HEM | White Blood Cell Disorder

- White Blood Cell Disorders
- Leukocytosis, Leukopenia, and Absolute Cell Counts
- Leukocytosis: Pathogenesis
- Neutrophilia
- Neutrophilia (cont.) and Leukemoid Reaction
- Leukoerythroblastosis
- Eosinophilia
- Basophilia
- Monocytosis
- Neutropenia / Agranulocytosis
- Neutropenia / Agranulocytosis (cont.) Morphologic and Clinical Findings

White Blood Cell Disorders

White blood cell disorders can be reactive (non-neoplastic) or neoplastic disorders. Both reactive and neoplastic disorders can be characterized as either a proliferative disorder due to an expansion of one or more leukocyte cell lines (leukocytosis) or can present as a leukopenia due to a deficiency of one or more types of white cells. Reactive white cell disorders are more common. Neoplastic white cell diseases (i.e., leukemias and lymphomas) are less common but more important clinically and cause approximately 10% of adult cancer-related deaths and up to 40% of cancer-related deaths in children under the age of 15.

Leukocytosis, Leukopenia, and Absolute Cell Counts

Leukocytosis and leukopenia can be further classified based on which white cell line(s) are increased or decreased by examining the total white blood cell (WBC) count and the white blood cell differential and absolute counts. Although changes in the relative WBC percentage of each cell type can give early clues in white cell disorders, changes in the relative WBC percentage can at times be misleading. As such it is best to determine the clinical significance of the WBC count based on increases or decreases in the absolute count of each WBC type.

Absolute cell count = total WBC X % cell type

For example, if the total WBC is 20,000/µL with 80% segmented neutrophils and 20% lymphocytes then:

- Absolute neutrophil count = 20,000 X 0.80 = 16,000/µL
- Absolute lymphocyte count = 20,000 X 0.20 = 4,000/µL

Normal adult absolute cell counts:

Segmented neutrophils	1500 - 8000/µl
Lymphocytes	1300 - 4000/µl
Monocytes	0 - 1000/µl
Eosinophils	0 - 450/µl
Basophils	0 - 200/µl

Leukocytosis: Pathogenesis

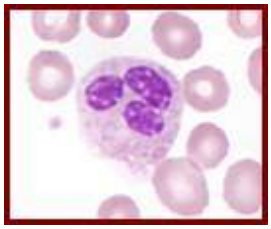
Peripheral blood leukocytes counts can be affected by multiple factors including:

- The size of precursor and storage pools if different cell types in the bone marrow, thymus, circulation, and tissues
- Rate of release from storage pools into circulation
- The number of marginated white cells (i.e., cells which are intravascular but adherent to endothelial vessel lining and not circulating-not in WBC count)
- Rate of extravasation or migration of cells from blood into the tissues

Various pathologic stimuli may cause the release of cytokines and growth factors which preferentially stimulate the proliferation of one type of white cell which can cause a leukocytosis of each of the five major types of circulating white cells: neutrophilia, eosinophilia, basophilia, monocytosis, and lymphocytosis. The first four categories

of leukocytosis will be further discussed here while lymphocytosis will be discussed separately (during lymphocytic disorder lectures)

Neutrophilia



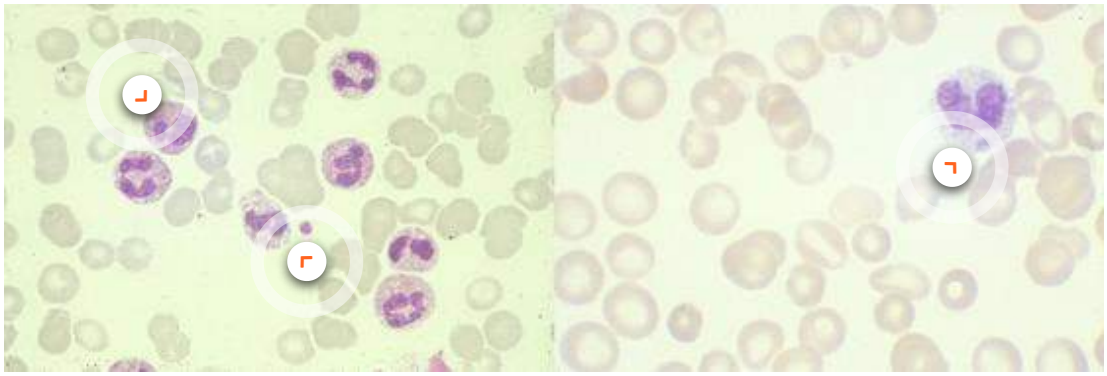
Neutrophilia is primarily due to a rapid increase in the release of marginated neutrophils and release of mature neutrophils from the bone marrow storage pools into the circulation which can be caused by various mechanisms. If the cause of the neutrophilia is prolonged, then various cytokines/growth factors can cause an sustained increase in neutrophil production. One of the most common causes of neutrophilia is acute bacterial infection and less commonly can be seen with other types of infection such fungal or the early phase of viral infection. Other causes of neutrophilia include medications or drugs including steroid (glucocorticoids) or catecholamines such as epinephrine, or various causes of sterile inflammation such as tissue necrosis or as a reaction to post-surgical stress.

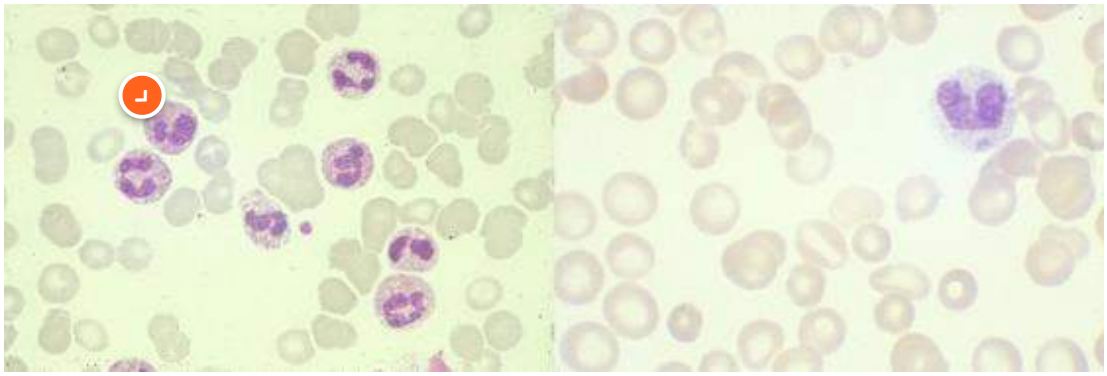
Morphologic changes in the neutrophils can be seen in severe infection or inflammatory disorders such as sepsis.

The morphologic changes can include:

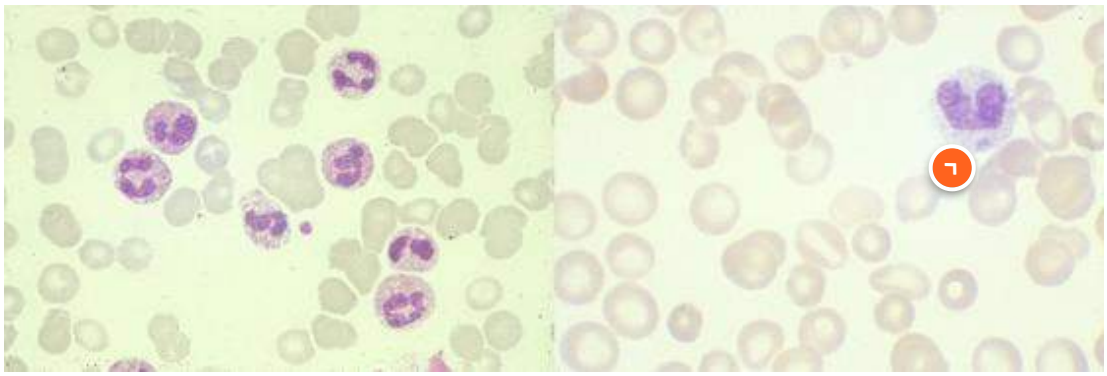
- Toxic granulation: coarser and increased number of neutrophil granules
- Cytoplasmic vacuolization
- Presence of Dohle bodies: Patches of dilated endoplasmic reticulum / ribosomes; look like cytoplasmic light blue or "sky" blue puddles

Identify which marker below identifies each of the following: *Cytoplasmic Vacuoles, Dohle Body, & Toxic Granules.*

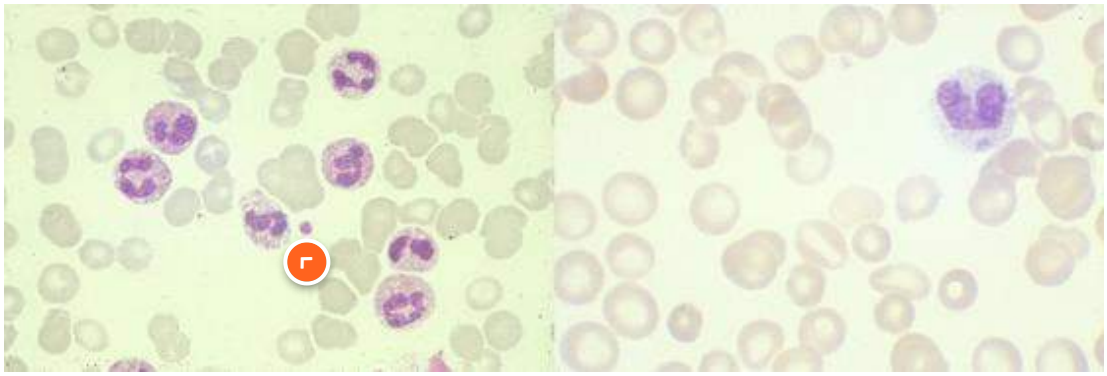




Toxic Granules



Dohle Body

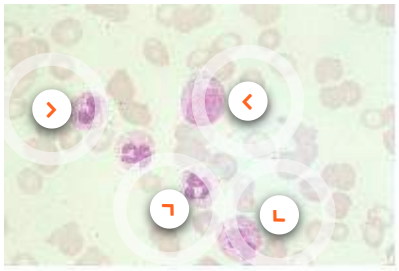


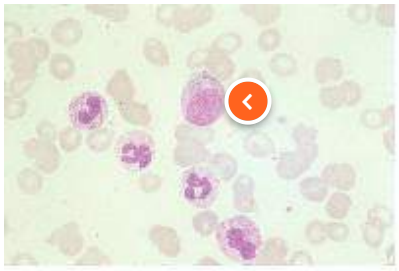
Cytoplasmic Vacuoles

Neutrophilia (cont.) and Leukemoid Reaction

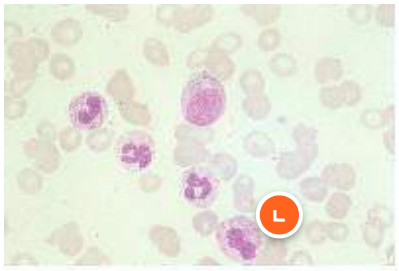
With some particularity severe and/or sustained infections, neutrophilia may be accompanied by the appearance of many immature granulocytes (i.e. metamyelocytes and myelocytes). The WBC results and peripheral blood smear morphology in these cases can mimic the appearance of a myeloid leukemia and as such are referred to as a leukemoid reaction. A reactive leukemoid reaction can often be differentiated from a neoplastic myeloid leukemia based on certain characteristics. In a leukemoid reaction, mature neutrophils forms (segmented cells and bands) are typically more numerous than immature forms (metamyelocytes and myelocytes), more immature forms such as promyelocytes or blasts are typically not seen, and leukemoid reactions may also have toxic granulation and Dohle bodies.

Identify which marker below identifies each of the following: *Toxic Granules and Rare Vacuoles, Band, Segmented Neutrophil, & Myelocyte.*

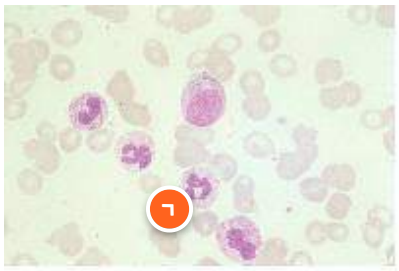




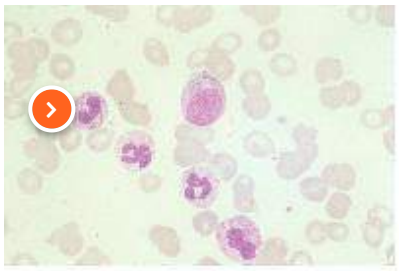
Myelocyte



Toxic Granules and Rare Vacuoles



Segmented Neutrophil

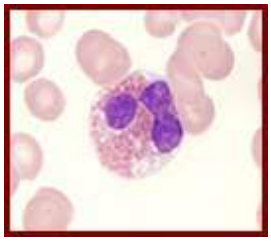


Band

Leukoerythroblastosis

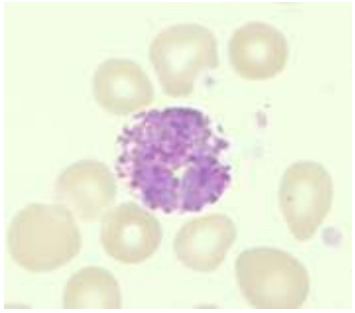
Leukoerythroblastosis is an abnormal release of immature cells into the peripheral blood which includes both immature neutrophils and nucleated red blood cells in the blood. The total white blood cell count can be increased, normal, or decreased. The primary cause of leukoerythroblastosis is a space-occupying lesion in the bone marrow which causes distortion or replacement of normal marrow elements. These types of space-occupying lesions are also sometimes referred to as a myelophthisic process, and examples of causes could include tumors (i.e. metastatic carcinoma), granulomatous disorders/infections, or marrow fibrosis. Rarely, a leukemoid reaction can also be seen due to severe marrow stress caused by severe hemorrhage, hemolysis, or infection.

Eosinophilia



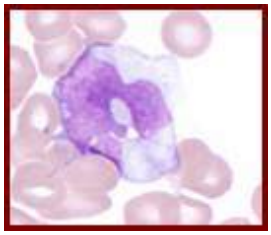
Eosinophilia (absolute eosinophil count >450/µL) can be caused by a variety of disorders including: allergic disorders (asthma, hay fever), parasitic infections, medications/drugs, autoimmune disorders, and as a reactive paraneoplastic process caused by certain malignancies (such as various lymphomas).

Basophilia



Basophilia (absolute basophil count >200/µL) is rare. While basophilia can rarely be caused by reactive conditions such as allergic reactions; it is most often part of a myeloproliferative disorder such as chronic myeloid leukemia.

Monocytosis



Monocytosis (absolute monocyte count >1000/µL) can be caused by a variety of disorders including: chronic infections, (i.e., tuberculosis), bacterial endocarditis, autoimmune disorders, inflammatory bowel disease, or rarely as part of some hematopoietic neoplasms.

Neutropenia / Agranulocytosis

Neutropenia is a reduction in the number of circulating neutrophils but the exact definition can vary according to different sources in part because the lower limit of the normal range for neutrophils is influenced patient age and race. Generally neutropenia is defined as <1,500/µL and is subclassified as follows:

Mild Neutropenia: 1,000 to <1,500/µL

Moderate Neutropenia: 500 to 999/µL

Severe Neutropenia: <500/µL (also known as "agranulocytosis")

There are a wide variety of causes of neutropenia which can be placed in broad categories with specific causes as below:

- Decreased production: due to a space-occupying lesion (aka myelophthisic processes) such as tumors, suppression of normal marrow elements as seen in aplastic anemia, or due to medication/drug.

- Ineffective production: megaloblastic anemias or myelodysplastic syndromes and due to defective precursors dying while still in the marrow.

- Accelerated removal or decreased survival: overwhelming infection, splenic sequestration, immune-mediated injury, or due to medication/drugs.

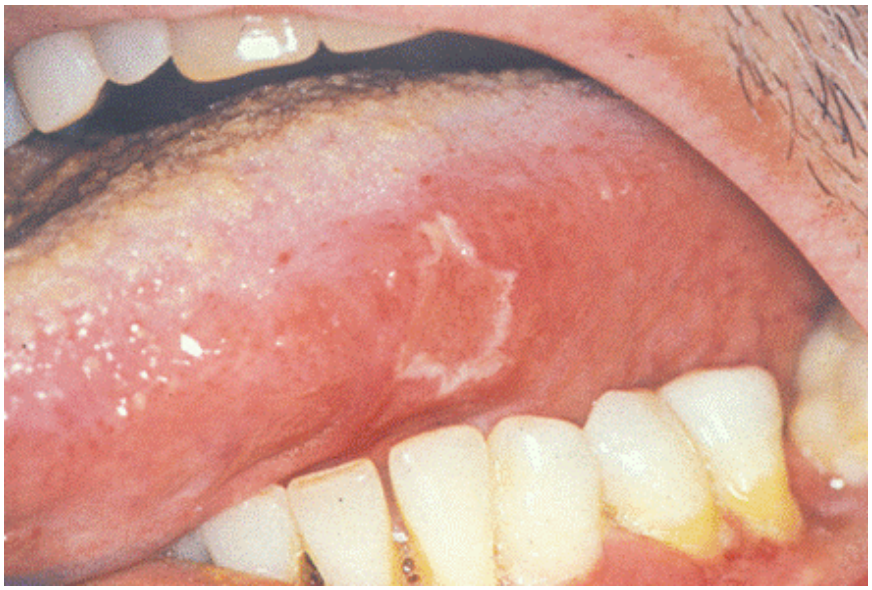
Medication/drug toxicity is the most common cause of neutropenia and as above can be mediated by decreased production due to direct toxicity or can be related to increased destruction. The drug toxicity may be dose-dependent or idiosyncratic in nature.

Neutropenia / Agranulocytosis (cont.) Morphologic and Clinical Findings

Bone marrow morphology varies based on the cause. For causes associated with increased destruction or ineffective production the bone marrow is hypercellular and there is typically a compensatory granulocytic hyperplasia. If the cause is suppression or destruction of granulocytic precursors, then the marrow will be hypocellular.

Patients with severe neutropenia (aka agranulocytosis) are at the highest risk of having increased susceptibility to bacterial and fungal infections, which can be overwhelming and potentially life-threatening.

Patients with neutropenia can develop characteristic deep, ulcerating, necrotizing lesions of the oral cavity. These ulcers may have massive overgrowth of bacterial or fungal organisms with little inflammatory response.



Severe invasive infections can occur in many organs including the lungs, urinary tract, and kidneys.

Neutropenic patients often present with symptoms and signs associated with infection including fever, chills, malaise, followed by weakness and fatigue. These patients are referred to as having a neutropenic fever. In addition to correlating with clinical symptoms/signs of possible localized infection, these patients are often "pan" cultured including blood, urine, and sputum/respiratory cultures. In some patients the neutropenic fever is unexplained if a source of infection cannot be identified and as such the patient is typically treated with empiric antibacterial and/or antifungal medications.

A patient who underwent chemotherapy treatment 6 days ago presents to clinic with complaint of subjective fever and not feeling well. A CBC is performed and

shows:

-WBC count of 2,000 / uL with 5% neutrophils, 80% lymphocytes, and 15% monocytes

-Hemoglobin of 7.8 g/dL

-Platelet count of 60,000 / ul

Which CBC finding is most concerning and could warrant further evaluation and treatment?

- ○ Lymphocytosis
- ○ Monocytosis
- ○ Neutropenia
- ○ Anemia
- ○ Thrombocytopenia

SUBMIT

Qualitative Disorders of Granulocytes / Chronic Granulomatous Disease

A variety of inherited and acquired disorders can cause functional or qualitative defects in granulocyte/neutrophil function.

One example is chronic granulomatous disease which is a group of constitutional disorders most commonly inherited in an X-linked recessive or less commonly autosomal recessive pattern which results from mutations/defects of genes encoding components of the NADPH oxidase. As a result, the patient's white blood cells can phagocytize but not effectively kill/destroy ingested organisms due to failure oxidative reactions (i.e. respiratory burst). Patients have increased susceptibility to recurrent infections which can affect multiple organs. Activated macrophages attempt to control/contain the spread of infection which results in widespread formation of granulomas in multiple organs.