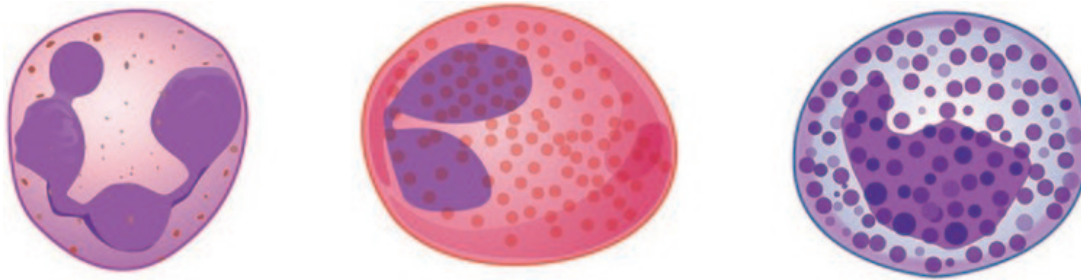


Hematopoiesis and Benign Blood Cell Disorders: Symptoms and Treatment

[See online here](#)

Hematopoiesis is the process of blood cell formation. It begins in embryogenesis and progresses to adulthood to replenish the cellular component of blood. The sites of hematopoiesis include the yolk sac at the embryological age of 0 - 2 months and the liver and spleen during the embryological age of 2 - 7 months. The bone marrow and thymus are definitive sites of hematopoiesis that take over the function from 8 months to adulthood. Extramedullary hematopoiesis in the spleen and liver can either the bone marrow is destroyed and cannot fulfill the function anymore.



Overview

Hematopoiesis begins with a pluripotential stem cell in the bone marrow, which can either reproduce itself or differentiate into more specific cells. **The pluripotent stem cells resemble a small/medium-sized lymphocyte** that is CD34+ or CD38+ on immunological testing.

For a pluripotent stem cell to produce blood cells, it must take the pathway of differentiation into more specific cells. This begins with the formation of hematopoietic progenitor cells which, unlike the pluripotent cells, have a limited potential to develop into various cells. They could either be lymphoid lineage progenitors or myeloid lineage progenitors. They also lack self-renewal properties.

The common lymphoid progenitor cells undergo **various differentiation processes to form B lymphocytes, T lymphocytes or natural killer cells**, while the common myeloid progenitor cells undergo further differentiation to form granulocytes, erythrocytes, macrophages, and megakaryocytes. After the cells are produced from the hematopoietic sites, they are then released into circulation to carry out their various functions.

Differentiation

1. Erythrocytes carry oxygen and nutrients into the blood to peripheral organs. They also remove waste products from these organs.
2. Lymphocyte cells are tasked with fighting infections and protect the body.
3. Myelocytic cells include:
 - Granulocytes and macrophages that also boost the body's immunity.
 - Megakaryocytes that help with blood coagulation to prevent bleeding.

Groups of blood cell disorders

- Malignant blood disorders
- Benign blood disorders
- Red blood cell disorders
- Anemia
- Erythrocytosis
- Disorders of lymphocyte cells
- Lymphocytosis
- Lymphopenia
- Disorders of myelocytic cells
- Leukocytosis
- Monocytic leukocytosis
- Eosinophilic leukocytosis
- Basophilic leukocytosis
- Neutrophilic leukocytosis
- Granulocytopenia/agranulocytosis/neutropenia

Lymphocytosis

Lymphocytosis is an increase in the number of white blood cells in peripheral circulation to a level higher than $4.0 \times 10^9/L$. The condition is a common finding, especially in infectious processes that produce a neutrophilic reaction.

Etiology

Common causes of lymphocytosis include:

- Glandular fever, which is characterized by fever, sore throat, lymphadenopathy, and abnormal lymphocytes. This state is seen in viral infections, such as the Epstein Barr virus, cytomegalovirus, and human immunodeficiency virus.
- Chronic infections, such as herpes simplex, hepatitis, and toxoplasmosis, or chronic infections, such as tuberculosis and brucellosis
- Chronic lymphoid leukemia
- Acute lymphoblastic leukemia
- Non-Hodgkin's lymphoma
- Thyrotoxicosis
- Infectious mononucleosis is a rise in lymphocyte count that arises from primary Epstein Barr virus infection, leading to suppression of B lymphocytes and a clonal T cell expansion and lymphocytosis. It is marked by heterophile antibodies that react with sheep and horse antibodies.

Epidemiology

Lymphocytosis is more common between the ages of 15 and 45 years. It is mainly associated with infectious processes.

Presentation

The condition presents with a **prodromal phase that mainly involves lethargy, general body malaise, headache, stiff neck, and cough**. An established disease presents with lymphadenopathy, which mainly affects the cervical region bilaterally. However, 50% of patients have generalized lymphadenopathy. The palpable lymph nodes may be tender and discrete. It also presents with inflamed oral or pharyngeal mucosal membranes, fever, morbilliform rash, headache, photophobia, and periorbital edema.

Other forms include the following:

- Hepatosplenomegaly
- Purpura
- Peripheral neuropathy
- Anemia

Investigations

Complete Blood Count

A **complete blood count (CBC) indicates a white blood cell count that is greater than $4.0 \times 10^9/L$** . Patients may also show signs of mild leukocytosis.

Peripheral Blood Film

Peripheral blood film (PBF) shows atypical lymphocytes that may possess abnormal morphology or granules within the cytoplasm.

Serum Heterophilic Antibodies

Serum heterophilic antibodies are present, as seen in the Paul-Burnell test. Other markers of infection, such as EBV antibodies, HIV, and DNA-PCR may be sought in other tests to identify the cause of lymphocytosis.

Differential Diagnosis

Acute and chronic leukemias present with alterations in other cell lines. They are malignant blood cell disorders and present with a more aggressive clinical picture of bleeding, infections, and wasting. Infections that may cause lymphocytes, such as toxoplasmosis and tuberculosis, should be ruled out.

Treatment

Symptomatic treatment focuses on the patient's comfort by the administration of antipyretics to control fevers and nutritional support for wasting.

In severe infections or elevations of the lymphocyte count, immunosuppression with corticosteroid therapy is considered.

Leukocytosis

Leukocytosis is an **increase in the number of white blood cells in peripheral circulation due to any cause**. A white blood cell count of greater than $8.5 \times 10^3/\text{mm}^3$ is considered abnormal. The condition is a common finding, especially in infectious processes that produce a neutrophilic reaction.

Classification

Leukocytosis may be **classified based on the type of cells** that are affected by:

Neutrophilia, eosinophilia/ eosinophilic leukocytosis, basophilia/ basophilic leukocytosis, and monocytosis. The conditions may occur singly or in combination.

Causes of Neutrophilia

- Bacterial infections with pyogenic bacteria
- Inflammation/tissue necrosis such as seen in myositis and vasculitis
- Metabolic disorders such as uremic acidosis and gout
- Neoplastic processes such as lymphoma and melanoma
- Drugs such as lithium and steroids
- Myeloproliferative diseases
- Asplenia

Causes of Eosinophilic Leukocytosis

- Allergic reactions, such as bronchial asthma, hay fever, and urticaria
- Parasitic infections, such as amoebiasis, hookworm, ascariasis, and schistosomiasis
- Skin diseases. such as pemphigus and psoriasis
- Drug sensitivity
- Polyarteritis nodosa
- Hodgkin's disease
- Metastatic malignancy
- Hypereosinophilic syndrome

Causes of Monocytosis

- Chronic bacterial infections, such as tuberculosis and brucella
- Connective tissue diseases, such as systemic lupus erythematosus
- Chronic neutropenia
- Hodgkin's disease
- Malignancies such as acute myelogenous leukemia

Epidemiology

Leukocytosis is one of the most commonly observed blood changes. It is readily seen in acutely ill patients and **in response to a variety of infections, hemorrhage, cancer processes, or drug exposure**. It is seen in up to 33% of patients with upper gastrointestinal bleeding.

Presentation

- Fever due to release of leucocyte pyrogens in excessive amounts
- Bleeding/easy bruisability due to depression of other cell lines in most conditions
- General body malaise
- Peripheral neuropathy
- Poor appetite and loss of weight
- Difficulty in breathing or seeing

Investigations

Complete blood count (CBC) indicates an elevated white blood cell count.

Peripheral blood film (PBF) shows a shift to the left with band forms, such as metamyelocytes, identified in circulation. Abnormal morphologies of white blood cells, such as toxic granulations and dole bodies, may be seen. The elevated neutrophil alkaline phosphatase (NAP) score is greater than 100.

Differential Diagnosis

Malignant blood disorders, such as lymphoproliferative diseases, must be ruled out since they present with leukocytosis as part of the symptomatology. Leukocytosis may also indicate lymphoma, infectious processes, such as viral infection with tuberculosis, viral infection, and drug-induced toxicities.

Treatment

Steroids are administered to lower the amount of inflammation and provide symptomatic relief.

Control of fevers, pain, and malaise with supportive therapy has been encouraged. **IV fluids and electrolyte supplementation to correct deficits in tumor lysis syndrome** are also common.

Leukapheresis can separate the blood cells from the fluid part of blood and reduce the number of white blood cells.

Prognosis

Leukocytosis is associated with high mortality and morbidity for patients with hyperleukocytosis and resulting in tumor lysis syndrome due to a breakdown of the cells in the body.

Neutropenia (Agranulocytosis)

Neutropenia is **characterized by a neutrophil count of less than $2.5 \times 10^9/L$ or an absolute count of 2500**. Any level below $0.5 \times 10^9/L$ or an absolute count of less than 500 indicates severe neutropenia, and the patient is susceptible to all forms of infections.

Etiology

Common Causes

- Chemotherapy, such as methotrexate use

- Acute and chronic leukemia
- Kostmann's syndrome, which is a rare congenital disease characterized by a low neutrophil count and an increased risk of infection since childhood. It mainly presents in children who are one year old.
- Myelokathexis – a rare neutrophil disorder where the neutrophil function is compromised.
- Myelofibrosis
- Myelodysplastic syndromes
- Chronic alcohol abuse
- Vitamin deficiency
- Hepatitis A, B, and other viral infections
- Rheumatoid arthritis
- Antibiotic use such as chloramphenicol
- Hypersplenism, where there is an abnormally high level of neutrophil destruction in the spleen.
- Autoimmune conditions, such as systemic lupus erythematosus and felty syndrome
- Drug-induced neutropenia, as seen with phenothiazines use

Epidemiology

Neutropenia may occur alone or in the setting of pancytopenia. **It affects 1.0 - 3.4 million people, with the elderly population being more affected.** It is more common among females, and drug-induced neutropenia is a common form due to dose-dependent or idiosyncratic drug reaction.

Pathophysiology

Neutropenia may arise from any of the three pathogenic pathways:

1. Insufficient bone marrow production as seen in the destruction of the bone marrow and infiltration of the bone marrow by infection.
2. The neutrophils shift from the circulating pool of cells
3. Increased destruction of the circulating pool of neutrophils. The neutrophilic injury may arise from immunological disorders such as systemic lupus erythematosus, drug toxicities, and splenic sequestration.

Presentation

The condition presents with:

- Recurrent mucosal infections, mostly in the mouth, throat, and skin due to low immunity
- Septicemia
- Fever, chills, and prostration
- Stomatitis and periodontitis
- Splenomegaly
- Petechial bleeds and easy bruising due to depression or other cell lines in most conditions
- Growth retardation
- Fever and general body malaise
- Poor appetite and loss of weight

Investigations

A complete blood count (CBC) indicates a low neutrophil count in the peripheral circulation.

Bone marrow aspirate and biopsy (BMA) show the presence of multiple precursors in myelodysplasia and infiltration. There may be a hypercellular marrow indicating peripheral destruction, or a hypocellular marrow, indicating marrow infiltration and bone marrow failure. Further workups can identify a focus of infection, such as cultures, urinalysis, sputum, and stool examinations.

Differential Diagnosis

- Leukemias, such as acute myelogenous leukemia
- Sepsis that may depress all cell lines
- Aplastic anemia
- Lymphoma

Treatment

Discontinue offending drugs, if any. Treat any infections with **antibiotics, antifungals, and antiviral agents**. Administer prophylactic agents if the infective process is not yet identified. Hemopoietic growth factors, such as G-CSF, will replenish the level of neutrophils. Steroid therapy is effective where autoimmune causes have been identified. Splenectomy may be necessary to avoid overt neutrophil destruction.

Prognosis

It depends on the etiology, severity, and presence of comorbidities. The **survival of these patients depends on the effectiveness of infection control** that can be achieved by broad-spectrum antibiotic coverage and replenishment of neutrophils. Mortality is mainly due to severe infections that mostly arise during periods of severe neutropenia.

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[Neutropenia](#) via emedicine.medscape.com (2017, August 2)

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