INHERITED NEUTROPENIAS

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Objectives

- Review neutropenia classifications
- Define chronic severe neutropenia
- Review diagnostic approach to neutropenia
- Categorize various congenital neutropenic syndromes
- Review various (not all) congenital neutropenic syndromes
- Review key disease characteristics of inherited neutropenic disorders
Why is this important?

- In polling a handful of recent graduates who took hematology boards they reported ~3-4 questions about this topic was on their boards (also on in-service)
How this talk is going to go...

- Bolded in red are genes that are associated with each disease
- Bolded in purple are things are that are important or unique to that particular disease
- I recognize this is not the most exhilarating talk and it is 7AM so...
Neutropenia Classification

- **Children** (age 2 months to 12 months): lower limit of normal is ANC of 1000 and after 12 months increases to 1500

- **Adults:**
  - *Mild Neutropenia: 1000-1500*
  - *Moderate Neutropenia: 500-1000*
  - *Severe Neutropenia: < 500*

- Note: lower values may exist for those of African descent
  - Duffy-Antigen Receptor Chemokine (DARC): thought a productive mechanism against malaria however uncertain of effects on PMN
Chronic Severe Neutropenia

- Definition:
  - ANC < 500 for > 3 months
  - Checked several times (at least three times)

- Risk:
  - Severe pyogenic infections
Table 1. Diagnostic approach to neutropenia etiologies

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Associated clinical diagnoses</th>
</tr>
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<tbody>
<tr>
<td><strong>Initial evaluation</strong></td>
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<tr>
<td>History of acute or chronic leukopenia</td>
<td>Congenital syndromes (see Table 3)</td>
</tr>
<tr>
<td>General medical history</td>
<td></td>
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<tr>
<td>Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies</td>
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<tr>
<td>Spleen size</td>
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<tr>
<td>History of drug exposure</td>
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<tr>
<td>CBC with differential and reticulocyte counts</td>
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<tr>
<td><strong>If ANC &lt; 1000/μL</strong></td>
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<tr>
<td>Evaluation of acute onset neutropenia</td>
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<tr>
<td>Repeat blood counts in 3-4 weeks</td>
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<td>Serology and cultures for infectious agents</td>
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<tr>
<td>Complement activation</td>
<td></td>
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<tr>
<td>Discontinue drug(s) associated with neutropenia</td>
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<tr>
<td>Test for antineutrophil Abs</td>
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<tr>
<td>Measure quantitative Igs (IgG, IgA, and IgM), lymphocyte subsets</td>
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<tr>
<td><strong>If ANC &lt; 500/μL on 3 separate tests</strong></td>
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<tr>
<td>BM aspiration and biopsy with cytogenetics</td>
<td>SCN</td>
</tr>
<tr>
<td>Serial CBCs (3/week for 6 weeks)</td>
<td>Cyclic neutropenia</td>
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<tr>
<td>Exocrine pancreatic function</td>
<td>Shwachman-Diamond syndrome</td>
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<tr>
<td>Skeletal radiographs</td>
<td>Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia</td>
</tr>
<tr>
<td><strong>If absolute lymphocyte count &lt; 1000/μL</strong></td>
<td></td>
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<tr>
<td>Repeat blood counts in 3-4 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>If ALC &lt; 1000/μL on 3 separate tests</strong></td>
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</tr>
<tr>
<td>HIV-1 Ab test</td>
<td>Transient leukopenia (eg, viral)</td>
</tr>
<tr>
<td>Quantitative Igs (IgG, IgA, and IgM) and lymphocyte subsets</td>
<td>HIV-1 infection, AIDS</td>
</tr>
<tr>
<td><strong>If there is pancytopenia</strong></td>
<td>Congenital (see Table 3) or acquired disorders of immune function</td>
</tr>
<tr>
<td>BM aspiration and biopsy</td>
<td>BM replacement by malignancy, fibrosis, granuloma, storage cells</td>
</tr>
<tr>
<td>BM cytogenetics</td>
<td>Myelodysplasia, leukemia</td>
</tr>
<tr>
<td>B12 and folate levels</td>
<td>Vitamin deficiencies</td>
</tr>
<tr>
<td>Cytometry for PI-linked proteins</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>TCR rearrangement</td>
<td>LGL leukemia often associated with Fehley syndrome</td>
</tr>
</tbody>
</table>
Congenital Neutropenia Syndromes

Granulopoiesis
1. Reticular Dysgenesis
2. Cyclic Neutropenia
3. Severe Congenital Neutropenia
4. Kostmann Disease

Ribosomal Dysfuntion
1. Shwachman-Diamond
2. Dyskeratosis Congenital

Metabolism
1. Barth Syndrome
2. Glycogen Storage Disease Type 1b
3. Pearson’s Syndrome

Vesicular Transport
1. Chediak-Higashi Syndrome
2. Cohen Syndrome
3. Griscelli Syndrome Type II
4. Hermansky-Pudlak Syndrome Type II
5. P14 Deficiency

Adapted from: Boxer, How to approach neutropenia, Hematology 2012)
Granulocytopoiesis
A 3-month-old male infant is hospitalized for his third serious bacterial infection. His absolute neutrophil count has been persistently below 200 cells/μL, and the remainder of the complete blood count is within normal ranges except for variably elevated monocyte counts. Bone marrow evaluation shows a normocellular marrow with maturation arrest at the promyelocyte stage. Bone marrow cytogenetic analysis shows a normal male karyotype. Which of the following medications is most appropriate for this patient?

A: Interferon-α
B. Intravenous immunoglobulin
C. Prednisone
D. Recombinant granulocyte colony-stimulating factor
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Severe Congential Neutopenia (SCN)

- **Definition**: umbrella term of varying inheritance patterns (AR and AD) that have ANC consistently below 200 with recurrent severe infections
- **Incidence**: 2-3 per million and usually Caucasian
- **Bone Marrow**: shows a myeloid maturation arrest at the promyelocyte-myelocyte stage
- **Infections**: chronic gingivitis, oral ulcers, skin abscesses, recurrent pneumonias
- **Mutations**: ELANE mutations found in 40-60% (rare others GFI1, G6PC3)
- **Associations**: ~25% at 25 years with leukemia and MDS requiring quarterly CBC and annual bone marrow evaluations
- **Treatment**: more than 90% response to G-CSF with increased PMNs and decreased infections however can get mutations in G-CSF receptor rendering decreased response
Kostmann Disease

- **Definition**: type of severe congenital neutropenia that is autosomal recessive
- **Mutation**: HAX1 deficiency
  - **Pathophysiology**: encodes a mitochondrial protein and when deficient causes decreased in cellular membrane potential and accelerated cell apoptosis
- **Associations**:
  - MDS/AML per previous slide
  - Cognitive Disorders
Cyclical Neutropenia

- **Incidence**: 0.6/1,000,00
- **Inheritance**: autosomal-dominance
- **Mutation**: ELANE or ELA-2 (usually exon 4 and 5)
  - Mutation in gene for neutrophil elastase
- **Presentation**:
  - Regular oscillations of peripheral PMN counts with severe neutropenia lastly 4-6 days every 21 days
  - During periods of neutropenia can get painful mouth sores, fever, and bacterial infection
- **Lab**: serial CBC at least 3 per week over a 6 week periods to observe two nadirs which helps differentiate from severe congenital neutropenia (SCN)
- **Association**: unlike SCN is not associated with increase leukemia or MDS
Figure 1. Pattern in a patient thought to have cyclic neutropenia compared with an individual with classic cyclic neutropenia. (Left) ANC and absolute monocyte count in a patient with congenital neutropenia over time. (Right) ANC and absolute monocyte count in a patient with cyclic neutropenia over time.
Reticular Agenesis

- **Definition**: complete failure of myeloid and lymphoid development which leads to severe leukopenia, defective cellular and humoral immunity, and absent lymphoid tissues
  - *Note: erythroid and megakaryocyte development is normal*
  - *One of rarest and most severe forms of SCID (severe combined immunodeficiency)*

- **Mutation**: *Adenylate Kinase 2 (AK2 gene)*

- **Treatment**: hematopoietic stem cell transplantation
Ribosomal Dysfunction
A 12-month-old girl is referred for evaluation of neutropenia that has persisted over the past 2 months. She has had no infections but has a history of chronic diarrhea and failure to thrive, which are under evaluation by her pediatrician. Other than her short stature and low weight, the physical examination is normal. Laboratory values include the following:

**CBC:** WBC: 5.1, Hgb 10.6, Plt 442 (4% PMN, 85% Lymph, 10% Mono)

**Liver:** AST/ALT: 183/248; T bil: 0.3

**Trypsinogen** < 1.2

**Bone Marrow:** Evaluation of a bone marrow aspiration and biopsy specimen shows a cellular marrow with maturing trilineage hematopoiesis with granulocytic left shift and mild to moderate dysgranulopoiesis with decreased granulation and abnormal nuclear segmentation. **Vacuolization is not observed.**

**Which of the following analyses is most likely to yield a molecular diagnosis?**

A: ELANE Gene Sequence

B. FANCA Gene Sequence

C. Mitochondrial Genome Analysis

D. SBDS Gene Sequence
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Shwachman-Diamond Syndrome (SDS)

- **Inheritance:** autosomal recessive
- **Presentation** (multi-organ):
  - *Neutropenia* (ANC < 1,000 in 2/3’s of patients)
  - *Pancreatic Exocrine Insufficiency* (worse in early infancy)
  - *Short Stature*
  - *Metaphyseal Dysplasia* (50%)
    - Rib-cage defects, clinodactyl, syndactyly, kyphosis, and osteopenia
- **Risk:**
  - a) Progressive Bone Marrow Failure
  - b) AML
  - c) MDS
- **Mutation:** **SBDS (90%)**
  - *Issues with ribosomal RNA (60S subunit)*
- **Treatment:**
  - a) pancreatic enzyme supplement
  - b) G-CSF if having infections
  - c) CBC to watch for MDS/AML
  - d) uncertain role of HSCT at this time
- **Pearls:** MDS/AML (15-25%) and treated with conventional therapy fail to regain normal hematopoiesis thus treatment is often allogeneic SCT. Males are 3:1 more like to progress/transform to AML

Images from Washington University at Saint Louis
A 12-year-old boy presents for evaluation of moderate thrombocytopenia and neutropenia. He has an unremarkable personal history, although his family history is notable for idiopathic pulmonary fibrosis in his maternal grandfather, diagnosed at the age of 50 years, and myelodysplastic syndrome in his maternal aunt, diagnosed at age 32. His mother has not seen a physician but recalls that she has been told she has blood count abnormalities. Physical examination of the boy shows reticulated skin hyperpigmentation, most notable on his upper chest and neck, and a few fingernails that appear dystrophic. Which of the following tests will establish the underlying diagnosis in this patient?

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B. Chromosome breakage analysis  
C. High-resolution karyotype  
D. Skin punch biopsy  
E. Telomere length testing
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B. Chromosome breakage analysis
C. High-resolution karyotype
D. Skin punch biopsy
E. Telomere length testing
Dyskeratosis Congenita

- **Classical Presentation**: triad of (1) abnormal skin pigmentation (2) nail dystrophy (3) oral leukoplakia
  - Additional: epiphoria, developmental delay, lung disease, esophageal webs, hair and tooth loss
- **Hematological**: pancytopenia is hallmark with average age of 10 and ~50% develop aplastic anemia which often precedes the classic triad and leads to death in 2/3’s of patients
- **Mutation**:
  - **DKC1** (X-linked-both recessive and dominant): encodes the nucleolar protein dyskerin that in turn results in ribosomal dysfunction; accounts for about 50% of cases
  - **TERT or TERC** (autosomal dominant): mutation in telomerase components and accounts for about 10% of cases
- **Treatment**: (a) anabolic steroid—danazol—can produce improvement and 2/3s will respond (b) BMT (increased mortality/morbidity than other bone marrow failure)
- **Pearls**: increased risk MDS, AML, and **squamous cell carcinomas**
Clinical characteristics of dyskeratosis congenita

Expert Reviews in Molecular Medicine ©2004 Cambridge University Press

Figure 1. Clinical characteristics of dyskeratosis congenita. Dyskeratosis congenita (DC) is characterised by a triad of cutaneous features and is also associated with many additional clinical features (Table 1). A selection of these features are shown in this 32-year-old X-linked recessive DC patient: abnormal skin pigmentation (a, b, c), premature greying of hair (a), leukoplakia (d), premature loss of teeth (d), and nail dystrophy (e, f).
Disorders of Metabolism
Pearson’s Syndrome

- **Issue:** *large deletions in mitochondrial DNA* and likely leads to impaired hematopoiesis through activation of capases and accelerated apoptosis

- **Presentation:** fatal congenital disorder involving the *pancreas*, liver, kidneys, and hematopoietic system
  - *Macrocytic anemia presents in infancy often with neutropenia and/or thrombocytopenia*

- **Bone Marrow:** normal cellularity but with *striking vacuolization of erythroid and myeloid precursors*, hemosiderosis, and ringed sideroblasts

- **Pearls:** often die in infancy
Bone marrow from a patient with PS. Left: vacuoles in myeloid precursors; right: a ringed sideroblast. See Figure 1E in the article by Gagne et al that begins on page 437.
Glycogen Storage Disease Type 1b (von Gierka Disease)

- **Issue**: inborn disorder of metabolism caused by inherited defects of the glucose 6-phosphatase complex (chromosome 11)

- **Presentation**:  
  - Hypoglycemia, hyperlactacidemia, hyperuricemia, hepatomegaly, growth retardation, osteopenia, enlarged kidneys, and neutropenia with neutrophil dysfunction (often ANC < 500)

- **Bone Marrow**: both myeloid hyper and hypo-cellularity have been reported

- **Etiology of Neutropenia**: PMNs have a striking tendency to undergo apoptosis in circulation

- **Treatment**: G-CSF reduces incidence of infection
Barth Syndrome

- **Inheritance**: X-linked recessive (thus nearly exclusive in males)
- **Mutation**: Tafazzin gene
- **Presentation**: cardiomyopathy, skeletal muscle weakness, neutropenia (ANC 500-1500), and growth retardation
- **Problem**: patient with reduced concentrations and altered composition of cardiolipin (a mitochondrial phospholipid) and etiology of neutropenia is not known
Disorders of Vesicular Transport
3 year female with fair skin and silvery hair is evaluated for recurrent bacterial infections and easy bruising. Medicine team calls you to review case and smear (below)

What disease do you suspect?
A: GATA 2 deficiency
B: Chediak-Higashi Syndrome
C: Congenital Amegakaryocytic Thrombocytopenia
D: WHIM Syndrome
What disease do you suspect?

- GATA 2 deficiency
- Chediak-Higashi Syndrome
- Congenital Amegakaryocytic...

WHIM Syndrome

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Chediak-Higashi Syndrome

- **Inheritance**: autosomal recessive
- **Issue**: defective intracellular granule movement
- **Presentation**: partial albinism, mild bleeding diathesis, peripheral neuropathy, predisposition to hemophagocytic syndromes after viral infection (i.e. EBV), mild neutropenia as well ineffective erythropoiesis
- **Mutation**: LYST (lysosomal trafficking gene) that encodes a protein necessary for vesicle transport
- **Treatment**: only curative therapy is HSCT
Figure 15-2 Photomicrographs of blood smears showing typical neutrophil morphology from (a) a healthy individual; (b) a patient with sepsis showing Döhle bodies (arrow) and toxic granulations; (c) a patient with Chédiak-Higashi syndrome showing large cytoplasmic inclusions.
Even more rare vesicular transport disorders
Cohen Syndrome

- **Inheritance**: autosomal recessive
- **Mutation**: COH1
- **Presentation**: developmental delay, facial dysmorphism (microcephaly), pigmentary retinopathy, and neutropenia
Griscelli Syndrome

- **Inheritance**: autosomal recessive
- **Mutation**: **RAB27a** which encodes a small GTPase involved in function of the intracellular-regulated secretory pathway
- **Presentation**: pigmentary dilution of skin, silver grey sheen of hair with large clumps of pigment at hair shaft
- **Labs**: mild neutropenia and unlike Chediak-Higashi syndrome do not have giant granules
- **Associations**: high risk of hemophagocytic syndrome
Hermansky-Pudlak Syndrome Type II

- **Inheritance:** autosomal recessive
- **Issue:** disruption of **adaptor protein 3 complex** (which plays a fundamental role in vesicle formation and in cargo selection in vesicular trafficking)
- **Presentation:** oculocutaneous albinism, platelet defects due to absences of platelet dense bodies, severe neutropenia with diminished neutrophil elastase
p14 Deficiency

- **Inheritance:** autosomal recessive
- **Presentation:** congenital neutropenia with ANC < 500, partial albinism, short stature, and B and T cell deficiency
- **Why is p14 needed?**
  - *Required for proper biogenesis of endosomes and the subcellular relocation of late endosomes*
Disorders of Immune Function
A 17-year-old man is referred for evaluation of chronic neutropenia. He has had recurrent fevers, multiple episodes of cellulitis, chronic sinusitis, and generalized *verrucae vulgar*es. Bone marrow examination demonstrates *hypercellularity and myelokathexis*. Other than the generalized warts, his physical examination appears normal. In which of the following genes is this patient likely to have a mutation?

A: CXCR4  
B. G6PC3  
C. GATA2  
D. DOCK8
Which of the following genes is this patient likely to have a mutation in?

- CACR4
- G6PC3
- GATA2
- CK8
A 17-year-old man is referred for evaluation of chronic neutropenia. He has had recurrent fevers, multiple episodes of cellulitis, chronic sinusitis, and generalized verrucae vulgares. Bone marrow examination demonstrates hypercellularity and myelokathexis. Other than the generalized warts, his physical examination appears normal. In which of the following genes is this patient likely to have a mutation?

A: CXCR4  
B. G6PC3  
C. GATA2  
D. DOCK8
WHIM Syndrome

- **Inheritance:** rare autosomal dominant
- **Presentation:** moderate to severe peripheral neutropenia with neutrophil hyperplasia in bone marrow with degenerative changes in PMNs with cytoplasmic vacuoles and prominent granules.
  - Warts (1-2 decade of life), Hypogammaglobuleniemia, Infections, and Myelokathexis (retention of neutrophils on marrow)
- **Issue:** CXCR-4 mutation and as a result myeloid cells fail to be mobilized from bone marrow and thus undergo apoptosis
  - Mutation results in enhanced CXCR4 signaling
- **Treatment:** partially correction with G-CSF therapy and IVIG therapy
Bone marrow smear from a patient with neutropenia due to myelokathexis. There is an increased number of mature and hypersegmented neutrophils. The myelokathexis morphology is characterized by pyknotic nuclei with lengthening and thinning of intrassegmented filaments and vacuoles.

*Courtesy of Robert L Baehner, MD.*
Cartilage-Hair Hypoplasia

- **Inheritance**: autosomal recessive

- **Presentation**: short-limbed dwarfism, fine hair, immunodeficiency, hyper-extendable digits, and increase incidence of cancer. Moderate to severe neutropenia is seen

- **Mutation**: RMRPG gene (encodes the RNA component of ribonuclear protein ribonuclease)

- **Treatment**: may response to G-CSF
Hyper-IgM Syndrome

- **Inheritance**: X-linked recessive (most common), autosomal recessive
- **Gene**: CD40L
  - *Recall that CD40 ligand on T cells interacts with CD40 on B cells to induce class switching from IgM to IgG and IgA and thus get elevated IgM and deceased IgA and IgG*
- **Presentations**: infections, autoimmune disease and hepatic malignancies
  - *Neutropenia: seen most often in X-linked recessive and can be cyclic or episodic and uncertain of why*
Schimke Immuno-Osseous Dysplasia

- **Inheritance**: autosomal recessive
- **Presentation**: spondyloepiphyseal dysplasia, growth delay, proteinuria, renal failure, lymphopenia and neutropenia with defective cellular immunity
- **Mutation**: **SMARCAL1** Gene (swi/snf-related matrix-associated actin-dependent regulator of chromatin)
- **Treatment**: HSCT and neutropenia responds to GCSF in 40% of patient
Conclusions
<table>
<thead>
<tr>
<th>Diagnostic Feature</th>
<th>Disease</th>
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<tr>
<td>Oculocutaneous albinism, peripheral neuropathy, and large granules in WBC</td>
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<td>Warts</td>
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<td>Hypoglycemia, growth retardation, hepatomegaly</td>
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<tr>
<td>Short-limbed, short stature, hypoplastic hair</td>
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<tr>
<td>Skeletal myopathy, dilated cardiomyopathy</td>
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<tr>
<td>Hypotonia, microcephaly, mental retardation</td>
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</tbody>
</table>
References

- Bertuch, Alison and Dokal Indergeet. ASH SEP. Myeloid Disorders and Inherited Marrow Failure Syndromes (Chapter 15). 2017.
A 16-year-old boy presents to his doctor with a history of skin changes, nail abnormalities, and bruising. Following referral to the hematologist, examination shows he has significant nail dystrophy and reticulate skin pigmentation around the neck. Blood count reveals a nonsevere pancytopenia, and the BM cellularity is found to be markedly reduced. Peripheral blood chromosomal breakage analysis following exposure to DEB is normal. Subsequent tests, however, show he has very short telomeres and a missense mutation in the \textit{DKC1} gene, confirming a diagnosis of