White cell disorders non neoplastic

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INTRODUCTION

- THINK- PAIR- SHARE
  - DESCRIBE DEVELOPMENT OF HEMATOLOGIC SYSTEM
  - LIST DOWN HEAMATOLOGIC CELLS
  - **Sites of haematopoesis during different developmental stages**

Normal values

Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 µkat/L	13–100 µ/L
Count (WBC)	WB	3.54–9.06×10^9/L	3.54–9.06×10^3/mm^3
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 µm^3
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	p		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 µg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in collagen, ristocetin, ar
Platelet count	WB	165–415×10^9/L	165–415×10^3/mm^3

Normal values

TABLE 13-1 -- Adult Reference Ranges for Blood Cells

Cell Type	
White cells (× 10^3/μL)	4.8–10.8
Granulocytes (%)	40–70
Neutrophils (× 10^3/μL)	1.4–6.5
Lymphocytes (× 10^3/μL)	1.2–3.4
Monocytes (× 10^3/μL)	0.1–0.6
Eosinophils (× 10^3/μL)	0–0.5
Basophils (× 10^3/μL)	0–0.2
Red cells (× 10^3/μL)	4.3–5, men; 3.5–5.0, women
Platelets (× 10^3/μL)	150–450

Pediatric CBC

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (USA)		CONVERSION FACTOR	REFERENCE VALUES (SI)	COMMENTS
COMPLETE BLOOD COUNT						
Hematocrit (HCT, Hct)	W(E)		% of packed red cells (V red cells/V whole blood cells ? 100		Volume fraction (V red cells/V whole blood)	
Calculated from mean corpuscular volume (MCV) and RBC count (electronic displacement or laser)		0-30 days	44-70%	?0.01	0.44-0.70	
		1-23 mo	32-42%		0.32-0.42	
		2-9 yr	33-43%		0.33-0.43	
		10-17 yr M	36-47%		0.36-0.47	
		F	35-45%		0.35-0.45	
		>18-99 yr M	42-52%		0.42-0.52	
		F	37-47%		0.37-0.47	
Hemoglobin (Hb)	W(E)		g/dL		mmol/L	
		0-30 days	15.0-24.0	?0.155	2.32-3.72	MW Hb = 64,500
		1-23 mo	10.5-14.0		1.63-2.17	
		2-9 yr	11.5-14.5		1.78-2.25	
		10-17 yr M	12.5-16.1		1.93-2.50	
		F	12.0-15.0		1.86-2.32	
		>18-99 yr M	13.5-18.0		2.09-2.79	
		F	12.5-16.0		1.93-2.48	
	P(H)	See *Chemical Elements*				

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Erythrocyte indices (RBC indices)					
Mean corpuscular hemoglobin (MCH)	W(E)		pg/cell		fmol/cell
		0-30 days	33-39	?0.0155	0.51-0.60
		1-23 mo	24-30		0.37-0.46
		2-9 yr	25-31		0.39-0.48
		10-17 yr M	26-32		0.26-0.32
		F	26-32		0.26-0.32
		>18-99 yr M	27-31		0.27-0.31
		F	27-31		0.27-0.31
Mean corpuscular hemoglobin concentration (MCHC)	W(E)		% Hb/cell or g Hb/dL RBC		mmol Hb/L RBC
			32-36	?0.155	4.96-5.58
Mean corpuscular volume (MCV)	W(E)		?m^3		fL
		0-30 days	99-115	?1	99-115
		1-23 mo	72-88		72-88
		2-9 yr	76-90		76-90
		10-17 yr	78-95		78-95
		>18-99 yr	78-100		78-100
Leukocyte count (WBC count)	W(E)	?1,000 cells/mm^3 (?L)			?10^9 cells/L
		0-30 days	9.1-34.0	?1	9.1-34.0
		1-23 mo	6.0-14.0		6.0-14.0
		2-9 yr	4.0-12.0		45.0-12.0
		10-17 yr	4.0-10.5		4.0-10.5
		18-99 yr	4.0-10.5		4.0-10.5

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Leukocyte differential	W(E)	%		Number fraction
Myelocytes		0%	?0.01	0
Neutrophils ("bands")		3-5%		0.03-0.05
Neutrophils ("segs")		54-62%		0.54-0.62
Lymphocytes		25-33%		0.25-0.33
Monocytes		3-7%		0.03-0.07
Eosinophils		1-3%		0.01-0.03
Basophils		0-0.75%		0-0.0075
		Cells/mm^3 (?L)		?10^6 cells/L
Myelocytes		0	?1	0
Neutrophils ("bands")		150-400		150-400
Neutrophils ("segs")		3,000-5,800		3,000-5,800
Lymphocytes		1,500-3,000		1,500-3,000
Monocytes		285-500		285-500
Eosinophils		50-250		50-250
Basophils		15-50		15-50
	W(E)	?10^3/mm^3 (?L)		?10^9/L
Platelet count (thrombocyte count)		Newborn 84-478 (after 1 wk, same as adult)	?10^6	84-478
		Adult 150-400		150-400

- Disorders of white blood cells can be classified into two broad categories:
- *proliferative disorders*, in which there is an expansion of leukocytes
  - *reactive*
  - *neoplastic*
- *leukopenias*, which are defined as a deficiency of leukocytes.

Leukopenia

- An abnormally low white cell count *(leukopenia)* usually results from reduced numbers of
  - Neutrophils *(neutropenia*, *granulocytopenia)*.
  - *Lymphopenia* is less common; most commonly observed in advanced human immunodeficiency virus (HIV) infection, therapy with glucocorticoids or cytotoxic drugs, autoimmune disorders, malnutrition, and certain acute viral infections.

NEUTROPENIA, AGRANULOCYTOSIS

- *Neutropenia*, a reduction in the number of neutrophils in the blood, occurs in a wide variety of circumstances.
- *Agranulocytosis*, a clinically significant reduction in neutrophils, has the serious consequence of making individuals susceptible to bacterial and fungal infections.

Pathogenesis

- A reduction in circulating granulocytes occurs if there is:

(1) inadequate or ineffective granulopoiesis,

(2) accelerated removal of neutrophils from the blood.

- *Inadequate or ineffective granulopoiesis* is observed in the setting of
  - *Suppression of hematopoietic stem cells*, as occurs in aplastic anemia and a variety of infiltrative marrow disorders (tumors, granulomatous disease, etc.);
  - *Suppression of committed granulocytic precursors* by exposure to certain drugs
  - Disease states associated with *ineffective hematopoiesis*, such as megaloblastic anemias and myelodysplastic syndromes, where defective precursors die in the marrow
  - Rare *congenital conditions* (such as Kostmann syndrome) in which inherited defects in specific genes impair granulocytic differentiation

- *Accelerated removal or destruction of neutrophils* occurs with
  - *Immunologically mediated injury* to neutrophils, which can be idiopathic, associated with a well-defined immunological disorder (e.g., systemic lupus erythematosus), or caused by exposure to drugs
  - *Splenomegaly*, in which splenic sequestration of neutrophils leads to excessive destruction.
  - *Increased peripheral utilization*, which can occur in overwhelming bacterial, fungal, or rickettsial infections

- *The most common cause of agranulocytosis is drug toxicity*.
- Certain drugs, such as alkylating agents and antimetabolites used in cancer treatment, produce agranulocytosis in a predictable, dose-related fashion.
- Because such drugs cause a generalized suppression of the bone marrow, production of red cells and platelets is also affected.

- Agranulocytosis can also occur as an idiosyncratic reaction to a large variety of agents.
  - The roster of implicated drugs includes aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, thiouracil, and phenylbutazone.
  - The neutropenia induced by chlorpromazine and related phenothiazines results from a toxic effect on granulocytic precursors in the bone marrow.

- Morphology.
  - The alterations in the bone marrow vary with cause. With excessive destruction of neutrophils in the periphery, the marrow is usually hypercellular due to a compensatory increase in granulocytic precursors. Hypercellularity is also the rule with neutropenias caused by ineffective granulopoiesis, as occurs in megaloblastic anemias and myelodysplastic syndromes.
  - Agranulocytosis caused by agents that suppress or destroy granulocytic precursors is understandably associated with marrow hypocellularity.

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- Infections are a common consequence of agranulocytosis.
- Ulcerating necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa, pharynx, or elsewhere in the oral cavity (agranulocytic angina) are quite characteristic.
- These are typically deep, undermined, and covered by gray to green-black necrotic membranes from which numerous bacteria or fungi can be isolated.

- Clinical Features.
  - The symptoms and signs of neutropenia are related to infection, and include malaise, chills, and fever, often followed by marked weakness and fatigability.
  - Serious infections are most likely when the neutrophil count falls below 500 per mm^3.
  - Because infections are often fulminant, broad-spectrum antibiotics must be given expeditiously whenever signs or symptoms appear.
  - In some instances, such as following myelosuppressive chemotherapy, neutropenia is treated with G-CSF, a growth factor that stimulates the production of granulocytes from marrow precursors

- Reactive (Inflammatory) Proliferations of White Cells and Lymph Nodes
  - *Leukocytosis refers to an increase in the number of white cells in the blood*. It is a common reaction to a variety of inflammatory states.

- Pathogenesis.
- The peripheral blood leukocyte count is influenced by several factors,
  - The size of the myeloid and lymphoid precursor and storage cell pools in the bone marrow, thymus, circulation, and peripheral tissues
  - The rate of release of cells from the storage pools into the circulation
  - The proportion of cells that are adherent to blood vessel walls at any time (the marginal pool)
  - The rate of extravasation of cells from the blood into tissues

INCREASED PRODUCTION IN THE MARROW
Chronic infection or inflammation (growth factor-dependent)
Paraneoplastic (e.g., Hodgkin lymphoma; growth factor-dependent)
Myeloproliferative disorders (e.g., chronic myeloid leukemia; growth factor-independent)
INCREASED RELEASE FROM MARROW STORES
Endotoxemia
Infection
Hypoxia
DECREASED MARGINATION
Exercise
Catecholamines
DECREASED EXTRAVASATION INTO TISSUES
Glucocorticoids

- Acute infection there is a rapid increase in the egress of mature granulocytes from the bone marrow pool.
- If the infection is prolonged, the release of interleukin-1 (IL-1), tumor necrosis factor (TNF), and other inflammatory cytokines stimulates bone marrow stromal cells and T cells to produce increased amounts of hematopoietic growth factors, which enhance the proliferation and differentiation of committed granulocytic progenitors and, over several days, cause a sustained increase in neutrophil production.

Causes

- Neutrophilic leukocytosis
  - **Acute bacterial infections**, especially those caused by pyogenic organisms; **sterile inflammation** caused by, for example, tissue necrosis (myocardial infarction, burns)
- Eosinophilic leukocytosis (eosinophilia)
  - **Allergic disorders** such as asthma, hay fever; certain skin diseases (e.g., pemphigus, dermatitis herpetiformis); **parasitic infestations**; drug reactions; certain malignancies (e.g., Hodgkin and some non-Hodgkin lymphomas); **collagen vascular disorders** and some vasculitides; atheroembolic disease (transient)

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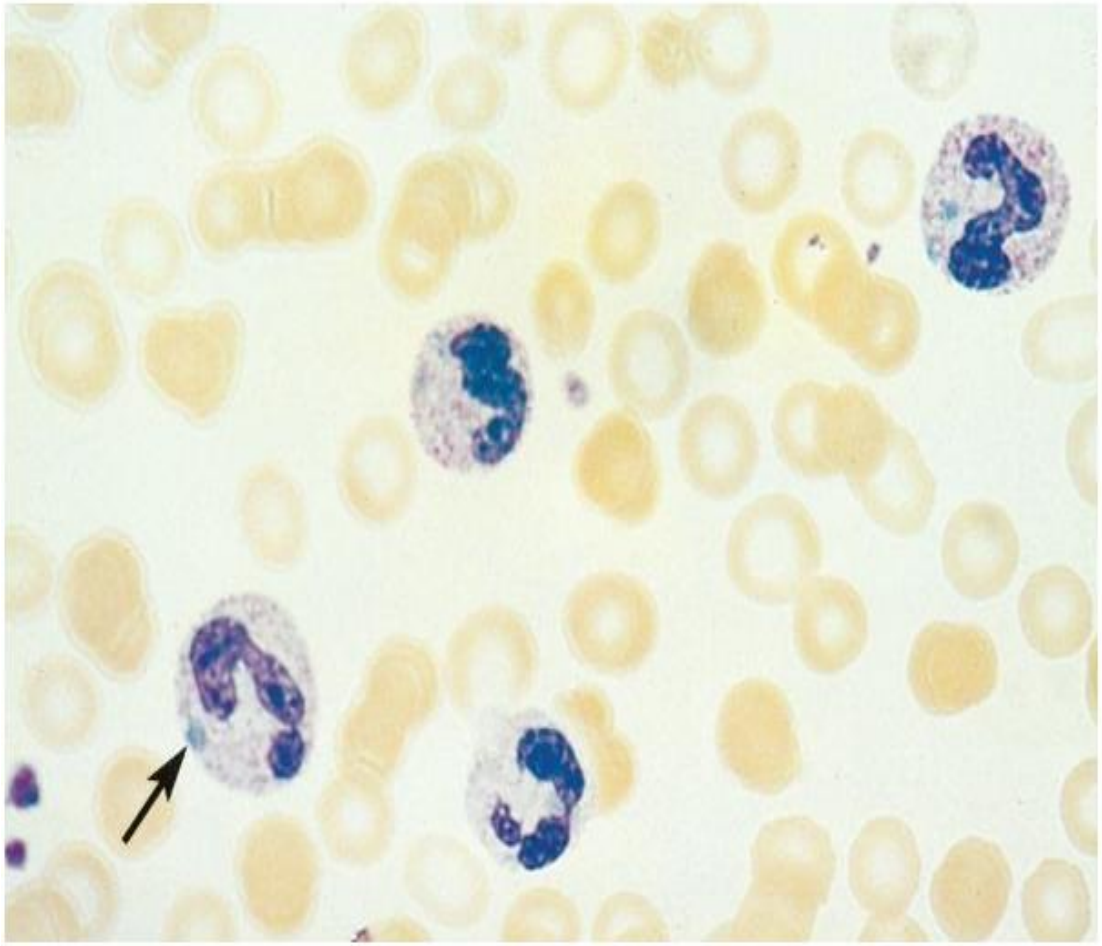
- Basophilic leukocytosis (basophilia) Rare,
  - often indicative of a myeloproliferative disease (e.g., **chronic myeloid leukemia)**
- Monocytosis
  - Chronic infections (e.g., **tuberculosis**), bacterial endocarditis, rickettsiosis, and malaria; collagen vascular diseases (e.g., systemic lupus erythematosus**); inflammatory bowel diseases (e.g., ulcerative colitis)**
- Lymphocytosis
  - Accompanies monocytosis in many disorders associated with chronic immunological stimulation (e.g., **tuberculosis, brucellosis)**; **viral infections** (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); *Bordetella pertussis* infection

Morphology



Neutrophils containing coarse purple cytoplasmic granules (toxic granulations) and blue cytoplasmic patches of dilated endoplasmic reticulum (Döhle bodies)

- *Reading assignment*
  - *Acute Nonspecific Lymphadenitis*