Chapter 5
Leukocytosis in the Critically Ill Patient

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5.1 Introduction

Leukocytosis (for definitions see below) is a very common laboratory finding with a broad assortment of possible clinical interpretations since it is a physiological response to many stimuli and it may be observed in a wide variety of diseases.

Patients admitted in Intensive Care Units (ICU) usually are prone to infections due to their critical condition that may impair their immune system and the presence of invasive devices, including central and peripheral venous catheters, arterial lines, urinary bladder catheters, etc., and invasive monitoring. Moreover, they can have several comorbidities and sometimes it may be difficult to recognize the underlying cause of leukocytosis even if the infection is the most likely one. The aim of this chapter is to address the most common causes of leukocytosis in order to indicate the potential differential diagnoses in critically ill patients.

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G. Berlot, G. Pozzato (eds.), *Hematologic Problems in the Critically Ill*,
DOI 10.1007/978-88-470-5301-4_5,

5.2 The Biology of the White Blood Cells (WBC)

The peripheral count of the different classes of WBC reflects the equilibrium of several compartments or pools. The bone marrow contains a mitotic pool, a maturation pool, and a storage pool. Once released into the bloodstream, the WBC can be subdivided in the circulating pool and marginated pool, which primarily consists of neutrophils adherent to the vascular endothelium; other WBC are located in the tissues. Then, the absolute and relative WBC count reflects only the circulating pool. A complex interplay of factors regulates production of granulocytes and their movement from one pool to another. After maturation into the bone marrow, mature neutrophils are released into the bloodstream, and this process can be accelerated in response to inflammation, leading to the appearance of immature cells. A number of substances induce neutrophil movement from the bone marrow into the blood, including endotoxin, glucocorticoids, a leukocyte-mobilizing factor derived from the third component of complement (C3e), chemoattractants such as C5a, cytokines such as tumor necrosis factor-α (TNF-α), etc. Increased neutrophil production can be stimulated by myeloid growth factors and inflammatory stimuli. The maturation of WBCs is influenced by Granulocyte-colony stimulating factors (G-CSFs), several interleukins (ILs), TNF-α, and different complement factors. In normal subjects with a functioning bone marrow, the myeloid growth factors induce neutrophilia by at least two mechanisms acting in different time frames: (a) a rapid response, occurring in few hours after the administration, which induces a release of neutrophils; and (b) a slower response, occurring after few days, which is characterized by the production of new neutrophils along with a rise of RBC, megakaryocytes, eosinophils, basophils, and monocytes. Proliferation of the common progenitor is stimulated by several growth factors,

including IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF), while later differentiation is regulated by G-CSF. The release of neutrophils from the marrow storage pool can result in a two-to-threefold increase in the neutrophil count within 4–5 h. At any given time, more than one-half of the neutrophils in the peripheral circulation adhere to the vascular endothelium. These marginated neutrophils can be released almost immediately (within minutes) under stressful conditions and this effect is mediated in part by the epinephrine released due to the activation of the hypothalamic–adrenal axis [1].

5.3 Definitions

The WBC count in adults varies from 4,400 to 11,000 cells/mL (4.4–11.0 × 10^9/L), the majority of which (~60 %) are mature neutrophils. Leukocytosis is defined as a total WBC count greater than 11,000/mL in adults.

By convention, leukocytosis values in excess of 50,000 cells/mL, when due to causes other than leukemia, is termed a leukemoid reaction or hyperleukocytosis.

Leukocytosis is most commonly due to an increase in the absolute number of mature neutrophils, but it can also reflect a marked increase in the absolute numbers of lymphocytes, eosinophils, monocytes, or, more rarely, basophils.

To guide the differential diagnosis, leukocytosis should be divided into the following classes:

- *Neutrophilia*, when the absolute neutrophil count exceeds 7,700 cells/mL in adults. Neutrophil leukocytosis is commonly seen in infection, stress, smoking, pregnancy, and following exercise. It can also occur in the chronic myeloproliferative disorders, such as polycythemia vera and chronic myeloid leukemia (CML).

- *Lymphocytosis*, indicating a lymphocyte count greater than 4,000 cells/mL. Lymphocytic leukocytosis can be seen following infections such as infectious mononucleosis and pertussis or in lymphoproliferative disorders such as the acute and chronic lymphocytic leukemia (ALC and CLL, respectively).
- *Monocytosis*, when the monocyte count is greater than 800 cells/mL. A monocytic leukocytosis can occur either in hematologic malignancies including the acute and chronic monocytic variants of leukemia and in acute bacterial infection or tuberculosis, chronic infections, autoimmune disorders, and after a splenectomy.
- *Eosinophilia and basophilia* indicate an eosinophil or basophil count exceeding 500/mL or 200/mL, respectively. Eosinophilic leukocytosis can occur in variant forms of chronic leukemia, solid tumors, infection with helminthic parasites, allergic reactions, and following treatment with Interleukin-2. The most common causes of basophilia include myeloproliferative disorders (myelodysplastic syndromes), other hematologic malignancies (basophilic leukemia, mastocytosis, hypereosinophilic syndrome, and atypical acute and chronic leukemias), allergic or inflammatory reactions, endocrinopathies, administration of estrogens, and infections (including viral infections, tuberculosis, and helminthes-associated infections). Basophilic leukocytosis is a distinctly unusual condition, and is most often associated with basophilic or mast cell variants of acute or chronic leukemia.
- *Hyperleukocytosis or leukemoid reaction* indicates a total white blood cell (WBC) count greater than 50,000–100,000/mL, which is often characterized by a significant increase in early neutrophil precursors along with increased numbers of band forms. In the bone marrow, a proliferation of all the normal myeloid elements is observed in contrast to acute leukemia, in which the most immature elements (e.g., promyelocytes, myeloblasts) predominate. Neutrophilic leukemoid

reactions can occur during infections but any strong stimulus to the bone marrow can trigger this reaction. In the presence of leukemoid reaction with a strong prevalence of neutrophils, a biopsy of the bone marrow is warranted in order to exclude acute and chronic myeloid leukemias (AML and CML, respectively) and other myelodysplastic/myeloproliferative neoplasms, which can present some morphologic overlap. Immature granulocytes (i.e., promyelocytes, myelocytes, and metamyelocytes) may be seen with either reactive neutrophilia or myeloid neoplasms such as CML [1–5].

- *Leukostasis* represents a condition of hyperleukocytosis characterized by an extremely elevated blast cell count and symptoms of decreased tissue perfusion due to the plugging of the microvascular network caused by aggregates of immature cells. This circumstance represents a medical emergency most commonly in patients AML or CML in blast crisis. Clinically, leukostasis is diagnosed empirically when a patient with leukemia and hyperleukocytosis presents with respiratory or neurological symptoms. Prompt treatment is indicated since, if left untreated, the 1-week mortality rate is approximately 20–40 %. In general, symptoms of leukostasis are more common in leukemias with large, poorly deformable blasts, as occurring in ALM [1, 6].

5.4 Major Causes of Leukocytosis

Leukocytosis may reflect either a primary disorder of bone-marrow production, which can be congenital or acquired (such as leukemias), or a secondary one in response to a pathologic process or the expositions to drugs or toxins. In critically ill patients, neutrophilia is far more common than increases in the absolute numbers of lymphocytes, eosinophils, monocytes, or basophils.

We will focus on the two following main lineages: neutrophils and lymphocytes.

5.4.1 Neutrophilia

As explained above, different mechanisms can account for the increase of circulating neutrophils, including (a) their increased production, whose effects appear after some days even with intense stimulation; (b) the accelerated release of mature cells from the marrow into the blood, which occurs within a few hours; (c) the shift between the marginated and circulating, which occurs in few minutes; (d) the reduced egress of neutrophils from the blood to tissues (primary disorder); and, finally, (e) a combination of all the mechanisms mentioned above.

The increase of the number of neutrophils occurring only in few minutes after the application of a stimulus is termed pseudoneutrophilia and is caused both by the detachment of neutrophils adhering to the endothelial walls mechanism, and on the redistribution from other vascular beds, including the pulmonary and splenic capillaries.

The increase in lymphocytes, monocytes, and neutrophils may be helpful in distinguishing pseudoneutrophilia from the neutrophilia in response to infections, protracted stress, or glucocorticoid administration. Actually, in this last condition, neutrophil counts are elevated, but lymphocyte and monocyte counts are generally depressed.

Acute neutrophilia is determined by the release of neutrophils from the marrow storage pool in response to inflammation and infections. In this circumstance, immature forms including metamyelocytes are not released into the bloodstream except under extreme circumstances.

Exposure of blood to foreign surfaces, such as hemodialysis membranes, activates the complement system and causes

Table 5.1 Causes of acute neutrophilia

Causes	Examples
Physical stimuli	Cold, heat, exercise, convulsions, pain
Emotional stimuli	Panic, rage, depression
Germs	Localized and systemic acute bacterial, rickettsial, and spirochetal infections
Tissue inflammation/necrosis	Trauma, burns, acute pancreatitis, electric shock, vasculitis, gout
Drugs and hormones	Epinephrine, glucocorticoids, tobacco, vaccines

transient neutropenia, followed by neutrophilia resulting from release of marrow neutrophils.

Colony stimulating factors (G-CSF and GM-CSF) cause acute and chronic neutrophilia by mobilizing cells from the marrow reserve and stimulate neutrophil production.

Chronic neutrophilia follows a prolonged stimulus to proliferation of neutrophil precursors. Mechanisms are not fully understood.

Many chronic noninfectious conditions cause neutrophilia, including many nonhematologic malignancies (lung, gastrointestinal, particularly when they metastasized to the liver and lung). In some cases, tumor cells produce colony stimulating factors. Neutrophilia as a manifestation of a hematologic disorder can be encountered in myeloproliferative syndromes including chronic neutrophilic leukemia and neutrophilic chronic myelogenous leukemia.

Neutrophilia in response to drugs is uncommon except for the well-known effects of epinephrine, other catecholamines, and glucocorticoids. Lithium salts cause sustained neutrophilia. The counts return to normal when the drug is discontinued [1]. The main causes of acute and chronic neutrophilia are summarized in Tables 5.1 and 5.2.

Table 5.2 Causes of chronic neutrophilia

Causes	Examples
Germs	Noneradicated infections causing acute neutrophilia
Tumors	Solid tumors, AML, CML
Drugs	Continued exposure to agents causing acute neutrophilia, lithium
Non-leukemic hematologic conditions	Rebound from agranulocytosis, therapy of megaloblastic anemia, asplenia
Hormones	Thyroid storm, pre-eclampisa and eclampisa, Cushing's Syndrome

5.4.2 Lymphocytosis

Circulating blood lymphocytes include populations of T cells, B cells, and natural killer cells. Levels of blood lymphocytes are higher in neonates and young children (within 12 years) with an absolute lymphocyte count as high as 8,000 cells/μL. In subjects older than 12 years, lymphocytosis is defined as an absolute count greater than 4,000 cells/μL.

Lymphocytosis can be due to a reactive proliferation or to a clonal expansion. The most common cause is infection. Reactive lymphocytosis is a physiologic or pathophysiologic response to infection, toxins, cytokines, or unknown factors. Normally it is characterized by polyclonal populations of lymphocytes with a pleomorphic morphology. Infectious mononucleosis (EBV) is the most common reactive cause. In this case, infected B cells stimulate the proliferation of atypical polyclonal T or NK cells which are observed peripherally. Pertussis infection, which is most often seen in pediatric populations, is an important exception. In fact, it is characterized by monomorphic lymphocytes. Nonclonal lymphocytes proliferation rarely exceeds 30,000 cell/ μL.

Table 5.3 Causes of reactive lymphocytosis

Causes	Examples
Acute and chronic infections	EBV and other mononucleosis syndromes
Hypersensitivity reactions	Insects bites, drugs
Tumors	Malignant thymoma
Others	Stress, autoimmune disorders, trauma, vaccines, postsplenectomy, smoking

Table 5.4 Causes of primary lymphocytosis

Causes	Examples
Malignancies, premalignancies	Acute lymphocytic leukemia, chronic lymphocytic leukemia, essential monoclonal B-cell lymphocytosis

Lymphoproliferative disorders are also associated with peripheral lymphocytosis and in early phases it may be difficult to distinguish them from a reactive lymphocytosis. The morphologic appearance of lymphocytes may help in this way. In fact, a monomorphic lymphocytosis favors a neoplastic proliferation. Major causes of lymphocytosis are summarized in Tables 5.3 and 5.4 [1–5].

5.5 Diagnostic Approach to Leukocytosis in the Critically Ill Patients

The differential diagnosis of leukocytosis includes physiologic responses to a broad range of infectious and inflammatory processes, as well as numerous primary hematologic disorders such as leukemias, lymphomas, and myeloproliferative neoplasms. Especially in critically ill patients with abnormally elevated WBC count with sepsis and sepsis-related conditions, the

presence of an infection as well must be primarily assessed; at the same time, other less common causes of leukocytosis must be looked for. Sampling errors, spurious leukocytosis, and all other possible confounding factors must be excluded. Spurious leukocytosis occurs in the presence of platelet clumping, fibrin clumping or cryoglobulinemia. In these cases, leukocytes count can be overestimated as clumps of platelets or agglutinated cryoglobulines can be counted as leukocytes. A peripheral blood smear is necessary either to confirm the elevated WBC count and to identify immature cells of the different lineages [7, 8].

Leukocytosis in response to drugs is commonly observed after the administration of corticosteroids and cathecolamines; in this case, leukocytes should not rise above 20,000–30,000/mL (mild-to-moderate leukocytosis) [1]. Many inflammatory stress conditions observed in intensive care unit (trauma, surgery, burns) can cause leukocytosis. Also, blood exposure to hemodialysis membranes can cause a secondary leukocytosis.

Leukocytosis associated with hypotension or shock may be related to a severe infection process or may be due to an important blood loss causing the release of neutrophils from the endothelial wall into the bloodstream; in these conditions, or in case of doubt, the measurement of C-reactive protein and procalcitonin may be of help to determine the presence of an infection. Actually, it should be noted that other clinical signs associated with leukocytosis like fever, anemia, thrombocytopenia, or thrombocytosis can be commonly observed both in infective and neoplastic diseases.

The diagnosis of a myeloproliferative disease should be considered if leukocytosis is caused by myelocytes and promyelocytes, increased basophils, and unexplained splenomegaly. In the presence of hyperleukocytosis, a leukemoid reaction must be excluded. Distinguishing myeloid–leukemoid reactions from myeloid malignancies can be challenging The presence of dysplasia, basophilia, WBC count greater than 50,000/mL, with a pronounced left shift (predominance of immature granulocytes), and increased blast count in the peripheral blood greater than

20 % address the diagnosis toward a myeloid malignancy. In this case, a bone marrow examination is recommended along with an appropriate ancillary testing.

Lymphocytosis differential diagnosis depends on patient age, clinical history, and morphologic findings. In adults, the first step will be excluding an infectious mononucleosis. The diagnosis can be made by a rapid test for heterophil antibodies. If these are negative, but the clinical suspicion of infectious mononucleosis is high, the serum sample should be tested for specific EBV antibodies. Furthermore, there may be a clinical overlap with acute lymphoblastic leukemia as the two disorders are distinguished on the basis of bone-marrow examination, lymphocyte immunophenotyping, and serological findings. Lymphocytosis is rarely seen in bacterial infections, with the exception of Bordetella pertussis infection [1–5].

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