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Leukocytosis

- Leukocytosis is defined as a total WBC count that is more than two standard deviations greater than the mean for age.
- The normal WBC range is 4400-11,000 cells/ μ L in adults but is age dependent in children, total WBCs seen within the first 2 weeks of life highest.
- a gradual decrease to adult normal ranges by early adolescence.

Leukocytosis

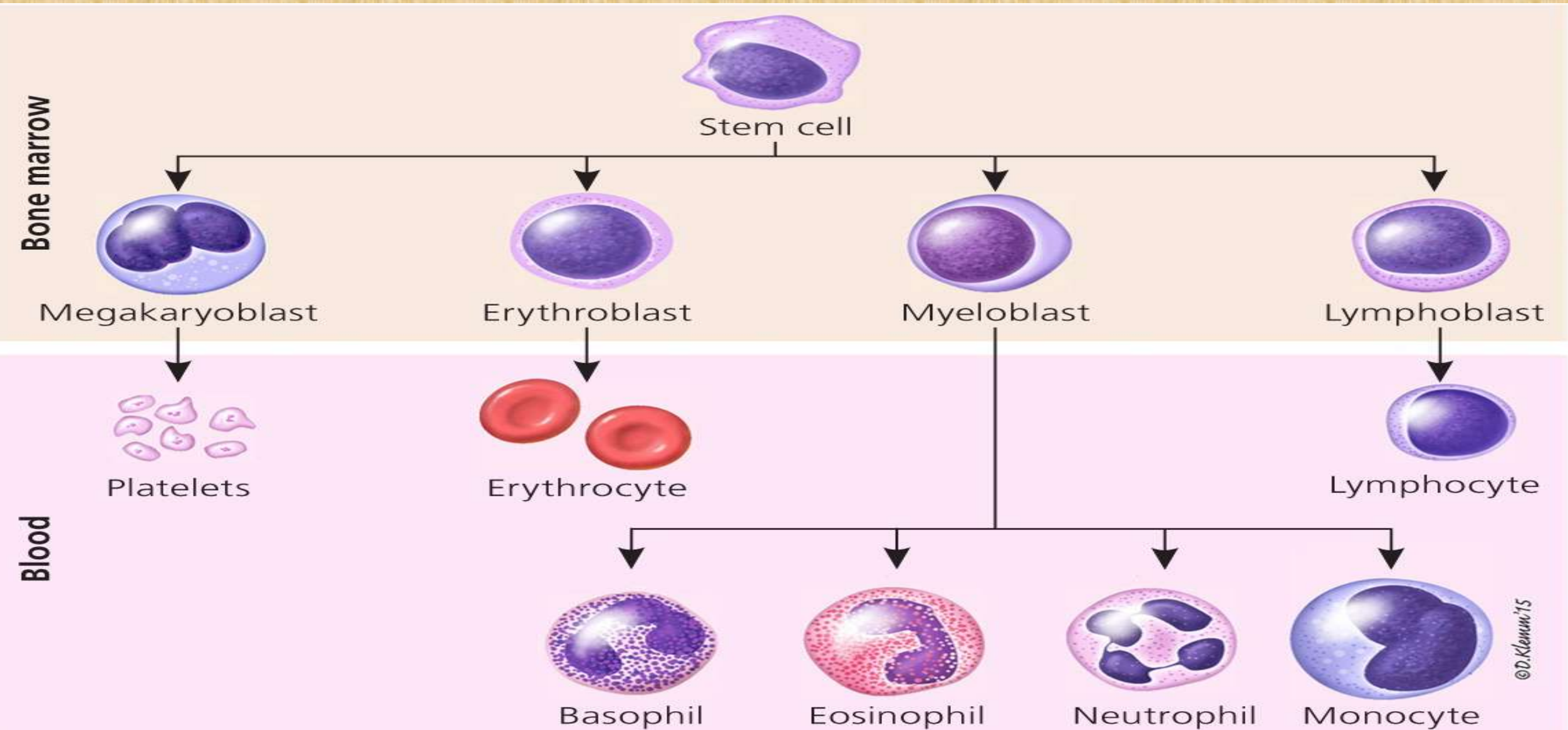
- **leukocytosis is secondary to an excess of mature neutrophils; however, it may be due to a marked increase in lymphocytes, monocytes, eosinophils, and/or basophils**
- **The clinical evaluation of leukocytosis is strongly influenced by which cell type is involved, the duration of the leukocytosis, and any associated findings.**

Table 1. White Blood Cell Count Variation with Age and Pregnancy

<i>Patient characteristic</i>	<i>Normal total leukocyte count</i>
Newborn infant	13,000 to 38,000 per mm ³ (13.0 to 38.0 × 10 ⁹ per L)
Infant two weeks of age	5,000 to 20,000 per mm ³ (5.0 to 20.0 × 10 ⁹ per L)
Adult	4,500 to 11,000 per mm ³ (4.5 to 11.0 × 10 ⁹ per L)
Pregnant female (third trimester)	5,800 to 13,200 per mm ³ (5.8 to 13.2 × 10 ⁹ per L)

Information from reference 3.

Normal Leukocyte Life Cycle and Responses



- WBCs have matured within the bone marrow, 80% to 90% remain in storage in the bone marrow.
- small pool (2% to 3%) of leukocytes circulate freely in the peripheral blood.
- the rest stay deposited along the margins of blood vessel walls or in the spleen.
- Leukocytes spend most of their life span in storage.
- Once a leukocyte is released into circulation and peripheral tissues, its life span ranges from **two to 16** days, depending on the type of cell.

Age	Total leukocytes		Neutrophils			Lymphocytes			Monocytes		Eosinophils	
	Mean	(Range)	Mean	(Range)	%	Mean	(Range)	%	Mean	%	Mean	%
Birth	18.1	(9.0-30.0)	11.0	(6.0-26.0)	61	5.5	(2.0-11.0)	31	1.1	6	0.4	2
12 h	22.8	(13.0-38.0)	15.5	(6.0-28.0)	68	5.5	(2.0-11.0)	24	1.2	5	0.5	2
24 h	18.9	(9.4-34.0)	11.5	(5.0-21.0)	61	5.8	(2.0-11.5)	31	1.1	6	0.5	2
1 week	12.2	(5.0-21.0)	5.5	(1.5-10.0)	45	5.0	(2.0-17.0)	41	1.1	9	0.5	4
2 weeks	11.4	(5.0-20.0)	4.5	(1.0-9.5)	40	5.5	(2.0-17.0)	48	1.0	9	0.4	3
1 month	10.8	(5.0-19.5)	3.8	(1.0-9.0)	35	6.0	(2.5-16.5)	56	0.7	7	0.3	3
6 months	11.9	(6.0-17.5)	3.8	(1.0-8.5)	32	7.3	(4.0-13.5)	61	0.6	5	0.3	3
1 year	11.4	(6.0-17.5)	3.5	(1.5-8.5)	31	7.0	(4.0-10.5)	61	0.6	5	0.3	3
2 years	10.6	(6.0-17.0)	3.5	(1.5-8.5)	33	6.3	(3.0-9.5)	59	0.5	5	0.3	3
4 years	9.1	(5.5-15.5)	3.8	(1.5-8.5)	42	4.5	(2.0-8.0)	50	0.5	5	0.3	3
6 years	8.5	(5.0-14.5)	4.3	(1.5-8.0)	51	3.5	(1.5-7.0)	42	0.4	5	0.2	3
8 years	8.3	(4.5-13.5)	4.4	(1.5-8.0)	53	3.3	(1.5-6.8)	39	0.4	4	0.2	2
10 years	8.1	(4.5-13.5)	4.4	(1.8-8.0)	54	3.1	(1.5-6.5)	38	0.4	4	0.2	2
16 years	7.8	(4.5-13.0)	4.4	(1.8-8.0)	57	2.8	(1.2-5.2)	35	0.4	5	0.2	3
21 years	7.4	(4.5-11.0)	4.4	(1.8-7.7)	59	2.5	(1.0-4.8)	34	0.3	4	0.2	3

Numbers of leukocytes are in thousands per mm³; ranges are estimates of 95% confidence limits and percentages refer to differential counts. Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few days of life.

Modified from Dallman, P.R., 1977. Blood and blood-forming tissues. In: Rudolph, A.M. (Ed.), *Pediatrics, sixth ed.* Appleton-Century-Crofts, Norwalk, CT.

Table 2. Normal White Blood Cell Distribution

<i>White blood cell line</i>	<i>Normal percentage of total leukocyte count</i>
Neutrophils	40 to 60
Lymphocytes	20 to 40
Monocytes	2 to 8
Eosinophils	1 to 4
Basophils	0.5 to 1

Information from reference 8.

Normal WBC Count Variations

- **Age-Specific Ranges:**
 - Newborn: 13,000–38,000 per mm³ (13.0–38.0 × 10⁹ per L)
 - Two weeks old: 5,000–20,000 per mm³ (5.0–20.0 × 10⁹ per L)
 - Adult: 4,500–11,000 per mm³ (4.5–11.0 × 10⁹ per L)
 - Pregnancy (3rd trimester): 5,800–13,200 per mm³ (5.8–13.2 × 10⁹ per L)
- **Ethnic Variation:** Black African descent may have lower WBC count by ~1,000 per mm³
- **Pregnancy Note:** Leukocytosis not reliable for postpartum bacterial infection

Types of Leukocytosis

- **Neutrophilia:** $>7,000$ per mm^3 (7.0×10^9 per L)
 - Causes: Infections, stress, chronic inflammation, medications
- **Lymphocytosis:** $>4,500$ per mm^3 (4.5×10^9 per L) or $>40\%$ of WBC
 - Causes: Viral infections, pertussis, leukemia/lymphoma
- **Monocytosis:** >880 per mm^3 (0.88×10^9 per L) or $>8\%$ of WBC
 - Causes: Tuberculosis, autoimmune diseases, malignancy
- **Eosinophilia:** Seen in parasitic or allergic conditions

Leukemoid Reaction

- **Definition:** WBC count 50,000–100,000 per mm³ (50.0–100.0 × 10⁹ per L)
- **Causes:**
 - Severe infections (e.g., Clostridium difficile, sepsis)
 - Organ rejection
 - Solid tumors
- **Distinguishing Feature:** Not typically malignant, but requires evaluation

Table 3. Nonmalignant Causes of Neutrophilia

<i>Cause</i>	<i>Distinguishing features</i>	<i>Evaluation</i>
Patient characteristics	Pregnancy, obesity, race, age	Reference appropriate WBC count by age or pregnancy trimester Compare WBC count to recent baseline (if available)
Infection	Fever, system-specific symptoms Physical examination findings	Obtain system-specific cultures and imaging (e.g., sputum cultures, chest radiography) Consider empiric antibiotics Consider use of other biomarkers, such as CRP and procalcitonin
Reactive neutrophilia	Exercise, physical stress (e.g., postsurgical, febrile seizures), emotional stress (e.g., panic attacks), smoking	Confirm with history
Chronic inflammation	Rheumatic disease, inflammatory bowel disease, granulomatous disease, vasculitides, chronic hepatitis	Obtain personal and family medical history Consider erythrocyte sedimentation rate and CRP levels, specific rheumatology laboratories Consider subspecialist consultation (e.g., rheumatology, gastroenterology)
Medication induced	Corticosteroids, beta agonists, lithium, epinephrine, colony-stimulating factors	Confirm with history; consider discontinuation of medication, if warranted
Bone marrow stimulation	Hemolytic anemia, immune thrombocytopenia, bone marrow suppression recovery, colony-stimulating factors	Complete blood count differential; compare with baseline values (if available) Examine peripheral smear Consider reticulocyte and lactate dehydrogenase levels Consider flow cytometry, bone marrow examination, hematology/oncology consultation
Splenectomy	History of trauma or sickle cell disease	Confirm with history
Congenital	Hereditary/chronic idiopathic neutrophilia, Down syndrome, leukocyte adhesion deficiency	Obtain family, developmental history Consider hematology/oncology, genetics, and immunology consultations

NOTE: After patient characteristics, causes are listed in approximate order of frequency.
CRP = C-reactive protein; WBC = white blood cell.
Information from references 1 through 7, 9, and 10.

Table 4. Selected Conditions Associated with Elevations in Certain White Blood Cell Types

<i>White blood cell line</i>	<i>Conditions that typically cause elevations</i>
Basophils	Allergic conditions, leukemias
Eosinophils	Allergic conditions, dermatologic conditions, eosinophilic esophagitis, idiopathic hypereosinophilic syndrome, malignancies, medication reactions, parasitic infections
Lymphocytes	Acute or chronic leukemia, hypersensitivity reaction, infections (viral, pertussis)
Monocytes	Autoimmune disease, infections (Epstein-Barr virus, fungal, protozoan, rickettsial, tuberculosis), splenectomy
Neutrophils	Bone marrow stimulation, chronic inflammation, congenital, infection, medication induced, reactive, splenectomy

Reactive Leukocytosis

- **Range: 11,000 to 30,000 per mm³ (11.0 to 30.0 × 10⁹ per L)**
- **Causes: Stress (surgery, exercise, trauma, burns, emotional stress)**
- **Medications: Corticosteroids, lithium, colony-stimulating factors, beta agonists, epinephrine**
- **Recovery phase after hemorrhage or hemolysis**

Leukocytosis in Infection

- **Hallmark of bacterial infections (mature/immature neutrophils)**
- **“Left shift”: Release of less-mature bands and metamyelocytes**
- **Some bacterial infections cause neutropenia (e.g., typhoid fever, rickettsial infections, brucellosis, dengue)**
- **Viral infections: Early leukocytosis, not typically sustained except in some childhood viral infections**

Leukocytosis as Infection Marker

- Suggestive but not definitive for significant infection
- Example: Acute appendicitis sensitivity (62%), specificity (75%)
- Poor predictor of bacteremia; not an indication for blood cultures alone
- Other biomarkers (CRP, procalcitonin) often more discriminatory

Findings Suggestive of Hematologic Malignancies in the Setting of Leukocytosis

- Symptoms
- **Bruising/bleeding tendency:** Indicates possible thrombocytopenia or coagulopathy, common in leukemias (e.g., acute lymphoblastic leukemia [ALL] or acute myeloid leukemia [AML]) or bone marrow infiltration.
- **Fatigue, weakness:** Likely due to anemia (low red blood cell count or hemoglobin) or systemic effects of malignancy.
- **Fever > 100.4°F (38°C):** Suggests infection (common in immunosuppressed states) or a paraneoplastic process.
- **Immunosuppression:** Increases risk of infections; seen in leukemias, lymphomas, or bone marrow failure.
- **Night sweats:** A "B symptom" associated with lymphomas (e.g., Hodgkin or non-Hodgkin lymphoma).
- **Unintentional weight loss:** Another systemic symptom, often linked to malignancy or chronic infection.

Physical Examination Findings: continue

- **Lymphadenopathy:** Enlarged lymph nodes, common in lymphomas or chronic lymphocytic leukemia (CLL).
- **Petechiae:** Small hemorrhagic spots due to low platelets or vascular issues, often seen in leukemia or bone marrow disorders.
- **Splenomegaly or hepatomegaly:** Suggests organ infiltration by malignant cells (e.g., leukemia, lymphoma) or extramedullary hematopoiesis.

Laboratory Abnormalities : continue

- **Decreased red blood cell count or hemoglobin/hematocrit levels:** Indicates anemia, which could result from bone marrow suppression, infiltration, or chronic disease.
- **Increased or decreased platelet count:** Thrombocytopenia is common in leukemias due to marrow replacement; thrombocytosis may occur in some myeloproliferative disorders.
- **Monomorphic lymphocytosis on peripheral smear:** Suggests chronic lymphocytic leukemia (CLL) or other lymphoproliferative disorders.
- **Predominantly immature cells on peripheral smear:** Highly suggestive of acute leukemia (e.g., ALL or AML), where blasts predominate.
- **White blood cell count > 30,000 per mm³ (or > 20,000 per mm³ after initial management):** Indicates significant leukocytosis, often seen in leukemias (e.g., CLL, AML, ALL) or leukemoid reactions.

a diagnostic flowchart for leukocytosis (white blood cell count $> 11,000$ per mm^3 or 11.0×10^9 per L). It outlines the following steps

- **Repeat complete blood count and order peripheral smear:** Confirm leukocytosis.
- If not confirmed, no further workup is necessary.
- If confirmed, proceed with additional history and physical examination.
- **Additional history and physical examination:**
 - Assess for patient characteristics explaining leukocytosis (e.g., pregnancy, newborn, splenectomy, smoking, medications).
 - If explained, no further workup is necessary.
 - If not explained, proceed based on patient presentation

- **Patient presents with:** Weight loss, fatigue, night sweats, fevers
- Abnormal red blood cell and platelet count
- Immature leukocyte forms (blasts)
- Chronic duration (weeks or years)
- History of risk factors for malignancy (e.g., splenomegaly, lymphadenopathy, bruising)
 - If no, consider nonmalignant etiologies and determine which cell line is affected.
 - If yes, consider malignancy; consult hematology/oncology and consider additional testing (flow cytometry, cytogenetic testing, or molecular testing of bone marrow or peripheral blood).

Nonmalignant etiologies based on affected cell line

- **Neutrophilia ($>7,000$ per mm^3 or 7.0×10^9 per L):** Infection, inflammation, stressors, medication-induced, bone marrow stimulation, splenectomy, tobacco use.
- **Consider:** Medical history, family, travel, sick contact, social history, ESR, CRP, ANA measurement, pathogen isolation (blood cultures, lumbar puncture), additional imaging (system-specific).
- **Monocytosis (>880 per mm^3 or 0.88×10^9 per L):** Infections (Epstein-Barr virus, tuberculosis, fungal, protozoan, rickettsial), autoimmune disease, splenectomy.
- **Consider:** Sick contact, surgical, travel history, imaging (chest radiography), pathogen-specific testing (mononucleosis spot test, purified protein derivative, ESR, CRP, ANA measurement).

- **Lymphocytosis ($>4,500$ per mm^3 or 4.5×10^9 per L):**Infections (viral, pertussis), hypersensitivity reaction.Consider: Sick contact and immunization history, imaging (chest radiography), pathogen-specific testing (viral panels).
- **Basophilia (>100 per mm^3 or 0.1×10^9 per L; rare):**Search for malignancy (or allergic condition, much less likely).
- **Eosinophilia (>500 per mm^3 or 0.5×10^9 per L):**Allergic conditions, eosinophilic esophagitis, medication reactions, dermatologic conditions, parasitic infections.

Consider: Medication, travel history, full skin examination, skin biopsy if warranted, allergy/immunology testing (stool ova and parasites), upper endoscopy.



Leukopenia

- Leukopenia refers to an abnormally low number of white blood cells
- (WBCs) in the circulating blood secondary to a paucity of **lymphocytes, granulocytes** or both.
- For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hr through the 1st wk of life. Thereafter, values are stable until 1 yr of age

After which a slow steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence.

NEUTROPENIA

- Neutropenia is defined as a decrease in the absolute number of circulating
- The absolute neutrophil count (ANC) is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands.
- Normal neutrophil counts must be stratified for age and race.
- Neutrophils predominate at birth but rapidly decrease in the 1st few
- days of life.
- **During infancy, neutrophils constitute 20-30% of circulating leukocyte populations.**

NEUTROPENIA

- Near equal numbers of neutrophils and lymphocytes are found in the peripheral circulation **at 5 yr of age.**
- the characteristic **70%** predominance of neutrophils that occurs in adulthood is usually attained during puberty.
- For white children older than 12 mo of age, the lower limit of normal for the ANC is 1,500/ μ L; for black children older than 12 mo of age the lower limit of normal is 1,200/ μ L.

NEUTROPENIA

- mild neutropenia, with an ANC of 1,000-1,500/ μ L.
- moderate neutropenia, with an ANC of 500-1,000/ μ L.
- severe neutropenia, with an ANC <500/ μ L.
- ANC <200 is also termed *agranulocytosis*.
- *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection.*

NEUTROPENIA

- **Acute neutropenia** evolves over a few days and is often a result of rapid neutrophil use and/or compromised neutrophil production.
- **Chronic neutropenia** by definition lasts longer than 3 mo and arises from reduced production, increased destruction or excessive splenic sequestration of neutrophils.
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Table 131-1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION <ul style="list-style-type: none">• History of acute or chronic leukopenia• General medical history• Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies• Spleen size• History of drug exposure• Complete blood count with differential and reticulocyte counts	<ul style="list-style-type: none">• Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport)• Hypersplenism• Drug-associated neutropenia• Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/μL <i>Evaluation of Acute Onset Neutropenia</i> <ul style="list-style-type: none">• Repeat blood counts in 3-4 weeks• Serology and cultures for infectious agents• Discontinue drug(s) associated with neutropenia• Test for antineutrophil antibodies• Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets	<ul style="list-style-type: none">• Transient myelosuppression (e.g., viral)• Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia• Drug-associated neutropenia• Autoimmune neutropenia• Neutropenia associated with disorders of immune function
IF ANC <500/μL ON 3 SEPARATE TESTS <ul style="list-style-type: none">• Bone marrow aspiration and biopsy, with cytogenetics• Glucocorticoid stimulation test• Serial CBCs (3/wk for 6 wk)• Exocrine pancreatic function• Skeletal radiographs	<ul style="list-style-type: none">• Severe congenital neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia• Chronic benign or idiopathic neutropenia, some autoimmune neutropenias• Cyclic neutropenia• Shwachman-Diamond syndrome• Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1000/μL <ul style="list-style-type: none">• Repeat blood counts in 3-4 weeks	<ul style="list-style-type: none">• Transient leukopenia (e.g., viral)
IF ALC <1000/μL ON 3 SEPARATE TESTS <ul style="list-style-type: none">• HIV-1 antibody or RNA test• Quantitative immunoglobulins (G, A, and M), lymphocyte subsets	<ul style="list-style-type: none">• HIV-1 infection, AIDS• Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA <ul style="list-style-type: none">• Bone marrow aspiration and biopsy• Bone marrow cytogenetics• Vitamin B₁₂ and folate levels	<ul style="list-style-type: none">• Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia• Myelodysplasia, leukemia• Vitamin deficiencies

Clinical Manifestations of Neutropenia

- Individuals with neutrophil counts $<500/\mu\text{L}$ are at substantial risk for
- developing infections, primarily from their endogenous flora as well as from nosocomial organisms.
- However, some patients with isolated
- chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias.
-

Clinical Manifestations of Neutropenia

- Children whose neutropenia is secondary to acquired disorders of production such as with cytotoxic therapy, immunosuppressive drugs, or radiation therapy are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised.
- Neutropenia associated with additional monocytopenia or lymphocytopenia, is more highly associated with serious infection
- **The integrity of skin** and mucous membranes, the **vascular** supply to tissues, and **nutritional** status also influence the risk of infection.

Clinical Manifestations of Neutropenia

- The most common **clinical presentation of profound neutropenia** includes fever, aphthous stomatitis, and gingivitis.
- Infections commonly associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis.
- The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and Gram-negative bacteria.

Laboratory Findings

- For patients with chronic neutropenia since infancy, recurrent fevers, and chronic gingivitis, perform WBC and differential counts 3 times/week for 6-8 weeks to assess for cyclic neutropenia.
- Bone marrow aspiration/biopsy may be needed to evaluate cellularity and myeloid maturation in select cases.
- If malignancy is not suspected, test ANC before and 4-6 hours after a single dose of **glucocorticosteroid (prednisone 1-2 mg/kg)** to assess bone marrow neutrophil reserve.
- A normal or slightly low ANC post-dose suggests chronic benign or idiopathic neutropenia, potentially avoiding marrow examination. Further tests depend on neutropenia duration, severity, and physical exam findings.

Acquired Neutropenia (Infection-Related)

- Transient neutropenia is common in childhood, occurs during the 1st 24-48 hr often linked to viral infections like influenza, adenovirus, RSV, enteroviruses, and others, typically lasting 3-8 days during viremia .
- It results from **neutrophil redistribution or sequestration** due to tissue damage or splenomegaly.
- Severe bacterial, protozoal, rickettsial, or fungal infections, especially bacterial sepsis in young infants and premature neonates, can also cause significant neutropenia, with neonates at higher risk due to limited marrow reserves.

Acquired Neutropenia (Infection-Related)

- **Chronic neutropenia with Epstein-Barr virus,**
- **cytomegalovirus,**
- **or HIV,**
- **often due to viral bone marrow suppression or antibody-mediated destruction.**

Table 131-4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella
Bacterial	<i>Anaplasma</i> (formerly <i>Ehrlichia</i>) <i>phagocytophilum</i> , brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

Drug-Induced Neutropenia

- particularly in adults over 65
- result from various drugs, including antimicrobials, antithyroid drugs, antipsychotics, antipyretics, and antirheumatics,
- through mechanisms like **immune-mediated** reactions, **toxicity**, **idiosyncratic** responses, or **hypersensitivity**.
- Immune-mediated neutropenia often develops suddenly with fever and resolves within a week after stopping the drug.
- Toxic or idiosyncratic reactions may vary in onset and severity,
- hypersensitivity reactions can involve multiple symptoms like fever, rash, and organ issues.

Drug-Induced Neutropenia

- **Management involves discontinuing nonessential drugs.**
- **If symptoms like infection occur, granulocyte colony-stimulating factor (filgrastim) may be used.**
- **Asymptomatic cases may allow continued drug use with close monitoring.**
- **Neutropenia is also predictable after anticancer drugs or radiation, typically appearing 7-10 days post-treatment and increasing infection risk due to compromised immunity.**
- **Extended use of certain antibiotics, phenytoin, or nutritional deficiencies can also cause neutropenia**

Table 131-5

Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

Nutrition-Related Neutropenia

- **Poor nutrition, particularly deficiencies in vitamin B12 or folic acid, can cause neutropenia by impairing myelopoiesis.**
- **Extended use of antibiotics (e.g., trimethoprim-sulfamethoxazole), phenytoin, or small intestine resection can disrupt folate metabolism, leading to megaloblastic pancytopenia.**
- **Neutropenia may also occur in starvation, marasmus, anorexia nervosa, or prolonged parenteral nutrition without vitamin supplementation.**

Neutropenia Secondary to Bone Marrow Replacement

- **Acquired bone marrow disorders like**
- **leukemia,**
- **lymphoma,**
- **metastatic tumors,**
- **aplastic anemia,**
- **myelodysplastic syndromes**
- **cause neutropenia, often with anemia and thrombocytopenia. Treatment focuses on managing the underlying disease.**

Neutropenia Secondary to Reticuloendothelial Sequestration

- splenic enlargement from various causes (e.g., storage diseases, portal hypertension, inflammation, or neoplasia) leads to mild-to-moderate neutropenia, often with anemia and thrombocytopenia.
- Severity depends on spleen size and bone marrow compensation.
- Treating the underlying condition may resolve neutropenia;
- splenectomy is considered in severe cases but increases infection risk, requiring immunizations and possible antibiotic prophylaxis. Splenectomy is avoided in immunodeficiencies due to high sepsis risk.

Chronic benign neutropenia of childhood

- common condition with mild to moderate neutropenia,
- typically not increasing the risk of serious infections.
- It may resolve spontaneously,
- though some cases might be misdiagnosed as autoimmune neutropenia (AIN) of infancy, which often resolves in childhood.
- It can be sporadic or inherited (dominant or recessive) and usually requires no treatment due to low infection risk.
- Idiopathic chronic neutropenia begins after age 2 with no clear cause. (ANC) consistently below $500/\mu\text{L}$
- recurrent infections affecting the skin, mucous membranes, lungs, and lymph nodes. Bone marrow analysis shows varied myeloid development, often with maturation arrest between the myelocyte and later stages.

- **Shwachman-Diamond Syndrome (SDS):**
- autosomal recessive caused by SBDS gene mutations, neutropenia, pancreatic insufficiency, short stature, and skeletal abnormalities. Symptoms include steatorrhea, failure to thrive, respiratory issues, and frequent infections.
- **Dyskeratosis Congenita:** nail dystrophy, leukoplakia, malformed teeth, and skin hyperpigmentation. Young patients may lack these signs
- **Chédiak-Higashi Syndrome:** Caused by LYST gene mutations, leading to giant granules in granulocytes, increased infection risk, bleeding issues, neuropathy, and HLH. Treated with hematopoietic stem cell transplantation.
- **Griscelli Syndrome Type II:** Caused by RAB27a mutations, features neutropenia, partial albinism, hypogammaglobulinemia, and HLH risk. Treated with stem cell transplantation

- **Metabolic Disorders (GSDIb):** Caused by G6PT1 mutations, leading to glycogen storage, hepatomegaly, growth retardation, neutropenia, and recurrent infections due to defective neutrophil motility and apoptosis.
- Filgrastim corrects neutropenia but not functional defects.
- **Immune Dysfunction Disorders:** Severe neutropenia is seen in X-linked agammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiencies, autoimmune lymphoproliferative syndrome, hyper-IgM syndrome, WHIM syndrome, and other rare immunodeficiencies

LYMPHOPENIA

- For children younger than 12 mo old, lymphopenia is defined as an ALC $<3,000$ cells/ μL .
- For older children and adults, an ALC $<1,000$ cells/ μL is considered lymphopenia.

Table 131-7 Causes of Lymphocytopenia**ACQUIRED**

Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury

INHERITED

Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome
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PUVA, psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

**Thanks FOR Your
Attention**