A Practical Approach to Leukopenia/Neutropenia in Children

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Disclosures

• EPIC trial → MAST Therapeutics
• SUSTAIN trial → Selexys Pharmaceuticals
• Neither relevant to this presentation
• No off label medication discussions
Objectives

• To describe the initial steps in the evaluation and management of a child with neutropenia

• To summarize the differential diagnosis of a child with leukopenia/neutropenia
Overview

• Define leukopenia and neutropenia
• Discuss the differential diagnosis of neutropenia
• Review key points of the history and physical examination when evaluating a child with neutropenia
• Provide a framework for ordering tests in a child with neutropenia
• Briefly review the management of neutropenia
• Define and discuss the differential diagnosis of lymphopenia
Case

- 2 year old WM seen for a WCC
- Recent viral illness/URI
- No clinical concerns
- Labs obtained that showed an ANC of 300/mm$^3$
Definition of Leukopenia

- Normal WBC count 5-15K
- Total WBC count less important than the differential
- What is the ANC and ALC
Neutropenia
Absolute neutrophil count $<1500/mm^3$

<table>
<thead>
<tr>
<th>Category</th>
<th>ANC*</th>
<th>Infection risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1000-1500</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>500-1000</td>
<td>Minimal</td>
</tr>
<tr>
<td>Severe</td>
<td>$&lt;500$</td>
<td>Moderate to Severe (Highest if $&lt;200$)</td>
</tr>
</tbody>
</table>

- Recurrent bacterial or fungal infections are the hallmark of symptomatic neutropenia!

*ANC = WBC X % (PMNs + Bands) / 100
How to approach neutropenia

- Normal vs. abnormal
- Malignant vs. non-malignant
- Congenital vs. acquired
- Is the patient symptomatic
- Transient, recurrent, cyclic, or persistent
How to approach neutropenia

• Adequate vs. decreased marrow reserve
• Decreased production vs. increased destruction/sequestration
Decreased neutrophil production

• Primary
  – Malignancy/leukemia/marrow infiltration
  – Aplastic anemia
  – Congenital marrow failure syndromes

• Secondary
  – Infectious
  – Drug-induced
  – Nutritional
    • B12, folate, copper
Increased neutrophil destruction/sequestration

- Immune-mediated
- Drug-induced
- Hypersplenism
- Pseudo-neutropenia
Congenital marrow failure syndromes

- Severe congenital neutropenia/Kostmann’s syndrome
  - Severe neutropenia and recurrent infections
  - Inheritance: AD, AR, or sporadic
  - Genetics: ELA2/ELANE, HAX-1, and others

- Shwachman-Diamond syndrome
  - Triad of neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities
  - May also have neutrophil dysfunction
  - Inheritance: AR
Congenital marrow failure syndromes

- Cyclic neutropenia
  - AD inheritance
  - Neutrophil elastase gene
  - Prevalence: 1 per million
  - Really cyclic hematopoiesis
  - Cycles 14-28 days (average 21 days)
  - Neutropenia lasts 3-5 days
  - 10% patients develop life-threatening infections
Typical Cyclical Pattern
Infection associated neutropenia

- Most common cause of neutropenia
- Typically viral infections
  - EBV, CMV, RSV, Influenza, HIV
- Resolves in a few days to months
- Multiple mechanisms
  - Increased utilization/margination
  - Marrow suppression
  - Antibody production/immune-mediated
Immune-mediated neutropenias

• Benign neutropenia of infancy/childhood
  – Affects 1 in 100,000 children between infancy and 10 years of age
  – Most common between 3 and 30 months of age
  – Median duration of neutropenia is 30 months
  – 95% of children recover by 4 years of age

• May be associated with other autoimmune disorders, especially in adolescents

• Generally not associated with an increased risk of infection
Autoimmune Neutropenias

### Table 1. Infections Present at the Time of Diagnosis

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of Events</th>
<th>Percentage of Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infections</td>
<td>49</td>
<td>19</td>
</tr>
<tr>
<td>Otitis media</td>
<td>44</td>
<td>17</td>
</tr>
<tr>
<td>Pyodermia</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Abscess</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Lymphadenitis colli</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Urogenital infections</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Phlegmonia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The total number of events is 260.

Bux et al, Blood 1998
Neonatal neutropenias

• Immune-mediated
  – Alloimmune neonatal neutropenia
  – Neonatal autoimmune neutropenia
  – Autoimmune neutropenia of infancy

• Placental insufficiency/PIH

• Congenital infections (TORCH)

• Necrotizing enterocolitis
History

• Recurrent or unusual infections
  – bacteremia, pneumonia, skin (cellulitis/abscess)
• Recurrent or recent fevers
• Growth
• Aphthous ulcers
• Periodontal disease
• Bone or extremity pain
• Rashes/petechiae
• Abdominal pain
• Family history of neutropenia
Physical Exam

• Potential red flags
  – Fever or ill-appearance
  – FTT or dysmorphic features
  – Lymphadenopathy (nodes > 1-2 cms in size)
  – Periodontal disease, aphthous ulcers, or oral lesions
  – Skin changes (don’t forget the fingernails)
  – Organomegaly
  – Arthritis
  – Abnormal bruising/petechiae
  – Pallor/jaundice
Dyskeratosis congenita
Laboratory Evaluation

• CBC with differential
  – Hgb/Hct and platelet counts
  – Don’t forget about the MCV

• CMP

• Peripheral blood smear

• Quantitative immunoglobulins

• Anti-neutrophil antibody screen
  – Does not rule out autoimmune neutropenia
Additional Tests

• Leukemia
  – LDH, uric acid, CXR

• Bone marrow failure syndromes
  – Hgb electropheresis (Fetal Hgb), skeletal survey, fecal elastase

• Autoimmune
  – ANA, anti-DNA abs, C3/C4

• Viral titers
  – EBV, CMV
Management of Neutropenia

- Depends on the clinical situation and underlying diagnosis
- Often no specific management is required
- Consider G-CSF for certain diagnoses or recurrent infections
- Conservative fever management
- Follow-up is important
- Periodontal management
Management of fever in the setting of neutropenia

• Largely dependent upon age, etiology, severity of neutropenia, and patient’s history of infections

• Get input from Hematology

• Fever > 101 F and ANC < 500/mm$^3$
  – CBC with differential and blood cultures
  – Empiric, broad-spectrum antibiotics
  – Treat any source (cellulitis, pneumonia, etc.) appropriately
Lymphopenia

- Absolute lymphocyte count (ALC) = WBC X % (lymphocytes) / 100
- Normal values are age dependent
  - Adults have a mean ALC of 1,800/mm$^3$
  - Higher ALCs in infants (mean 6,700/mm$^3$)
- Generally, less than 1,000/mm$^3$ is abnormal
  - ALC < 1,000-2,000/mm$^3$ in an infant < 2 months of age is highly abnormal
Differential Diagnosis of Lymphopenia

- Decreased production vs. increased destruction
- NOT A T-CELL
- Normal variant/no disease, occult carcinoma, TB/infections, AIDS/immunodeficiency, thoracic duct drainage/chylothorax, cytotoxic drugs/chemotherapy, eating disorders/malnutrition, lymphoma, lupus/autoimmune
- Infant with lymphopenia, FTT, chronic diarrhea, rash → think SCID
Case

• 2 year old WM seen for a WCC
• Recent viral illness/URI
• No clinical concerns
• Labs obtained that showed an ANC of 300/mm$^3$
• Hb, PLTs, and MCV normal for age
Case

• Review history and physical exam including growth curve → call if red flags!!!
• Is there a history of recurrent or unusual infections → refer if yes
• Review prior labs → refer if recurrent and severe
• If no to above, would continue to monitor
• Repeat CBC in one week, sooner if febrile
Case Follow-up

- Neutropenia resolved ➞ continue WCC
- Neutropenia persistent ➞ consider further work-up or referral
- Can start with a neutrophil ab screen and review of the peripheral blood smear
- Refer if neutropenia persists > 1 month in the absence of documented etiology
Additional Reading


• Nathan and Oski’s Hematology of Infancy and Childhood, 7th Ed. Orkin et al, editors. Chpt. 21 – Phagocyte system and disorders of granulopoiesis and granulocyte function