"NON-NEOPLASTIC DISORDERS OF WHITE BLOOD CELLS" 🩸

I. NORMAL HEMATOPOIESIS (OVERVIEW) 🌱

Hematopoietic Stem Cell (HSC)

- Pluripotent stem cell in bone marrow
- Gives rise to myeloid and lymphoid lineages

Lineage Differentiation 🔁

- Pluripotent HSC → Myeloid stem cell (CFU-GEMM) → Erythroid, granulocytic, monocytic, megakaryocytic cells
- Pluripotent HSC → Lymphoid stem cell → B-cells, T-cells, NK cells

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II. GRANULOPOIESIS (Neutrophil series) 🧬

Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → Band (stab) cell → Mature neutrophil

📌 Exam pearl:

- Myelocyte = last stage capable of division
- Band forms ↑ = left shift

III. ERYTHROPOIESIS ❤️

CFU-E → Proerythroblast → Basophilic erythroblast → Polychromatic erythroblast → Orthochromatic erythroblast (normoblast) → Nuclear extrusion → Reticulocyte → Erythrocyte

📌 Reticulocytes indicate marrow response

IV. MONOCYTOPOIESIS 🦠

CFU-GM → Monoblast → Promonocyte → Monocyte → Tissue macrophage

V. LYMPHOCYTOPOIESIS 🧠

CFU-L

- B-lymphocytes → Mature in bone marrow → Plasma cells
- T-lymphocytes → Mature in thymus
- NK cells

📌 Organ association

- B-cells → Lymph nodes, spleen
- T-cells → Thymus

VI. THROMBOPOIESIS (Megakaryocytopoiesis) 🧩

CFU-Meg → Megakaryoblast → Promegakaryocyte → Megakaryocyte → Platelets

📌 Platelets are cytoplasmic fragments, not true cells

NON-NEOPLASTIC DISORDERS OF WBCs 🩸

Classification 🧠

Quantitative Disorders

- Leukocytosis → ↑ WBC count
- Leukopenia → ↓ WBC count

Etiologic

- Reactive
- Neoplastic (excluded here)

VII. DEFINITIONS (VERY HIGH-YIELD) ⭐

Parameter	Cut-off
Leukocytosis	> 11,000 /cmm
Leukopenia	< 4,000 /cmm
Neutrophilia	> 7,500 /cmm
Neutropenia	< 2,000 /cmm
Lymphocytosis	> 4,000 /cmm

Lymphocytopenia	< 1,500 /cmm
Eosinophilia	> 600 /cmm
Monocytosis	> 1,000 /cmm
Basophilia	> 100 /cmm

📌 MCQ favorite: exact numeric cut-offs

VIII. LEUKOPENIA / NEUTROPENIA 🚫🦠

Causes

- Infections (viral common)
- Drugs (chemotherapy, antithyroid, antibiotics)
- Aplastic anemia
- Bone marrow infiltration (tumors)
- Autoimmune disorders (SLE)
- Splenomegaly
- Congenital immunodeficiency

Pathogenesis (Flowchart) 🔁

A. ↓ GRANULOPOIESIS

- Suppression of HSC → Aplastic anemia → Infiltrative disorders
- Drug-induced suppression of granulocytic precursors
- Ineffective hematopoiesis → MDS → Megaloblastic anemia
- Congenital disorders → Kostmann syndrome

B. ↑ DESTRUCTION / REMOVAL

- Immune-mediated destruction (SLE)
- Hypersplenism
- Increased utilization → Severe bacterial / fungal infections

📌 Exam pearl:

Neutropenia = risk of life-threatening infections

IX. LEUKOCYTOSIS 🔥

Mechanisms 🧠

- Increased marrow production
- Increased release from marrow
- Decreased margination
- Decreased tissue migration

Causes of Leukocytosis (TABLE – VERY IMPORTANT) 📊

Cell type	Causes
Neutrophils	Bacterial infections, inflammation, corticosteroids, acute hemorrhage
Eosinophils	Allergy, parasitic infestation, hyper-eosinophilic syndrome
Basophils	CML, basophilic leukemia
Monocytes	TB, typhoid, sarcoidosis
Lymphocytes	Viral infections, CLL, lymphoma

X. LYMPHOCYTOSIS 🧠🦠

Acute Causes

- Infectious mononucleosis
- Acute infectious lymphocytosis
- Viral hepatitis, mumps
- Toxoplasmosis
- Acute lymphoblastic leukemia

Chronic Causes

- Tuberculosis
- Chronic lymphocytic leukemia
- Collagen vascular diseases
- Lymphoma
- Thyrotoxicosis

Pathogenesis of Leukocytosis (GENERAL) 🔁

- ↑ Production / release from marrow → Chronic infections, inflammation, hypoxia
- ↓ Margination → Exercise, catecholamines
- ↓ Extravasation into tissues → Glucocorticoids

📌 Steroids cause neutrophilia by demargination

XI. LEUKEMOID REACTION (VERY EXAM-FAVORITE) ⭐⭐

Definition

- Excessive reactive neutrophilia
- WBC count < 50×10^9 /L
- Mimics leukemia but non-neoplastic

Causes

- Severe infections (TB, shigellosis, colitis)
- Sepsis
- Solid tumors
- Organ transplant rejection
- Severe hemorrhage / hemolysis

Peripheral Blood Findings 🔬

- Marked neutrophilia
- Left shift:
    - Bands
    - Metamyelocytes
    - Myelocytes
- Occasional promyelocytes / myeloblasts
- Toxic granulation
- Döhle bodies
- Cytoplasmic vacuolations

📌 Key difference from CML

- LR → High LAP score
- CML → Low LAP score

XII. CASE BASED LEARNING 🩺

Findings in a Case of LR

- High-grade fever + chills
- Enlarged tonsils

- WBC 31,700 /µL
- Neutrophils 85%
- Toxic changes present

Diagnosis

➡ Reactive neutrophilia / Leukemoid reaction due to acute bacterial infection

📌 Not leukemia because:

- Clinical infection present
- Reactive picture
- No blast predominance

FINAL EXAM PEARLS 💡

- Leukemoid reaction ≠ leukemia
- Band forms = left shift
- Steroids cause neutrophilia by demargination
- Toxic granulation = severe infection

INFECTIOUS MONONUCLEOSIS (IM) 🦠🩸

Definition

- Acute, self-limiting lymphoproliferative disorder
- Common in adolescents & young adults
- Caused by Epstein-Barr Virus (EBV)

📌 Exam buzzwords: EBV, atypical lymphocytes, heterophil antibodies, splenomegaly

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Etiologic Agent

- Epstein-Barr virus (EBV)
- Member of Herpesvirus family

PATHOGENESIS (VERY IMPORTANT) 🔁

Stepwise Flowchart 🧠

EBV entry → Infection of oropharyngeal epithelial cells → Spread to underlying lymphoid tissue (tonsils) → Infection of mature B cells

Infected B cells → Proliferation & transformation → Some undergo lysis → viral shedding → Others enter latency

Host immune response → Activation of $CD8^+$ cytotoxic T cells → Appear in blood as atypical lymphocytes

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Key Pathogenetic Points ⭐

- EBV infects B lymphocytes
- Infected B cells:
    - Become latent
    - Secrete antibodies
- Polyclonal B-cell activation → Production of IgM heterophil antibodies → Later class switch to IgG

📌 Atypical lymphocytes are NOT B cells ➡ They are reactive $CD8^+$ T cells

IMMUNOLOGICAL ASPECT 🧬

- Infected B cells express:
  - LYDMA (Lymphocyte-determined membrane antigen)
- Recognized by:
  - Cytotoxic $CD8^+$ T cells
- Result:
  - Control of B-cell proliferation
  - Latent EBV-infected B cells escape immune clearance

📌 This latency explains EBV persistence for life

CLINICAL FEATURES 🩺

- Fever 🌡️
- Sore throat
- Tender lymphadenopathy (cervical)

- Splenomegaly ⚠️ (risk of rupture)
- Tonsillar enlargement

LABORATORY DIAGNOSIS 🔬

Peripheral Blood Findings

- Leukocytosis
- Absolute lymphocytosis
- Presence of atypical lymphocytes

Atypical Lymphocyte (Downey cell) Morphology 🧫

Feature	Description
Size	Larger than normal lymphocyte
Cytoplasm	Abundant, basophilic, may show vacuoles
Nucleus	Oval / irregular
Chromatin	Coarse, clumped
Nucleoli	Prominent

📌 These are activated $CD8^+$ T cells

Serology ⭐

Test	Finding
Heterophil antibody test	Positive (Monospot test)
Anti-VCA (viral capsid antigen)	Present
Anti-EA (early antigen)	Present
Leukocyte count	Leukocytosis with atypical lymphocytosis

📌 Monospot test detects IgM heterophil antibodies

LYMPH NODE CHANGES IN IM 🧠

- Reactive lymphadenitis
- Paracortical hyperplasia (T-cell zone expansion)

REACTIVE LYMPHADENITIS 🧬🦠

Definition

- Non-neoplastic enlargement of lymph nodes
- Due to immune response to infections or inflammation

TYPES OF REACTIVE LYMPHADENITIS 📊

❑ Acute Non-Specific Lymphadenitis

Causes

- Local infection (draining lymph nodes)
- Generalized bacterial or viral infections

Gross Appearance

- Swollen
- Gray-red
- Congested

Microscopy 🔬

- Enlarged germinal centers

- Numerous mitotic figures
- Possible abscess formation in severe infection

📌 Nodes are tender & painful

2️⃣ Chronic Non-Specific Lymphadenitis

A. Follicular Hyperplasia 🧠 (B-cell response)

Pathogenesis

- Chronic antigenic stimulation
- Activation of B cells

Microscopy

- Enlarged & variably sized germinal centers
- Prominent mantle zone
- Numerous macrophages
- Preserved lymph node architecture

Causes

- Rheumatoid arthritis

- Toxoplasmosis
- Early HIV infection

📌 Reactive follicles vary in size → helps differentiate from lymphoma

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B. Paracortical Hyperplasia 🧠 (T-cell response)

Pathogenesis

- T-cell antigenic stimulation
- Transformation into immunoblasts
- Effacement of B-cell follicles

Causes

- Infectious mononucleosis ⭐
- Acute viral infections
- Vaccination
- Drug reactions

📌 IM = Paracortical hyperplasia

C. Sinus Histiocytosis 🦠

Features

- Dilated lymphatic sinusoids
- Increased macrophages
- Hypertrophy of sinus lining cells

Seen in

- Immune responses
- Infections
- Nodes draining malignancies

CAT-SCRATCH DISEASE 🐱🦠

Etiology

- Bartonella henselae

Clinical Features

- Self-limited disease
- Mostly children & young adults
- Regional lymphadenopathy
- Resolves in 2–4 months

⚠️ Rare complications:

- Encephalitis
- Osteomyelitis
- Thrombocytopenia

Morphology 🔬

- Irregular stellate necrotizing granulomas
- Central necrosis

📌 Classic exam image: stellate granuloma

CASE BASED LEARNING 🎯

A 16-year-old boy has sore throat, enlarged tender cervical lymphadenopathy, and low-grade fever for one week. On examination, he has splenomegaly. His CBC shows TLC 20,000/µl and DLC reveals lymphocytosis. Peripheral smear shows atypical lymphocytes. What is the possible diagnosis?

Case Summary

- 16-year-old boy
- Sore throat
- Tender cervical lymphadenopathy
- Low-grade fever
- Splenomegaly
- TLC: 20,000/µL
- Lymphocytosis
- Atypical lymphocytes on smear

Most Likely Diagnosis ✅

➡ Infectious Mononucleosis

Why NOT others?

- ❌ Acute lymphoblastic leukemia → blasts, not reactive lymphocytes
- ❌ Hodgkin lymphoma → Reed-Sternberg cells
- ❌ Non-Hodgkin lymphoma → monoclonal population

FINAL EXAM PEARLS 💡

- IM = EBV + atypical $CD8^+$ T cells
- Heterophil antibody = IgM
- Splenomegaly → avoid contact sports
- Paracortical hyperplasia = T-cell response
- Reactive follicles vary in size → not lymphoma

-> The End <-