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Myeloid Cell Disorders: Goals

• Define members of the myeloid series
• Understand:
  – white blood cell maturation
  – the white blood cell count and differential
  – ‘philias’ and ‘penias’ of the myeloid series members and associated clinical settings
  – recruitment of WBC from the circulation.
• Associate white blood cell defects with function
Maturation of Myeloid Cells

G-CSF → Myeloblast → N. Promyelocyte → N. Myelocyte → Immature Monocyte → Megakaryocyte

GM-CSF → Myeloid Stem Cell → Pronormoblast → Basophilic Normoblast → Polychromatric Normoblast

Platelets → Erythrocyte → Lymphocyte
Mature Myeloid Cells

Neutrophil

Eosinophil

Basophil

Monocyte
Assessment of Circulating WBC

• The total white blood cell count (WBC) and differential are measured in an automated counter

• WBC reflects the **circulating** pool of myeloid and lymphoid cells

• WBC in each microliter (µl;mm³) is reported

• **Relative proportion** of each type of WBC is indicated by a percentage

• **Absolute number** is the percentage of each type of WBC multiplied by the total WBC
# White Blood Cell Counts: Normal Ranges

<table>
<thead>
<tr>
<th>Age</th>
<th>WBC</th>
<th>PMN</th>
<th>Band</th>
<th>Lymph</th>
<th>Mono</th>
<th>Eos</th>
<th>Baso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth (0-1m)</td>
<td>6-30K</td>
<td>42-80%</td>
<td>2%</td>
<td>26-36%</td>
<td>3-8%</td>
<td>0-5%</td>
<td>0-2%</td>
</tr>
<tr>
<td>Child (1m – 12m)</td>
<td>6-18K</td>
<td>18-44%</td>
<td>3%</td>
<td>46-76%</td>
<td>3-8%</td>
<td>0-5%</td>
<td>0-2%</td>
</tr>
<tr>
<td>Child (1y – 16y)</td>
<td>5-14K</td>
<td>37-75%</td>
<td>3%</td>
<td>25-57%</td>
<td>3-8%</td>
<td>0-5%</td>
<td>0-2%</td>
</tr>
<tr>
<td>Adult</td>
<td>4-10K</td>
<td>36-75%</td>
<td>2%</td>
<td>20-50%</td>
<td>3-8%</td>
<td>0-5%</td>
<td>0-2%</td>
</tr>
</tbody>
</table>
## White Blood Cell Counts: Disease States

<table>
<thead>
<tr>
<th></th>
<th>WBC</th>
<th>PMN</th>
<th>Band</th>
<th>Lymph</th>
<th>Mono</th>
<th>Eos</th>
<th>Baso</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial Infection</strong></td>
<td>16K↑</td>
<td>79%↑</td>
<td>8%↑</td>
<td>8%</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Steroid Therapy</strong></td>
<td>12K↑</td>
<td>79%↑</td>
<td>4%</td>
<td>14%</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Splenectomy</strong></td>
<td>13K↑</td>
<td>50%</td>
<td>2%</td>
<td>40%</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Viral Infection</strong></td>
<td>3.5K↓</td>
<td>50%</td>
<td>2%</td>
<td>40%</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Chemo</strong></td>
<td>&lt;3K↓</td>
<td>65%</td>
<td>0%</td>
<td>20%</td>
<td>12%↑</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**J. Levine**
Neutrophil Maturation

Bone Marrow

<table>
<thead>
<tr>
<th>Phase</th>
<th>Percentage</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td>25%</td>
<td>6-7 days</td>
</tr>
<tr>
<td>Maturation</td>
<td>65%</td>
<td>6-7 days</td>
</tr>
<tr>
<td>Intravascular</td>
<td>8%</td>
<td>12 h</td>
</tr>
<tr>
<td>Tissues</td>
<td>2%</td>
<td>12 h</td>
</tr>
</tbody>
</table>

J. Levine
Neutrophil Maturation - Proliferative Phase

Proliferation 25%

Source Undetermined (All Slides)

Myeloblast Promyelocyte Myelocyte
65% of myeloid cells

Maturation 6-7 days

Metamyelocyte → Band → Neutrophil

Source Undetermined (All Slides)
Fate of the mature neutrophil

<table>
<thead>
<tr>
<th>Circulating</th>
<th>Marginating</th>
</tr>
</thead>
<tbody>
<tr>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Intravascular 12 h  Tissues 12 h

Approximately 10% of the developing neutrophils are in the circulation, marginated or in the tissue.
Disorders of Neutrophil Numbers

Definition

Neutropenia
Less than 1500/µl

Acquired
Or
Inherited

Neutrophilia
Greater than 7700/µl
Definition of Neutrophilia - too many

- Normal ANC is 1500-7700/µl
- Neutrophilia: abnormally high ANC
- Shift to the left: ↑’d release of precursors from the bone marrow
  – not necessarily associated with neutrophilia
Neutrophilia

• Acute shift from marginalizing to circulating pool
  – ↑ measured WBC, not total WBC

• Causes:
  – Steroid treatment
  – Exercise
  – Epinephrine
  – Hypoxia
  – Seizures
  – Other stress

• Chronic Stimulation
  – Excess cytokine stimulates proliferative pool

• Causes:
  – Infection
  – Down's Syndrome
  – Pregnancy/Eclampsia
  – Chemotherapy recovery
  – Myeloproliferative disorders
  – Marrow metastases
Example: exercise induced neutrophilia
Neutropenia: too few

• Neutropenia
  – Definition: ANC < 1500/µl
  – ANC 500-1000 increased risk of infection from exposure
  – ANC < 500: increased risk of infection from host organisms

• African-Americans: lower normal neutrophil counts (1000-1200)
# Acquired Causes of Neutropenia

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Increased Destruction</th>
<th>Shift to Marginating Pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Peripheral circulation</td>
<td>Move from the circulating pool to attach along the vessel wall</td>
</tr>
<tr>
<td>Medication:</td>
<td>Autoimmune diseases</td>
<td>Severe infection</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>(Rheumatoid arthritis, SLE, etc)</td>
<td>Endotoxin release</td>
</tr>
<tr>
<td>Antibiotics, etc</td>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiopulmonary bypass</td>
</tr>
</tbody>
</table>
Increased Destruction

Anti-neutrophil antibody

Neutrophil-Antibody Complex

Uptake and destruction of neutrophil by the RE system
Shift to Marginating Pool

Severe infection / Endotoxin release
Hemodialysis
Cardiopulmonary bypass
Evaluation of Neutropenia

• If visit prompted by a fever and ANC is low, treat promptly for infection
• Suspect medication: major cause of neutropenia
• If no culprits, bone marrow exam for:
  – Malignancy
  – Infiltration by non-marrow cells
  – Arrest of cell growth
  – Myeloproliferative disorder
Cyclic Neutropenia

- 21 day cycle
- autosomal dominant
- fever, mouth ulcers
- Treatment G-CSF
- usually improves after puberty

Figure: Blood cell counts of Patient No. 15 show regular 21 day cyclic variation. Note that monocytes and reticulocytes tend to rise when the neutrophils fall.
Congenital Neutropenia

- Maturation arrest
- Frequent infections, often serious
- Mouth sores
  - May lose teeth or develop severe gum infections
- Increased risk of leukemia
- Tx: G-CSF, BMT
Role of Neutrophil

- Responds to **chemotactic factors** released from damaged tissue
- **Rolls and attaches** to the endothelial cell wall
  - protein and carbohydrate interactions (selectins and their ligands).
- Becomes **activated** by chemotactic factors
- **Tightly adheres** through the integrin family of proteins.
- **Migrates** across the endothelial cell wall.
- **Phagocytizes** organisms so that they are contained within a vesicle or phagosome.
- **Releases granule products** and reduced oxygen species (e.g. hydrogen peroxide and superoxide) to kill organisms.
Function of the Circulating Neutrophil

Attachment/rolling  Activation  Adhesion  Migration

Chemoattractant  Phagocytosis

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Disruption of Neutrophil Function

• Steps where defects in structural components of neutrophils results in impaired ability to fight infection
  – Recruitment from the circulation
  – Adhesion and subsequent migration
  – Defective production in active oxygen metabolites
  – Deficiency in granules
Defect in Attachment/Rolling

Attachment/rolling

Cell surface molecules expressing Sialyl Lewis X interact with selectin proteins on the cell surface of endothelial cells.

Sialyl Lewis X

Selectins

LAD-2 Impaired expression of sialyl LewisX - Neutrophils do not attach and are not recruited to the site of inflammation.

Chemoattractant

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Defect in Adhesion

Integrins on the surface of neutrophils mediate tight adhesion to the endothelial cell wall. Cells then migrate.

LAD-1 results from a defect in leukocyte integrins. Decreased to absent expression on the cell surface. Cells cannot adhere and subsequently cannot migrate.
Clinical manifestations: LAD
Phagocytosis

Chemoattractant

Chediak-Higashi Syndrome: Defect in granule formation

CGD: NADPH-Oxidase-defective
Cannot produce active oxygen species

Bacteria are engulfed and contained in a phagosome.
Contents of the granules are released.
Oxygen metabolites (superoxide and H$_2$O$_2$) kill bacteria

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- Oculocutaneous albinism
  - Photophobia
  - Sun sensitivity
- Neuropathy
- Infections, esp Staph aureus

- TX: BMT
Chronic granulomatous disease (CGD)
Chronic granulomatous disease: CGD

- Catalase positive organisms
  - Staph aureus
  - Serratia marcescens
  - Burkholderia cepacia
  - Fungal
- Skin, lungs, bones, abscesses
- Granuloma formation from chronic infection
Myeloperoxidase deficiency

• One of the more common disorders
  – 1: 4000
• Decreased production of hypochlorous acid (HOCl)
• Killing takes longer than normal
• Clinically silent for most people
## Diseases with Neutrophil Defects

<table>
<thead>
<tr>
<th>Disease</th>
<th>Step</th>
<th>Molecular Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD-2</td>
<td>Rolling</td>
<td>Sialyl Lewis X Carbohydrate</td>
</tr>
<tr>
<td>LAD-1</td>
<td>Adhesion</td>
<td>Integrin expression</td>
</tr>
<tr>
<td></td>
<td>Phagocytosis</td>
<td></td>
</tr>
<tr>
<td>Chediak-Higashi Syndrome</td>
<td>Migration</td>
<td>Vacuolar sorting protein (large granules interfere with traversing endothelial wall)</td>
</tr>
</tbody>
</table>
## Diseases with Neutrophil Defects

<table>
<thead>
<tr>
<th>Disease</th>
<th>Step</th>
<th>Molecular Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGD</td>
<td>Oxidative burst</td>
<td>NADPH oxidase</td>
</tr>
<tr>
<td>Myeloperoxidase Deficiency</td>
<td>Oxidative burst</td>
<td>HOCl Production</td>
</tr>
</tbody>
</table>
Monocyte-Macrophages

- Monocytes: circulating precursor of the tissue macrophage.
- Also known as the reticuloendothelial system
- Average count 300 cells/µl
- Range 0-800 cells/µl
Monocyte Differentiation

- Proliferation: 30-48 hours
- Maturation: 24 hours
- Intravascular: 72 h
- Tissue: Differentiation into Macrophages

Bone Marrow

Source Undetermined
Function of Monocytes and Macrophages

Antigen presentation of phagocytized particles to T Cells

Cytokines/chemokines
Monocyte Function

Follow neutrophils to sites of inflammation within 12-24h
Number 1/30th that of neutrophils
Pts w/ CGD, CHS and LAD also have defects in monocyte fxn
Disturbances in Monocytes

• Low counts
  – glucocorticoids
  – stress

• Elevated counts
  – Malignancy
  – Granulomatous disease
  – Marrow recovery
  – Infections
    • malaria
    • TB
    • Rocky Mountain Spotted fever
    • leishmaniasis
    • brucellosis
Eosinophils

Proliferation

Maturation

Intravascular

Tissues

9 days

2.5 days

3-8 hours

Bone Marrow

Myelocyte

Eosinophil

Source Undetermined (Both Slides)
Eosinophil Function

- Bright red granules
- IgE on cell surface (not on neutrophils)
- Play a key role in killing parasites
- Average absolute count 200/µl
- Non allergic individuals usually <400/µl
Eosinophilia

• **Conditions:**
  – **Neoplasm** (Hodgkin’s disease, lymphoma other tumors)
  – **Allergies**—drugs, environmental (grass, trees, dust)
  – **Asthma**
  – **Collagen vascular diseases**—vasculitis
  – **Parasitic infection**

• **Idiopathic hypereosinophilia:** elevated eosinophil count associated with organ dysfunction (GI, skin, CNS, cardiovascular).
  – > 5000/µl requires treatment with immunosuppressives and antihistamines
Maturation of Basophils and Mast Cells

Intravascular Tissues

Proliferation

Maturation

2.5 days

7 days

days

Basophil

Mast Cell

Proliferation

Maturation in Tissues

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Basophil Function

• Basophils and mast cells
  – Function remains obscure but may play a role in host defense against certain parasites
Disturbances in Basophil Count

- Low count
  - hypersensitivity
  - glucocorticoids

- High count
  - Allergies
  - infection
  - endocrinopathies
  - myeloproliferative disorders
  - Systemic mastocytosis
    - symptoms due to excess histamine release
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