LEUKOCYTOSIS
AND LEUKOPENIA

Nancy Berliner, M.D.
Chief, Division of Hematology
Brigham and Women’s Hospital
Intensive Review of Internal Medicine
I have no financial relationships to disclose. 

AND

I will NOT include discussion of off-label or investigational use of any products in my presentation.
Nancy Berliner, M.D.

H. Franklin Bunn Professor of Medicine
Chief, Division of Hematology, BWH

Yale Medical School
Residency and Chief Residency at BWH
Hematology Fellowship at BWH

Editor-in-Chief, Blood
Objectives

Use a series of cases to:

• Review the approach to the patient with neutrophilia
• Review the approach to the patient with neutropenia
A 43-year-old woman with elevated WBC

Previously healthy woman seen for routine office visit is noted to have a WBC 12K, with normal differential. Repeated three weeks later- no change.
Hct 42; Plts 230K
LEUKOCYTOSIS: DIFFERENTIAL DIAGNOSIS

SECONDARY TO OTHER ILLNESSES
   Infection
      Acute: Demargination/release storage pool
      Chronic: Granulomatous dx (leukoerythroblastic)
   Stress
   Drug-induced (steroids, β-agonists, lithium)
   Chronic inflammation
   Post-splenectomy
   Non-hematologic malignancy
   Marrow stimulation (ITP, hemolysis, CMT)

PRIMARY HEMATOLOGIC DISEASE
   CML
   Other MPD
Neutophilia is usually reactive, indicative of a normal functioning bone marrow. Bone marrow evaluation is often unnecessary.

- Repeat WBC to R/O factitious or artifactual elevation
- Evaluation for acute/chronic infection or inflammation
- LAP score—of limited value since bcr-abl testing available
- FISH for bcr-abl
- Bone marrow exam: r/o granulomatous dx, fungus
A 1-month-old boy with elevated WBC

1 month old infant with delayed umbilical cord separation
High grade fever, MRSA infection, and WBC of 90,000
Poorly healing skin lesions, otitis, failure to thrive
Poor response to antibiotics
What to do??

Adapted from Pediatr Transplantation 11:453-5, 2007
LEUKOCYTOSIS: DIFFERENTIAL DIAGNOSIS

PRIMARY HEMATOLOGIC DISEASE

Congenital
- Hereditary neutrophilia
- Down’s sx
- Leukocyte Adhesion Deficiency
Pathogenesis:

Defective integrin receptor common β chain of integrin receptors (LAD I)

Loss of expression of LFA-1, Mac-1 (C3bi receptor), and gp150;95.

Results in inability to ingest and kill microbes opsonized by C3bi

Can also arise by an abnormality of selectin glycosylation that impairs leukocyte adhesion (LAD II)

<table>
<thead>
<tr>
<th>β2 Integrins</th>
<th>Present</th>
<th>H1 Absent</th>
<th>Defective</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectin ligand (PSGL-1)</td>
<td>Present</td>
<td>Normal</td>
<td>Normal</td>
<td>Defective</td>
</tr>
</tbody>
</table>
Clinical manifestations:
- elevated WBC
- recurrent infections, mainly cutaneous abscesses, gingivitis
- Many die before age 2

Treatment:
- Stem cell transplant: treatment of choice (performed on the patient described here)
- G-CSF has been tried experimentally
NEUTROPENIA

The Textbook:

>1500 Normal

1000-1500 May be normal; no significant increased infection

500-1000 Some increased risk of infection; fever mx as outpt

<500 Significant risk of infection; fevers managed w/ iv abx as inpatient; often few signs of infection

The Patient

<500 Significant risk of infection in patient with *acute* neutropenia
Most don’t get into trouble until the count is < 200.

*In chronic neutropenia, patients frequently have little or no manifestations of neutropenia with counts of 50-100*
NEUTROPENIA: DIFFERENTIAL DIAGNOSIS

CONGENITAL NEUTROPENIAS

Benign neutropenia
   Constitutional neutropenia
   Benign neutropenia (familial, idiopathic)

Congenital
   Severe congenital neutropenia, including Kostmann’s syndrome

Cyclic neutropenia

Other rare disorders
   Chediak-Higashi
   Schwachmann-Diamond
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Gene (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic neutropenia Normal Duffy A-B- WBC</td>
<td>?</td>
<td>DARC SNPS</td>
</tr>
<tr>
<td>Benign familial neutropenia</td>
<td>AD</td>
<td>Unknown</td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>AD</td>
<td>ELANE (55-60%)</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>HAX1 and G6PC3 (&lt;5%)</td>
</tr>
<tr>
<td></td>
<td>X-linked</td>
<td>WASP (&lt;5%)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Unknown (40%)</td>
</tr>
<tr>
<td>Cyclic neutropenia</td>
<td>AD</td>
<td>ELANE (95-100%)</td>
</tr>
<tr>
<td><strong>Immunodeficiency Syndromes Associated with Neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwachman-Diamond Syndrome</td>
<td>AR</td>
<td>SBDS (100%)</td>
</tr>
<tr>
<td>Fanconi Anemia</td>
<td>AR and X-linked</td>
<td>FANC A-P genes</td>
</tr>
<tr>
<td>Dyskeratosis Congenita</td>
<td>X-linked</td>
<td>DKC1 (80%)</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>TERC (0-20%)</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>TERT (0-20%)</td>
</tr>
<tr>
<td>Glycogen storage disease Ib</td>
<td>AR</td>
<td>SLC37A4 (100%)</td>
</tr>
<tr>
<td>Myelokathexis</td>
<td>AD</td>
<td>CXCR4 (100%)</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>AR</td>
<td>LYST (100%)</td>
</tr>
<tr>
<td>Griscelli syndrome II</td>
<td>AR</td>
<td>RAB27A (100%)</td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome II</td>
<td>AR</td>
<td>AP3B1 (100%)</td>
</tr>
<tr>
<td>Cartilage-hair hypoplasia</td>
<td>AR</td>
<td>RMRP (100%)</td>
</tr>
</tbody>
</table>
Congenital agranulocytosis

- rare
- autosomal dominant, recessive, and sporadic cases reported.
- severe infections; survival dramatically changed by treatment with G-CSF
- high incidence (30% over 10 years) of evolution to AML.
SEVERE CONGENITAL NEUTROPENIA

**Autosomal dominant form of SCN:**

- linked to mutations in the neutrophil elastase gene (ELANE)
- Mutant ELANE accumulates in the cytoplasm, and activates the “unfolded protein response,” a cellular stress response that results in apoptosis
- AML associated with a truncation mutation of the G-CSF receptor of uncertain pathogenetic significance

**Autosomal recessive SCN:**

- Kostmann’s Syndrome: syndrome described 50 years ago
- Linked to mutations in HAX1, a mitochondrial protein associated with signal transduction
- Disruption of HAX1 in myeloid cells destabilizes the mitochondrial membrane and leads to apoptosis
CYCLIC NEUTROPENIA

Dominantly inherited disorder
- cycle of neutropenia q 15-35 days
- marrow during neutropenia: myelocyte arrest
- Usually benign; patients with severe infections may require G-CSF

Like autosomal dominant SCN, cyclic neutropenia has been linked to mutations in elastase

ELANE (ELA2) mutations found in essentially 100% of cyclic neutropenia

NOT associated with an increased risk of AML
Primary AIN:
- Seen primarily in children
- Associated with abs against common ags

Secondary AIN
- Seen primarily in adults
- Associated with AID
- Associated with LGL
- Associated (rare) with leukemia/lymphoma
A disease of childhood caused by $\alpha$-neutrophil antibodies

- Average age of onset: 6-12 months
- Moderate to severe neutropenia
- Spontaneous remission over 2 yrs: 95%
- Treatment: Prophylactic antibiotics; G-CSF only with severe/recurrent infection
Occurs in approximately 50% of SLE patients

- Marker of disease activity
- Little impact on the course of the disease
- Infectious complications correlate with immunosuppressive therapy rather than height of neutrophil count

**Pathophysiology:**

- Neutrophil-specific antibodies
- Immune-complex mediated destruction
- Increased apoptosis of neutrophils
- Decreased marrow neutrophil production
Felty’s syndrome
- Typically in patients with longstanding RA
- Associated with end-organ RA manifestations (pulmonary fibrosis, vasculitis, rheumatoid nodules, Sjogren’s syndrome)
- Splenomegaly
- Considerable morbidity from bacterial infection

LGL-associated neutropenia
- Shares many features with Felty’s syndrome
- Monoclonal neoplastic disorder, while Felty’s traditionally is polyclonal

Both have a very high (90%) incidence of HLADR4, suggesting they are a spectrum of the same disease
False positive results

- abundant Fc receptors on neutrophils
  - high circulating antibody
  - circulating immune complexes
- spontaneous fluorescence of neutrophils
- spontaneous aggregation of neutrophils
- fragility, with spontaneous lysis

Effect on outcome remains undefined

- no “gold standard”
- non-neutropenic populations often have detectable antibody
- poor correlation between level of antibody and degree of neutropenia
WHEN DO I CHECK ANTI-WBC ABS IN ADULTS w/ NEUTROPENIA?

NEVER
CASE PRESENTATION

65 yo man with sore throat and fever

PMH: chronic CHF and has been taking several cardiac drugs for 2 months

CBC: Hb 12; Plts 190K; WBC 0.7 with ANC 50

Drugs most commonly associated with DIA

| Anti-thyroid medications | Carbamizole  
|                          | Methimazole   
|                          | Thiouracil    
| Antibiotics              | Cephalosporins  
|                          | Penicillins   
|                          | Sulfonamides  
|                          | Chloramphenicol  
| Anticonvulsants          | Carbamazapine  
|                          | Valproic Acid  |
DRUG-INDUCED NEUTROPENIA

• Idiosyncratic drug reaction leading to profound neutropenia or agranulocytosis
• Pathogenesis poorly understood, and studies are difficult it is rare, sporadic, and transient

Anti-neutrophil antibodies
  Autoantibodies
  Drug-dependent antibodies
  Complement binding in some cases
  Graves’ disease: antibodies that cross-react with TSH

Unlike chronic neutropenia, DIN is associated with significant morbidity and a mortality of 10%
A 31-year-old woman referred for neutropenia

**HISTORY:**
Age 16:
- Episodic abdominal pain, fever, and vomiting
- After multiple episodes: dx appendicitis
- Symptoms resolved after appendectomy
Post-operatively, WBC fell to 2000 with an ANC of 500
Neutropenia has persisted ever since

**PMH:**
In retrospect: frequent upper respiratory illnesses as a child, including several episodes of pneumonia
1 year ago: begun on weekly G-CSF

**ROS:** LUQ pain, nausea and vomiting 1-2 days after taking G-CSF
NON-IMMUNE CHRONIC NEUTROPENIA

Chronic neutropenia

- Normal marrow cytogenetics; variable cellularity
- No evidence of autoimmune disease, nutritional deficiency, myelodysplasia
- Benign clinical course, often diagnosed on routine blood tests in asymptomatic patients
- Variable need for cytokine support

Pathophysiology

- NO IDEA!! Probably a heterogeneous disorder.
MANAGEMENT OF THE NEUTROPENIC PATIENT

Diagnostic
- Stop potential offending drugs
- Bone marrow aspiration/biopsy
- Serologic studies: ANA, viral titers, anti-neutrophil antibodies
- R/O Primary malignancy:
  - Chromosome analysis
  - Sucrose-hemolysis test; flow cytometry

Therapeutic
- Aggressive treatment of infections
- Immune neutropenia: steroids, IgG
- LGL: low dose MTX
- G-CSF: SCN, CH, recovery from drugs
- Stem cell transplant: SCN
TREATMENT OF NEUTROPENIA: G-CSF OR NO??

Responses to G-CSF documented in neonatal, primary and secondary immune, and NI-CINA

• Treatment is frequently unnecessary
• Reserved for recurrent or serious infections
• May cause flare of joint disease in setting of RA

Shortens the time to neutrophil recovery in drug-induced neutropenia/agranulocytosis

• Evidence-based data lacking: only randomized trial had only 24 patients, and used a subtherapeutic dose of G-CSF
• Meta-analyses & retrospective analyses suggest shorter time to WBC recovery, reduced cost, ? reduced mortality
• 10% mortality rate, safety and efficacy justify G-CSF use in this setting
“TAKE-HOME MESSAGES”

• Leukocytosis is usually reactive and the sign of a healthy bone marrow responding to external signals.

• Peripheral smear and PCR findings can usually provide clues to the less common primary marrow disorders associated with elevated neutrophils. Don’t miss CML!

• Neutropenia is more commonly a manifestation of a primary marrow problem, although autoimmune disease and sequestration both occur.

• Although rare, study of congenital neutropenia has provided key insights into neutrophil biology and AML.

• Acquired chronic neutropenia is usually benign although the pathophysiology is poorly understood.
A patient with hyperthyroidism is started on propylthiouracil. Six weeks later she comes to the emergency room with a fever of 102°F and a tonsillar exudate. CBC shows a WBC of 1500 with 5% neutrophils, with a normal with H/H and platelet count. The PTU is discontinued. Appropriate therapy should include:

A. Start the patient on amoxicillin and schedule her to return to clinic the following day for follow-up of his throat culture.
B. Admit the patient to the hospital and begin broad-spectrum antibiotics and G-CSF.
C. Start the patient on amoxicillin and admit for observation.
D. Admit the patient to the hospital and begin on broad-spectrum antibiotics.
QUESTION 1

• In the presence of a normal hematocrit and platelet count, acute development of a very low neutrophil count is essentially always related to drugs or toxins. This is true even in the setting of HIV, where there are many possible etiologies for neutropenia.

• This patient’s agranulocytosis is almost certainly induced by PTU, since it is one of the drugs most commonly associated with agranulocytosis. Her absolute neutrophil count is 75. She needs emergent treatment for her neutropenia with broad-spectrum antibiotics.

• The recovery of the WBC can be speeded by G-CSF. Although no controlled clinical trials have shown increased survival with G-CSF Rx, DIN is associated with high mortality. G-CSF is recommended to reduce the time to neutrophil recovery.
A 19-year-old Nigerian woman has recently emigrated to the US and has been accepted to college. She goes to have her pre-admission physical and her health forms at the University Health services. A CBC reveals neutropenia, and her physician advises her to wait to move into a dorm until she has seen you for evaluation. She is healthy with no history of infections, and has a completely negative past medical history. Her exam is normal. CBC shows: WBC 3400 w/ 30% neutrophils, Hct 41, Plts 200K. What should you advise her?

A. She should have a bone marrow to rule out a bone marrow process causing neutropenia
B. She should have serial blood counts to rule out cyclic neutropenia
C. She should move into the dorm without any further evaluation
D. She should have chromosome analysis of her peripheral blood
The normal neutrophil count is partially determined by ethnic background. African males frequently have a neutrophil count of 1000-1500, and African women may have counts that are even lower. Many may actually have counts below 1000. With a total neutrophil count of 1120, a normal hematocrit and platelet count, and an unremarkable history and physical, the patient should be diagnosed with “normal WBC in a Duffy A-B-individual.” This requires no further evaluation, and the patient should be reassured that these counts are normal for her and present no undue risk. She should matriculate in college as planned.
References

- Horwitz M, Benson KF, Person RE, Aprikyan AG, Dale DC. Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological clock in cyclic hematopoiesis. Nature Genetics 23:433, 1999