CELLULAR COMPONENTS

Hematopoiesis is a polyclonal process that is 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. In the early 1960s, Till and McCulloch began analyzing the bone marrow to find out which components were responsible for regenerating blood. They defined what have remained the two hallmarks of an HSC: it can renew itself, and it can produce cells that give rise to all the different types of blood cells (1). Now it is also known that these cells 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 unnecessary 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 lymphoid (T, B, and natural killer lymphocytes), myeloid (granulocytes, monocytes), erythrocytes, and megakaryocytes (platelets) cell lineages, while maintaining sufficient numbers of pluripotent stem cells to sustain hematopoiesis throughout adult life. These cells can be found in a small population of cells characterized by the surface expression of CD34 molecule and by lack of markers of differentiation.

The production of differentiated blood cells is the real work of HSCs and progenitor cells. Progenitor or precursor cells are partially differentiated cells that divide and give rise to differentiated “specialized” cells. Such cells are usually regarded as “committed” to differentiating along a particular cellular development pathway. The HSC population supports a tremendous production of blood cells over an animal’s life span, e.g., 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 hematopoietic stem cell 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 these stem cells, 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 innate 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). Under normal conditions, most HSCs and many progenitors are quiescent in the G0 phase of the cell cycle; however, many of the more mature progenitors are proliferating and producing mature offspring (7). In the absence of any stresses, this is balanced by the rate of apoptosis in progenitors and mature cells (5).

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 (8); additionally, fewer progenitors and mature cells undergo apoptosis (9,10). Furthermore, quiescent progenitors and HSCs are stimulated by various growth factors to proliferate and differentiate into mature white cells, red blood cells, 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.

Humoral Mediators

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. As the progenitors differentiate, the phenotype-specific receptors evolve so that only certain cytokines can affect these new and more mature cells, while others maintain stem cell self-renewal and expansion (11). 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. These include erythropoietin (epoetin alfa, or long-acting darbepoetin alfa) for erythrocyte production, granulocyte colony-stimulating factor (G-CSF, filgrastim or long-acting pegfilgrastim), and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) for neutrophil production, as well as stem cell harvest for transplantation and interleukin-11 (oprelvekin) for...


**DECREASED BLOOD COUNTS**

Anemias

Anemia (hemoglobin concentration less than 12 g/dL) is present in 95% of patients to the intensive care unit, with about one third of those having upon admission concentration of less than 10 g/dL. In the assessment, particular attention should be paid to the time of onset, patient's ethnic origin, concurrent illness, procedures patient has undergone, drugs patient is receiving, and history of transfusions. One practical approach is to classify anemia into two major categories: anemia resulting from underproduction versus anemia due to increased destruction of red blood cells (RBC) (Table 173.1). These considerations will affect the type of laboratory tests and the need for transfusions.

Every effort should be exerted to obtain diagnostic tests prior to any transfusions. These should include a complete blood count, including hematocrit, hemoglobin, mean corpuscular volume (MCV) and hemoglobin (MCH), a reticulocyte count, and a stained blood smear. In addition, serum bilirubin and lactate dehydrogenase are useful to determine the presence of hemolysis. If immune hemolysis is suspected, direct Coombs test should be ordered (indirect Coombs test is done routinely with any cross-match request sent to the blood bank), or if hemoglobinopathy is suspected, hemoglobin electrophoresis should be obtained before transfusion.

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 and/or with critical illness (17). 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 (17–19). 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.

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**Table 173.1**

**ANEMIA CLASSIFICATION**

<table>
<thead>
<tr>
<th>ANEMIAS SECONDARY TO MARROW</th>
<th>UNDERPRODUCTION</th>
</tr>
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<tbody>
<tr>
<td>Decreased erythropoietin production</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Endocrine deficiency</td>
<td>Stimulation</td>
</tr>
<tr>
<td>Inadequate response to erythropoietin</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Folic acid deficiency</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>Anemia due to marrow failure</td>
<td>Marrow infiltration</td>
</tr>
<tr>
<td>Congenital erythropoietic anemia</td>
<td>Sideroblastic anemia</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>Tissue failure</td>
</tr>
<tr>
<td>Toxic marrow damage</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ANEMIAS SECONDARY TO INCREASED DESTRUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
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</table>

TTP, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular coagulation.
Patients with acute myocardial infarction or unstable angina (17), and some cancer patients, may benefit from a higher hemoglobin level. Patients with a hemoglobin greater than or equal to 10 g/dL are unlikely to benefit from blood transfusion.

Anemia in Critical Illness

Anemia of hemoglobin less than or equal to about 8.5 g/dL is the most frequent type of anemia encountered in the ICU. As a result, more than 50% of these patients receive RBC transfusions during their ICU stay, as do more than 85% of patients with an ICU length of stay longer than 7 days. This trend was confirmed by two more recent studies: the CRIT study in the United States (20) and the ABC trial in Europe (21). Both studies also showed that the number of RBC transfusions a patient received was independently associated with longer ICU stay and increase in mortality. These and other similar epidemiologic studies have 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.

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 proinflammatory 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 (19).

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 (22). This discovery should lead to studies focused on the role of hepcidin in the anemia of the critically ill patient and better understanding of its pathogenesis.

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 (23,24). Since 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, because there have been anaphylactoid reactions reported with iron dextran, iron gluconate is the preferred formulation. Iron gluconate is administered at a dose of 125 mg diluted in 100 mL saline over 1 hour infusion or undiluted at a rate of 12.5 mg/minute daily for eight sessions, to a total cumulative dose of 1,000 mg.

Autoimmune Hemolytic Anemia

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 (greater than 2) identifying the mechanism of the anemia as hemolytic, 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. 173.1). In some instances, the urine may be discolored
red, brown, or black if there has been sufficient intravascular hemolysis to produce hemoglobinuria. A positive result on direct antiglobulin (Coombs) testing indicates that immunoglobulin or complement is on the surface of the circulating red cells, identifies the immune etiology of the hemolysis. In the absence of recent transfusion, the diagnosis of AIHA is confirmed. 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. The mechanisms whereby drugs produce immune hemolysis are not absolutely clear, but evidence suggests an alteration of red cell surface antigens by the drug and production of antibodies that lead to hemolysis (25). 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 (26). In some instances, the AIHA may be the presenting manifestation of the underlying disease. In other instances, the AIHA may be associated with idiopathic thrombocytopenic purpura (ITP) as part of Evans syndrome.

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 gammaglobulin, rituximab chimeric anti-CD20 antibody, alemtuzumab humanized anti-CD52 antibody, or treatment with 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 red blood cells 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 the patient with AIHA with a critical degree of anemia, transfusion must be considered (27,28). It may be possible to find compatible red blood cells 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 or eicosanoids.

In massive hemolysis, therapeutic efforts should be directed at maintenance of blood pressure, renal blood flow, and urinary output. Intravascular fluids and diuretics such as furosemide should be used to maintain a urine flow of 100 mL/hour.

**Hemolytic Anemia from G6PD Deficiency**

Red blood cell 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 U.S. 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%) (29). The red cell G6PD levels in affected men are 8% to 20% of normal. Clinically significant hemolysis occurs when red cells are subjected to an oxidative metabolic challenge, as may occur with exposure to certain drugs or with certain illnesses. 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.

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**

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—for example, heart valves, vascular grafts, and shunts—and disorders affecting blood vessels that
result in microangiopathic hemolytic disease, such as disseminated intravascular coagulation or thrombotic microangiopathy (TMA).

TMA encompasses the spectrum of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome. 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 (30). Because hemolysis is intravascular, hemoglobinemia and hemoglobinuria may be present. Characteristically, the blood smear shows red cell fragmentation producing micropoikilocytes (schistocytes, similar to that shown in Fig. 173.1). Typically, the TMA patient will also have thrombocytopenia, fever, and possibly neurologic and renal involvement.

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. 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.

**Sickle Cell Anemia**

Sickle cell hemoglobin (hemoglobin S) is the result of a single nucleotide mutation in the sixth codon of the \( \beta \) globin gene (\( \beta^S \)). Heterozygous inheritance of hemoglobin S does not usually cause disease or symptoms but is detectable as sickle cell trait (31). Homozygous inheritance or compound heterozygous inheritance with another \( \beta \) globin gene results in disease. The discussion here is directed primarily toward homozygous sickle cell disease which includes those genotypes associated with chronic hemolytic anemia and vaso-occlusive pain: homozygous sickle cell disease (hemoglobin SS), hemoglobin SC disease (hemoglobin SC), sickle-\( \beta^0 \) thalassemia (hemoglobin S\( \beta^0 \)), and sickle-\( \beta^+ \) thalassemia (hemoglobin S\( \beta^+ \)), and other less common hemoglobin mutants. The clinical manifestations are related to the degree of intracellular polymerization of deoxyhemoglobin S (Table 173.2), and it is different among the various genotypes.

The clinical symptoms of sickle cell disease (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, a frequent—and sometimes fatal—complication, affects more than 40% of all patients with SCD.

**Table 173.2**

<table>
<thead>
<tr>
<th>Hemoglobin electrophoresis</th>
<th>Hematologic values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease group</td>
<td>Clinical severity</td>
</tr>
<tr>
<td>SS</td>
<td>Usually marked</td>
</tr>
<tr>
<td>( \beta^0 ) Thal</td>
<td>Marked to moderate</td>
</tr>
<tr>
<td>( \beta^+ ) Thal</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>SC</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>S HPPH</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

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

*50 percent Hb C. 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.
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; autopsplenectomy with increased risk of fulminating septicaemia 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 (33).

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. Adequate relief of pain in the hospitalized patient usually requires parenteral administration of opioid analgesics at frequent fixed intervals. 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 acute chest syndrome. Because there is no 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.

Transfusions are not needed for the usual anemia or episodes of pain. 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 acute chest syndrome with hypoxia. Chronic red cell transfusions have been shown to prevent strokes in patients with SCD, although the optimal duration of transfusion is unknown. However, the risks of transfusions must be weighed against the benefits. These risks include alloimmunization, infections, and iron overload. For patients undergoing general anesthesia, preoperative transfusion to a hematocrit above 30% reduced postoperative complications. Leukocyte-depleted red cells that are phenotype matched for the antigens most frequently associated with immune response are preferred for transfusion. 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, such as stroke and severe acute chest syndrome, and in patients with striking cholestatic syndrome and signs of liver failure.

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; and hydroxyurea treatment to prevent complications. In a double-blind, placebo-controlled trial, hydroxyurea was shown to reduce the pain episodes, acute chest syndrome, blood transfusions, and hospitalizations (34). The improvements noted with hydroxyurea treatment correlate to increases in hemoglobin F levels and a decrease in granulocytes, monocytes, and reticulocytes (35). Hydroxyurea treatment should be reserved for patients with SCD who have severe complications. Other experimental treatments aimed at interrupting the disease mechanisms are in progress (36).

**Specific Clinical Problems**

1. If abdominal symptoms are present, the possibilities of cholecystitis and complications of cholelithiasis must be considered.
2. Rarely, bone marrow infarction may be extensive and may produce the syndrome of fat embolism. This syndrome is manifested by severe bone pain, fever, neurologic abnormalities, and respiratory distress. It may be fatal, and treatment by exchange transfusion can be life-saving. Fat embolism may be a cause of some cases of acute chest syndrome.
3. Hematuria occurs as a complication of the sickle cell diseases, including sickle cell trait, and may be severe. It is thought usually to result from sickling and vaso-occlusion in the renal medulla, but other causes unrelated to sickle disease must be excluded. Supportive treatment with hydration and, perhaps, urinary alkalization is often sufficient for this self-limited complication.
4. Priapism, a frequent and painful complication of sickle cell disease, arises from the vaso-occlusion that produces congestion and sickling in the corpora cavernosa. It may resolve spontaneously, and initial conservative treatment with analgesics, hydration, and alkalization is appropriate. Exchange transfusion and various surgical procedures have also been successful in terminating priapism.

**Aplastic Crisis in Hemolytic Anemia**

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 thrombocytopenia are often present. The aplastic nature of the anemia is demonstrated by an extremely low reticulocyte count and marked reduction in erythroid precursors in the bone marrow. The episode is self-limited, and recovery usually begins by 2 weeks. In the recovery phase, there is a return of vigorous erythropoiesis and often an outpouring of nucleated red cells and reticulocytes into the blood, frequently accompanied by leukocytosis and immature white blood cells. There is convincing evidence that parvovirus B19 is the cause of most aplastic crises (37).

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 red blood cells. 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, e.g., Africans, African Americans, and Yemenite Jews, without 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. Three patient groups are discussed as most pertinent to critical care situations: (a) Patients with neutropenia from primary bone marrow diseases or cytotoxic treatment; (b) patients in whom neutropenia exists alone or in combination with other cytopenias as an aplastic process; and (c) patients with neutropenia or agranulocytosis caused by immunologic mechanisms.

Primary Bone Marrow Diseases and Cytotoxic Treatment

This is the largest and most frequent entity that causes neutropenia. Bone marrow diseases such as leukemias, myelodysplastic syndrome, and marrow 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 with a rapid onset of septic shock. In current practice, the occurrence of neutropenic fever is an indication for hospitalization with the risk for infection-related complications or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (greater than 10 days) and profound (less than 0.1 × 10^9 cells/μL) neutropenia, age older than 65 years, uncontrolled primary disease, pneumonia, hypothermia, multorgan dysfunction, invasive fungal infection, or being hospitalized at the time of the development of the fever (41). On the other hand, colony-stimulating factors are recommended for primary and secondary prophylaxis used to prevent chemotherapy-induced neutropenia (41).

ICU physicians should be aware of respiratory status deterioration or acute respiratory distress syndrome (ARDS) during neutropenia recovery with or without the use of G-CSF (42,43). 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.

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 (44,45). 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 dichlorodiphenyltrichloroethylene (DDT) and other insecticides, are suspect. Tolune 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 chloramphenicol, phenylbutazone, indomethacin, diphenylhydantoin, sulfonamides, and gold preparations. In at least half the cases of aplastic anemia, no cause is found or suspected.

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 ther-
apy including antithymocyte globulin, and other supportive 
care measures such as antibiotic prophylaxis and colony-
stimulating factors.

**Immune and Drug-related Granulocytopenia**

Neutropenia in adults often occurs as an isolated finding or 
in association with autoimmune disease such as rheumatoid ar-
thritis, systemic lupus erythematosus, and other similar con-
ditions. The evaluation should include the following: periph-
eral blood smear to seek out large granular lymphocytes (LGL); 
measurement of antinuclear antibodies, rheumatoid factor, and 
other autoantibodies; and possibly a bone marrow examina-
tion. 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 an-
tibiotics, 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 immunosuppres-
sive therapy, such as methotrexate or cyclosporine, alone or 
with G-CSF. Chronic neutropenia in association with rheuma-
toid arthritis, or Felty syndrome, is usually seen in severe cases 
with elevated rheumatoid factor. These patients who have re-
current fevers and infection require treatment similar to pa-
tients with LGL syndrome. Splenectomy should be considered 
in refractory cases.

Drug-induced granulocytosis is a serious medical problem 
and occurs in 1% to 3% of patients treated with certain medica-
tions. The characteristic clinical syndrome includes high fever, 
chills, and severe sore throat (agranulocytic angina) caused 
bacterial infection. Oral and pharyngeal ulcers, necrotiz-
ing tonsillitis, pharyngeal abscesses, and bacteremia may oc-
cur. The blood will demonstrate a virtual absence of granulo-
cytes. The bone marrow may show absence of all granulocyte 
precursors or only the mature cells. The picture may super-
icially resemble acute leukemia, or a state of maturational ar-
rest; the disease mechanism is often unclear. In some cases, it 
is an antibody against the drug acting as a haptogen in associ-
ation with endogenous antigen on neutrophil surface. Other 
drugs may impair production of neutrophils by direct toxic 
mechanism.

Serum 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 ex-
amination 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.

**THROMBOCYTOPENIAS**

Thrombocytopenia is a common laboratory abnormality in 
ICU patients that has been associated with adverse outcomes. 
The incidence of thrombocytopenia—defined as a platelet 
count of less than 150 × 10^3 cells/μL—has been reported to 
be 23% to 41.3%, with mortality rates up to 54% (46). The 
incidence of more severe thrombocytopenia—less than 50 × 10^3 
cells/μL—is lower, about 10% to 17%, but is associated 
with greater mortality (46). The relationship between the time 
course of platelet counts and mortality in 1,449 critically ill pa-
tients was examined in a prospective multicenter observational 
study in 40 ICUs from Europe, the United States, and Australia 
(47). There was a documented increase in mortality in patients 
who had thrombocytopenia on day 4 of admission to the ICU 
and even higher mortality in those patients with documented 
thrombocytopenia by day 14.

Systematic evaluation of thrombocytopenia is essential to 
the identification of and management of the causes (46). There 
are numerous potential causes of thrombocytopenia in the ICU 
(Table 173.3). While sepsis is the most common cause, account-
foring for more than 48% of thrombocytopenia cases in the ICU, 
more than 25% of ICU patients have more than one cause (48). 
Drug-induced thrombocytopenia presents a diagnostic chal-
lenge inasmuch as many medications can cause thrombocy-
topenia, and critically ill patients often receive multiple drugs. 
One such drug is heparin, the most common cause of drug-
induced thrombocytopenia due to immune mechanisms (46).

The first step in the diagnosis of true thrombocytopenia is to 
consider the mechanism (49). Is the thrombocytopenia caused 
by increased destruction, decreased production, or se-
questration of platelets? As noted earlier, the presence of large 
platelets on the blood smear or by mean platelet volume (MPV) 
suggests active thrombopoiesis, though this finding may be 
equivocal. Therefore, examination of the bone marrow for the 
presence of megakaryocytes is often necessary to distinguish 
between increased destruction (presence of megakaryocytes) 
and decreased production (absence of megakaryocytes). The 
presence of splenomegaly raises the possibility of sequestration.

Other laboratory tests are not necessary to evaluate the throm-
boctopenia itself. The bleeding time is not useful in assess-
ing thrombocytopenia. There is also the possibility of platelet 
clumping induced by the commonly used anticoagulant EDTA; 
platelet cold agglutinins; partial cloting of the blood sample; 
and platelet satellitosis, a disorder in which platelets cluster 
around white blood cells. When pseudothrombocytopenia is 
suspected, examining the peripheral blood smear and close 
communication with the laboratory is necessary.

Treatment of thrombocytopenia depends on the cause and 
is discussed below under the specific entities. First, some gen-

![TABLE 173.3: POTENTIAL CAUSES OF THROMBOCYTOPENIA](image-url)
the same fate. Thus, platelet transfusions most often are of little benefit, and are reserved for treatment of severe bleeding. When thrombocytopenia is caused by decreased platelet production, as in hematologic malignancies or during recovery from stem cell transplantation, serious hemorrhage can be prevented by regular transfusion of platelets. It is generally acceptable to use prophylactic transfusion to keep the platelet count greater than 10,000 to 20,000 cells/μL. 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 platelet count within an hour posttransfusion. The effectiveness of platelet transfusions is diminished in febrile, infected patients who may require larger and more frequent transfusions. Actively bleeding patients require more frequent transfusion and a higher target of platelet count, usually above 30,000 cells/μL. Chronically transfused patients may become refractory to platelet transfusions from random donors because of alloimmunization. Single-donor platelets limit exposure to foreign antigens and may delay immunization. Platelets obtained from family members by platelet apheresis may be considered in patients who are at risk for bleeding and refractory to random-donor platelets.

### Thrombocytopenia with Infection

Mild and transient thrombocytopenia 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 become consumed because of disseminated intravascular coagulopathy, whereas in viral infection, platelet production may be suppressed. Thrombocytopenia is commonly associated with human immunodeficiency virus (HIV) infection, mainly due to decreased production, although sometimes an autoimmune mechanism is also involved. Thrombotic thrombocytopenic purpura (TTP) or thrombotic microangiopathy (TMA) may be associated with HIV as well as other infections such as streptococcal and Escherichia coli (51–53). Treating the underlying infection in most of these cases is usually adequate to correct the thrombocytopenia.

### Drug-induced Thrombocytopenia

Drug-induced thrombocytopenia presents a diagnostic challenge because many medications can cause thrombocytopenia, and patients in ICU are often on multiple medications (54). The most commonly reported drugs with probable or definite relation to thrombocytopenia were quinidine, quinine, rifampin, and trimethoprim-sulfamethoxazole. Many other drugs can cause thrombocytopenia, 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 drug-induced thrombocytopenia 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 Ib/IX and GPIIb/IIIa. The diagnosis of drug-induced thrombocytopenia is usually supported by recovery to a normal platelet count within 5 to 7 days.

Treatment of drug-induced thrombocytopenia may require only withdrawal of the offending drug. Prednisone may be given if the diagnosis of idiopathic autoimmune thrombocytopenia (ITP) cannot be ruled out. Patients with severe thrombocytopenia 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 (46). The diagnosis of HIT should be considered when the platelet count falls to less than 150 × 10³ cells/μL, or more than 50% decrease of the platelet count from baseline, between days 5 and 14 from start of heparin therapy (55). A high index of suspicion on the physician’s part is key in making the diagnosis. The thrombocytopenia 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% (46).

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 thrombocytopenia (46). Anti-PF4/heparin antibodies are transient and usually become undetectable within a median of 10 to 14 days. If heparin is readministered to a patient with high levels of HIT antibodies, abrupt thrombocytopenia can occur. However, this likely will be more than 100 days after the last exposure to heparin (46). 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 unfractionated heparin (UFH), as opposed to low-molecular-weight heparin (LMWH), are more likely to develop HIT.

The frequency of HIT in ICU patients was examined in two major studies (36,57). The results suggested that only a small minority of ICU patients with thrombocytopenia receiving UFH have HIT, and that the PF4/heparin-reactive antibodies are more likely to be detected by ELISA assay than serotonin release assay (SRA), suggesting a possible overdiagnosis—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 thrombocytopenia among patients treated with anticoagulants. The thrombotic sequelae of HIT carry significant morbidity and may even be lethal. Some of the morbid events include deep venous thrombosis (DVT), pulmonary embolism, skin necrosis, limb ischemia, thrombotic stroke, and
Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP), also known as immune thrombocytopenic purpura, is a common cause of thrombocytopenia in both adults and children. Although it is usually in the differential diagnosis of thrombocytopenia, the diagnosis of ITP can usually be made only after exclusion of other causes of thrombocytopenia. When the history, physical examination, and bone marrow with peripheral smear are consistent with ITP and do not suggest other causes of thrombocytopenia, 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. Thrombotic 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.

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 per day of prednisone. If the platelet count 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 platelet count 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—limit 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 (59). The overall goal in treating chronic/refractory ITP is to maintain a safe platelet count, defined as greater than 10,000 to 20,000 cell/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 thrombocytopenia in the fetus and newborn. The lowest platelet count 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 thrombocytopenia that occurs in about 3% of normal women with uncomplicated pregnancies. The most important clue to differentiating the two is a history of previous thrombocytopenia when the woman was not pregnant. Also, more severe thrombocytopenia occurring before the third trimester is more likely to be ITP.
Platelet counts less than 100,000 cells/μL are present in over one fourth of critically ill alcoholic patients (63). There are many possible causes for thrombocytopenia in such patients, including hypersplenism and folic acid deficiency. However, it is important to recognize that reversible severe thrombocytopenia 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 platelet survival. Abnormalities of platelet function may also 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 pro-drome of bloody diarrhea caused by the Shiga toxin-producing enterohemorrhagic strain of E. coli. The laboratory findings in TTP are basically those related to the above features: thrombocytopenia, hemolytic anemia with red cell fragmentation, and renal dysfunction. Elevation of serum lactic acid dehydrogenase from intravascular hemolysis, and perhaps also damage to other tissues, is an index of activity of the disease. Coagulation tests are usually normal.

The basic pathogenic mechanism behind these syndromes is most likely related to the vascular endothelial cells. A role for ultra large von Willebrand factor (vWF) multimers has been identified to this is linked to endothelial damage and the occurrence of disseminated platelet thrombi. Recently, a specific metalloprotease (ADAMTS13) that rapidly cleaves these multimers has been identified (60,61). Deficiency of this metalloprotease activity appears to be associated with many, but not all, TTP cases (62).

Plasma exchange has dramatically changed TTP-HUS prognosis and outcome. Plasma infusion is less effective in adults, but it could 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**

Thrombocytopenia 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: thrombocytopenia 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 thrombocytopenia and microangiopathic hemolytic anemia are sufficient to begin plasmapheresis.

The clinical presentation is variable, but the thrombocyto-penia 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 also include uremia, hematuria, and proteinuria. The reasons for fever are unclear.

Severe thrombocytopenia 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 threaten some of 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 to say, in the absence of a normal red cell mass—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.

True erythrocytosis results from one of two general mechanisms:

1. 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.
2. 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, stress, 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.

**Polycythemia Vera**

Criteria for the diagnosis of PV have been modified multiple times since the first criteria were published by Modan and Lilienthal (64) in 1965; modified diagnostic criteria are shown in Table 173.4 (65). 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 (66). Risks in uncontrolled PV are primarily hyperviscosity and thromboembolic or hemorrhagic events. Patients at highest risk are those whose disease has shown particularly active cell proliferation requiring extensive therapy, those with a prior history of complications, and
The elderly. The level of the hematocrit or platelet count is not a reliable predictor. 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. Thromboses may be arterial or venous. Fatigue, plethora, 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.

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 may be linked with increased risk of transformation to acute leukemia. Emergency plateletpheresis may also be considered in such emergencies to lower an elevated platelet count.

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.

Secondary Erythrocytosis or Polycythemia

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 (for example, secondary to tissue hypoxemia) or inappropriately increased RCM (for example, secondary to increased erythropoietin production). Additional studies are needed to differentiate the diverse causes of polycythemia. 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.

**Thrombocytosis**

With the availability of a platelet count as part of a routine blood count, an elevated platelet count, or thrombocytosis, has become an important clinical problem in hospitalized patients. Unlike thrombocytopenia, the literature dealing with thrombocytosis in ICU patients is very scant. Furthermore, unlike thrombocytopenia, the presence of thrombocytosis predicts a favorable outcome in ICU patients, whereas a blunted rise in platelet count may be associated with worse outcome. Thrombocytosis in hospitalized patients is classified according to its origin into primary (or clonal) and secondary (or reactive) forms. Primary thrombocytosis refers to a persistent elevation of platelet count due to clonal thrombopoiesis, as it occurs in myeloproliferative disorders including essential thrombocythemia (ET), PV, myelodysplastic syndrome, chronic myelogenous leukemia, and myelofibrosis. 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, post splenectomy, 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 (67–71) with an elevated platelet count (more than 500 × 10³ cells/L), and the main conclusions suggest that whereas most patients have secondary thrombocytosis, a higher platelet count and increased thromboembolic complications are significantly associated with primary thrombocytosis. In one study, even when using greater than or equal to 1,000 × 10³ cells/L as the basis for defining extreme thrombocytosis, 82% of 231 patients analyzed were found to have an elevated platelet count due to reactive (secondary) thrombocytosis (72). In this study, the risk of bleeding and/or thrombosis was 56% in primary thrombocyto-
older than 60 years, history of thromboembolism, a platelet count greater than 1,500,000 cells/L 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 cytoxic agent of choice for childbearing women. The aim should be to lower the platelet count to less than 400,000 cells/L. 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 (greater than 1,500,000 cells/L) 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**

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/L with shift to the left. The major causes for such a reaction include severe infections, severe hemorrhage, acute hemolysis, hypersensitivity, and malignancies (paraneoplastic syndrome). Hyperleukocytosis syndrome. This occurs in leukemic states when the white blood cell 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 hypotonia. 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, macrothrombi, and microvascular invasion (leukostatic tumors) (73). 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 white blood cell 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/L in acute myelogenous leukemia or the accelerated phase of CML is usually an alarming sign and an indication for prompt 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 hypersuricemia. Hydroxyurea (6 g by mouth) is frequently used initially to produce rapid leukemic cell kill.

**Chapter 173: Hematologic Conditions in the ICU**

**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 monoclonal gammopathy of IgM in Waldenstrom macroglobulinemia or IgG or 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 thrombocytopenia 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, multorgan failure, or septic shock, and have the highest mortality among cancer patients admitted to the ICU (74). Because of the generally poor outcome, especially for patients requiring mechanical ventilation, the utility of such support has been questioned (75,76). It is generally accepted that patients admitted to the ICU during the engraftment period should be fully supported because of better outcome (77). 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 intraabdominal bleeding. This topic is dealt with in more detail elsewhere in this text.

**SUMMARY**

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
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Section XIX: Hematologic and Oncologic Disease and Dysfunction

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 hematologic service in the evaluation and treatment of these specific entities are essential for better outcome and improved survival.

References


HYPERCALCEMIA

Hypercalcemia is the most common of the paraneoplastic syndromes, affecting 10% to 30% of all patients with malignancy at some time during their disease course (5–7). Breast cancer, lung cancer, and multiple myeloma represent the most common malignancies associated with hypercalcemia (5). The presence of hypercalcemia in a patient with cancer portends an extremely poor prognosis, particularly when elevated parathyroid hormone-related protein (PTHrP) levels are detected (8,9); approximately 50% of cancer patients with hypercalcemia will die within 30 days (10).

Pathophysiology

Hypercalcemia of malignancy results from increased bone resorption and subsequent release of calcium from bone into the extracellular fluid (11). Classification is based on the mechanism by which the elevated calcium is generated, of which there are four recognized types:

1. Humoral hypercalcemia of malignancy (HHM)
2. Local ostolytic hypercalcemia
3. Tumor production of the active form of vitamin D
4. Ectopic parathyroid hormone (PTH) secretion (5)

Humoral Hypercalcemia of Malignancy (HHM)

This is the most common cause of cancer-induced hypercalcemia, seen in 80% of cases (7,12). The mechanism is mediated by parathyroid hormone-related protein (PTHrP), which is secreted into the systemic circulation by malignant tumors (12)—most frequently squamous cell carcinoma, renal cell carcinoma, ovarian and endometrial carcinomas, human T-cell lymphoma/leukemia virus (HTLV)-associated lymphomas, and breast carcinoma (5). Normally, PTHrP is expressed in many
neoneoplastic adult and fetal tissues where it is involved in cell growth and differentiation but is not systematically secreted in significantly detectable levels. Because of its structural homology with parathyroid hormone at the amino terminal end, humoral PTHrp binds to PTH receptors in bone and kidney, causing an increase in bone resorption and distal tubular calcium resorption (5,13).

**Local Osteolytic Hypercalcemia**

Seen in about 20% of cases of malignant hypercalcemia, this form occurs when tumor cells present in bone metastases induce osteoclastic bone resorption by secreting cytokines—for example, tumor necrosis factor, interleukin-1, interleukin-6, macrophage inflammatory protein, and lymphotoxin—which, in turn, stimulate local macrophages within the tumor to differentiate into osteoclasts. Local osteolytic hypercalcemia occurs frequently in breast cancer, non-small cell lung cancer, and multiple myeloma (9).

**Tumor Production of the Active Form of 1,25-dehydroxyvitamin D**

Occurring in less than 1% of cases, this entity is seen in some lymphomas. The hypercalcemia is mediated by enhancement of both osteoclastic bone resorption and intestinal resorption of calcium.

**Ectopic Parathyroid Hormone (PTH) Secretion**

The final mechanism of hypercalcemia of malignancy is ectopic PTH secretion, which has been adequately described in only eight patients (5).

**Differential Diagnosis**

Malignancies and primary hyperparathyroidism account for approximately 90% of all cases of hypercalcemia and may co-exist in the critically ill cancer patient (14). Among hospitalized patients, neoplastic disease is the most common cause, accounting for more than 65% of cases (15,16). Renal failure, rhabdomyolysis, granulomatous diseases such as sarcoid and tuberculosis, adrenal insufficiency, immobilization, vitamin A or D intoxication, milk alkali syndrome, familial hypocalciuric hypercalcemia, and medications such as thiazide diuretics, lithium, estrogens, and tamoxifen are also included in the differential diagnosis of hypercalcemia (16,17).

**Clinical Presentation**

There are multiple symptoms of hypercalcemia (Table 174.1), which are nonspecific and often attributed to coexisting chronic or terminal illness (9). In general, the symptoms correlate with the absolute concentration and the rapidity in rise of the serum calcium (18). Neurologic, gastrointestinal, renal, cardiac, and bone-related manifestations may be present. Neurologic symptoms may be mild at lower serum calcium levels or when the hypercalcemia has developed slowly. Mild drowsiness or fatigue may progress to weakness, lethargy, stupor, and eventually coma in hypercalcemic crisis or in acutely rising hypercalcemia (11). Psychotic behavior, visual and speech abnormalities, hypotonia, and occasionally localizing signs on neurologic exam, often thought to be secondary to metastatic disease, may be exhibited, and may resolve with therapy that lowers serum calcium (16,19). In older patients, neurologic dysfunction may be more pronounced even at lower concentrations of serum calcium (5).

**Gastrointestinal Symptoms**

Gastrointestinal symptoms are related to smooth muscle hypotonicity and include anorexia, nausea, vomiting, constipation, and abdominal pain (11). Infrequently, hypercalcemia may present as peptic ulcer disease (18) and pancreatitis (20).

Renal manifestations result from the impairment of renal water-concentrating ability because antidiuretic hormone (ADH) secretion is inhibited by hypercalcemia. Subsequent dehydration decreases the glomerular filtration rate and reduces renal excretion of excess serum calcium. To expand the extracellular volume, compensatory proximal tubular resorption of sodium and calcium occurs, leading to a paradoxical increase in
In primary hyperparathyroidism—is often necessary to differentiate among the mechanisms of hypercalcemia. PTH lowers serum phosphate and increases serum chloride concentrations (14). A low serum chloride (less than 100 mEq/L) suggests hypercalcemia of malignancy, whereas elevation of serum chloride caused by hyperchloremic acidosis resulting from PTH-induced renal bicarbonate loss seen in hyperparathyroidism (9). Ectopic hyperparathyroidism is an extremely rare cause of malignant hypercalcemia, and elevations in PTH levels are more likely to indicate concomitant primary hyperparathyroidism in cancer patients with hypercalcemia (21). In contrast to PTH level measurement, determination of the serum PTHrP concentration is not routine. However, it may be useful in identifying the mechanism of hypercalcemia. For example, PTHrP levels are low in patients with primary hyperparathyroidism but high in patients with either HBM alone or concomitant primary hyperparathyroidism and malignant hypercalcemia (12,23). PTHrP also has been used in evaluating the response to bisphosphonate therapy; patients with PTHrP levels above 12 pmol/L were reported to be less responsive to pamidronate and more likely to develop recurrent hypercalcemia within 14 days (24).

**Diagnosis**

Calcium is present in the extracellular fluid (ECF) in three fractions: (i) 50% is the ionized free fraction, (ii) 40% is protein bound (primarily to albumin) and is not renally filtered, and (iii) 10% is complexed to anions (18). Hypercalcemia is diagnosed by measuring the ionized calcium level, as this is the biologically active level that correlates with the signs and symptoms of hypercalcemia. Except in the presence of hypercalcemia, the ionized calcium level can be inferred from the total plasma calcium. In cancer patients, hypercalcemia is common, and the total plasma calcium must be corrected to reflect the calcium level that would have been measured as if the albumin were in the normal range. In general, for each 1 g/dL decrease in serum albumin, there is a 0.8 mg/dL decrease in serum calcium. This method of calculation is inaccurate in the presence of calcium-binding immunoglobulins, as seen in multiple myeloma. This circumstance warrants measurement of the ionized calcium level because the total serum calcium level may significantly overestimate the ionized fraction (11). Although ionized calcium concentrations increase with acidosis and decrease with alkalosis, these changes are relatively small and do not lead to clinically significant events (22).

Once the diagnosis of hypercalcemia is confirmed by obtaining corrected calcium levels, measurement of the intact PTH level—suppressed in hypercalcemia of malignancy and elevated in primary hyperparathyroidism—is often necessary to differentiate among the mechanisms of hypercalcemia. PTH lowers serum phosphate and increases serum chloride concentrations (14). A low serum chloride (less than 100 mEq/L) suggests hypercalcemia of malignancy, whereas elevation of serum chloride caused by hyperchloremic acidosis resulting from PTH-induced renal bicarbonate loss seen in hyperparathyroidism (9). Ectopic hyperparathyroidism is an extremely rare cause of malignant hypercalcemia, and elevations in PTH levels are more likely to indicate concomitant primary hyperparathyroidism in cancer patients with hypercalcemia (21). In contrast to PTH level measurement, determination of the serum PTHrP concentration is not routine. However, it may be useful in identifying the mechanism of hypercalcemia. For example, PTHrP levels are low in patients with primary hyperparathyroidism but high in patients with either HBM alone or concomitant primary hyperparathyroidism and malignant hypercalcemia (12,23). PTHrP also has been used in evaluating the response to bisphosphonate therapy; patients with PTHrP levels above 12 pmol/L were reported to be less responsive to pamidronate and more likely to develop recurrent hypercalcemia within 14 days (24).

**Treatment**

The only effective long-term means of reversing malignancy-associated hypercalcemia is reduction in tumor burden (Table 174.2); antihypercalcemic therapy is a temporizing measure that does not affect survival (5). The aggressiveness of the therapeutic approach depends on the potential for palliation and cure. When all antitumor strategies have failed, or in patients who do not wish to pursue further treatment of their cancer, an ethical, humane, and appropriate approach may involve withholding antihypercalcemic treatment (5,9). Stewart (5) has classified hypercalcemia based on serum calcium levels into mild hypercalcemia (10.5–11.9 mg/dL), moderate hypercalcemia (12.0–13.9 mg/dL), and severe hypercalcemia (14.0 mg/dL or greater) as a guide to therapeutic interventions. In addition to the magnitude of hypercalcemia, the severity of symptoms and the cause of hypercalcemia are other important factors in formulating an appropriate treatment strategy. In general, severe hypercalcemia requires emergent, aggressive treatment in the presence or absence of symptoms, whereas interventions in mild to moderate hypercalcemia are contingent on the severity of the symptoms. Prior to initiating therapy, the clinician should assess the patient for correctable factors that may contribute to hypercalcemia. Exogenous sources of calcium such as calcium-containing intravenous fluids, parenteral nutrition, and oral calcium supplements should be removed. In addition, thiazide diuretics, vitamins A and D, calcitriol, lithium, and estrogen or antiestrogens used as therapy for breast carcinoma should be discontinued (11). Immobilization is a well-established cause of hypercalcemia, and weight-bearing ambulation is recommended whenever possible (25). Finally, in the presence of hypophosphatemia, hypercalcemia becomes more difficult to treat. Hypophosphatemia is frequently observed in cancer patients for multiple reasons including poor nutrition, saline diuresis, PTHrP effects, use of antacids and loop diuretics, and hypercalcemia itself. Oral or nasogastric phosphate supplementation should be administered to keep the calcium-phosphate product between 30 and 40. Intravenous phosphorus replacement may precipitate hypercalcemia, seizures, and acute renal failure, and is reserved for patients in whom oral or nasogastric administration cannot be performed (5).

**Fluids and Diuretics**

The initial intervention in the treatment of hypercalcemia is the administration of isotonic saline at a rate of 200 to 500 mL/hour based on the degree of hypovolemia and renal and cardiovascular dysfunction (5). Once the fluid deficit is replaced, the infusion rate should be decreased to 100 to 200 mL/hour in patients without cardiac or renal impairment (20). The patient must be carefully monitored to prevent fluid overload. Saline hydration reduces serum calcium level by increasing the glomerular filtration rate and increasing calcium delivery to the proximal tubule where urinary calcium excretion is augmented by the calciiac effects of saline (5).
## TABLE 174.2

### TREATMENT OF HYPERCALCEMIA OF MALIGNANCY

#### DEFINITIVE TREATMENT
- Antitumor therapy to reduce tumor burden

#### INITIAL TREATMENT
- **Removal of exogenous calcium sources:**
  - Intravenous fluids and parenteral nutrition, oral calcium supplements, thiazide diuretics, vitamins A and D, calcitriol, lithium, estrogens, antiestrogens
- **Weight-bearing ambulation**
- **Phosphate repletion**
- **Loop diuretics**
- **Saline hydration**

#### PHARMACOLOGIC TREATMENT
- **Bisphosphonate therapy**
  - Principal agents in hypercalcemic treatment
    - Zoledronate: 15-min infusion
    - Pamidronate: 2-h infusion
  - **Bisphosphonate adverse effects:** Acute and chronic renal failure, fever arthralgias, ocular inflammation, electrolyte imbalance, osteonecrosis of the jaw
- **Other Agents**
  - Calcitonin: Useful in congestive heart failure or renal failure
  - Glucocorticoids: Used in lymphomas with elevated levels of 1, 25-vitamin D
  - Mithramycin: Use limited by adverse effects: Thrombocytopenia, anemia, leukopenia, renal failure
  - Gallium nitrate: Use limited by 5-day continuous infusion, nephrotoxicity

#### DIALYSIS
- For patients with renal failure or congestive heart failure

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Loop diuretics inhibit calcium reabsorption at the loop of Henle, and, hence, also increase calciuresis. These agents should be used judiciously and only after euvalmia is achieved in hypovolemic patients or in patients who present with volume overload (5,9,16). Because of ensuing complications such as hypokalemia, hypomagnesemia, and volume depletion, and because of the availability of bisphosphonates, loop diuretics are used less favorably in clinical practice (26).

**Bisphosphonate Therapy**

Bisphosphonates inhibit osteoclastic bone resorption and are the principal agents used in the management of hypercalcemia of malignancy (27). When compared to saline and diuretics alone, and other antiresorptive agents including calcitonin, bisphosphonates are superior in treating hypercalcemia of malignancy (5). Because only 1% to 2% of oral bisphosphonates are absorbed, these drugs are administered intravenously (7). Pamidronate, and zoledronate are the most commonly used bisphosphonates, and are the two agents that have been approved by the Food and Drug Administration (FDA) for the treatment of hypercalcemia of malignancy. Clodronate and ibandronate are available in Europe and other countries. Patients respond to bisphosphonate therapy within 2 to 4 days, with a nadir in serum calcium occurring within 4 to 7 days; normocalcemia may persist for 2 to 4 weeks (5,18). Compared to pamidronate, zoledronate is 850 times more potent and is more efficacious, although this increased efficacy is of unclear clinical significance (9,28). In a pooled analysis of two randomized controlled trials comparing a single 4-mg dose of zoledronic acid to a 90-mg dose of pamidronate, serum calcium concentrations normalized within 10 days in 88% versus 70% of patients, respectively, and the duration of response was 32 days versus 18 days, respectively, within the two groups (28). Although pamidronate may be the less expensive of the two agents, zoledronate can be administered over a shorter interval of 15 minutes, making it advantageous in the outpatient setting; pamidronate requires a 2-hour infusion. Both zoledronate and pamidronate have been associated with acute and chronic renal
failure, with more adverse events reported with zoledronate. Dose reduction of zoledronate is recommended in patients with a creatinine clearance between 30 and 60 mL/min; however, the American Society of Clinical Oncology does not recommend changing the dose or infusion rate of pamidronate in patients with a creatinine clearance of less than 30 mL/min. However, the other complications of bisphosphonates include acute systemic inflammatory reactions such as fever and arthralgias, as well as ocular inflammation, electrolyte imbalance, and osteonecrosis of the jaw (29).

**Other Agents**
Calcitonin is a well-tolerated synthetic polypeptide analogue of salmon calcitonin, which reduces serum calcium levels by inhibiting bone resorption. When administered subcutaneously or intramuscularly, it produces a rapid but transient decrease in serum calcium levels within 12 to 24 hours (5,9). This agent is useful in patients with congestive heart failure or renal failure where saline, diuretics, and bisphosphonates may be contraindicated. Tachyphylaxis may occur with continued use (7). Glucocorticoids are effective in decreasing serum calcium in hypercalcemia of malignancy associated with some lymphomas, particularly Hodgkin lymphoma. Elevated levels of 1,25-vitamin D are present in Hodgkin’s lymphoma (7); glucocorticoids, in addition to increasing renal calcium excretion, block vitamin D-mediated calcium absorption in the gastrointestinal tract (11). These agents have limited utility in the acute setting because a reduction in serum calcium may not be observed for 1 to 2 weeks (11). Mithramycin, an inhibitor of osteoclast RNA synthesis and formerly a first-line hypocalcemic agent, has serious adverse effects including thrombocytopenia, anemia, leukopenia, and renal failure (5). Gallium nitrate has the disadvantage of requiring continuous infusion over 5 days and has potential nephrotoxicity. Finally, dialysis may be used to treat patients with hypercalcemia complicated by renal failure or congestive heart failure (5,18).

### ACUTE TUMOR LYSION SYNDROME

#### Definition
Acute tumor lysis syndrome (ATLS) occurs as a consequence of the rapid and massive destruction of tumor cells resulting in the release of intracellular metabolites into the circulation in quantities sufficient to exceed renal excretory capacity (30,31). The four biochemical disturbances generated by this process that characterize the syndrome are life threatening (32): 1. Hyperkalemia 2. Hyperphosphatemia 3. Hypocalcemia 4. Hyperuricemia

These metabolic abnormalities have widespread adverse effects on the cardiac, musculoskeletal, nervous, and renal systems.

Acute tumor lysis syndrome is most frequently observed after the administration of cytotoxic chemotherapy in patients with high-grade hematologic malignancies—classically, Burkitt’s lymphoma and acute lymphocytic leukemia (ALL) (7,33,34). The incidence of clinically significant ATLS in non-Hodgkin’s lymphoma and ALL has been reported as 6% (35) and 5.2% (7), respectively. Metabolic derangements in these patients may develop within a few hours to a few days after initiating chemotherapy (7,36). Other malignancies in which ATLS has been described include chronic leukemia, low-grade lymphoma, and, rarely, multiple solid tumors such as metastatic breast carcinoma, lung carcinoma, seminoma, thymoma, medulloblastoma, ovarian carcinoma, rhabdomyosarcoma, melanoma, vulvar carcinoma, and Merkel cell carcinoma (31). The syndrome can also occur after radiation therapy, immunotherapy (rituximab and interferon), and endocrine therapy (corticosteroids and tamoxifen) (7,31,33).

#### Pathophysiology
Rapid dissolution of cells with aggressive cytotoxic therapy results in an increase in plasma uric acid, potassium, and phosphorous levels. The hyperphosphatemia, in turn, precipitates secondary hypocalcemia. Hyperkalemia occurs as a consequence of high tumor cell turnover rates in these malignancies leads to hyperuricemia and consequent uric acid nephropathy (37,38). Prompt recognition of STLS is essential because it is associated with poor outcomes and high mortality rates (38). Predisposing factors for developing ATLS include large tumor burdens (33), bulky lymphadenopathy (7), extensive bone marrow involvement (33), rapid tumor cell proliferation, leukocyte (more than 50 × 10³ cells/L) (34), elevated lactate dehydrogenase (LDH) (more than 1,500 IU) (33), and high tumor chemosensitivity (7,32). Pretreatment hyperuricemia, renal dysfunction, and hypovolemia, as well as treatment with nephrotoxic agents, also confers an increased risk of ATLS (31).
nausea, vomiting, anorexia, and lethargy. Acute renal failure with associated oliguria, edema, hypertension, and altered sen-
sorium will be seen in untreated patients (33). Uric acid is
generated from purine metabolism in the liver. Adenosine and
guanosine nucleotides are degraded to hypoxanthine and xan-
thine, respectively, and xanthine oxidase converts these prod-
ucts to uric acid (7). Rapidly proliferating neoplastic cells have
high turnover rates with accelerated purine catabolism from
DNA and RNA degradation (41), and these cells contain large
amounts of purine nucleotides; consequently, with cytotoxic
therapy, there is a rapid rise in plasma uric acid (33). Uric acid
is excreted by the kidneys through the processes of glomeru-
lar filtration, partial proximal tubular reabsorption, and distal
tubular secretion (32). The clearance of uric acid is indepen-
dently proportional to intravascular volume status (31) and
the urinary flow rate (32), and may be significantly reduced
in the presence of dehydration or tubular obstruction from acute
nephrocalcinosis or uric acid nephropathy. Uric acid nephropa-
yth develops when uric acid crystals deposit in the renal tubules
and collecting ducts because of acidic conditions. The urinary
pH of uric acid is 5.4, and the luminal pH of the distal tubules
and collecting ducts is 5.0, resulting in the poor solubility of
uric acid in acidic urine (7). This poor solubility, coupled with
the marked hyperuricosuria present in ATLS, leads to uric acid
precipitation, intratubular obstruction, oliguria, and acute re-
nal failure (7,42). Acute renal failure (ARF) in ATLS may also
be mediated by renal calculi from phosphate and uric acid pre-
cipitation (31), as well as from ischemic acute tubular necrosis
cauised by renal hyperperfusion (33). Drug toxicity, sepsis, and
tumor-associated obstructive uropathy or renal parenchymal
infiltration may exacerbate ATLS-induced ARF (39).

Classification

Although no widely accepted definition of ATLS currently ex-
sists, Hande and Garrow (35) first classified ATLS into labora-
tory TLS and clinical TLS. Cairo and Bishop (39) have modified
and further developed this classification system into the Cairo-
Bishop definition, which uses laboratory and clinical data in
conjunction with a grading scale to assess the severity of ATLS.
Laboratory TLS (LITLS) is defined as two or more of the follow-
ing metabolic abnormalities occurring 3 days before or 7 days
after chemotherapy: uric acid 8 mg/dL or greater, potassium
6.6 mg/dL or greater, phosphorus 6.5 mg/dL or greater, or a
25% increase in baseline levels of these metabolites, and cal-
cium 7 mg/dL or less, or a 25% decrease from baseline level.
Clinical tumor lysis syndrome is defined as LTLS in addition
to one or more of the following findings: increased serum cre-
atinine (1.5 times the upper limit of normal), cardiac arrhyth-
mania/sudden death, or seizure. The grading of ATLS from 0
through 5 is determined by the presence or absence of LTLS,
the degree of serum creatinine elevation, and the presence and
severity of the cardiac arrhythmia and seizure (39).

Prevention and Treatment

Early recognition of patients at high risk for ATLS is an essential
component of the management strategy so that appropriate
prophylactic interventions can be instituted.

Fluids and Alkalinization

Except in patients at risk for congestive heart failure, aggres-
sive intravenous hydration with isotonic or hypotonic saline
(42) is the single most important intervention for both pre-
vention and treatment of ATLS. Cytotoxic therapy should be
delayed whenever possible to administer appropriate hydration
(7,42). Intravenous hydration should commence 2 days before
and for 2 to 3 days after chemotherapy (31,33) at a rate of
3,000 mL/m² per day (7,9,39), or two or four times the daily
fluid maintenance requirement to achieve a urine output of 100
mL/m²/hr or greater (31,39). Aggressive administration of in-
travenous fluid increases the intravascular volume, renal blood
flow, glomerular filtration rate, and urinary flow rate, result-
ing in correction of electrolyte derangements by dilution of the
extracellular fluid and prevention of phosphate and uric acid
precipitation by increasing urinary excretion of these metabo-
lites (31,39). Volume expansion alone may be insufficient to
maintain adequate urine output, necessitating the administra-
tion of diuretics. Once euvalemia is achieved, and no signs of
acute obstructive uropathy are present, a dose of furosemide—
0.5 to 1 mg/kg or 2 to 4 mg/kg for severe oliguria or anuria—
may induce or improve urine output (35). The effectiveness of
furosemide is diminished in the setting of uric acid precipita-
tion in the renal tubules; in this circumstance, mannitol, at a
dose of 0.5 mg/kg, may be administered.

Alkalization of the urine to a pH 7.0 or greater remains contro-
versial (7,9,39). This practice is based on the biochemical
properties of uric acid, that is, uric acid is 13 times more
soluble at pH 7.0 than at pH 5.0 (32), maximal solubility of
uric acid is attained at pH 7.5, and urine alkalization (pH
6.5 or greater) enhances renal excretion of uric acid (39).
What limits this approach is that calcium phosphate precipita-
tion with systemic alkalization, exacerbating nephrocalci-
nosis (7,31). Additionally, hyperxantine and xanthine solubil-
ity are substantially reduced, leading to xanthine nephropathy
with concurrent allopurinol therapy (9,31,39).

Management of Hyperuricemia

Allopurinol reduces the risk of ATLS when administered 2 to
3 days prior to chemotherapy by inhibiting the production of
uric acid (9). Allopurinol is both a synthetic structural
analogue of the purine base, hypoxanthine, and a competitive
inhibitor of xanthine oxidase (33), and, therefore, in the
presence of allopurinol, xanthine oxidase cannot catalyze the
conversion of hypoxanthine to xanthine and xanthine to uric
acid (31). Allopurinol is administered orally at 300 to 800
mg daily (10 mg/kg per day or up to 400 mg/m² per day) in
one to three divided doses, and should be titrated to uric acid
level. Intravenous allopurinol was approved by the FDA in
1999 and can be administered in doses of 200 to 400 mg/m²
per day (maximum 600 mg/day) in patients unable to tolerate
oral medications, although the cost per day ranges between
$400 and $1,000 (7,43). Dose adjustment of allopurinol is
required for reduced creatinine clearance (7,43). There are
several limitations with allopurinol therapy:

1. A reduction in serum uric acid level is not seen before 48
to 72 hours after initiating allopurinol because the drug in-
hibits the synthesis of uric acid but does not affect the pre-
treatment uric acid concentration (7).
2. Inhibition of xanthine oxidase by allopurinol leads to increased plasma levels of xanthine and hypoxanthine, which may precipitate in the renal tubules (31).

3. Three percent of patients develop hypersensitivity reactions, including Stevens-Johnson syndrome.

4. Allopurinol interacts with many drugs, including chemotherapy and azathioprine (42).

Another agent that lowers uric acid concentration is urate oxidase. Urate oxidase converts uric acid to allantoin, which is five to ten times more soluble in urine than uric acid. Present in many mammalian species, urate oxidase is not expressed in human beings as a result of a nonsense mutation in the coding region during hominoid evolution (44). A nonrecombinant form of urate oxidase was first obtained from Aspergillus flavus and has been used in France (1975) and Italy (1984) for treatment of hyperuricemia. Subsequently, a recombinant urate oxidase, rasburicase, was developed because of the 4.5% of hypersensitivity reactions that occurred with the nonrecombinant form (7,31,42). Rasburicase was FDA approved in 2002 for use in pediatric patients at risk for ATLS (48). An injectable dose of 0.15 to 0.20 mg/kg normalizes uric acid levels within 4 hours of administration in children and adults (7,42). This dose may be repeated daily for a total of 5 days, and chemotherapy should be initiated 4 to 24 hours after the first dose. In addition to being more effective than allopurinol in reducing pre-treatment and post-treatment uric acid levels, rasburicase does not generate increased xanthine and hypoxanthine levels, thereby minimizing the risk of uric acid nephropathy that may be seen with allopurinol use (7,31,42). Of note, rasburicase is contraindicated in patients with glucos-6-phosphate dehydrogenase (G6PD) deficiency. Bronchoospasm and anaphylaxis may rarely occur with rasburicase therapy (45). There is insufficient evidence to characterize the incidence of dialysis in ATLS, and because a 5-day course of therapy is approximately 2,000 to 3,000 times more expensive than a 5-day course of oral allopurinol (7,43), cost-effectiveness must be considered in formulating a treatment plan.

Correction of Electrolyte Abnormalities

Because of the potential for life-threatening arrhythmias, prompt recognition of electrolyte derangements is imperative. Laboratory monitoring should be performed every 4 to 6 hours in the first 24 hours of chemotherapy in patients at high risk for ATLS, and then every 6 to 8 hours thereafter (42). A baseline electrocardiogram (ECG) should be obtained to assess for cardiac effects related to electrolyte abnormalities. Hyperkalemia is treated with calcium gluconate to stabilize the cardiac membrane and with intravenous insulin/dextrose and inhaled beta agonists to facilitate intracellular shift of potassium. Although sodium bicarbonate may also shift potassium intracellularly by improving the metabolic acidosis, its use may result in inappropriate volume expansion. Potassium binding resins such as sodium polystyrene sulfate increase potassium elimination in the gastrointestinal (GI) tract and have a delayed hypokalemic effect. Diuretics can be administered to reduce serum potassium. Asymptomatic hypocalcemia should be left untreated to preclude calcium phosphate precipitation; however, symptomatic hypocalcemia is managed with intravenous calcium gluconate. Treatment of hyperphosphatemia with oral phosphate binders such as aluminum hydroxide or aluminum carbonate will usually concurrently correct the hypocalcemia (7,31).

Dialysis

Dialysis is indicated in patients with marked elevations in serum uric acid, phosphate, and potassium that do not respond to aggressive treatment, and in patients with ARF with volume overload, severe uremia, or acidosis (31,33,39). Hemodialysis is used in ATLS because it is superior to peritoneal dialysis in the clearance of both uric acid and phosphorous (31,39).

OBSTRUCTIVE SYNDROMES

Superior Vena Cava Syndrome

Definition

Superior vena cava syndrome (SVCS) describes the set of signs and symptoms associated with obstruction of the superior vena cava, which may be caused by extrinsic compression, vascular invasion, or intraluminal thrombosis of the vein (46–48). The SVC is a thin-walled, compliant, low-pressure middle mediastinal vessel, rendering it easily vulnerable to disease processes in the adjacent right lung, the paratracheal and peri hilar lymph nodes, the mainstem bronchi, the esophagus, and the thoracic spinal cord (48,49).

First described by William Hunter (50) in 1757 in a patient with an aortic aneurysm secondary to syphilis, SVCS was—prior to the widespread use of antibiotics—primarily a complication of infectious diseases, as seen in syphilitic aortitis, histoplasmosis-induced fibrosing mediastinitis, and tuberculous mediastinitis (51,52). Currently, malignancy is the most common cause of SVCS. The percentage of cases attributable to cancer varies widely in the literature from 78% (48,53) to as high as 90% to 97% (54–57). A more recent retrospective study, reviewing the outcome of 78 patients over 5 years, reported malignancy as the cause of SVCS in 60% of the patients, with an increasing proportion of benign causes related to the presence of intravascular devices, e.g., central venous catheters and pacemaker wires (71%) (58). Other benign causes of SVCS include fibrosing mediastinitis from prior irradiation or histoplasmosis, aortic dissection, and complications of surgery, such as aortic dissection repair (54,58). Bronchogenic carcinoma accounts for 83% to 90% of the malignancies in which SVCS presents (54,57). Overall, SVCS develops in 2% to 10% of lung malignancies (47,52,56,59,60), and the risk of SVCS is higher in small cell lung cancer, with an incidence of 6.6% to 12% (59) because it involves the central mediastinal structures. In addition, because of the anatomic location of the SVC, right-sided lung cancers cause SVCS four times as often as left-sided lung cancers (56). Other neoplasms include malignant lymphomas; although Hodgkin’s lymphoma more often involves the mediastinum, it rarely causes SVCS (48,54). Primary germ cell cancers, thymoma, mesothelioma (60), and metastatic disease (primarily breast carcinoma) constitute a small proportion of SVCS cases (54,58,60).

Clinical Presentation

SVCS may be the initial presentation of bronchogenic carcinoma and lymphoma, or may arise in patients with previously...
documented malignancy (53,58). The severity of signs and symptoms depends on the extent, location, and rapidity of onset of the SVC occlusion (55). In general, obstruction within or below the azygos vein results in more dramatic symptoms. Normally, azygos venous capacity increases from 11% to 35% to augment drainage of the head and neck (47), but impairment of flow from obstruction precludes this auxiliary function (47,54,60). With slowly developing SVCS, collateral vessels in the chest wall and upper extremities are recruited as a diversion for the existing SVC engorgement; hence, SVCS in this population is of insidious onset, as in fibrosing mediastinitis (55).

The most commonly reported symptom in SVCS is dyspnea followed by head and facial swelling (48,58). Other cardiopulmonary symptoms include cough, orthopnea, and chest pain. Associated signs are neck and arm vein distention, plethora or cyanosis of the head and neck (48), venous collateralization in the arms and upper chest wall (54), and chronic pleural effusions (54,55). More extensive airway or vascular obstruction is predicted when positional maneuvers such as lying supine or leaning forward exacerbate respiratory or cardiac symptoms; for example, respiratory insufficiency in the supine position worsens as the weight of the mediastinal structures impinges on the tracheobronchial tree. In the substantially compromised patient with SVCS, cardiopulmonary arrest may ensue simply with the administration of sedatives and general anesthesia (54). Other head and neck signs and symptoms range from conjunctival and periorbital edema, nasal congestion, dysphagia, and hoarseness due to laryngeal nerve compression (61) to proptosis, glossal edema, stridor secondary to laryngeal edema, and tracheal obstruction (54,55). Patients with central nervous system (CNS) metastasis may exhibit mild headaches, dizziness, and lethargy with progression to syncope (in rapidly developing or complete SVC obstruction) seizures, or coma (from cerebral edema and increased intracranial pressure) (47,54). Bleeding complications such as epistaxis, hemoptysis (54), and gastrointestinal hemorrhage from esophageal varices (in longstanding SVC) (55) may occur.

Diagnostic Investigations

Imaging. Once the clinical diagnosis of SVC syndrome is suspected, confirmation can be obtained using both radiologic and nuclear techniques. Chest radiography reveals widening of the superior mediastinum in approximately 60% of patients (53,54,56) and pleural effusions, most frequently right-sided, in up to 25% of patients (48,54). A normal chest radiograph does not exclude the diagnosis. Contrast-enhanced helical computed tomography (CT) accurately delineates the site, extent, and cause of the occlusion (56,60), as well as any associated thrombus and collateral vessel development (60). The radiologic diagnosis of SVCS is made by demonstrating both decreased or absent venous opacification below the level of obstruction and prominent collateral vessel opacification (56). MRI is an alternative imaging method in patients with in- dicated contrast allergy or without adequate venous access for contrast administration, but offers no distinct advantage over CT (48,54,62). Venography is most useful when planning bypass or stenting procedures (48,60). Although venography is superior to CT in identifying the site and extent of obstruction and in mapping the collateral circulation, it does not elucidate the underlying cause of the SVCS (62), unless SVC thrombosis alone is the causative factor (52,56,60). Radionuclide 99mTc-technetium venography is a less invasive alternative to standard venography but lacks the image resolution of the latter (48). Although not a well-established diagnostic modality in clinical practice, helical CT plethorography, which involves simultaneous bilateral cannulation of the femoral vein injection with intravenous contrast, produces both detailed CT images of the mediastinum and a CT venogram that correlates well with digital venography. Flow artifact (inhomogeneous contrast opacification) created by physiologic mixing of contrast-opacified and nonopacified blood may mimic intraluminal filling defects in patent vessels and remains the major limitation of this technique (62).

Histologic Diagnosis. Spuritus cytology, thoracentesis, percutaneous needle biopsy, bronchoscopy, mediastinoscopy, or thoracotomy are all methods used to obtain pathologic specimens. The diagnostic yields are as follows: bronchoscopy, 50% to 70%; transbronchial needle aspiration biopsy, 75%; mediastinoscopy or mediastinotomy, greater than 90% (63). Historically, the treatment practice was to administer emergent radiotherapy for SVCS without establishing a histologic diagnosis. This strategy was predicated on the following beliefs: SVCS was a life-threatening emergency necessitating immediate intervention; invasive diagnostic procedures were associated with a high risk of morbidity, including bleeding and anesthetic complications; and unresectable lung malignancy was the most probable cause of the SVCS (46,56,59). Presently, it is well established that in the absence of tracheal obstruction or severe laryngeal or cerebral edema, SVCS itself results in no life-threatening complications (58,60,64-66); that invasive investigative procedures such as percutaneous needle biopsy, bronchoscopy, mediastinoscopy, and thoracotomy can be performed safely and with minimal risk; and that ongoing a pathologic diagnosis is unjustified, except in severe airway obstruction or cerebral edema (56,58,67,68), because identification of the underlying condition guides appropriate treatment of the SVCSs in both benign and malignant disease.

Treatment

The primary goals of treatment are symptom relief and eradication or palliation of the underlying malignancy. Initial symptomatic management involves bed rest, head elevation to reduce venous pressure, and supplemental oxygen administration. Diuretics and sodium restriction may decrease edema, but reports are anecdotal. Use of glucocorticoids to minimize inflammatory responses to tumor or radiotherapy (XRT) is controversial (48,56), but steroids are a mainstay of treatment in non-Hodgkin lymphoma (NHL) (54,56).

Endovascular Stenting. If these conservative measures are ineffective in controlling symptoms, a percutaneously placed endovascular stent can be inserted with or without balloon angioplasty (56). In recent studies, relief of symptoms occurred immediately after stent placement in 80% to 95% of patients with few complications (69,70). A systematic review of the literature found that morbidity increased with stent insertion if thrombolytics were administered. One group advocates stent insertion as a first-line therapy for symptom relief because, after placement, symptoms were rapidly alleviated in 18/18 patients, enabling all to begin XRT the following day (71). In a study involving 52 patients with non-small cell lung cancer (NSCLC) and SVCS, immediate symptom relief permitted patients to receive the appropriate hydration required with full doses of platinum therapy (69). Recurrence of SVCS occurs in 10% to 30% of patients after primary therapy with chemotherapy.
and/or radiation, and, in these cases, stent placement may be used for palliation (56,72).

Thrombolysis. With the increased use of intravascular devices, thrombus now accounts for a larger proportion of the benign causes of SVCS (58). When SVC syndrome is attributable to thrombosis of a central versus catheter, and catheter preservation is desired, thrombolytic therapy given within 3 days of symptom onset is associated with an 88% success rate versus 25% after 5 days (56,72).

Radiotherapy and Chemotherapy. The treatmentmodality selected will be determined by the type of malignancy, stage, and performance status of each patient (52,60). Primary management of solid tumors and NSCLC involves XRT. NSCLC associated with SVCS carries a poor prognosis, with 1-year survival in one series 17% (48,73), and a review of 1,635 patients showed a median survival of 5 months (74). The treatment of choice in NSCLC is XRT and possible stent insertion (49). Within 72 hours of XRT, patients have relief of symptoms, and within 2 weeks, 70% to 90% of patients are symptom free (56).

In a large systematic review, 69% of the NSCLC patients had relief of SVCS after chemotherapya and/or radiotherapy, and SVCS recurred in 19% (60). Chemotherapy prolongs survival and improves quality of life in patients with small cell lung cancer (SCLC), and addition of thoracic irradiation may reduce the recurrence risk of SVCS. In the aforementioned systematic review, SVCS was relieved in 77% of patients receiving chemotherapy and/or radiation, with relapse in 17% of patients (60). Lymphoma and germ cell tumors are usually treated with chemotherapy based on the histologic type, grade, and stage of the disease. In Hodgkin’s lymphoma, chemotherapypassed by XRT to areas of bulky disease may be indicated (56). In non-Hodgkin’s lymphoma, XRT alone may be used in early-stage disease, and chemotherapy is the treatment for higher-stage tumors. Whether to irradiate areas of bulky disease in NHL after chemotherapeutic remission is less clear; however, with residual tumor or progression of disease after chemotherapy, radiotherapy is administered (56).

Surgery. Surgical bypass of the obstruction with vein grafts or prosthetic grafts may be appropriate in patients with benign causes of SVCS. In patients with malignancy, surgical intervention, when no further treatment options are possible, at best, is a palliative measure with poor long-term survival (56,55).

**ACUTE AIRWAY OBSTRUCTION**

**Oropharyngeal and Tracheal Obstruction**

Sudden upper airway obstruction (UAO) of the larynx, pharynx, or extrathoracic trachea is uncommon with cancers of the head and neck. Tumors of the larynx, pharynx, base of tongue, and thyroid are primarily slow growing and, as they progressively enlarge, obvious signs and symptoms of airway compromise are usually evident prior to the development of acute obstruction (75); tracheal masses, which take years to be discovered, first become symptomatic when the airway lumen is narrowed by 75% (76). Mechanisms of UAO include direct tracheal invasion as well as extrinsic tracheal compression (77).

In the head and neck, direct tracheal invasion is seen with locally advanced oropharyngeal tumors, laryngeal neoplasms associated with bulky or supraglottic lesions, and, rarely, thyroid cancer and primary tracheal tumors (75). In thyroid cancer, tracheal invasion develops in 1% to 6.5% of patients, and UAO is the most common cause of death in this group (78). Bilateral thyroid cancer may cause glottic obstruction from bilateral laryngeal nerve paralysis and resultant bilateral vocal cord paralysis (75). Direct tumor extension into the trachea from adjacent structures by malignancies of the lung, esophagus, and mediastinum occurs more frequently than metastatic disease spread (79).

Tracheal impingement in lung cancer occurs when there is tracheal ingrowth of the primary tumor originating in a main-stem bronchus or from enlarging paraatracheal or subcarinal lymph nodes. Bilateral vocal cord paralysis with recurrent laryngeal nerve paralysis may also be associated with lung malignancies (75,80). Extrathoracic malignancies may metastasize to mediastinal and endobronchial lymph nodes, causing airway obstruction. Renal cell carcinoma, sarcomas, breast cancer, and colon cancer are most commonly involved (81). Melanoma may arise as a primary tracheal tumor but more often is a metastatic lesion (79).

Tracheal compression, which is usually attributable to benign disease, is a secondary mechanism of UAO in neoplastic disease and is often the initial presentation of mediastinal tumors and extensive lymphoma (82).

**Clinical Presentation**

Patients may present with dysphagia, hoarseness, intractable cough, hemoptysis, dyspnea, or stridor (54,75). Important goals during physical examination are to determine whether impending airway obstruction is present and to localize the site of the lesion. Once stridor is apparent, the airway caliber has profoundly narrowed to approximately 6 mm, and without intervention, complete UAO is imminent. Inspiratory stridor implies an extrathoracic lesion at the level of the glottis or above, whereas expiratory stridor suggests an intrathoracic lesion. Bihapstridor may be indicative of a subglottic or tracheal mass. Voice alteration, such as muffling and hoarse-ness, accompanies subglottic lesions and unilateral vocal cord paralysis, respectively (47).

**Diagnostic Investigations**

A chest radiograph may identify an obstructive neck mass and consequent tracheal deviation. Flexible oropharyngeal or nasopharyngeal endoscopy can be performed to assess the airway. Once the airway is stabilized, high-resolution CT of the head and neck provides comprehensive evaluation of the sites of narrowing and the size and extent of the tumor in relation to adjacent structures. Spirometry demonstrates a plateau in the inspiratory limb of the flow-volume loop if there is a fixed obstructive lesion in the extrathoracic trachea (83).

**Treatment**

Initial management includes head elevation and administration of cool humidified oxygen. Case reports have demonstrated that inhalation of a helium-oxygen mixture, consequent to its lower density compared to oxygen supplementation alone, reduces the work of breathing (54,84,85). Airway obstruction in patients with bulky oropharyngeal, laryngeal, or thyroid carcinomas will require emergent or elective tracheostomy. Endotracheal intubation is not recommended for patients with...
bulky, friable, laryngeal, and/or pharyngeal disease, as it may exacerbate existing airway edema and hemorrhage (75). For intrathoracic lesions, bronchoscopy with interventions such as laser therapy (86,87), brachytherapy, photodynamic therapy, or stenting may be performed to rapidly alleviate symptoms (87). Stents are also useful in palliating symptomatic extrinsic compression (54,88). Endotracheal intubation or stenting may be used to maintain the airway when there is extrinsic compression from lymphoma (88) or other highly radiosensitive or chemosensitive tumors with anticipation of rapid reduction of tumor mass. Surgical resection is indicated for primary airway tumors (54,89) and for lung cancers with- out mediastinal lymph node involvement. In lung and thyroid cancers that directly invade the trachea, surgery may be curative (79); metastatic disease to the trachea requires palliative treatment.

Intrathoracic Obstruction

Intrathoracic airway obstruction may be present with intrinsic primary endobronchial tumors such as bronchogenic carci- nomea and carcinoid, with metastatic tumors or their associated lymphadenopathy (lung, renal, breast, thyroid, and colon can- cers, and sarcoma or melanoma), or with bulky disease caus- ing airway compression. Symptoms often progress slowly over time, and patients may complain of dyspnea, wheezing, or chest discomfort, leading to the misdiagnosis of asthma or bronchitis prior to the development of fulminant airway obstruction (90). Postobstructive pneumonia may be a finding on initial pre- sentation. With impending obstruction, patients may exhibit hypertension, tachycardia, tachypnea, and significant pulsus paradoxus. Poor air movement, use of accessory muscles, and mental status changes are indicators of severe obstruction. Progression symptoms may result in negative pressure pulmonary edema and anoxic brain injury (83). Chest examination may reveal a prolonged expiratory time and wheezing. Respiratory symptoms are unilateral with lesions below the carina (90), and the chest radiograph reveals asymmetric lung fields, par- ticularly on end-expiration. Stable patients should have a flow- volume loop performed. An intrathoracic, mobile tracheal le- sion above the carina will demonstrate airway compression during the expiratory phase, producing flattening of the ex- piratory limb of the flow-volume loop, whereas a plateau in both inspiratory and expiratory limbs will be observed with fixed obstructive lesions (83). Chest CT defines tumor extent and location, but rigid bronchoscopy is usually necessary to evaluate the airway in impending obstruction. When airway obstruction is severe, flexible bronchoscopy is hazardous be- cause this technique does not permit ventilatory support, and, additionally, the bronchoscope may obstruct the already nar- rowed airway lumen (90).

Treatment proceeds with the general measures of oxygen or helium/oxygen supplementation and, possibly, steroids. If endotracheal intubation is required, the clinician must recog- nize the potential for hemodynamic compromise associated with acute respiratory obstruction and significant increases in airway pressure distal to the obstruction (83). Bronchoscopy with vari- ous interventions, including debridement, dilatation, endotra- cheal stent placement, laser ablation, photodynamic therapy, and placement of brachytherapy catheters may relieve symp- toms (90). External beam radiotherapy may also play a role. In lung cancer, tracheal and carinal resection is indicated in patients without mediastinal lymph node involvement for a potential cure (54).

NEUROLOGIC SYNDROMES

Spinal Cord Compression

Etiology and Pathophysiology

Malignant spinal cord compression (MSCC) is a profoundly debilitating, but usually nonfatal, manifestation of metastatic cancer, occurring in 5% to 10% of cancer patients (91–93). The term, MSCC, refers to epidural, intramedullary, and lep- tomeningeal disease; however, the focus of this section is on epidural spinal cord compression (ESCC) because the literature primarily discusses this population (93). Although any malignancy capable of metastatic spread may give rise to MSCC, prostate, breast, and lung cancers are most commonly involved, with each accounting for 15% to 20% of cases (91,94) or, in combination, 60% of cases (93,95). The cumulative inci- dence of MSCC is specific to tumor type, with the highest rates occurring in multiple myeloma (8%), prostate cancer (7%), and nasopharyngeal cancer (6.5%) (95). Other tumors include non-Hodgkin’s lymphoma and renal cell carcinoma, with each representing 5% to 10% of cases (96), and gastrointestinal cancers, sarcoma, melanoma, thyroid cancer (92,93), and un- known primary carcinoma (95,96). Enlarging meningiomas, nerve sheath tumors, and leptomeningeal metastases may also compress the spinal cord. Nonmalignant causes of MSCC in the cancer patient are epidural abscesses in the presence of immune compromise and hematoma with bleeding diatheses (97).

MSCC has a proclivity for the thoracic spine (92,96,98– 100) and is estimated to occur in this location in approximately 60% to 66% of cases (97,99). Twenty percent of cases involve the lumbar spine (92,97), and MSCC in the cervical spine is uncommon in 7% to 10% of cases (99,100). Prostate and col- onrectal carcinomas favor the lumbarosacral spine (97). MSCC is the initial manifestation of malignancy in 20% of patients. One series found that carcinomas of the lung and unknown primary, multiple myeloma, and non-Hodgkin’s lymphoma accounted for 78% of patients with MSCC presenting with malignancy compared to 26% in patients with previously established ma- lignantancy (100).

The mechanisms by which MSCC occurs include vertebral body invasion by tumor with possible vertebral collapse caus- ing encroachment on the anterior spinal cord (85%); direct ex- tension into the intervertebral space by paraspinal lymphoma, sarcoma, or lung cancer, seen in 10% to 15% of cases (9,92); and epidural or intramedullary space invasion, seen in less than 5% of cases (92). The mechanism of injury to the spinal cord is mediated by white matter vasogenic edema and axonal swelling that result from cord compression. Venous hyperten- sion, decreased spinal cord blood flow, and cord infarction en- sure, resulting in ischemic hypoxic neuronal injury. Vascular endothelial growth factor (VEGF) is generated in association with spinal cord hypoxia, and it is thought that dexamethasone may down-regulate VEGF expression, resulting in the benefi- cial actions of steroids in MSCC (96).

Clinical Presentation

Pain, which may be characterized as localized, radicular, or re- ferred, is the primary presenting symptom in MSCC, occurring
in 83% to 95% (96,98,101) of patients for a median of 8 weeks prior to diagnosis (96,98). Focal bony pain is typically localized, dull or aching, and constant. Direct tenderness of the involved vertebral body may be evident with periostial destruct-

tion (102). With time, radicular pain occurs in the dermatome of the affected nerve root and is severe, deep, and lancinating. Radicular symptoms occur most often in the lumbar or sacral spine and may be unilateral or bilateral, the latter more frequent with thoracic spine involvement (97,103). Refrained pain does not radiate, but appears in a region distal to the area of pathology; for example, sacroiliac pain may result from L1 compression (103). The pain of MSCC is typified by worsening with recum-

bency secondary to distention of the epidural venous plexus (96,97). Coughing, sneezing, orValsalva maneuvers will also exacerbate the pain (103). Straight-leg raising identifies a lum-

bosacral radiculopathy, and neck flexion reproduces symptoms of thoracic radiculopathy (97,101,103).

Motor weakness is present in 60% to 85% of patients on diagnosis of MSCC. Although only one third of patients com-

plain of lower extremity weakness on initial presentation (97), two thirds are not ambulatory at the time of diagnosis (96,97). Motor deficits at the level of the conus medullaris or above gen-

erally have a symmetric distribution. Paralysis is usually seen in the extremities of the upper extremities or the flexors of the lower extremities, depending on the location of the lesion in the spine. Upper motor neuron signs such as spasticity, hyperreflexia, and Babinski responses, may be present. Cervical lesions may lead to quadriplegia and respiratory collapse (102).

Sensory deficits, reported as varying degrees of paresthesias, are less common than motor deficits but can be found in 40% to 90% of patients. The level of hypesthesia on examination occurs one to five levels below the actual anatomic level of cord compression (96). The sensation of an electric shock radiating through the spine and extremities with neck flexion, termed the Lhermitte's sign is seen infrequently with cervical or thoracic neoplasms. Perineal paresthesias may occur with cauda equina lesions. Urinary incontinence follows sensory loss impairment, but in the absence of sensory findings, impairment of the spinocere-

bellar tract should be considered.

Bowel and bladder dysfunction reflects autonomic dysfunc-
tion and is a late manifestation of MSCC (103). Patients re-

port urinary hesitancy and frequency, and both incontinence of urine, from poor sphincter tone or overflow of urine, and urinary retention may ensue. At the time of diagnosis, 50% of patients are incontinent or catheter-dependent (101). Patients may also exhibit erectile dysfunction and impotence. Constipa-
tion and incontinence of stool with diminished sphincter tone may be present (103). Narcotics are widely used in cancer pa-

tients and are capable of precipitating urinary retention and constipation; however, spinal lesions must be excluded in these patients before narcotic use is implicated.

Diagnostic Investigation

The imaging study of choice in evaluating MSCC is magnetic resonance imaging (MRI) because it is a noninvasive test that provides high resolution of the soft tissues, including bony metastases and intramedullary pathologies. One study found that MRI had a sensitivity, specificity, and overall accuracy of 93%, 97%, and 93%, respectively, in detecting MSCC in patients with known primary CNS tumors (104). It is fundamental to recognize that when the entire spine is imaged beyond the area of clinically determined cord compression, multiple epidural metastases (MEMs) are found in 30% of patients. Because the presence of MEMs may alter treatment strategy, several studies have purported using whole-

spine MRI in all patients with MSCC (94,104,105). With the relative paucity of cervical spine metastases, if the clinical presentation does not suggest cervical disease, it may be acceptable to image the thoracolumbar spine alone (106). Myelography with or without CT myelogram is a more inva-
sive tool than MRI and is used in imaging MSCC when MRI is contraindicated. CT alone does not adequately define the soft tissues and spinal cord, and plain radiographs and radionu-

clide testing have low sensitivity and specificity for demon-

strating MSCC. Plain films detect vertebral metastases at the site of known cord compression only 80% of the time (9,97), and many metastases are missed because the ability to visualize these lesions requires that 30% to 40% of the bone be eroded (107). Bone scintigraphy is the most cost-effective and sensitive technique in imaging vertebral metastases.

Treatment

The goals of therapy are pain control and preservation of neu-

rologic function to improve quality of life. Narcotic and corti-

costeroids administration, XRT, and surgery may all be used.

Corticosteroids. In a randomized trial that established the ef-

cacy of corticosteroids in cord compression, patients were

assigned to XRT with or without dexamethasone. At the con-

clusion of the study, 81% of those receiving corticosteroids and XRT versus 63% of those receiving XRT alone remained am-

bulatory. At 6 months, the percentages were 59% and 40% (93) respectively in the two groups, respectively (108). There are less well es-


tablished data regarding the use of high-dose dexamethasone regimens because, although higher doses (100mg versus 10-

mg bolus) may have greater clinical efficacy in improving posttreatment ambulation, they are associated with a higher propor-
tion of adverse effects. Typical regimens include a 10-

mg bolus, followed by 16 mg divided four times daily, tapered over 2 weeks. High-dose regimens (100-mg bolus, then 96 mg divided four times daily, tapered over 2 weeks) (93) may be reserved for patients with paresis or paraplegia. In ambulatory patients who are asymptomatic and undergoing XRT, cortico-

steroids may be withheld (93,94,109).

Surgery and Radiation. A recent randomized trial demon-

strated that direct decompressive surgery followed by radio-

therapy is superior to radiotherapy alone for patients with MSCC. Patients were assigned to either surgery followed by XRT or to XRT alone. The study was stopped early because the primary end point had been satisfied, and a therapeutic ad-

vantage of surgery plus XRT was observed: 84% of the surgery group versus 57% of the XRT group were ambulatory after surgery alone in the two groups, respectively (108). There are less well es-


tablished data regarding the use of high-dose dexamethasone regimens because, although higher doses (100mg versus 10-

mg bolus) may have greater clinical efficacy in improving posttreatment ambulation, they are associated with a higher propor-
tion of adverse effects. Typical regimens include a 10-

mg bolus, followed by 16 mg divided four times daily, tapered over 2 weeks. High-dose regimens (100-mg bolus, then 96 mg divided four times daily, tapered over 2 weeks) (93) may be reserved for patients with paresis or paraplegia. In ambulatory patients who are asymptomatic and undergoing XRT, cortico-

steroids may be withheld (93,94,109).
Prognosis

The median survival in MSCC patients receiving XRT is 3 to 6 months (96). Patients who initially present with paralysis or become paralyzed after treatment have a shorter life expectancy than those who are ambulatory (94). Multiple studies have shown that the ambulatory function on diagnosis of MSCC is the most important predictor of outcome of ambulatory function after irradiation. This finding underscores the need for education of both the clinician and the patient to ensure prompt recognition of MSCC. In one study, delay in diagnosis was attributed to the patient's failure to identify symptoms and diagnostic delays by the generalist and hospital practitioner, leading to deterioration in motor or bladder function (111).

Cardiac Tamponade

Primary neoplasms of the myocardium and pericardium are uncommon, but metastatic disease to the pericardial space is frequently seen (112). Primary pericardial tumors, of which mesothelioma represents the largest proportion, are 40 times less common than metastatic disease. Secondary malignancies include, most frequently, lung, breast, and ovarian carcinoma, and melanoma, lymphoma, and leukemia (113). Malignancy is a primary cause of pericardial effusion in the United States (114), and pericardial tamponade resulting from malignant pericardial effusion (MPCE) represents at least 50% of reported cases of pericardial fluid collection requiring intervention (115,116). Autopsy series have reported, with varying estimates, that MPCE is seen in 2% to 22% of cancer patients (47,114,115,117), and that these effusions are clinically quite esent, remaining unrecognized (47). In some patients, MPCE may be the initial presentation of cancer, but in any patient, it signifies a dismal prognosis, with most patients dying within 1 year (118). Pericardial effusions in some cancer patients may be attributable to comorbid conditions rather than to malignant disease, and other causes must be considered, such as radiation-induced pericarditis, infection, uremia, myocardial infarction, congestive heart failure, and pneumonia (113).

Pathophysiology

The pericardium is a fibroserous sac, composed of two layers that surround the heart. The outer layer is the fibrous pericardium, which attaches to the diaphragm and securely anchors the heart within the thoracic cavity. The serous pericardium is a single layer of mesothelial cells and its underlying connective tissue, which lines the fibrous pericardium. During embryonic development, the heart invaginates the walls of the serous pericardium, creating a potential space between an inner serous layer that is adherent to the heart (visceral pericardium) and an outer serous layer that lines the fibrous pericardium (parietal pericardium). The pericardial space is formed between the two serous layers, and it normally contains 15 to 50 mL of fluid for lubrication. The fluid is drained from the right pleural space into the right lymphatic duct, and from the parietal pericardium into the thoracic duct (119,120). Any interruption in this flow will result in accumulation of fluid and pericardial effusion. The mechanisms by which malignant disease generates MPECs include direct invasion of the pericardium or myocardium, and disruption of lymphatic flow from lymph node metastases or from prior radiotherapy to the chest or mediastinum (115,117). The tumors that invade the pericardium directly or hematogenously are most often lung cancer, followed by lymphoma and breast cancer (47,115).

With either of the aforementioned mechanisms, pericardial fluid accumulates and inhibits passive diastolic filling of the normally low-pressure right heart structures, producing jugular and abdominal venous hypertension (115). As the pericardial effusion expands, the heart is further compressed, leading to reduced diastolic compliance, decreased diastolic filling, and, ultimately, decreased stroke volume, cardiac output, and blood pressure. Right atrial and right ventricular collapse ensues, resulting in frank tamponade, which, untreated, will lead to shock (121). Pericardial reserve volume is approximately 10 to 20 mL, and is defined as the volume that will just distend the pericardium. As the pericardial effusion enlarges, capacity for stretch is exceeded. Therefore, when fluid accumulates rapidly, the pericardium cannot stretch rapidly enough to accommodate the added volume, and the heart becomes compressed (120). Under these circumstances, acute tamponade may occur with as little as 50 mL of fluid (121). When effusions develop chronically, the pericardium is able to compensate by stretching slowly over time—the phenomenon of stretch relaxation (120–122). In cancer patients, the MPCE develops slowly, and as much as 2 L of pericardial fluid may be present before critical symptoms occur (121).

Clinical Presentation

Patients may be asymptomatic with small pericardial effusions (9,113) and, in general, symptoms correlate with the compressive effect of the effusion on surrounding structures, including the lung, trachea, and esophagus. Symptoms include dyspnea, cough, chest pain, hoarseness, hiccupps, and dysphagia (120). The most commonly reported physical sign is distention of the jugular veins. The classic finding of the Beck’s triad of hypotension, increased jugular venous pressure, and quiet heart sounds may be present in addition to the Kussmaul’s sign, which is paradoxical jugular venous distention and increased jugular venous pressure on inspiration. Sinus tachycardia, hepatomegaly, and peripheral edema may all be apparent. On cardiac examination, dullness beyond the apical impulse and rales can be detected, and in patients with inflammatory effusions, a pericardial rub is often heard. A narrow pulse pressure is frequently noted, and pulsus paradoxus, a decrease in systolic blood pressure greater than 10 mm Hg, is observed in 77% of patients with acute tamponade; patients may report a feeling of uneasiness (121). When low-output shock results from failure of compensatory mechanisms to maintain cardiac output, the patient exhibits cold, clammy skin, cyanosis, oliguria, and altered mental status (122).

Diagnostic Investigations

Chest radiograph reveals a water bottle-shaped heart with widening of the cardiac silhouette and, occasionally, pericardial calcifications (121). Pleural effusions will be present in one third of cases (115). The electrocardiogram may demonstrate a low-voltage QRS or nonspecific ST-T wave changes (9).
Electrical alternans in the P wave and QRS complex is a rare finding, noted in 0% to 10% of patients (120), in which every other QRS complex has a lower voltage and/or reversed polarity (121). The echocardiogram precisely localizes the pericardial fluid, discerns the quality of the effusion (heterogeneous versus homogeneous), determines whether localizations or bulky tumor are present, assesses right and left ventricular function, and ascertains whether right atrial and right ventricular diastolic dysfunction are present. On echocardiography, the heart may be seen to swing in a pendular fashion within the pericardial fluid. Right heart catheterization is the definitive standard for further defining the pericardial effusion. Classically, there will be equalization of diastolic pressures across all cardiac chambers (115).

**Treatment**

Treatment strategy should be individualized to each patient based on age, comorbid conditions, malignancy type, and overall prognosis (114). Cardiac tamponade is a class I indication, as designated by the European Society of Cardiology Task Force, for performing pericardiocentesis, and the initial emergent intervention in malignant cardiac tamponade is to drain the effusion, usually in conjunction with echocardiographic guidance (113). Fluid should be sent for chemical analysis, microbiology, and cytology; the effusion is removed successfully in 97% of patients (123). The guidelines recommend that in the absence of tamponade, systemic chemotherapy be administered as baseline treatment (113), thereby precluding reaccumulation in 57% of cases (123). Systemic chemotherapy is effective in controlling malignant effusions when the tumors are chemo-sensitive, as in lymphoma, leukemia, and breast cancer. Notably, ART is highly effective (93%) in controlling malignant pericardial effusions in patients with lymphoma and leukemia, although radiation myocarditis or pericarditis is, in itself, a complication of radiotherapy (123). Pericardiocentesis should be performed in MPCE, especially when these are large, for symptomatic relief and to establish a cause. Because fluid reaccumulates within 88 hours of the initial pericardiocentesis (124), intrapericardial sclerosing or cytostatic agents, selected according to tumor type, should be administered to prevent recurrence. The mechanism of action of sclerosing agents is to effect symphysis of the visceral and parietal pericardia (113). A surgical approach to MPCE management is subxiphoid pericardiectomy to create a pericardial window. An advantage of this technique is that it is performed using local anesthesia and has a low recurrence rate. Additionally, tissue can be obtained for pathologic review. However, there is a small risk of myocardial infarction, pneumothorax, and mortality with this procedure. One study showed a 12% recurrence at 1 year and a 4% reaccumulation rate for subxiphoid pericardiectomy (114). Pleuropericardiectomy and pericardiectomy, which require general anesthesia, have higher morbidity and mortality rates, and are rarely used in MPCE management (113). Percutaneous balloon pericardiectomy may become the procedure of choice in the future. Requiring only local anesthesia, it facilitates passage of pericardial fluid into the left pleural or peritoneal spaces, which have greater resorptive capacity. The major side effect is asymptomatic pleural effusion in most patients (47,125). Percutaneous balloon pericardiectomy appears to be a safe and effective technique in patients with large MPCEs and recurrent tamponade (90% to 97%) (125,126). Reaccumulation rates with this method are 0% to 6%. Reaccumulation rates for other therapies that are administered after initial pericardiocentesis is performed are radiotherapy, 33%; systemic chemotherapy, 30%; sclerotherrapy with tetracycline, 15% to 30%; and mechanical therapies, including indwelling pericardial catheter placement, balloon pericardiomyotomy, and thoracotomy with pericardiomyotomy, 0% to 13% (47).

Even if there is no reaccumulation of fluid, cardiac function may remain impaired in the presence of epicardial infiltration by tumor. Diastolic dysfunction occurs because of the constrictive effect of a diseased epicardium surrounding the heart. Effusive-constrictive pericarditis results in a combination of tamponade and cardiac restriction. This entity must be considered in the differential diagnosis when a patient develops hemodynamic collapse a few days after pericardiocentesis. Pericardiectomy may be useful in alleviating the constrictive component; irrespective of this procedure, mortality is extremely high (47,127,128).

**Prognosis**

Survival after the development of a malignant pericardial effusion is extremely poor (124,128). The pericardial lesions either contribute to or directly cause death in 86% of untreated patients with symptomatic MPCE (128). In one series of 275 patients with MPCE, the median survival was 13.5 days, and the chance of surviving the first year was 26%. The findings of male gender, lung cancer, positive fluid cytology for malignant cells, and the clinical presentation of cardiac tamponade or hemodynamic collapse were independently associated with poor survival (124). In another series, which concluded that a poor prognosis was associated with positive fluid cytology, median survival was 7.3 weeks versus 29.7 weeks in the positive cytology and negative cytology groups, respectively, MPCE and abnormal cytology were found to be independent predictors of death (129). Taken together, these prognostic factors can be used to make practical and realistic treatment decisions.

**GASTROINTESTINAL EMERGENCIES**

**Neutropenic Enterocolitis**

Neutropenic enterocolitis (NE) is also known as necrotizing enteropathy, ileocecal syndrome, or typhlitis (130), from the Greek derivation of the word “typhlon,” or cecum (131). Necrotizing enteropathy was first described in adult patients with leukemia and lymphoma more than four decades ago (132), and typhlitis was recognized as an equivalent entity involving the cecum in children undergoing induction therapy for acute leukemia in 1970 (133). The disorder is a life-threatening inflammatory syndrome in the immunocompromised patient that involves the terminal ileum, ascending colon, and cecum (134). Because the disease affects both the small and large bowel, the term, neutropenic enterocolitis, is most commonly used (135). The cardinal features that define the syndrome are fever, abdominal pain, and bowel wall thickening in a patient with neutropenia (134,136), where neutropenia is defined as...
a neutrophil count of either less than 500 neutrophils/µL, or less than 1,000 neutrophils/µL with an expected precipitous decline to below 500/µL, and death (137,138). In its natural history, the disease may progress to bowel ulceration, necrosis, and perforation, and ultimately, sepsis and death (135).

Neutropenic enterocolitis (NE) occurs primarily in patients following aggressive cytotoxic therapy for acute leukemia (134,139) and other hematologic malignancies such as lymphoma (134,136), chronic leukemia (134), multiple myeloma (134–136), and rarely in solid tumors, such as colon, breast, testicular, lung (130,140), and pancreatic cancer (140). In leukemia, administration of drugs toxic to the bowel mucosa, such as cytosine arabinoside (141), which cause cellular atypia to frank ulceration, increases the risk of NE (140). Other agents include cytarabine, cisplatin, fluorouracil, vincristine, doxorubicin, 5-fluorouracil, thioguanine, and mercaptopurine (141). NE is rare in solid tumors, but there are case reports identifying the syndrome in breast cancer patients receiving taxanes (142–144). Interestingly, there are also case reports of acute leukemia patients presenting with NE in the absence of chemotherapy (136), indicating that drug toxicity is a predisposing factor rather than a prerequisite in the disease pathogenesis (136). Other immunocompromised patients in whom NE occurs include cases of aplastic anemia (134,136,139,145), cyclic neutropenia (146,147), agranulocytosis (148), Felty syndrome, thalassemia minor, systemic lupus erythematosus (134), and HIV disease (134,149). Patients receiving immunosuppressive therapy for bone marrow (150) or renal transplantation (151) are also at risk.

The incidence of NE in adults varies widely in the literature, ranging from 0.3% to 2.6%. In a recent systematic review, the pooled incidence rate for adults hospitalized for treatment of hematologic malignancies and solid tumors and for aplastic anemia was 5.3%. The incidence of NE in the acute leukemia group receiving myelosuppressive therapy, with the exclusion of transplant patients, was 5.6%. Extrapolating from these findings, the authors concluded that neutropenia rather than acute leukemia is the primary risk factor for NE (134). In another study, 88 (6%) of 1,450 consecutive patients treated for leukemia had clinical manifestations of NE (152). Although the incidence may be low, it is the high mortality rate associated with NE that underscores its designation as an oncologic emergency. Initial studies reported mortality rates ranging from 50% to 100% (153). The above systematic review stated that several authors observed a rate of 50% or higher, with other published figures ranging between 40% and 50% (154).

Pathogenesis

NE has a predilection for the terminal ileum, cecum, and appendix (154). One factor that may explain this predilection is the overall decreased blood supply to the colon (136). Also, inherent to the cecum is decreased vascularity and increased distensibility compared to other colonic segments (140,142), and progressive distention in the cecum may cause increasing intraluminal pressure and exacerbation of submucosal edema (140). The pathogenesis of NE is multifactorial and remains unclear (130,136). Drug-induced cytotoxic mucosal injury (130,131,140) initiates the process by limiting cellular proliferation and generating glandular epithelial atypia and necrosis (cytosine arabinoside), and by producing myenteric plexus degeneration (vincristine) (140). Subsequently, mucosal barrier integrity is breached because cells cannot rapidly regenerate to repare the damaged surface (137,138). Once mucosal damage develops, bacterial translocation occurs, resulting in microbial infection and sepsis (130,140). Marked neutropenia impairs host defense and promotes further microbial invasion; bowel flora becomes altered (136). Blood cultures are often positive for Clostridium septicum, C. difficile, Escherichia coli, Pseudomonas, Klebsiella, Enterobacter, and Staphylococcus (135,140). Candidiasis, primarily Candida albicans, which colonizes mucosal surfaces, is the most common fungal infection in neutropenic patients and is associated with a high morbidity and mortality (155). These microbial infections lead to inflammation and edema. With sustained profound neutropenia, bacterial invasion is unconstrained, resulting in transmural necrosis, hemorrhage, ulceration, and perforation (135,136,140,156). In addition to drug-induced mucosal injury, infiltration of mucosa with leukemic and lymphoproliferative cells and mucosal ischemia from sepsis-related hypotension may also participate in initiating and perpetuating mucosal injury (140,154).

Symptoms

The onset of NE is 7 to 10 days after treatment when neutropenia is evident. The clinical presentation includes fever, occurring in 90% of all hospitalized neutropenic patients at any time (140), nausea and vomiting, abdominal pain, and watery or bloody diarrhea. Physical examination may reveal stomatitis with diffuse mucositis, abdominal distention, and peritoneal signs suggestive of bowel perforation (140,141,157). In 60% to 80% of patients, right lower quadrant (RLQ) tenderness is elicited. Palpation of a mass in the RLQ usually indicates a thickened, dilated, fluid-filled cecum (140).

Differential Diagnosis

Neutropenic enterocolitis must be included in the differential diagnosis whenever a neutropenic patient presents with fever and abdominal pain, particularly RLQ pain. Other entities that may mimic NE are pseudomembranous colitis, acute appendicitis, acute cholecystitis, acute pancreatitis (152), diverticulitis (158), ischemic colitis, Ogilvie’s syndrome (colonic pseudo-obstruction) (159), chemotherapy-induced abdominal pain (130), and ileus secondary to vincristine toxicity (152). Gastrointestinal bleeding may occur in 35% of typhilitis cases, and hemorrhage should suggest NE rather than appendicitis (157).

Diagnostic Investigation

On laboratory analysis, in addition to neutropenia, thrombocytopenia may be seen. Blood cultures are positive in 50% to 82% of cases for bowel organisms as described above (135). Stool studies may be notable for absence of C. difficile toxin A because C. difficile is not the primary pathogen in NE (134,142).

Plain radiographs of the abdomen are usually normal or nonspecific. Findings may include a decrease in right lower quadrant gas with dilated small bowel loops and air fluid levels.
consistent with a distal bowel obstruction. Free intraperitoneal air after perforation, pneumatosis colci, or localized or diffuse “thumb-printing” characteristic of mucosal edema may be exhibited (130,140).

Sonography assists in confirming the diagnosis of NE and in excluding other differential diagnoses by detecting bowel wall thickening. Additionally, ultrasound is useful in following the clinical course of the disease (136,152). Sonographic manifestations of NE include a rounded mass with dense central echos and a wider hyperechoic periphery (130), pseudopolyloid changes of the cecal mucosa, and pericolic fluid collections (140). One study of neutropenic enterocolitis demonstrated that patients with sonographically detected bowel wall thickness of greater than 10 mm had a significantly higher mortality rate (60%) than did those with bowel wall thickness less than or equal to 10 mm (4.2%) (152).

Computed tomography is a more accurate modality for assessing cecal wall thickening and evaluating the extent of the colitis (130,136). It also has utility in differentiating NE from appendicitis, appendiceal abscess, or pseudomembranous colitis (159). CT findings include diffuse submucosal thickening and edema of the terminal ileum and ascending colon, mural hemorrhage, pericolic fluid collections, abscess formation, pneumatosis colci, and intraperitoneal free air (136). The false-negative rates in identifying NE for CT, ultrasound, and plain radiographs are 15%, 23%, and 48%, respectively (139).

Barium enema is unsafe because it may result in bowel perforation in the presence of severely damaged, necrotic bowel (131,160). Endoscopic examination is generally avoided because it involves a high risk of perforation in addition to hemorrhagic and infectious complications, and it may precipitate fulminating mural necrosis (130). Colonoscopy has been performed in a paucity of patients and will reveal irregular nodular mucosa, ulcerations, hemorrhagic friability, and a masquile lesion resembling carcinoma (131).

**Histopathology**

With the difficulty of obtaining biopsy specimens, a tissue diagnosis is not required to confirm NE. On gross examination, striking bowel wall thickening is evident. Scattered serosal echymoses give the bowel a dusky appearance. Microscopy demonstrates pronounced transmural submucosal edema, vasculitis, stromal hemorrhage, and patchy or complete epithelial necrosis, resulting in mucosal ulceration and pseudomembrane formation. With further damage, transmural necrosis leads to musculitis propria degeneration. Vascular injury affects intramural and intraluminal hemorrhage, and fibrous thrombi may be seen in the submucosal vessels. Polymicrobial infiltration with bacteria and fungi is observed in 53% of postmortem cases (134). Very few inflammatory cells are observed, and rarely, leukemic or lymphoproliferative infiltrates invade the bowel wall. Neutrophils are absent, and aneutrophilia in the setting of marked cell injury is pathognomonic for NE (134,154).

**Management**

Prospective trials or case control studies evaluating therapeutic interventions in NE are lacking (134). Management strategy remains controversial regarding the decision to proceed with early surgical intervention versus a conservative approach (161). Conservative management of NE involves bowel rest, intravenous fluid and blood product resuscitation, broad-spectrum antibiotics, granulocyte colony-stimulating factor (G-CSF), and frequently, parenteral nutrition (130,141). Use of omeprozole and gastric decompression is not advocated by some authors because these interventions facilitate bacterial migration from the bowel into the respiratory tract, predisposing the patient to pneumonia (134). Medications that inhibit bowel motility, such as antiadrenergic and narcotic agents should be avoided since they perpetuate ileus and promote bacterial overgrowth (141). Patients with chemotherapy-induced NE may suffer from repeated episodes of future treatment; therefore, further chemotherapy should be withheld until NE has completely resolved. Bowel decontamination may be helpful before subsequent chemotherapy, although this is not well-studied (131).

Selection of broad-spectrum antibiotics should incorporate the Infectious Diseases Society of America (ISDA) 2002 recommendations for febrile neutropenia (137) as well as the 2003 ISDA guidelines for complicated intra-abdominal infections (162). Without prompt antibiotic therapy, neutropenic patients with Gram-negative bacteremia have a mortality rate approaching 40% (163). The antibiotic(s) of choice in NE must demonstrate activity against both Gram-negative and anaerobic organisms. Options include the following: monotherapy with a carbapenem or piperacillin-tazobactam; duotherapy with another antipseudomonal β-lactam plus an aminoglycoside; or duotherapy with cefepime or ceftazidime plus metronidazole (134,141,162). Antifungal therapy with amphotericin B therapy should be considered for empiric therapy in profound neutropenic patients with severe sepsis or fungemia persisting beyond 5 days despite receiving appropriately dosed broad-spectrum antibiotics (137). Granulocyte colony-stimulating factor (G-CSF) increases cell division in myeloid precursor cells, decreases bowel motility, such as antidiarrheal and narcotic agents, food, oral and rectal antibiotics (162). Without prompt antibiotic therapy, neutropenic patients may have a mortality rate approaching 40% (163). The antibiotic(s) of choice in NE must demonstrate activity against both Gram-negative and anaerobic organisms. Options include the following: monotherapy with a carbapenem or piperacillin-tazobactam; duotherapy with another antipseudomonal β-lactam plus an aminoglycoside; or duotherapy with cefepime or ceftazidime plus metronidazole (134,141,162). Antifungal therapy with amphotericin B therapy should be considered for empiric therapy in profound neutropenic patients with severe sepsis or fungemia persisting beyond 5 days despite receiving appropriately dosed broad-spectrum antibiotics (137).
conservative therapy warrant consideration for surgery (142,167). Several authors recommend surgery for severe complications such as abscess, necrotic bowel, and obstruction (136). In general, definitive indications for surgery include intraperitoneal free air/perforation, generalized peritonitis, and persistent bleeding in spite of correction of coagulopathy (130,140). Important considerations that must influence the decision to surgically intervene are the patient’s prognosis and comorbidities because postoperative morbidity and mortality is greater in individuals with coexistent diseases (140). If surgery is warranted, the procedure of choice is colectomy with ileostomy and mucous fistula; a primary anastomosis is used in very few patients (168). Of note, the extent of mucosal necrosis may be underestimated by the appearance of the serosa. A surgeon must ensure complete resection of edematous bowel, even in the absence of necrosis and inflammation, to preclude a fatal outcome (140).

**TOXICITY OF CHEMOTHERAPY**

Most antineoplastic agents exert their therapeutic actions by targeting rapidly proliferating malignant cells. Because these agents interrupt fundamental cellular processes such as DNA, RNA, and protein synthesis, they are not completely specific to malignant cells and will also act on normal tissues, causing multiple toxicities. Rapidly regenerating cells, such as the hematopoietic lineage, gastrointestinal mucosa, hematopoietic, and hair follicles may suffer transient toxicity compared to cells that have limited regenerative capacity, including those of the myocardium, and nerves (169–171). This section focuses on the major life-threatening toxicities that occur with commonly used chemotherapeutic agents.

**Pulmonary Toxicities**

Pulmonary toxicity, both acute and chronic, is seen increasingly with numerous antineoplastic agents (172). Chemotherapy-induced lung disease (CLD) describes lung injury with multiple etiologic agents and varying pathophysiologic mechanisms. These major mechanisms include direct lung toxicity, immunologic response, and increased capillary permeability. The corresponding clinical presentations are interstitial pneumonitis/fibrosis, hypersensitivity syndrome, and capillary leak syndrome, respectively, and each may eventuate in fulminant respiratory failure. Symptoms can appear immediately or months after termination of therapy (173).

**Antitumor Antibiotics**

**Bleomycin.** Bleomycin is an antitumor antibiotic used in the treatment of lymphoma, germ cell tumors, cervical carcinoma, and head and neck squamous cell carcinoma. The absence of bleomycin hydrolyase in the skin and lungs prevents deactivation of the drug, accounting for its selective toxicity. Bleomycin interstitial pneumonitis is the most ominous toxicity, associated with a 3% mortality rate (174) and occurring in 0% to 46% of patients receiving bleomycin-containing regimens, either during treatment or up to 6 months after discontinuation (175). Toxicity is mediated by the mechanism of direct lung injury via generation of cytokines and free radicals, the sequelae of which are endothelial damage, inflammatory cell infiltration, fibroblast activation, and fibrosis (173,175). There is conflicting evidence in the literature as to whether preoperative oxygen supplementation exceeding a concentration of 24% fractional inspired oxygen causes synergistic toxicity with bleomycin through the production of free radicals (176,177).

**Mitomycin C.** This is an antibiotic used in treating solid tumors, primarily breast and lung carcinomas. The mechanism of injury is alkylation of endothelial cell DNA, precluding cell division. This agent is associated with the development of an interstitial pneumonitis/fibrosis (178,179), usually 3 to 12 months after therapy (179,180), with a 3% to 14% incidence. Mortality is as high as 14% to 50% (178,179,181). Risk factors include oxygen exposure, prior irradiation, and other cytotoxic drug administration, such as bleomycin, cisplatin, the vinca alkaloids, cyclophosphamide, and doxorubicin. Drug withdrawal, steroids, and avoidance of supplemental oxygen may be helpful (180).

Mitomycin–vinca alkaloid syndrome is a unique entity occurring with a 6% incidence after the vinca alkaloid is administered to patients receiving combination therapy with mitomycin and vinblastine but not with the vinca alkaloid alone. Severe hypoxemia ensues with development of interstitial infiltrates on chest radiograph. Most patients show acute improvement within 24 hours with oxygen, diuretics, and occasionally, mechanical ventilation, although chronic lung damage occurred in 60% of patients in one study (178).

**Alkylating Agents**

**Carmustine (BCNU).** This is a nitrosourea used in the management of central nervous system tumors and in conjunction with therapy for bone marrow transplantation (BMT). Its cytotoxicity is mediated by alkylation of guanine in DNA (172). Carmustine causes dose-dependent pulmonary fibrosis and carries the highest incidence of fibrosis among the nitrosoureas. The mortality rate ranges from 24% to as high as 90% in some reports (180,181). In 1% and 30% of the patients receiving high- and low-dose carmustine, respectively, early-onset fibrosis and alveolitis will occur. In up to 40% of the patients undergoing induction for BMT, pulmonary fibrosis will develop within 2 years. Late fibrosis can be observed up to 17 years after exposure. Concomitant radiotherapy, chronic obstructive pulmonary disease (COPD), and pneumoconioses increase the risk of carmustine toxicity. Sixty percent of patients will respond dramatically to steroids (180).

**Microtubule-targeting Agents**

**Taxanes.** Paclitaxel inhibits microtubule disassembly (182), and has activity against solid tumors such as non-small cell lung carcinoma, breast carcinoma, and ovarian carcinoma (173); it is prepared in Cremophor, a castor oil-based solution (173,182). A type I hypersensitivity reaction, characterized by urticaria, bronchospasm, angioedema, and hypotension, occurs within 2 to 10 minutes of infusion of paclitaxel (182,183) with a 3% to 10% incidence (180), and is attributable to the Cremophor vehicle rather than paclitaxel itself (173). Premedication with steroids and H$_2$ and H$_3$ blockers can curtail this reaction (182).

**Antimetabolites**

**Cytosine Arabinoside.** Ara-C is a substituted nucleoside antimetabolite that disrupts DNA replication and is used in the
therapy of leukemia and non-Hodgkin’s lymphoma. One of its toxicities is the abrupt onset of endothelial inflammation and capillary leak syndrome (173), causing noncardiogenic pulmon-ary edema, acute dyspnea, and a diffuse interstitial and alveolar pattern. Management is supportive and includes oxy-gen, diuretics, and mechanical ventilation when needed (180).

Gemcitabine. This is a pyrimidine analogue, structurally similar to ara-C (183), that has activity against tumors of the pancreas, lung (NSCLC), breast, and ovaries. Recent large series report an incidence of lung toxicity of less than 1% to 1.4% (184). The proposed mechanism of injury involves pulmonary endothelial cell damage resulting in capillary leak syndrome (173,183). The symptoms of gemcitabine pulmonary toxicity range from mild dyspnea to a fatal acute respiratory distress syndrome. Increasing age, pulmonary neoplasm, and prior radiotherapy may be contributing risk factors (173,185). Patients respond rapidly to corticosteroids (173), but fatalities do occur (173,181,183,185,186).

Differentiation Agents
All-trans-Retinoic Acid. ATRA is a differentiation agent used for the treatment of acute promyelocytic leukemia (APL). It is associated with retinoic acid syndrome, developing in 20% to 50% of APL patients receiving ATRA (187) a median of 7 days (range 0–35 days) after induction therapy (188). The clinical presentation includes fluid retention, weight gain, fever, and musculoskeletal pain, with progression to respiratory distress, pulmonary infiltrates, pleural (187) and pericardial ef-fusions (180), renal insufficiency, skin infiltrates, hypotension, and death (187). Corticosteroids are highly effective when the syndrome commences but have limited utility once pulmonary symptoms are apparent. The putative mechanism of the pulmon-ary toxicity of ATRA is a capillary leak syndrome (180).

Monoclonal Antibodies
Trastuzumab. This is a humanized monoclonal antibody that targets the epidermal growth factor type 2 (HER2) receptor (189). In approximately 25% of breast cancers, the HER2 re-ceptor is overexpressed (183) and is associated with a poor prognosis (190), a finding that provides the rationale for use of trastuzumab in HER2 receptor-positive metastatic breast cancer. A retrospective analysis of 25,000 patients identified bronchospasm as the only manifestation of pulmonary toxic-ity. Nine cases (0.04%) attributable to trastuzumab infusion were fatal; most serious reactions commenced within 2 hours of infusion, and most fatalities were observed in patients with poor performance status and severe underlying pulmonary dis-ease (191).

Bevacizumab. This is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF) that inhibits binding of VEGF to its receptors, hence impairing angiogenesis. The drug is approved for first-line treatment of advanced colorectal cancer in combination ther-apy (183). In a phase II randomized trial of 99 patients with ad-vanced or recurrent NSCLC, the incidence of hemoptysis in pa-tients with NSCLC was demonstrably higher in patients treated with bevacizumab, carboplatin, and paclitaxel (20%) than in those treated with carboplatin and paclitaxel alone (6%). Four patients in the bevacizumab group had severe hemoptysis, which occurred with an incidence of 8.1% and was associ-ated with squamous cell pathology, tumor necrosis and cavi-ration, and centrally located tumors in close proximity to ma-jor blood vessels (192). A recent study excluded patients with pre-existing hemoptysis and squamous cell pathology based on the premise that squamous carcinomas, as a consequence of their location and ability to cavitate, are more prone to bleed-ing. With these exclusions, a 1.9% incidence of life-threatening hemorrhage with bevacizumab was observed (193).

Alentuzumab. This is a monoclonal antibody to the lympho-cyte and monocyte cell surface antigen CD52 and is used as a salvage therapy for chronic lymphocytic leukemia (194). In a series of 16 patients with B-cell chronic lymphocytic leukemia (B-CLL), the associated pulmonary toxicity in one patient was severe bronchospasm that responded to corticosteroids (195).

Cardiac Toxicities
Antitumor Antibiotics
Anthracyclines. These are red-pigmented antibiotics (rhodo-myocins), which include doxorubicin, daunorubicin, idarubicin, and epirubicin (196). They are active against a broad spec-trum of tumors, such as breast and esophageal carcinomas, Hodgkin’s and non-Hodgkin’s lymphomas, osteosarcomas, Kaposi’s sarcoma, and soft-tissue sarcomas. Three mechanisms that lead to oxidative stress (197) contribute to the cardiac toxicity of these agents: mitochondrial dysfunction and con-sequent adenosine triphosphate depletion; free radical lipid peroxidation by iron–doxorubicin complexes; and glutathione peroxidase depletion (196). Histopathology demonstrates myofibril dropout, vacuolization of myocardial cells, and necrosis (196,197). Acute cardiotoxicities include nonspe-cific ST-T wave changes (198), supraventricular tachycardia (SVT), ventricular arrhythmias, myocarditis, cardiomy-opathy, and sudden death. The cardiomyopathy is dose depen-dent, and is classified as subacute and late. Subacute cardiomy-opathy presents within 8 months of therapy, with a peak onset of 3 months, whereas late cardiomyopathy is observed after 5 or more years. A continual decline in left ventricular func-tion results in congestive heart failure (CHF) (196); liposomal doxorubicin may play a role in reducing cardiotoxicity (199). Dexrazoxane, an iron chelator with cardioprotective prop-erties, has been demonstrated to substantially reduce toxic-i ty (197,200). Toxic effects may be compounded by other therapies, including trastuzumab, cyclophosphamide, dacitino-myocin, mithramycin, mitomycin, etoposide, melphalan vin-cristine, bleomycin, dacarbazine (196), and taxanes (201,202).

Mitoxantrone. This agent has structural similarity to the an-thracyclines, and is used in managing metastatic breast can-cer, acute myeloid leukemia, and non-Hodgkin’s lymphoma (202). The mechanism of cardiac injury, like that of the an-thracyclines, may involve iron chelation complexes (203); ar-rhythmias and dose-dependent heart failure are toxicities. The incidence of a moderate to severe decrease in left ventricu-lar ejection fraction (LVEF) and of CHF is 13% and 2.6%, respectively, with a cumulative dose of less than or equal to 140 mg/m². Doses below 110 mg/m² decrease the incidence of heart failure, whereas incidence increases with doses greater than 160 mg/m² (196).
Mitomycin C. In addition to its lung toxicity, mitomycin is cardiotoxic, resulting in an increased incidence of cardiac failure with cumulative doses exceeding 30 mg/m² (196,204). Additive cardiotoxicity occurs when mitomycin is used in conjunction with anthracyclines (204); superoxide free radicals may mediate this toxicity (196).

Alkylating Agents

Cyclophosphamide. This agent is a nitrogen mustard alkylating agent effective in treating leukemia, lymphoma, multiple myeloma, mycosis fungoides, neuroblastoma, and ovarian and testicular tumors. Acute cardiotoxicity may develop with doses of 120 mg/kg to 170 mg/kg given over 1 to 7 days in preparation for bone marrow transplantation. Electrocardiogram may reveal decreased QRS amplitude, nonspecific T-wave abnormalities, poor R-wave progression, supraventricular and ventricular tachyarrhythmias, and second-degree atrioventricular block (203). Acute fulminant CHF may occur in up to 28% of patients treated with high-dose cyclophosphamide (196), but CHF is usually short lived and reversible (203). The drug is metabolized to its active form in the liver by the cytochrome P-450, and more rapid metabolism amplifies the risk of CHF (205). Another cyclophosphamide-related cardiotoxicity is hemorrhagic myocarditis, putatively mediated by endothelial capillary injury, which results in pericardial effusion, tamponade, and death; most effusions are treatable with corticosteroids and analgesics. When the purine analogue pentostatin (198) is used in bone marrow conditioning regimens in combination with cyclophosphamide, there is an increased incidence of fatal cardiac toxicity (196) that includes myocardial infarction, CHF, and arrhythmias (198). There may be an additive effect of cyclophosphamide and anthracycline-induced cardiomyopathy, but the data are conflicting (196).

Ifosfamide. This is an alkylating agent, with similar properties to cyclophosphamide, used to treat lymphoma, leukemia, and testicular and bladder tumors. Arhythmias and transient, reversible, dose-dependent CHF—as with cyclophosphamide—may be seen (203,206).

Cisplatin. This agent cross-links interstrand DNA. It is used in treating cancers of the testes, bladder, ovaries, and other tumors. Bradycardia, supraventricular tachycardia (196), acute ischemia (207), myocardial infarction, and ischemic cardiomyopathy may be observed (196). Acute chest pain and palpitations may be associated with cisplatin infusion. Late complications can occur 10 to 20 years after therapy. Hypomagnesemia and hypokalemia generated by cisplatin-induced tubular defects (196) may exacerbate arrhythmias (198).

Microtubule-targeting Agents

Vinca Alkaloids. Vinca alkaloids include vincristine and vinblastine, which are used for management of hematologic malignancies and solid tumors, and vinorelbin, a semisynthetic derivative used in NSCLC therapy. These agents exert their toxicity by inhibiting microtubule assembly, and all possess vasoconstrictive properties. Hypertension, vasoepicardic myocardial ischemia, and myocardial infarction may be seen (198). Vinorelbine toxicity is more common in women than men (208).

Taxanes. (See also Pulmonary Toxicities, above.) Hypertension (196) and cardiac arrhythmias, most commonly transient asymptomatic bradycardia (182), are observed with paclitaxel. In a large series, the incidence of more significant bradycardia—Mobitz type I and II heart block and complete heart block—was 0.1% (209). Rarely, atrial and ventricular tachycardias, myocardial ischemia, and myocardial infarction occur, often in patients with underlying cardiac disease or electrolyte derangements (196). Doxetaxel may lead to the potentiation of anthracycline cardiomyopathy (202).

Antimetabolites

5-Fluorouracil and Capecitabine. 5-Fluorouracil (5-FU) is a synthetic pyrimidine antimetabolite used in regimens for managing multiple solid tumors including gastrointestinal, breast, ovarian, and head and neck malignancies. Myocardial ischemia, possibly triggered by coronary vasospasm, is a well-known cardiac toxicity that occurs with increased frequency in combination with cisplatin. In one study, silent ischemic ECG changes were identified during 24 hours of observation in up to 68% of patients receiving a continuous 5-FU infusion (210). Other cardiac manifestations include chest pain, angina, atrial and ventricular arrhythmias, myocardial infarction, persistent ventricular dysfunction, sudden death, and cardiogenic shock (196,203) requiring isotropic support (196). Pre-existing cardiac morbidity significantly increases the risk of cardiotoxicity compared to no prior cardiac disease (15.1% vs. 1.5%) (203). Given the potential for severe cardiotoxicity, infusions should be terminated when chest pain occurs. The oral equivalent of infused 5-FU is capecitabine, which exhibits a similar cardiotoxicity profile to 5-FU (211).

Topoisomerase Inhibitors

Etoposide. This agent is a topoisomerase II inhibitor used primarily for treatment of refractory testicular tumors and small cell lung carcinoma. Hypotension is the most common side effect (198). Myocardial infarction (198,212) and vasoplastic angina (196) may also occur. Prior chemotherapy or mediastinal irradiation may increase the risk of myocardial infarction after etoposide therapy (196).

Biologic Response Modifiers

Interferons. These are glycoprotein biologic response modifiers classified according to their respective derivations: interferon-alpha (leukocytes), interferon-beta (fibroblasts), and interferon-gamma (lymphocytes) (196). They are used to treat various tumors including renal cell carcinoma, metastatic melanoma, multiple myeloma, Kaposi sarcoma, and some leukemias and lymphomas. Cardiovascular toxicities include hypertension or hypotension (198), ischemia in patients with coronary artery disease, myocardial infarction, arrhythmias (20% incidence) (213), sudden death, and cardiomyopathy characterized by resolution with termination of the infusion (214).

Interleukin-2 (IL-2). This is a glycoprotein biologic response modifier derived from helper T-lymphocytes, and is approved for the treatment of metastatic renal cell cancer. Most patients develop capillary leak syndrome and hypotension associated with decreased peripheral vascular resistance necessitating vasopressors (196). In a study of 423 treatment courses with IL-2, 65% required pressor support for hypotension (215). In patients with coronary artery disease, direct myocardial toxicity precipitates ischemia, myocardial infarction, arrhythmias, and...
death. IL-2 may also predispose patients to venricular and supraventricular arrhythmias, which are seen in 14% to 21% of patients (196).

**Differentiation Agents**

**All-trans-Retinoic Acid.** (See also Pulmonary Toxicities.) Peri-Tamoxifen and the aro-

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This agent is a human/mouse chimeric mono-

clonal antibody designed to target the human epidermal growth factor receptor. It is used alone or in combination therapy with 

trastuzumab, rather than temporally separated 

administration, compared to those receiving tamoxifen, the incidence in-

creases to 0.4% over 5 years and 1.4% to 1.7% over 5 years, 

ment, compared to those receiving tamoxifen, the incidence in-

creases to 0.4% over 5 years and 1.4% to 1.7% over 5 years, 

the CD20 antigen, present on normal and malig-

drome. Prolongation of the QT interval is another complication 

seen in up to 63% of patients, leading to torsades de points (196) and sudden death. The degree of QT prolongation 

is higher in the presence of hypokalemia (216); therefore, careful 

monitoring of electrolytes and maintaining levels in the high 

normal range is prudent.

**Monoclonal Antibodies**

**Trastuzumab.** (See also Pulmonary Toxicities.) There is an in-

creased risk of cardiac toxicity associated with trastuzumab, which is highest in patients receiving concurrent anthracy-

cline plus cyclophosphamide (27%) compared to concomitant trastuzumab and paclitaxel (13%) or trastuzumab alone (3%– 

7%) (217). The mechanism of cardiac toxicity of trastuzumab is not well understood, but cardiac erbB2 is essential for my-

ocyte function, and trastuzumab targets both HER2 and erbB2 receptors (203,218). Early following initial treatment, there may 

be an asymptomatic decline in LVEF with late progression 

to dilated cardiomyopathy (203). Risk factors for cardiovascu-

lar toxicity include older age, cumulative doxorubicin dosage 

400 mg/m² or greater (217), and concurrent anthracycline and 

trastuzumab administration, rather than temporally separated 

dosing (218).

**Rituximab.** The CD20 antigen, present on normal and malig-

nant B cells, is the target of the chimeric marine/human mon-

oclonal antibody rituximab, which is used to treat leukemias 

and lymphomas, as well as benign diseases. Cardiac toxicity 

involves arrhythmias and angina in less than 1% of infusions (196). Most adverse effects with rituximab are infusion related, 

usually occurring within 2 hours of the first infusion (219). 

Acute infusion-related deaths have been reported in 0.04% to 

0.07% of cases. The clinical presentation in these patients in-

cludes hypoxia, pulmonary infiltrates, adult respiratory distress 

syndrome, myocardial infarction, ventricular fibrillation, and 

cardiogenic shock (196). Hypersensitivity reactions, including 

hypotension, angioedema, hypoxia, or bronchospasm, may oc-

cur in up to 10% of cases. Management is supportive, using 

intravenous fluids, antihistamines, acetaminophen, bronchodilata-

tors, and vasopressors (198).

**Cetuximab.** This agent is a human/mouse chimeric mono-

clonal antibody designed to target the human epidermal growth factor receptor. It is used alone or in combination therapy with 

irinotecan to treat metastatic colorectal cancer. Life-threatening 

infusion reactions occur in 3% of patients with bronchospasm, 

urticaria, and hypotension (220). Intestinal stenomitis with 

noncardiogenic pulmonary edema is a rare toxicity (198).

**Bevacizumab.** (See also Pulmonary Toxicities.) This agent is 

associated with CHF, hypertension, and arterial thromboem-

bolism. With bevacizumab monotherapy, 2% of patients devel-

oped moderate to life-threatening (grades 2 to 4) left ventricular 

dysfunction (221). CHF developed in 14% of patients concur-

rently receiving anthracyclines, and in 8% of patients who had 

previously received anthracyclines or left chest wall irradiation 

(196,198). Clinical trials have also documented hypertension 

in 5% of patients, with reports of hypertensive crisis, hyperten-

sive encephalopathy, and subarachnoid hemorrhage (198). The 

FDA has issued a warning to health care providers announcing 

that bevacizumab has demonstrated an increased risk of ar-

terial thromboembolic events, which include cerebrovascular 

accident, transient ischemic attack, myocardial infarction, and 

angina (222). In addition, the risk of fatal arterial thrombotic 

events is doubled to 5% in patients receiving intravenous S-FU 

and bevacizumab (222,223).

**Hematologic Toxicities**

**Thalidomide**

Thalidomide is a sedative-hypnotic agent with anti-inflam-

matory properties, used in multiple myeloma patients to treat 

advanced and chemotherapy-refractory disease (224,225). Its 

mechanism of action is unclear, but immune modulation, an-

tiangiogenesis, and tumor necrosis factor-alpha may play a 

role (226). There is an increased risk of venous thromboem-

bolism (VTE) associated with thalidomide, occurring at a mean 

of 2 months of therapy (227). Lower extremity deep venous 

thrombosis (DVT) is the most frequent thrombotic complica-

tion occurring with thalidomide treatment, and approximately 

50% of these patients will develop PE. The mechanism of 

thalidomide-induced DVT is not well defined. Thalidomide 

can also cause a direct effect on endothelial cells that have been 

injured by other chemotherapy agents such as doxorubicin 

(226). In one study, VTE rates with thalidomide monother-

apy, thalidomide–dexamethasone, thalidomide–doxorubicin, 

and thalidomide–dexamethasone–doxorubicin were less than 

5%, 9%, 12%, and 22%, respectively (228). These findings 

suggest a role for VTE prophylaxis, and further investigation 

is warranted.

**Hormones**

Estramustine. Estramustine phosphate has hormonal proper-

ties because it contains nor-nitrogen mustard linked to 17 beta-

estradiol. It is used in the treatment of prostate cancer. In up 

to 10% of patients receiving estramustine, venous thrombo-

sis, pulmonary emboli, and myocardial and cerebrovascular 

ischemia may occur (196).

Tamoxifen and Aromatase Inhibitors. Tamoxifen and the aro-

matase inhibitors—anastrozole, letrozole, and exemestane— 

are used as adjuvant therapy for early-stage estrogen recep-

tor-positive breast carcinoma (229). It is well known that there is 

an increased risk of VTE with tamoxifen. The following data 

clearly quantifies the risk: the incidence of VTE in the general 

population is 0.12% per year and 0.09% per year in women. 

In women with early-stage breast cancer and no adjuvant treat-

ment, compared to those receiving tamoxifen, the incidence in-

creases to 0.4% over 5 years and 1.4% to 1.7% over 5 years,
respectively. This incidence escalates to 10.8% over 5 years in the same population of women who receive concurrent tamoxifen and chemotherapy. Aromatase inhibitors (AI) are generally associated with a lower risk of VTE than tamoxifen. In the ATAC trial (Arimidex, Tamoxifen, Alone, or in Combination) at 5 years, the incidence of VTE with anastrozole was 1.6% versus 2.4% with tamoxifen (230).

### Gastrointestinal Toxicities

**Bevacizumab**

This agent is associated with both bowel perforation and gastrointestinal hemorrhage. In a randomized controlled trial in patients with metastatic colon cancer, subjects received either irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, or IFL alone. Gastrointestinal perforation was observed in six patients (1.5%) treated with IFL plus bevacizumab with one fatality compared to no patients in the control group (231). A more recent phase II trial adding bevacizumab to bolus 5-FU and leucovorin reported bowel perforation in 2% of cases (223). In a phase II trial of bevacizumab in combination with fluorouracil and leucovorin in advanced refractory colorectal cancer, severe to life-threatening gastrointestinal hemorrhage (grades 3 and 4) was seen in 3.8% of patients (232).

### Genitourinary Toxicities

**Cyclophosphamide and Ifosfamide**

Cyclophosphamide and ifosfamide induce an early (within 72 hours of administration) hemorrhagic cystitis via their metabolite, acrolein, that causes denudation of the bladder mucosa and bleeding (233,234). In the past, early hemorrhagic cystitis was observed in over 40% of bone marrow transplants, but that rate has dramatically declined to 5% with aggressive hydration regimens and administration of the thiol mesna. Mesna is a type of thiol that inactivates acrolein in the bladder after itself being converted to the active form in the kidneys. It must be administered prior to cyclophosphamide infusion and continued after the infusion is terminated consequent to its shorter half-life. In cases of hemorrhagic cystitis that have progressed to intractable or profuse bleeding, bladder irrigation and cystoscopy with clot extraction and fulguration may be necessary to achieve hemostasis (234). Cystectomy, vascular ligation, or hyperbaric therapy (233) may be required in recalcitrant cases. Late occurring hemorrhagic cystitis commences 72 hours after administration of preparatory regimens in bone marrow transplantation, with risk factors including viral infections, busulfan use, pelvic irradiation, older age at transplantation, allogenic transplantation, and graft versus host disease (235).

**Mitomycin C**

Mitomycin C has been discussed with reference to its pulmonary and cardiac toxicities. Another life-threatening manifestation associated with mitomycin C is the thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TPP-HUS). This entity is a distinct multiorgan disorder distinguished by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and tissue ischemia precipitated by platelet agglutination in the arterial microvasculature (236). The classic pentad—fever thrombocytopenia, MAHA, renal failure, and neurologic dysfunction—is no longer required to make the diagnosis. Instead, the new definition encompasses a broad spectrum of conditions in which unexplained thrombocytopenia and MAHA are present (237). Of the chemotherapeutic agents associated with TTP-HUS, mitomycin is the most common, but bleomycin, cisplatin, and gemcitabine are also causes of the syndrome (238). The pathogenic mechanism of mitomycin C–induced TTP-HUS may involve chemotherapy-induced endothelial cell injury (238,239) and circulating immune complexes against tumor-related antigens (239). In some cancer patients, it may be difficult to attribute TTP-HUS to mitomycin, because malignancy-induced TTP-HUS is clinically indistinguishable from mitomycin-induced disease. TTP-HUS is typically seen 4 to 8 weeks following the final dose of mitomycin. Patients usually present with dyspnea from noncardiogenic pulmonary edema, which may progress to adult respiratory distress syndrome, and may mimic mitomycin lung toxicity. Renal failure is generally present, whereas neurologic symptoms are infrequent (237). Unfortunately, patients with mitomycin-induced TTP-HUS do not respond to plasmapheresis. Immunoabsorption of plasma over a thiolated polystyrene particle column to remove immune complexes may be effective in these patients (240). The prognosis of mitomycin-induced TTP-HUS is poor, with most patients succumbing to pulmonary or renal failure or to their underlying malignancy within 4 months (237).

### References

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