Hematologic Complications of Critical Illness

Anemia, Neutropenia, Thrombocytopenia, and More

Nancy Munro, RN, MN, CCRN, ACNP

ABSTRACT

All critically ill patients are at risk for hematological complications during their hospitalization. It is essential that critical care nurses understand the hematological system and common complications. The purpose of this article is to briefly review some basic hematologic concepts involving each of the 3 cell lines: the white blood cell, the red blood cell, and platelets. The content focuses on how to assess these cell lines when there is dysfunction. Examples of disease processes involving the increased and decreased production of each cell line as well as destruction processes are discussed from a critical care perspective. The critical care nurse needs to continually incorporate this information into practice as research continues to formulate critical care practice. Keywords: anemia, leukocytosis, neutropenia, thrombocytopenia

Hematopoiesis

Hematopoiesis, or the production of blood cells, occurs primarily in the bone marrow. The liver, spleen, lymph nodes, and thymus are involved in hematopoiesis during embryonic development, but the liver and spleen can also respond throughout the life span if provoked by disease processes. The stem cell is an undifferentiated cell that has the capacity to reproduce itself and to mature into any of the different types of blood cells. As the stem cell divides and matures, it differentiates into 1 of 2 committed cell lines: lymphoid or myeloid progenitor cells. The committed lymphoid progenitor cell eventually matures.
into T and B lymphocytes and natural killer cells. The committed myeloid stem progenitor cell develops into (1) the megakaryocyte-erythrocyte precursors leading to the development of platelets and RBCs and (2) the granulocyte-monocyte precursors leading to the development of the WBC (ie, granulocyte and monocyte). Maturation of these cell lines is influenced by multiple growth factors such as granulocyte colony stimulating factor (G-CSF), erythropoietin, thrombopoietin, interleukins, interferon, and many others. Figure 1 shows a model for hematopoietic cell differentiation.

**White Blood Cells**

The primary role of the WBC (leukocyte) is to recognize and protect the body against invasion of foreign bodies. White blood cells can be divided into 2 major categories: phagocytes and lymphocytes. The principal role of phagocytes is to locate and kill invading microorganisms or foreign antigens. The primary role of lymphocytes is to initiate and direct the immune response including the antigen/antibody interaction. White blood cells travel throughout the body and migrate into different tissues depending on chemical mediators that signal the cells. Phagocytes perform their role primarily at the site of an inflammation where they mobilize to the site by chemotaxis and kill microbes by phagocytosis. Many substances stimulate this chemotactic migration. Phagocytic cells are divided into 2 subgroups: granulocytes (exhibit granular substances within the cell after staining) and monocytes. The granulocytes include neutrophils (also called “polys” for polymorphonuclear neutrophils or PMNs), basophils, and eosinophils. Neutrophils compose 60% to 70% of all WBCs and their main function is to find and kill bacteria. They also play an important role in acute inflammatory processes. Neutrophils are one of the first phagocytic cells to appear at the site of an acute inflammation.

During severe inflammatory reactions, neutrophils can actually cause damage to surrounding tissues by releasing proteolytic enzymes and oxygen-free radicals. Once in the bloodstream, some of the neutrophils freely circulate, whereas others linger along the blood vessel wall, which is called margination. Adhesion molecules emanating from an injury or an organism make the blood vessel wall sticky so that the marginated neutrophils adhere to the vessel walls. The neutrophil releases substances that allow the endothelial cells to separate and permit the neutrophil to crawl into the connective tissue (diapedesis). The neutrophil migrates to the area of injury through chemotaxis. Opsonization is a process in which molecules in the plasma coat the microorganism, making it more recognizable to the neutrophil. With the increased demand for WBCs with inflammation or invasion, the bone marrow will produce more cells faster, causing immature cells or “bands” to appear in the count. It is another sign of the body’s attempt to fight foreign bodies.

Eosinophils and basophils are granular WBCs that have specific functions that are also important in the defense of the body. Eosinophils compose approximately 4% of a
normal WBC count. They have proinflammatory and cytotoxic activity and play a role in the pathogenesis in parasitic, neoplastic, and allergic disorders. Basophils account for only 0.5% to 1% of the total WBC count. Their role (and their tissue equivalent, mast cells) is pivotal in the immediate hypersensitivity reaction and may require the release of heparin and histamine. Monocytes constitute 4% to 8% of the total WBC count. Agranular leukocytes are WBCs without granular substances within the cells after staining. Monocytes and lymphocytes are agranular leukocytes. Within 24 to 36 hours of entering the circulation, they migrate into the tissues where they undergo further maturation and are called macrophages (ie, Kupffer cells). When in the bloodstream, monocytes have functions similar to those of the neutrophil. However, monocytes and macrophages play a crucial role in recognizing foreign invaders and presenting these foreign antigens to lymphocytes, thus stimulating the immune response. In addition to their phagocytic activity, macrophages secrete biologically active products, including cytokines that modulate the immune response. This system serves as a 2-fold attack on foreign substances. The neutrophils serve as a first line of attack but are short-lived. The lymphocytes are the second line of protection that provide “memory” of the antigen for a lasting intervention (Table 1).

Lymphocytes are essential components of the immune system. They recognize and are instrumental in the elimination of foreign proteins, pathogens, and tumor cells. Lymphocytes control the intensity and specificity of the immune response. There are 2 general types of lymphocytes, T lymphocytes (or T cells), which provide cell-mediated immunity, and B lymphocytes (B cells), which produce the antibodies of humoral immunity. Stem cell differentiation for the production of lymphocytes occurs in the bone marrow. It is in the thymus that T cells learn to differentiate self from non-self. Cell-mediated activities are of great importance in delayed hypersensitivity reactions; graft rejection; graft-versus-host disease; and in defense against fungal, protozoal, and most viral infections. Another important function of T cells is to regulate immune activities through the secretion of lymphokines.

B lymphocytes mature into cells that respond to stimulation from foreign proteins by differentiating into memory cells and plasma cells. The plasma cells produce specific antibodies that inactivate or destroy foreign proteins and pathogens such as bacteria and some viruses. The helper cells of the T cells stimulate B cells to produce antibodies. Natural killer cells, another subset of lymphocytes, kill tumor cells and cells infected by viruses. The activities of phagocytes and immune cells overlap in numerous mutually beneficial ways. White blood cells are the first line of attack protecting the body against foreign invaders.

White blood cells have a limited life span and need to be replaced constantly. The number of cells produced is fairly constant, but depending on environmental stimuli such as bleeding, infection, or inflammation various cells may be needed in larger than normal quantities at times. Thus, each of these cell lines is regulated by cytokines that influence the rate of growth and differentiation of the stem cells in the marrow. Cytokines are proteins that are made by cells of the immune system and regulate the immune response. An example of a cytokine is G-CSF, which stimulates the growth of granulocytes and macrophages. Cytokines also stimulate the function of mature immune cells. The WBC count is composed of various types of cells and is referred to as the differential. To assist with quantifying the number of these types of cells, an absolute cell count can be calculated. The absolute neutrophil count (ANC) is the most commonly used calculation when treating oncology or immunocompromised patients. This calculation is used for decision making about oncologic interventions or empiric

| Table 1: White Blood Cell Differential Count* |
|-----------------|-----------------|
| **Cell Type**    | **Cell Count**   |
| White Blood Cells| 5–11000/μL (5–11 × 10^9/L) |
| Bands           |                  |
| Neutrophils     | 4–6000/μL (4–6 × 10^9/L) |
| Lymphocytes     | 2–5000/μL (2–5 × 10^9/L) |
| Monocytes       | 500–1000/μL (0.5–1 × 10^9/L) |
| Eosinophils     | <450/μL (<0.45 × 10^9/L) |
| Basophils       | <50/μL (<0.05 × 10^9/L) |

*Adapted from Hillman et al. 2
duced cells. Interleukin 1 (IL-1) and other cytokines will stimulate the production of the associated monocyte colony stimulating factor, which will cause leukocytosis. The other types of WBC can also have an absolute cell count calculated and can be used when deciding on diagnosis, treatments, or interventions (see Table 1).

**Abnormalities in WBC Production**

**Increased Production**

When analyzing abnormal WBC production, there are 2 options. There is either an increase or a decrease in production, which encompasses most causes of abnormal WBC counts. The most common WBC finding in a critically ill patient is an increase in the WBC count (leukocytosis). The first question that needs to be asked in the clinical setting is why is the WBC count rising and what is the supporting evidence for the cause of the increasing count. Within hours of the onset of a bacterial infection, the WBC count can increase up to 4 times the baseline. The usual hematopoietic response includes the release of multiple cytokines including G-CSF, granulocyte macrophage stimulating factor, and monocyte colony stimulating factor, which will stimulate the production of the associated cells. Interleukin 1 (IL-1) and other interleukins will be released to help stimulate the immune response led by the lymphocytes. Therefore, there will be an increase in both mature and immature leukocytes as the demand increases. The increased appearance of immature cells is referred to as the “shift to the left” phenomenon in which bands or immature neutrophils increase above normal levels as the defense system attempts to deal with foreign antigens.

However, there are factors other than infection that will cause an increase in the WBC count. Stress, trauma, hemorrhage, marked hypoxia, or other conditions that lead to an increase in catecholamines will affect the leukocytes that have marginated along the vessel walls and force them to be released into circulation. This phenomenon is called demargination. Systemic inflammatory response syndrome can mimic the symptoms of an infection and it becomes challenging to determine the true cause of the increased WBC. Glucocorticoid therapy is another intervention that will cause leukocytosis because steroids interfere with the egress of leukocytes into the tissue, thus masking infection. Prednisone doses of 60 to 100 mg daily are thought to increase the WBC count to 15 000 to 20 000/μL and higher doses can lead to WBC counts of 30 000/μL. Careful examination of the differential count can assist with detection of other types of nonbacterial infections. Reactive monocytosis (>1000/μL) can be seen in tuberculosis, whereas parasitic infestations are characterized by increased basophils (>50/μL). It is important to determine whether infection is truly present because initiation of antibiotics in a noninfective, inflammatory situation is one reason for the rise of antibiotic resistance.

Severe infections can lead to a leukemoid reaction in which the WBC count can increase to 150 000 to 200 000/μL. The major characteristics of a leukemoid reaction are (1) no evidence of leukemia, (2) WBC count greater than 50 000/μL with or without the presence of immature cells, and (3) presence of immature cells. However, if the WBC count remains consistently greater than 50 000/μL, malignancy must be considered in the differential diagnosis. The increased production of WBCs is due to bone marrow dysfunction. One of the most common reasons for this dysfunction is myeloproliferative disorders such as chronic myelogenous leukemia. The WBC count can increase to as high as 200 000/μL with many immature myeloid progenitor cells in the differential due to abnormal production. Because the WBC is a larger cell, high numbers of WBCs can lead to abnormal blood flow. Hyperviscosity of the blood can cause poor perfusion and lead to multiple organ failure and lactic acidosis. Unless the WBC cell line is
treated either with chemotherapy or with drugs directed at correcting gene malfunction, abnormal blood flow will continue.\(^2\) Plasmapheresis can also be used to remove WBCs while concurrently treating the direct cause of the extreme leukocytosis. Higher lymphocyte counts may also indicate lymphomas that can have a similar impact.

**Decreased Production**

There are multiple triggers that decrease the WBC count (leukopenia). When the WBC count drops, the subcategories will also drop and the major focus is on neutropenia or a decrease in neutrophils, the first responder to invasion of the body. One of the most common reasons for a neutropenic reaction is drugs. Many of the chemotherapy agents will decrease neutrophils due to their effects on the stem cell and myelocytic progenitor proliferation.\(^2\) Some antimicrobials (eg, trimethoprim/sulfamethoxazole [Bactrim] and linezolid [Zyvox]) can also depress bone marrow function especially in immunocompromised patients. Many drugs can impact the WBC count and cause occasional neutropenia\(^2\) (Table 2). Theoretically, any drug can affect bone marrow function and must be one of the first considerations if neutropenia occurs. Once the drug is discontinued, the WBC/neutrophil count should return to normal if the drug was the solitary cause.

Sepsis can also impact the neutrophil production causing a significant neutropenia.

<table>
<thead>
<tr>
<th>Table 2: Drugs That Cause Occasional Neutropenia(^a)</th>
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<td>Gold salts</td>
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<td>Chloramphenicol</td>
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<td>Antithyroid medications</td>
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<td>Phenacetin</td>
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<td>Tricyclic antidepressants</td>
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<td>Phenothiazines</td>
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\(^a\)Adapted from Hillman et al.\(^2\)

Overwhelming infection will stimulate the bone marrow to increase production but will then consume neutrophils at an alarming rate, which is reflected in a very low WBC count and thus a low ANC.\(^2\) When significant neutropenia is seen in patients with pneumococcal sepsis or peritonitis, prognosis is very poor.\(^2\)

Alcoholic patients represent another common patient population in the intensive care unit (ICU) in which hematologic consequences occur. Alcohol has a direct toxic effect on the bone marrow that can lead to pancytopenia or depression of all cell lines.\(^2\) The differential diagnosis for a neutropenic patient with an alcohol abuse history must rule out infection, but healthcare providers must also be mindful of alcohol’s effect on the bone marrow.

Cancer plays a prominent role in the development of neutropenia. Acute myeloid leukemias reflect a dysfunction in the very early progenitor cell that leads to the increased numbers of immature myeloid cells in the marrow and blood. An ironic consequence when treating leukemias is that the treatment will also induce significant neutropenia that may cause this patient population to be admitted to the ICU with neutropenic fever. A balance must then be found in treating the neutropenic fever with empiric antibiotics that can also make the neutropenia worse. The lymphocyte count can sometimes be overlooked when evaluating the WBC differential. Absolute lymphopenia is defined as a count less than 1500/\(\mu\)L.\(^2\) This deficit may indicate an immune deficiency that could be caused by viral (especially human immunodeficiency virus), fungal, or other opportunistic infections and may have a more subtle impact on the overall WBC count. The WBC is not the only cell line to experience these extremes in levels, so we must also study the other cell lines including the RBCs.

**Red Blood Erythrocytes**

The major role of the RBC is to participate in the exchange of gases or respiration. The mature RBC is a biconcave disc with no nucleus filled with hemoglobin. The lack of a nucleus allows the RBC to change shape and facilitates movement through small capillary beds.\(^2\) Normal RBC values differ according to gender. Men have a higher normal range (4.7–6.1 million cells per microliter), whereas the range for women is lower due to menses (4.2–5.4 million cells per microliter). Heme,
the iron-containing pigment, is the actual oxygen-transporting portion of the hemoglobin molecule. Oxygen diffuses from the alveoli into the alveolar capillaries and binds to each of 4 sites on the heme portion of hemoglobin. One gram of hemoglobin can carry 1.34 to 1.36 mL of oxygen. The remarkable oxygen-binding capacity of the RBC is influenced by 3 factors that affect the oxyhemoglobin dissociation curve: pH, temperature, and the amount of 2,3 diphosphoglycerate. Carbon dioxide, a tissue metabolism waste product, is also transported from the tissues by the RBC.

The rate of bone marrow stem cell differentiation into erythrocytes is controlled by erythropoietin, which is produced primarily by the kidney. The creation of RBC is influenced by the oxygen content of the blood as sensed by the kidneys. Production is augmented by substrates including vitamin B12, vitamin B6, folic acid, and iron. The vitamins, iron, and folic acid are obtained from dietary sources. However, most iron is gained through the recycling of the RBC in the spleen. Red blood cell production is increased at times of blood loss, at high altitude, and in pulmonary diseases which result in hypoxia. Red blood cells live approximately 120 days, at which time they are recycled by the spleen. The spleen is a “testing ground” for the viability of the RBC. Blood from the arterioles is presented to the splenic RBC pulp where plasma volume is reduced and the cell is subjected to a relative hypoxic environment, testing the metabolic pathways of older RBCs. If the RBC successfully completes this viability trial, it then has to squeeze through 2- to 5-mm openings in the sinusoidal wall in order to escape from the spleen. These destruction and production processes are continually balanced to maintain adequate numbers of RBCs, but pathologies will influence and distort the normal physiology.

**Increased Destruction**

The normal cycle of the RBC ends when the cell is no longer able to navigate the narrow capillaries. The membranes of the older RBC are more fragile and allow the macrophages in the spleen, liver, and marrow to easily phagocytize the aging cells. This hemolysis process allows the hemoglobin to be recycled by cleaving the globin and heme portions off the cell. Globin continues to be degraded into amino acids, whereas iron is removed from the heme protein and attaches to the plasma protein transferrin, which is the transporter of iron. This complex is transported to muscle fiber and liver cells where the macrophages detach the iron molecule from transferrin and attach it to ferritin for storage. When the stored iron is recalled, it will again be transported by transferrin to the marrow for use by the precursor cells. The noniron portion of heme is converted to biliverdin and then to bilirubin. It is transported to the liver whose cells secrete conjugated bilirubin in bile. Once the bile enters the intestine, bilirubin is converted by bacteria into urobilinogen and is reabsorbed back into the blood and converted to urobilin. The rest of the urobilinogen is converted into stercobilin and eliminated in the feces (see Figure 2).

This normal process of RBC destruction can be overwhelmed when the rate of RBC cell destruction is accelerated by pathologic processes. The RBC can be destroyed because of defects in the hemoglobin molecule, the RBC membrane, or the metabolic machinery of the cell. These causes are usually hereditary in nature, such as sickle cell disease, thalassemia, or glucose-6-phosphate dehydrogenase deficiency. However, the more common presentation for hemolysis in critical care is hemolysis caused by extrinsic causes. Hemolysis associated with transfusion reactions is due to antibody activity directed against the RBC membrane. Destruction of RBCs due to stasis or trapping with an enlarged spleen can also be seen. Malfunctioning aortic valves can lead to high jet velocity damage to RBCs and hemolysis. Direct destruction to the RBC can occur with malaria or babesiosis.

**Figure 2**: Life cycle of red blood cell (RBC).
Once hemolysis starts by one of the above mechanisms, the by-products of the process will be cleared through an extravascular or intravascular pathway. The extravascular pathway includes phagocytosis by the reticuloendothelial cells, hemoglobin reduction, iron recovery, and final breakdown of bilirubin in the liver. The intravascular pathway starts with free hemoglobin binding with haptoglobin or hemopexin or converting to methemalbumin and then clears these proteins in the liver through the breakdown of bilirubin. The mechanism for RBC destruction can vary but the diagnosis using laboratory results has consistent features.

The most obvious laboratory finding with hemolysis is a decrease in the hemoglobin and hematocrit. The speed of hemolysis can differ depending on the cause. The faster the process, the more likely the body’s compensation ability will be overwhelmed and the faster the abnormal laboratory results will appear. This relationship may also dictate the criticality of the patient’s condition. Serial hemoglobin/hematocrit measurements should always be coupled with high index of clinical suspicion. Blood loss must first be eliminated as the cause of the drop in hemoglobin/hematocrit. Once that premise is established, signs of hemolysis need to be examined. With blood destruction, the bone marrow production is increased and the percentage of reticulocytes will increase by 4% to 5%, assuming the marrow is functioning properly. An increase in the reticulocyte count is usually seen in situations of chronic hemolysis (eg, sickle cell disease). Factors such as recent chemotherapy, significant infection, or other drugs should always be considered. Red blood cell destruction will release lactate dehydrogenase, a common enzyme found in the cytoplasm of RBCs, into the blood. The lactate dehydrogenase levels may rise to 1000 IU (normal range is 105–333 IU/L) with significant hemolysis but levels greater than 5000 IU are not uncommon. Haptoglobin is an alpha globulin that binds with free hemoglobin and assists with transport of free hemoglobin to the liver for further degradation. Normal levels of haptoglobin range from 50 to 200 mg/dL but with hemolysis, the levels are decreased or may even be depleted as all the globulin is bound with free hemoglobin in cases of significant hemolysis. This finding is more common in acute hemolysis clinical situations.

The serum bilirubin is also affected by excessive hemolysis. The conventional formation of bilirubin described earlier is referred to as conjugated or direct bilirubin. However, the indirect or unconjugated level of bilirubin is the marker that is elevated when excessive hemolysis occurs. Macrophages in the spleen will process the heme portion of hemoglobin into unconjugated bilirubin, which is insoluble and needs to be further processed by the liver. However, the liver is unable to respond to the increased volume of unconjugated bilirubin with excessive hemolysis, which will be reflected in an elevated indirect bilirubin level. Another marker of hemolysis can be seen in the peripheral blood smear. Fragmented RBCs can be visualized microscopically and are called schistocytes. When there is increased destruction, the number of schistocytes per field will increase and will help determine the cause of the hemolysis.

Increased Production
An increase in RBCs can have different causes. One of the more common presentations in critical care would be hypoxic polycythemia. Hypoxia will drive an increase in the production of erythropoietin and RBCs. Cardiopulmonary disease such as congenital heart disease with cyanosis results in hemoglobin levels greater than 22 g/dL. Pulmonary disease due to mechanical hypoventilation in the morbidly obese patient may lead to high levels of hemoglobin. Patients with chronic obstructive pulmonary disease or interstitial lung disease may also have abnormal RBC counts. Malignancy is another cause of polycythemia but it is rare. The danger of high hemoglobin levels is increased blood viscosity, which can become life threatening when severe because it will lead to decreased perfusion of organs. All interventions are directed toward correction of the cause of the elevated RBC count.

Decreased Production
A decrease in RBCs can be due to a decrease in production or a loss of cells. Blood loss in critical care is common and has many causes. The gastrointestinal tract is a common source of blood loss although pulmonary bleeding does occur. Colorectal and genitourinary cancer may also be a cause of blood loss. Bleeding at a recent surgical site is another source of blood loss. However, there are many patients in
critical care who experience a gradual decline in the hemoglobin/hematocrit.

Anemia is defined as a hemoglobin value less than 12 g/dL. A hemoglobin value of 11 g/dL would be considered an excellent laboratory value in an ICU patient, but it may be a sign that the patient has anemia of chronic disease (ACD). This disease is also known as anemia of chronic inflammation, which is helpful in understanding the origin of this common critical care phenomenon. Any disease that is associated with a major inflammatory response will probably result in a hypoproliferative state or ACD. Conditions that cause the release of cytokines such as interleukins and tumor necrosis factor α through monocyte activation may ultimately develop this type of anemia. Monocytes are the second line of attack against foreign bodies. One of their roles is to attract lymphocytes to the affected site. The T lymphocytes will release interferons (beta and gamma) that have been shown to produce the clinical presentation of ACD in animal models. The mechanisms for ACD are thought to be related to bone marrow RBC production issues, but frequent blood sampling can contribute to the level of anemia. Iron metabolism is disrupted because of iron trapping in macrophages and leads to decreased availability of iron for hemoglobin synthesis. Normal bone marrow will not be able to mount a normal erythropoietin response to the anemia and result in a relative decrease in production. The RBC also has a decreased survival rate with ACD. Laboratory findings associated with ACD include mild (hemoglobin level 10–11 g/dL) to severe anemia (hemoglobin level <8 g/dL). Low reticulocyte counts are expected with more severe anemia. Total iron-binding capacity, which is the serum iron concentration, and transferrin levels will be low. Treatment of ACD is directed at the correction of the underlying disorder. Additional interventions including erythropoiesis-stimulating factor, erythropoietin, and supplemental iron may also be added to increase production.

Platelets
Platelets (thrombocytes) are small cell fragments that are produced by the disintegration of megakaryocytes in the bone marrow and released in large numbers into the circulation. Because of their small size and disc shape, they are capable of changing shape and have a high metabolic rate. Platelets have a relatively short cell life and circulate in the bloodstream for approximately 10 days. The production of platelets is regulated by thrombopoietin, which is another stimulating factor that will influence bone marrow function. They play a major role in hemostasis by adhering to a damaged blood vessel wall and aggregating together to form a mechanical barrier to the flow of blood, thereby preventing blood loss. Platelets will then release various mediators to attract other cells and components to the site so that fibrin formation can start. There are multiple elements needed to optimize platelet adhesion, aggregation, and activation. Alpha granules within the cytoplasm of the platelet contain glycoprotein receptors on their membrane that assist with adhesion. Dense granules release serotonin and adenosine diphosphate to supply the energy needed for clot formation. Both von Willebrand factor and fibrinogen are required for platelet adhesion and aggregation by interacting with glycoprotein IIb/IIIa receptors. Thromboxane A2, platelet factor 4 (PF4), and β-thromboglobulin are cytokines that play an active role in activating and optimizing platelet function. Platelets are sequestered in the spleen and are released as needed to combat bleeding.

Increased Production
Increased number of platelets (thrombocytosis) is seen in critical care but is not a common disorder. It is usually associated with infection or chronic inflammatory conditions that can lead to platelet counts up to 1 000 000/μL. It is more likely to appear with chronic infection or recovery from infection or may be due to the overproduction of proinflammatory cytokines such as interleukins. Patients who have had a splenectomy may also have thrombocytosis because there is no longer a storage depot for the platelets. In the noncancer patient, it is considered a benign disorder but thrombosis could be a complication of this condition. Malignancy can also be a cause for increased production just as in the other 2 cell lines and is usually associated with a myeloproliferative disorder.

Decreased Production
Thrombocytopenia or decreased platelet count is very common in critical care and has several causes. Decreased production is commonly the
result of malignancies (eg, aplastic anemia, acute leukemias, or multiple myeloma). Certain drugs can also produce thrombocytopenia including chemotherapy, thiazides, alcohol, and estrogens as well as exposure to radiation therapy. Reversal of this condition is achieved by treating the underlying cause or stopping exposure to the toxic agent.

**Increased Destruction/Consumption**

Knowledge about platelet destruction is rapidly progressing with cellular biology and immunology advances. Thrombocytopenia can be the result of nonimmune conditions. Disseminated intravascular coagulation is the consumption of platelets as the coagulation pathways are activated commonly because of infection but can be due to any cause leading to the activation of the endothelium (see Dressler). When the endothelium is injured, the platelets are activated and stick to the injury area to initiate the formation of a fibrin clot.

Heparin-induced thrombocytopenia (HIT) has become a major challenge in critical care today. The occurrence of HIT is increasing because of increasing exposure to heparin and is difficult to diagnose, leading to false-positive diagnoses. Unlike other clotting disorders, HIT is the result of an immunohematologic reaction. The development of the pathogenic immunoglobin G (IgG) is the key to this disorder. The heparin binds with PF4, which leads to the development of a highly reactive antigenic complex and activates the platelets. The major target antigen is a macromolecular complex comprising heparin or other high-sulfated oligosaccharides and PF4 that binds to the platelet surface.

“HIT is an immune-mediated adverse drug reaction that is caused by heparin-dependent, platelet-activating IgG antibodies that recognize complexes of PF4 bound to heparin.” These antibodies are the HIT antibodies because once they recognize heparin, the autoimmune response is triggered and they become anti-PF4/heparin, platelet-activating IgG antibodies. Once activated, platelets release procoagulants and PF4 neutralizes heparin leading to increased thrombin generation. The HIT antibodies can also activate the endothelium and monocytes leading to the expression of tissue factor at cell surfaces. These events increase thrombin formation and create a potentially devastating thrombotic situation.

Heparin-induced thrombocytopenia can have varying time onsets because it is an immune response that requires time to develop. The usual onset for 70% of patients is a decrease in platelet count 5 to 10 days after starting heparin (first day of heparin use = day 0). If patients have an exposure to heparin within the past few weeks or months leading to HIT antibody development, a “rapid onset” HIT presentation can occur within 24 hours of subsequent heparin administration. When the platelet count decreases after all heparin has been stopped, this is a “delayed presentation” HIT and thought to be due to high levels of circulating antibodies. Although HIT can develop in any patient who has exposure to heparin, there are certain patient populations that seem to have a higher incidence. These risk factors include (1) duration of heparin use greater than 1 week, (2) exposure to unfractionated heparin, (3) postsurgical thromboprophylaxis, and (4) being female. It is important to note that the postoperative patient’s “baseline” platelet count is the highest postoperative count prior to the decrease suspected with HIT. The presentation of HIT includes venous thrombotic complications such as deep vein thrombosis (50%) and pulmonary embolism (25%). Arterial thrombotic complications include limb artery thrombosis, thrombotic stroke, myocardial infarction, or other arterial thrombosis (mesentery or spinal).

The diagnosis of HIT is based on the patient’s exposure to heparin, which can extend to 100 days before the event. Thrombocytopenia after heparin exposure is the hallmark sign for HIT. Because of the complexity of diagnosing HIT, Warkentin has developed a 4 “Ts” scoring system (thrombocytopenia, timing, thrombosis, and other cause of thrombocytopenia) to help estimate the probability of HIT.

Platelet activation assays are the newer tests that test patient serum against donor platelets “washed” in apyrase-containing buffer (potentiator of HIT antibody-induced platelet activation) and have high sensitivity. PF4-dependent enzyme immunoassays were one of the original tests developed for HIT and a negative test essentially rules out the diagnosis of HIT. However, the enzyme immunoassays detect more clinically insignificant antibodies, which can lead to overdiagnosis of HIT.
Varying laboratory practices in North America may impact the correct detection of the HIT diagnosis.\textsuperscript{11} The presence of antibodies may not always confirm the diagnosis of HIT. Clinical as well as laboratory data need to be compiled and interpreted to properly diagnose this disorder.

Once HIT is diagnosed, anticoagulation is started using the thrombin inhibitors approved for the treatment of HIT: danaparoid (withdrawn from the US market but still used in Europe and Canada), lepirudin, and argatroban. Bivalirudin and fondaparinux are used for treating HIT, but their use is not supported by controlled studies.\textsuperscript{6} With early recognition and initiation of appropriate treatment, morbidity and mortality associated with HIT can be improved.

**Summary**

The influence of hematologic and immunologic pathophysiology principles on critical care practice is becoming more prevalent. All 3 cell lines demonstrate the influences of these principles in many pathologic conditions. The cell lines can experience an increase or a decrease in production usually caused by malignancies but also affected by drugs or other toxins. Cell destruction is another mechanism that can affect a cell line, and if the destruction is rapid, normal compensatory mechanisms are overwhelmed and the body will reflect the serious adverse effects of this disruption. The pathophysiology of some diseases can consume cells at a rapid rate and thereby imitate a significant reduction of that cell. The critical care nurse must be able to recognize these disorders quickly in order to make a difference in patient outcomes.

**References**