of HIT is recognized, heparin should promptly be substituted with a direct thrombin inhibitor, such as argatroban or lepirudin, or the heparinoid danaparoid—which is not available in the United States—to reduce the risk of life-threatening thromboembolic events. Because warfarin can temporarily reduce the synthesis of protein C and S, causing a hypercoagulable state, it should never be used alone in the initial treatment of HIT, and its use should be postponed until substantial platelet recovery has occurred. Consultation with a hematologist in these situations should be considered in all critically ill patients. The argatroban dose is 2 μg/kg/min in continuous infusion and dilution of 1 mg/mL. Dose adjustment is needed for hepatic impairment (use 25% of the dose), with the aim of a 1.5 to 3 times prolongation of activated partial thromboplastin time (aPTT) in comparison to baseline. On the other hand, lepirudin treatment consists of a bolus 0.4 mg/kg (maximum of 44 mg), given over 10 to 15 seconds and followed by continuous infusion at 0.15 mg/kg/hr, with the goal of a 1.5 to 3 times prolongation of aPTT over baseline. The dose should be modified if creatinine is more than 1.5 mg/dL or clearance is less than 60 mL/min. If given with warfarin, discontinue lepirudin when an international normalized ratio (INR) of 2.0 is obtained.

**IDIOPATHIC THROMBOCYTOPENIC PURPURA**

**Pathophysiology and Diagnosis**

ITP, also known as immune thrombocytopenic purpura, is a common cause of TP in both adults and children. Although it is usually in the differential diagnosis of TP, the diagnosis of ITP can usually be made only after exclusion of other causes. When the history, physical examination, and blood count with peripheral smear are consistent with ITP and do not suggest other causes of TP, few diagnostic tests are necessary. Bone marrow examination may be important to rule out other primary marrow diseases such as myelodysplastic syndrome or lymphoproliferative disorders. In ITP, the marrow will show an increased number of megakaryocytes with immature forms and normal erythroid and myeloid lineages. A test for HIV is important in patients with risk factors for infection with this agent. Tests for platelet antibodies are not helpful because of lack of limited specificity and sensitivity. Thrombocytopenic purpura also may occur as one of the autoimmune complications of collagen vascular diseases such as systemic lupus erythematosus, or lymphoproliferative diseases such as chronic lymphocytic leukemia, and may even be the presenting manifestation of these disorders. ITP is categorized as acute, chronic, and refractory.

**Treatment**

Many forms of treatment have demonstrated effectiveness in ITP. Because of the numerous therapeutic options, individualization of therapy is possible. Platelet transfusions are used only in the case of severe, life-threatening hemorrhage. Initial therapy is usually with corticosteroids in a dosage equivalent to 1 mg/kg/day of prednisone. If the PC does not rise substantially within 2 to 3 weeks, splenectomy is usually the next step. Splenectomy produces prolonged remissions in two-thirds of cases, with additional partial remission in 15% of patients. Splenectomy also may be necessary in patients who have responded to steroids but cannot be weaned from the drug without the recurrence of thrombocytopenia. The 10% to 20% of patients who fail to respond to splenectomy may benefit from treatment with vincristine or immunosuppressive agents such as cyclophosphamide. The anabolic steroid, danazol, when given for periods of several months, also has been effective in some cases of ITP. Large doses of intravenous gamma globulin also may increase the PC in ITP, perhaps through blockage of reticuloendothelial sites of platelet destruction. The high cost of this therapy and the short duration of responses—usually 2 to 3 weeks—limits its use to certain specific circumstances such as active bleeding or prior to surgery. Anti-D therapy is effective only in Rh(D)+ patients and is not effective in splenectomized patients. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to be effective in chronic ITP. The overall goal in treating chronic/refractory ITP is to maintain a safe PC, defined as greater than about 10,000 to 20,000 cells/μL, and minimal therapy to minimize the morbidity and mortality associated with treatment.

When ITP occurs during pregnancy, there is an additional concern that the IgG autoantibody may cross the placenta and produce TP in the fetus and newborn. The lowest PC is
usually seen several days after birth. The current practice is to use standard obstetric management of pregnancy and delivery. ITP should be differentiated from gestational TP that occurs in about 5% of normal women with uncomplicated pregnancies. The most important clue to differentiating the two is a history of previous TP when the woman was not pregnant. Additionally, more severe TP occurring before the third trimester is more likely to be ITP.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Pathophysiology and Diagnosis

TTP and its closely related disorders—HUS, TMA, and peripartum HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome—may be catastrophic and rapidly fatal. This disease entity was discussed in the first section of this chapter in regard to microangiopathic hemolytic anemia. TTP was defined by a pentad of abnormalities: TP from increased platelet destruction; microangiopathic hemolytic anemia caused by mechanical damage to red cells as a result of the vascular lesions; neurologic abnormalities; renal abnormalities; and fever. With the advent of curative plasma exchange in the 1970s, the urgency to establish a diagnosis and start treatment has resulted in using limited diagnostic criteria. Now only TP and microangiopathic hemolytic anemia are sufficient to begin plasmapheresis.

The clinical presentation is variable, but the TP and hemolytic anemia are often severe. A wide variety of fluctuating neurologic abnormalities may be present, including seizures, altered consciousness, delirium, and paresis. Renal abnormalities may include uremia, hematuria, and proteinuria. The reasons for fever are unclear. The typical presentation for young children is to have a prodrome of bloody diarrhea caused by the Shiga toxin-producing enterohemorrhagic strain of E. coli. The laboratory findings in TTP are basically those related above: TP, hemolytic anemia with red cell fragmentation, and renal dysfunction. Elevation of serum lactic acidosis and outcome. Plasma infusion is less effective in adults, but plasma exchange has dramatically changed TTP-HUS prognosis and outcome. Plasma infusion is less effective in adults, but it may be adequate in congenital TTP caused by ADAMTS13 deficiency. The duration of plasma exchange is unpredictable. Long durations, up to several months, may be required in patients with repeated relapses. The efficacy of additional treatments such as prednisone, platelet aggregation inhibitors, and splenectomy is unknown (see http://moon.ouhsc.edu/jgeorge).

Alcoholism-Associated Thrombocytopenia

Platelet counts less than 100,000 cells/μL are present in over one-fourth of critically ill alcoholic patients. There are many possible causes for TP in such patients, including hypersplenism and folic acid deficiency. However, it is important to recognize that reversible severe TP may occur as a direct effect of alcohol ingestion in some patients. Studies of the mechanism have demonstrated elements of both decreased effective platelet production and shortened platelet survival; abnormalities of platelet function have been noted as well. Recovery begins 2 to 3 days after cessation of alcohol ingestion, and maximum PC is reached in 1 to 3 weeks. There is often an overshoot to abnormally high platelet counts, which then return to baseline levels. Therapy consists of having the patient discontinue alcohol ingestion and providing appropriate supportive measures.

Thrombocytopenia Associated with Bone Marrow Disorders

Severe TP from impaired platelet production is a frequent concomitant of bone marrow disorders, such as aplastic anemia, leukemia, or other malignancies metastatic to the bone marrow, as well as cytotoxic chemotherapy of such disorders. Treatment is directed at the underlying disease.

INCREASED BLOOD COUNTS

Erythrocytosis

Erythrocytosis, defined as an abnormally increased red cell mass, may require critical care due to complications of blood hyperviscosity or because of hemorrhagic or thromboembolic complications that may threaten these patients. The initial clue to the presence of erythrocytosis is usually a high value for hematocrit or hemoglobin concentration. Such values may be present without true erythrocytosis—that is, in the presence of a normal red cell mass—if the plasma volume is contracted. This circumstance is usually apparent, although it is often advisable to quantify the red cell mass (RCM) by direct measurement using radioisotopic red cell labels. The RCM is usually increased when the hematocrit is above 60% in a man or 57% in a woman.

Pathophysiology

True erythrocytosis results from one of two general mechanisms:

- Polycythemia vera (PV) is a clonal abnormality of bone marrow stem cells resulting in autonomous overproduction of red cells and often of granulocytes and platelets;
- Secondary erythrocytosis results from excess erythropoietin production in response to hypoxemia, abnormalities of oxygen release from hemoglobin, or autonomous hormone production (e.g., by renal or other tumors).

When the RCM is expanded and the hematocrit increased, blood viscosity is increased, and diminished blood flow, stasis, thrombosis, and tissue hypoxia may ensue. On the other hand, hemorrhagic tendency is also increased, particularly in PV, where elevated platelet counts and abnormalities of platelet function may also be present.
Diagnosis

Criteria for the diagnosis of PV have been modified multiple times since the first criteria were published by Modan and Lifshitz in 1965; modified diagnostic criteria are shown in Table 146.5 (64). The detection by PCR of Janus kinase 2 (JAK2) tyrosine kinase in up to 97% of patients with PV increases the sensitivity and specificity of early diagnosis. The JAK2 V617F point mutation makes hematopoietic progenitors hypersensitive to the different growth factors, resulting in proliferation of all lineages (65). Risks in uncontrolled PV are primarily hyperviscosity and thromboembolic or hemorrhagic events. Symptoms resulting from decreased cerebral flow, such as headache, dizziness, and changes in vision are the most common manifestations of hyperviscosity. Hemorrhage or thrombosis can affect almost any body part; peptic ulcer disease with bleeding is common and thromboses may be arterial or venous. Fatigue, pruritus, particularly with hot bath, excessive sweating, paresthesias (erythromelalgia), fullness in the left upper abdomen (splenomegaly), and shortness of breath are also some manifestations of PV. Surgery poses an enormous risk in the patient with uncontrolled PV because of a high incidence of thrombotic or hemorrhagic complications.

The diagnosis of secondary erythrocytosis is made in a patient with an increased RCM in whom the criteria for PV are not met. These patients could either have physiologically appropriate increased RCM (e.g., secondary to tissue hypoxia) or inappropriate increased RCM (e.g., secondary to increased erythropoietin production). Additional studies are needed to differentiate the diverse causes of polycythemia.

Treatment

Patients with uncontrolled PV may present as medical emergencies requiring ICU care and urgent therapy. The mainstay of such therapy is phlebotomy to reduce hematocrit to less than 45%. This may be done as rapidly as 1 unit of blood every other day in young adults. Electrolyte solutions or plasma expanders should be administered with phlebotomy, as necessary, to avoid circulatory instability from sudden changes in blood volume. Elderly patients may tolerate phlebotomy less well, so that removal of volumes of 200 to 300 mL at less frequent intervals may be necessary. Because of the clinical observations of increased thrombosis with aggressive phlebotomy, the simultaneous use of cytotoxic chemotherapy is recommended as part of the initial therapy of patients older than 60 years of age, as well as in younger patients with thrombotic risk factors or a history of thrombosis. Hydroxyurea is often used for this purpose in an initial dose of 15 to 30 mg/kg/day. Emergency platelethapheresis may also be considered in such emergencies to lower an elevated platelet count. The FDA approved a new drug in December 2014, Jakafi (ruxolitinib, a JAK2 inhibitor), to be used in PV patients who have an inadequate response to or intolerance to hydroxyurea.

Other treatment options include low-dose aspirin (81 mg/day), interferon-α, and anagrelide; these may be used together with phlebotomy as needed. In general, patients with PV should avoid practices and habits that augment hypercoagulability such as smoking, use of oral contraceptives, or hormone replacement therapy. Aggressive antithrombotic prophylaxis should be given postoperatively in addition to maintaining normal hematocrit and platelet counts.

Indications for phlebotomy in secondary erythrocytosis are less clear than in PV. The best current advice is to individualize therapy so as to maximize the patient’s exercise tolerance and overall sense of well-being.

TABLE 146.5 Proposed Modified Criteria for the Diagnosis of Polycythemia Vera

<table>
<thead>
<tr>
<th>Symptom categories</th>
<th>Diagnostic scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>A2</td>
</tr>
<tr>
<td>Raised red cell mass (&gt;25% above mean normal predicted value, or a hematocrit value &gt;50% in males or &gt;56% in females)</td>
<td>Absence of causes of secondary erythrocytosis</td>
</tr>
<tr>
<td>A1 + A2 + A3 or A4 establishes polycythemia vera.</td>
<td>A1 + A2 + two of B establishes polycythemia vera.</td>
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Thrombocytosis

With the availability of a PC as part of a routine blood count, an elevated platelet count, or thrombocytosis, has become an important clinical problem in hospitalized patients. Unlike TP, the literature dealing with thrombocytosis in ICU patients is very scant, however the presence of thrombocytosis predicts a favorable outcome in ICU patients, whereas a blunted rise in PC may be associated with worse outcome.

Pathophysiology and Diagnosis

Thrombocytosis in hospitalized patients is classified into primary (clonal) and secondary (reactive) forms. Primary thrombocytosis refers to a persistent elevation of PC due to clonal thrombopoiesis, as it occurs in myeloproliferative disorders including essential thrombocythemia (ET), PV, myelodysplastic syndrome, chronic myelogenous leukemia, and primary myelofibrosis (PMF). The discovery of JAK2 V617F and MPL exon 10 mutations allows for the positive identification of ET in more than 50% of patients, although differentiation from PV and PMF is still needed. Secondary thrombocytosis is due to various conditions, some of them short-lived, such as acute bleeding, infection, trauma or other tissue injury, and surgery; other causes, such as malignancy, postsplenectomy, chronic infection, iron deficiency, or chronic inflammatory disease may persist for a longer time. Multiple studies have been conducted on adult and pediatric hospitalized patients (66–70) with an elevated PC (>500 x 10³ cells/μL), and the main conclusions suggest that whereas most patients have secondary thrombocytosis, a higher PC and increased thromboembolic complications are significantly associated with primary thrombocytosis. In one study, even when using greater than or equal
to 1,000 × 10⁹ cells/μL as the basis for defining extreme thrombocytosis, 82% of 231 patients analyzed were found to have an elevated PC due to reactive (secondary) thrombocytosis (71). In this study, the risk of bleeding and/or thrombosis was 56% in primary thrombocytosis, but only 4% in the secondary type. Unless additional risk factors are present, secondary thrombocytosis is not associated with an increased risk of thromboembolic events.

Treatment

Treatment for primary thrombocytosis, such as ET, is based on risks for thrombosis or bleeding in the presence of vasomotor symptoms. Patients at increased risk (age >60 years, history of thromboembolism, PC >1,500,000 cells/μL) should receive platelet-lowering agents such as hydroxyurea, anagrelide, or interferon-α (IFN-α). Low-dose aspirin can be used for the relief of vasomotor symptoms, but if there is no relief, platelet-lowering agents should be added. Hydroxyurea is the recommended drug in patients 60 years of age or older, whereas IFN-α is the cytodestructive agent of choice for childbearing women. The aim should be to lower the PC to less than 400,000 cells/μL. Arterial or venous thrombosis should be treated with heparin and, possibly, thrombolysis in some arterial events; plateletpheresis may be indicated in both types of events. Low-dose aspirin may be useful in arterial thrombosis. In hemorrhage, it is appropriate to stop antiplatelet agents and transfuse platelets if the bleeding is persistent. Some patients with uncontrolled thrombocytosis (>1,500,000 cells/μL) were found to have an acquired defect of von Willebrand factor, which contributes to the risk of bleeding. Thus, DDAVP, cryoprecipitate, or factor VIII concentrate may be indicated to treat hemorrhage in these patients.

LEUKOCYTOSIS

Pathophysiology

As in thrombocytosis, leukocytosis can be due to primary bone marrow disorders or secondary disorders in response to acute infection or inflammation. Secondary leukocytosis is physiologic and transient, resolving after treating the underlying cause. Leukemoid reaction refers to a persistent leukocytosis of more than 50,000 cells/μL, with shift to the left. The major causes for such a reaction include severe infections, severe hemorrhage, acute hemolysis, hypersensitivity, and a malignancy-induced paraneoplastic syndrome.

Diagnosis

Leukocytosis due to a primary bone marrow disorder with uncontrolled clonal growth of immature cells can result in an emergency situation known as the hyperleukocytosis syndrome. This occurs in leukemic states when the WBC count is high. Signs and symptoms are most commonly related to the central nervous system, eyes, and lungs. They include stupor, altered mentation, dizziness, visual blurring, retinal abnormalities, dyspnea, tachypnea, and hypoxia. Intracranial and pulmonary infarction or hemorrhage and sudden death may occur. Priapism and peripheral vascular insufficiency have also been linked with the syndrome. Although the pathogenesis is incompletely understood, autopsies have shown white cell aggregates, microthrombi, and microvascular invasion (leukostatic tumors). The syndrome occurs more commonly in acute (AML) and chronic myelogenous leukemia (CML) than in acute lymphoblastic leukemia, and occurs rarely, if ever, in chronic lymphocytic leukemia. The level of the WBC count at which the syndrome appears is variable, depending perhaps on the maturity and size of the white blood cells present and the degree of coexisting anemia. A white count exceeding 100,000 cells/μL in acute myelogenous leukemia or the accelerated phase of CML is usually an alarming sign and an indication for prompt treatment.

Treatment

If there are signs or symptoms attributable to the hyperleukocytosis syndrome, then leukopheresis is indicated to rapidly and safely decrease the white count. At the same time, chemotherapy should be initiated, and treatment with allopurinol and intravenous hydration with urine alkalinization should be started in anticipation of the hyperuricemia. Hydroxyurea (6 g by mouth) is frequently used initially to produce rapid leukemic cell kill.

OTHER HEMATOLOGIC DISORDERS

Plasma Cell Dyscrasias

The presenting symptoms for these malignant disorders may include severe infection, spinal cord compression, or hyperviscosity syndrome that can lead to admission to the ICU. Total serum protein will be abnormally high on routine chemistry blood test. Subsequent evaluation will reveal an IgM monoclonal gammopathy in Waldenstrom macroglobulinemia or IgG/IgA in multiple myeloma. Hyperviscosity syndrome is rare and less frequent when IgG or IgA, respectively, are the abnormal proteins. The most common manifestations of the hyperviscosity syndrome are neurologic and include headache, visual disturbances, hearing loss, vertigo, altered consciousness—ranging from stupor to coma—paresis, seizures, and peripheral neuropathy. A bleeding tendency may exist because of the associated TP or interference by the abnormal protein with the function of platelets or plasma coagulation factors. The most rapidly effective form of therapy for hyperviscosity from serum protein abnormalities is plasmapheresis. At the same time, hydration and specific therapy for the underlying disease should be started.

STEM CELL TRANSPLANTATION

Patients after stem cell transplantation (SCT)—mainly allogeneic—constitute a large proportion of those with hematologic disorders who are admitted to the ICU. These patients are usually admitted with respiratory distress requiring mechanical ventilation, multiorgan failure, or septic shock, and have the highest mortality among cancer patients admitted to the ICU (72,73). Because of the generally poor outcome, especially for patients requiring mechanical ventilation, the utility of such support has been questioned (74,75). It is generally accepted that patients admitted to the ICU during the
engraftment period should be fully supported because of better outcome (76). These patients may have the engraftment syndrome, which can result in cytokine-induced capillary leak syndrome with multiorgan failure or alveolar hemorrhage; early high-dose steroids can dramatically reverse the downhill course. These patients should also undergo bronchoscopy to rule out infection while receiving the steroid therapy. Early intervention and transfer to ICU in septic shock will result in improved outcome. After autologous SCT, patients usually have better survival in the ICU than after allogeneic SCT, even those requiring mechanical ventilation.

Admission to the surgical ICU is less frequent for patients after SCT, but some of the most frequent reasons include intestinal perforation and intracranial bleeding. This topic is dealt with in more detail elsewhere in this textbook.

**Key Points**

- Benign and malignant hematologic disorders are frequently encountered in patients admitted to the intensive care units. Some of these disorders develop while patients are in the ICU for other reasons, such as anemia, HIT, TTP, and other drug-induced cytopenias.
- Other disorders are the primary reason for admission to the ICU and include neutropenic fever and septic shock, respiratory distress, serious life-threatening bleeding, and other disease-specific and chemotherapy-related complications.
- Familiarity with these problems and the early involvement of the hematology service in the evaluation and treatment of these specific entities are essential for better outcome and improved survival.
- The approach to patients with suspected (4Ts score 4 or more) or confirmed HIT includes the following:
  - Discontinuation of all heparin.
  - Administration of alternative nonheparin anticoagulation, such as argatroban or lepirudin.
  - Testing for anti-PF4/heparin antibodies, followed, if positive, by an SRA.
  - Avoiding prophylactic platelet transfusions.
  - Allowing platelet recovery before starting warfarin.
  - Assessing for lower extremity DVT.
- Patients with previous HIT:
  - Those who are antibody-negative and require cardiac surgery should receive UFH in preference to other anticoagulants, which are less validated for this purpose.
  - Preoperative and postoperative anticoagulation should be handled with an anticoagulant other than UFH or LMWH.
  - Patients with recent or active HIT should have surgery delayed until antibody is negative, if possible; otherwise, an alternative anticoagulant should be used (77).

### References


34. Rice L, Teruya M. Sickle cell patients face death in the ICU. JAMA. 2014;312(12):1261.


