The Maroon Bells
View from the Pine Creek Cookhouse
Bone Marrow Failure

- Final common endpoint rather than a distinct disease entity
  - Congenital, environmental, genetic influences
  - Starting point for investigation as to why it happened

- Congenital (constitutional) or acquired
  - Can present at any age, but inherited/constitutional usually present in childhood or young adulthood

- Single lineage or multiple lineages
  - Some initially single lineage but then progress into multilineage with pancytopenia and more extensive marrow hypoplasia
Bone Marrow Failure

- Important to consider constitutional syndromes
  - Treatment may differ, especially if the child goes to BMT
    - Radiation sensitivity
  - Many have increased risk of MDS, leukemias and/or solid tumors – will need surveillance
  - Early onset of abnormal blood/bone marrow findings, family history, dysmorphic physical findings, ethnicity may be helpful, often genetic or other testing (chromosomal breakage, telomere length) will be confirmatory
Inherited Bone Marrow Failure

- Most germline inherited disorders are single gene disorders, inheritance patterns vary
  - Autosomal recessive
  - Autosomal dominant
  - X-linked recessive

- Many have disease specific genetic mutations identified, although can be variable within any particular disease, and often not all genes/mutations known
Bone Marrow Failure

- Although peripheral blood changes may be present (high MCV for example), circulating cells usually have normal function.

- Many of the inherited syndrome have increased risk of MDS and/or acute leukemia:
  - Some have increased risk of solid tumors also.

- Variable genetic expressivity and penetrance within any given disorder.
Inherited Bone Marrow Failure

- Many patients have associated dysmorphic features or physical abnormalities (skeletal, others) identified in early infancy or at birth, but many patients will not necessarily have the obvious physical manifestations.
  - Some develop over time and may become more obvious in later childhood, young adulthood (dyskeratosis congenita).
  - Cytopenias, marrow failure may be first manifestation of the disorder.
Inherited Bone Marrow Failure

- If anemic, may have evidence of fetal type hematopoiesis
  - Macrocytosis
  - Increased Hgb F (F cells)
Fig. 1. Overlapping syndromes. The differential diagnosis for apparently acquired aplastic anemia includes paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and inherited bone marrow failure syndromes (IBMFS).
<table>
<thead>
<tr>
<th><strong>Table 2</strong> Features suggestive of inherited bone marrow failure syndromes (IBMFS) in a patient with pancytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
</tr>
<tr>
<td>Clinical history</td>
</tr>
<tr>
<td>- Failure to thrive</td>
</tr>
<tr>
<td>- History of cytopenia, easy bruising, frequent infections</td>
</tr>
<tr>
<td>- Malabsorption/maldigestion</td>
</tr>
<tr>
<td>- Developmental delay</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>- Family members with cytopenias, myelodysplastic syndrome, or leukemia</td>
</tr>
<tr>
<td>- Cancer of the breast, lung, esophagus, head and neck in multiple family members</td>
</tr>
<tr>
<td>- Pulmonary fibrosis, liver fibrosis, early osteoporosis</td>
</tr>
<tr>
<td>- Family members with congenital anomalies associated with IBMFS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>+FH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
</tr>
<tr>
<td>- Short stature, congenital anomalies, dysmorphologies</td>
</tr>
<tr>
<td>- Abnormal skin pigmentation, birth marks</td>
</tr>
<tr>
<td>- Nail abnormalities</td>
</tr>
<tr>
<td>- Limb (especially forearm) abnormalities</td>
</tr>
<tr>
<td>- Other skeletal abnormalities</td>
</tr>
<tr>
<td>- Renal and genitourinary abnormalities</td>
</tr>
<tr>
<td>- Cardiac abnormalities</td>
</tr>
<tr>
<td>- Eye abnormalities</td>
</tr>
<tr>
<td>- Cleft lip/palate</td>
</tr>
<tr>
<td>- Hair or teeth abnormalities</td>
</tr>
<tr>
<td>- Developmental delay</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Abnormal PE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory workup</td>
</tr>
<tr>
<td>- Increased chromosomal breakage after exposure to cross-linking agents</td>
</tr>
<tr>
<td>- Very short telomere lengths in lymphocytes</td>
</tr>
<tr>
<td>- Macrocytosis</td>
</tr>
<tr>
<td>- Increased fetal hemoglobin</td>
</tr>
</tbody>
</table>
Bone Marrow Morphology in Bone Marrow Failure

- Features are often non-specific - hypoplastic marrow with decline in one or more cell lineages
- In general, no specific morphologic abnormalities other than the decrease in hematopoietic elements
- Clinical correlation and laboratory studies are key to establish the diagnosis
Inherited/Constitutional Causes: Multilineage

- Fanconi’s anemia
- Dyskeratosis congenita
- Congenital amegakaryocytic thrombocytopenia
- Shwachman-Diamond syndrome
- Some Diamond-Blackfan anemia
- Pearson marrow-pancreas syndrome
- Familial aplastic anemia
- Reticular dysgenesis
- Nonhematologic syndromes (Down’s, Dubowitz’, Seckel’s syndromes, familial HLH, metabolic storage disorders, osteopetrosis)
Acquired Causes: Multilineage

- Acquired aplastic anemia (often immune destruction of stem cells)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Radiation exposure, chemotherapy
- Idiosyncratic drug or toxin effect
  - Antibiotics: chloramphenicol, sulfonamides
  - NSAIDS: phenylbutazone, indomethacin
  - Anticonvulsants: felbamate, carbamazepine, phenytoin
- Infections
  - Hepatitis A, B, G
  - HIV
  - EBV, CMV
Acquired Causes: Multilineage

- Hepatitis associated
- Immune disorders (SLE, GVHD, transfusion associated GVHD, eosinophilic fasciitis)
- Pregnancy
- Bone marrow effacement
  - Primary/secondary neoplasm
  - Fibrosis (neoplastic or non-neoplastic)
- Nutritional deficiency (B12, folate)
- Myelodysplastic syndrome
Constitutional Single Lineage Disorders

- Diamond-Blackfan anemia
- Congenital dyserythropoietic anemia
- Congenital sideroblastic anemias
- Schwachman-Diamond syndrome
- Severe congenital neutropenia/Kostmann syndrome
- Cyclic neutropenia
- Thrombocytopenia with absent radii
Acquired Causes: Single lineage – Erythroids

- Viral infection (Parvovirus B19 – esp immune suppressed pts)
- Transient erythroblastopenia of childhood
- Neoplasm associated
  - Thymoma
- Immune related
- Iron deficiency anemia
- Anemia of chronic disease
- Idiosyncratic drug or toxin effects
- Other/idiopathic
Acquired Causes: Single lineage – Myeloids

- Drugs/ Medication related
- Infections
  - Viral: EBV, CMV, varicella, rubella, Thai hemorrhagic fever
  - Bacterial: meningococcus
- Toxin-related
- Levamisole-tainted cocaine
- Nutritional deficiencies
  - Megaloblastic anemia
Acquired Myeloid Production Problems

- Infiltration of the bone marrow (metastatic cancer, myelofibrosis)
- Other acquired toxic/ environmental/ immune causes
- Other/idiopathic
Meg/platelet Production Problems: Congenital

- Bernard Soulier syndrome
- May-Hegglin anomaly
- Fechtner syndrome
- Sebastian syndrome
- Epstein syndrome
- Montreal platelet syndrome
- Fanconi anemia
- Wiskott-Aldrich syndrome
- Thrombocytopenia with absent radii (TAR)
- Congenital amegakaryocytic thrombocytopenia
- Autosomal dominant & X-linked thrombocytopenia
Acquired Causes:
Single lineage – Megs

- Rare
- Medication effect
- Other/idiopathic
Acquired – Drugs Causing Marrow Suppression of Platelets

- Chemotherapy
- Zidovudine
- Ethanol – long periods of ingestion
- Interferon therapy
- Large doses of estrogen, or DES
- Anticonvulsants
- Tranquilizers
- Some antibiotics (chloramphenicol)
Case #1

16 year old girl with pancytopenia
Case #1 - Diagnosis

Bone marrow failure
(patient has very severe aplastic anemia)
Idiopathic Aplastic Anemia

- Frequency of 1-4/million
- Occurs in all age groups
- Hematopoietic stem cell failure
- Progressive pancytopenia
- Bone marrow hypoproliferation
- Other causes of secondary aplastic anemia due to marrow injury should be ruled out
  - Drugs/toxins
  - Radiation
  - Infections (including viral hepatitis)
## Etiology associated with AA

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Nutritional</th>
<th>Drugs</th>
<th>Chemical</th>
<th>Other associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis-associated, typically seronegative</td>
<td>Copper deficiency</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Benzene</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Vitamin B₁₂</td>
<td>Antibiotics</td>
<td>Insecticides</td>
<td>Inflammatory and autoimmune (e.g., systemic lupus erythematosus)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Folic acid</td>
<td>Anticonvulsants</td>
<td>Pesticides</td>
<td>Graft-versus-host disease</td>
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<tr>
<td>Parvovirus</td>
<td></td>
<td>Sulfonamides</td>
<td>Solvents</td>
<td></td>
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<tr>
<td>Mycobacterial infections</td>
<td></td>
<td>Gold salts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td></td>
<td>Idiosyncratic</td>
<td></td>
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</tr>
<tr>
<td>Human herpesvirus 6</td>
<td></td>
<td>Many additional agents rarely associated with aplastic anemia</td>
<td></td>
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</tr>
<tr>
<td>Varicella zoster virus</td>
<td></td>
<td>Chloramphenicol</td>
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<tr>
<td>Measles</td>
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<td></td>
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<tr>
<td>Adenovirus</td>
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<td></td>
<td></td>
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<tr>
<td>And others</td>
<td></td>
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</tbody>
</table>

Idiopathic                                      | Of unknown etiology, this term is increasingly replaced by “immune-mediated AA” |
Aplastic Anemia: Morphology

- Cellularity <25% of normal
- All cell lines down, but relatively normal maturation
- When severe, main cellularity is lymphocytes, plasma cells, +/- mast cells
- Differential diagnosis
  - Constitutional syndromes
  - Hypocellular MDS or AML
Bone Marrow Failure: Aplastic Anemia

- Progressive pancytopenia & marrow hypoplasia
- Acquired causes secondary to an inciting event, infection, toxin, etc usually has more acute presentation than idiopathic or inherited
- Some cases present a few months after an episode of hepatitis
  - No definite virus or other etiology identified
- Primary or “idiopathic” cases majority of patients
  - More insidious presentation
- Need to rule out constitutional causes
  - Treatment, planning for BMT regimen
1. Presentation of Aberrant Auto-antigen by APC

2. Dysregulated Activation of Auto-reactive T cells

3. T Cell Expansion and Differentiation

4. Cytokine-driven HSC Apoptosis and Reduction in Cell Cycling Leading to Bone Marrow Aplasia

ATG + CSA
Alemtuzumab
CY
MMF

IFN-γ
TNFα
FASL
HSC

Pediatr Clin N Am 60 (2013) 1311–1336
## Evaluation of Aplastic Anemia

<table>
<thead>
<tr>
<th>Establish BM Failure is present &amp; severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Establishing diagnosis and severity of AA</td>
</tr>
<tr>
<td>Clinical history and physical examination</td>
</tr>
<tr>
<td>Complete blood count and differential</td>
</tr>
<tr>
<td>Reticulocyte count</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy</td>
</tr>
<tr>
<td>Bone marrow cytogenetics</td>
</tr>
<tr>
<td>Liver function tests, serum bilirubin, lactate dehydrogenase</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Rule out an inherited disorder</th>
</tr>
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<tbody>
<tr>
<td>2. Exclusion of inherited bone marrow failure syndromes (IBMFS)</td>
</tr>
<tr>
<td>Clinical history</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Physical examination</td>
</tr>
<tr>
<td>Chromosomal breakage studies in peripheral blood</td>
</tr>
<tr>
<td>Telomere length measurement in peripheral blood</td>
</tr>
<tr>
<td>Increased fetal hemoglobin (several IBMFS)</td>
</tr>
<tr>
<td>Consider c-mpl testing</td>
</tr>
<tr>
<td>Consider additional diagnostic and genetic testing for IBMFS if suspected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Look for a specific cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Assess for specific causes and association</td>
</tr>
<tr>
<td>Viral serology (hepatitis virus panel, CMV, EBV, parvovirus, VZV, HSV, HHV6, HIV, adenovirus)</td>
</tr>
<tr>
<td>Flow cytometry of peripheral blood for paroxysmal nocturnal hemoglobinuria (PNH)</td>
</tr>
<tr>
<td>Vitamin B₁₂ and folate</td>
</tr>
<tr>
<td>Copper, ceruloplasmin, zinc</td>
</tr>
<tr>
<td>Immunology: lymphocyte subsets (including CD4+, CD25+ regulatory T cells), quantitative immunoglobulins</td>
</tr>
<tr>
<td>Autoimmune or inflammatory disease evaluation</td>
</tr>
<tr>
<td>HLA typing</td>
</tr>
<tr>
<td>Pregnancy test</td>
</tr>
<tr>
<td>T-cell receptor rearrangement</td>
</tr>
</tbody>
</table>
Marrow Findings in Aplastic Anemia

- Classified as mild, moderate, severe, or very severe based on marrow cellularity, CBC
- Cellularity usually 5-10%
  - No greater than ¼ of the age-related normal range
- Decrease in all hematopoietic lineages
  - Morphology may be normal, or may see mild megaloblastic changes, nuclear/cytoplasmic asynchrony, dyserythropoiesis
- Residual cellularity – stromal cells, macrophages, mast cells, lymphs, plasma cells
  - Often perivascular in distribution – you’ll see them in the particles
<table>
<thead>
<tr>
<th>Definition of severity of aplastic anemia (AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate or nonsevere (NSAA)</strong></td>
</tr>
<tr>
<td><strong>Severe (SAA)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
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<td></td>
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<tr>
<td><strong>Very severe (vSAA)&lt;sup&gt;c&lt;/sup&gt;</strong></td>
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</tbody>
</table>


<sup>b</sup> Automated reticulocyte counts (or manual counts of 20,000 × 10<sup>6</sup>/L).

Inherited Marrow Failure Syndromes
Fanconi Anemia

- Very rare, 1 in 350,000 – 1,000,000 births
  - Increased in Ashkenazi Jews
- Autosomal recessive
- Due to mutations in FANC family of genes
- DNA repair defect
- Most patients present in first decade of life (median 8 years), but can vary and even present in adulthood
<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Mutations</th>
<th>% of patients</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>FANCA</td>
<td>16q24.3</td>
<td>355</td>
<td>60</td>
<td>AR</td>
</tr>
<tr>
<td>FANCB</td>
<td>Xp22.31</td>
<td>14</td>
<td>2</td>
<td>XLR</td>
</tr>
<tr>
<td>FANCC</td>
<td>9q22.3</td>
<td>54</td>
<td>14</td>
<td>AR</td>
</tr>
<tr>
<td>FANCD1/BRCA2</td>
<td>13q12.3</td>
<td>35</td>
<td>3</td>
<td>AR</td>
</tr>
<tr>
<td>FANCD2</td>
<td>3p25.3</td>
<td>33</td>
<td>3</td>
<td>AR</td>
</tr>
<tr>
<td>FANCE</td>
<td>6p21.3</td>
<td>24</td>
<td>3</td>
<td>AR</td>
</tr>
<tr>
<td>FANCF</td>
<td>11p15</td>
<td>14</td>
<td>2</td>
<td>AR</td>
</tr>
<tr>
<td>FANCG/XRCC9</td>
<td>9p13</td>
<td>49</td>
<td>10</td>
<td>AR</td>
</tr>
<tr>
<td>FANCI</td>
<td>15q25-26</td>
<td>20</td>
<td>1</td>
<td>AR</td>
</tr>
<tr>
<td>FANCJ/BACH1/BRIP1</td>
<td>17q22.3</td>
<td>12</td>
<td>2</td>
<td>AR</td>
</tr>
<tr>
<td>FANCL</td>
<td>2p16.1</td>
<td>3</td>
<td>0.2</td>
<td>AR</td>
</tr>
<tr>
<td>FANCM</td>
<td>14q21.3</td>
<td>3</td>
<td>0.2</td>
<td>AR</td>
</tr>
<tr>
<td>FANCN/PALB2</td>
<td>16p12.1</td>
<td>15</td>
<td>0.7</td>
<td>AR</td>
</tr>
</tbody>
</table>
Fanconi Anemia

- Characteristic physical abnormalities (not present in up to 1/3 of patients)
  - Facial dysmorphism (hypertelorism, microcephaly)
  - Upper limb/hand anomalies (absent radii & thumbs)
  - Short stature
  - Skin abnormalities (café au lait spots, other pigmentation abnormalities)
  - Visceral organ defects
    - Gastrointestinal, renal, GU, cardiac)
Fanconi Anemia

- Hematologic findings
  - Progressive pancytopenia
    - Usually starts with leukopenia and/or thrombocytopenia then progresses to pancytopenia
  - Progressive marrow hypocellularity

- Confirmatory testing
  - Increased chromosomal breakage on exposure to certain agents (diepoxybutane)

- Treatment
  - Patients respond to androgens, hematopoietic growth factors, transfusions, bone marrow transplant
Fanconi Anemia

Prognosis

- Median survival 30 years
- Death due to marrow failure
- Increased risk for solid tumors, MDS, and AML
Dyskeratosis Congenita

- Very rare
- Variable inheritance patterns: X-linked, autosomal recessive, autosomal dominant
- Due to mutations in genes involved in telomere maintenance and the telomere complex
  - DKC1 (X-linked form)
  - TERC (AD form)
  - TERT, NOP10, NHP2, TIN2, C16orf57
  - Some genotype – phenotype correlations
- Physical Abnormalities
  - Triad of skin hyperpigmentation (reticulated hyperpigmentation), dystrophic nails, mucosal leukoplakia
  - May develop over time but may be subtle in early life
  - Variety of other physical anomalies described
Physical Findings in DKC
Table 1
Diagnostic criteria of dyskeratosis congenita and its variants.

A. Dyskeratosis congenita
   1. Simultaneous presence of abnormal skin pigmentation, nail dystrophy and leukoplakia.
   2. Presence of one of the mucocutaneous triad, bone marrow failure, and two of the other somatic features of DC.
   3. Presence of two or more features seen in DC associated with very short telomeres (below the first percentile in multiple leukocyte subsets).

B. Hoyeraal-Hreidarsson syndrome
   1. Presence of four or more of the features growth retardation, developmental delay, microcephaly, bone-marrow failure, immunodeficiency and cerebellar hypoplasia.
   2. Cerebellar hypoplasia and additional manifestations of DC.

C. Revesz syndrome
   1. Bilateral exudative retinopathy and additional manifestations of DC.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Mutations</th>
<th>~% of patients</th>
<th>Genetics</th>
</tr>
</thead>
</table>
| **B) Dyskeratosis congenita**
  DKC1                  | Xq28     | ~40       | 35%            | XLR      |
  TINF2                 | 14q11.2  | ~15       | 10–20%         | AD       |
  TERC                  | 3q26.3   | ~5        | 10%            | AD       |
  TERT                  | 5p15.53  | ~10       | 5%             | AD, AR   |
  NOP10/NOLA3           | 15q14-q15| 1         | <1%            | AR       |
  NHP2/NOLA2            | 5q35.5   | 1         | <1%            | AR       |
The Telomere Complex
Dyskeratosis Congenita

- 50% of patients will have bone marrow failure by the 2\textsuperscript{nd} decade of life
  - Median age is 16 years
  - Autosomal dominant form may present in 3\textsuperscript{rd} decade

- Hematologic findings
  - Progressive pancytopenia
    - Starts with anemia (high MCV, incr Hgb F) and/or thromocytopenia
  - Progressive marrow hypoplasia

- Marrow failure may be 1\textsuperscript{st} indication that patient has this syndrome
Dyskeratosis Congenita

- Confirmatory testing
  - Telomere length – these patients have extremely short telomeres
  - Tested by flow-FISH (combination of flow cytometry and FISH)

- Prognosis
  - Median survival of 30 years
  - AD type has longer survival, but is at risk of developing solid tumors
Flow-FISH for the diagnosis of dyskeratosis congenita

Survival in DKC

Case #2 – 11 week old boy with pallor

Hgb = 2.9 g/dL
Hct = 8.8%
MCV = 91.1 fL
Platelet = 813 K/ul
WBC = 12.61 K/ul
Retic = 0.1%
Diagnosis

Pure red cell aplasia
(Diamond Blackfan anemia)
Diamond Blackfan Anemia

- Usually autosomal dominant, autosomal recessive in some cases
  - Most cases are actually sporadic (75%)
- Incidence 5-7/100,000 live births
- Ribosomal protein RPS19 at 19q13.2 mutated in 25% of patients
  - Another subset of patients have linkage to 8p23.2-22
- Typically presents at birth or early infancy with profound, often macrocytic anemia
- Low reticulocyte count
- 30-40% have skeletal defects (upper limb, other), short stature, eye abnormalities
<table>
<thead>
<tr>
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<th>~% of patients</th>
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<tbody>
<tr>
<td>RPS19</td>
<td>19q13.3</td>
<td>50</td>
<td>25</td>
<td>AD</td>
</tr>
<tr>
<td>RPS24</td>
<td>10q22-23</td>
<td>3</td>
<td>2</td>
<td>AD</td>
</tr>
<tr>
<td>RPS17</td>
<td>15q25</td>
<td>1</td>
<td>Rare</td>
<td>AD</td>
</tr>
<tr>
<td>RPL5</td>
<td>1p22.1</td>
<td>18</td>
<td>9</td>
<td>AD</td>
</tr>
<tr>
<td>RPL11</td>
<td>1p36.1-35</td>
<td>13</td>
<td>6</td>
<td>AD</td>
</tr>
<tr>
<td>RPL35A</td>
<td>3q29-qter</td>
<td>2</td>
<td>2</td>
<td>AD</td>
</tr>
</tbody>
</table>

C) Diamond-Blackfan anemia

Diamond Blackfan Anemia

- Additional laboratory testing
  - Increased red cell adenosine deaminase (ADA) & Hgb F
- Long term survivors may develop multilineage hypoplasia and additional cytopenias
  - Neutropenia & thrombocytopenia
- Small increased risk of cancer
- Patients often respond to early steroid therapy, also treated with transfusions, and possibly bone marrow transplant
- Median survival 40-50 years; 20-25% may spontaneously remit
Marrow Findings in Diamond Blackfan Anemia

- Isolated profound erythroid hypoplasia
- Only scattered unremarkable erythroblasts
- May see increased hematogones
- Eosinophilia may be seen
- At least initially, normal myelopoiesis and megakaryocytes
Case #3

6 week old girl with severe neutropenia
Diagnosis

Severe congenital neutropenia
Severe Congenital Neutropenia (SCN)

- Severe congenital neutropenia
  - Also called infantile agranulocytosis
- Very rare
- Variable modes of inheritance
  - Most autosomal dominant and sporadic new mutations, rare autosomal recessive or X-linked
- Genetics
  - 35-84% with *ELA2* mutations
    - Generally worse disease, lower neutrophil counts, increased risk of malignancy
  - Other mutations: *GFI1*, *WASP*, *HAX1*, *CSF3R*
<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM #</th>
<th>Locus</th>
<th>Mutations</th>
<th>~% of patients</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELA-2/ELANE</td>
<td>202700</td>
<td>19p13.3</td>
<td>75</td>
<td>60</td>
<td>AD</td>
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<tr>
<td>GFI1</td>
<td>613107</td>
<td>1p22</td>
<td>2</td>
<td>&lt;1</td>
<td>AD</td>
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<tr>
<td>HAX1</td>
<td>610738</td>
<td>1q21.3</td>
<td>~10</td>
<td>1</td>
<td>AR</td>
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<tr>
<td>WAS</td>
<td>300299</td>
<td>Xp11.33-11.22</td>
<td>3</td>
<td>&lt;1</td>
<td>XLR</td>
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<tr>
<td>G6PC3</td>
<td>612541</td>
<td>17q21.31</td>
<td>4</td>
<td>&lt;1</td>
<td>AR</td>
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</table>
A Number of Disorders are Associated with Neutropenia

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>MIM #</th>
<th>Gene</th>
<th>Genetics, locus</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticular dysgenesis</td>
<td>267500</td>
<td>AK2</td>
<td>AR, 1p34</td>
<td>Severe combined immunodeficiency, hearing loss, mitochondrial function</td>
</tr>
<tr>
<td>WHIM syndrome</td>
<td>193670</td>
<td>CXCR4</td>
<td>AD, 2q21</td>
<td>Warts, hypogammaglobulinemia, immunodeficiency, myelokathexis</td>
</tr>
<tr>
<td>Glycogen storage disease 1b</td>
<td>232220</td>
<td>SLC37A4</td>
<td>AR, 11q23</td>
<td>Glycogen metabolism</td>
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<tr>
<td>Barth syndrome</td>
<td>302060</td>
<td>TAZ</td>
<td>XLR, Xq28</td>
<td>Dilated cardiac and skeletal myopathy, increased 3-methylglutaconic aciduria</td>
</tr>
<tr>
<td>Cartilage hair hypoplasia</td>
<td>250250</td>
<td>RMRP</td>
<td>AR, 9p21-9p12</td>
<td>Immunodeficiency, abnormal hair, skeletal hypoplasia</td>
</tr>
<tr>
<td>Chediak–Higashi syndrome</td>
<td>214500</td>
<td>LYST</td>
<td>AR, 1q42.1-42.2</td>
<td>Partial albinism, neurologic, lymphoma</td>
</tr>
<tr>
<td>Griscelli syndrome, type 1</td>
<td>214450</td>
<td>MY05A</td>
<td>AR, 15q21</td>
<td>Partial albinism, neurologic</td>
</tr>
<tr>
<td>Griscelli syndrome, type 2</td>
<td>603868</td>
<td>RAB27A</td>
<td>AR, 15q21</td>
<td>Partial albinism, neurologic, hemophagocytic syndrome</td>
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<tr>
<td>Hemansky–Pudlak syndrome</td>
<td>608233</td>
<td>AP3B1</td>
<td>AR, 5q14.1</td>
<td>Oculocutaneous albinism, immunodeficiency, abnormal platelets</td>
</tr>
<tr>
<td>P14-deficiency</td>
<td>610389</td>
<td>MAPBPIP</td>
<td>AR, 1q22</td>
<td>Growth failure, hypopigmentation, immunodeficiency</td>
</tr>
<tr>
<td>Cohen syndrome</td>
<td>216550</td>
<td>VPS13B</td>
<td>AR, 8q22-q23</td>
<td>Retardation, skeletal anomalies, pigmented retinopathy</td>
</tr>
<tr>
<td>Charcot–Marie–Tooth disease, type 2</td>
<td>606482</td>
<td>DNM2</td>
<td>AD, 19p13.2</td>
<td>Axonal demyelinating neuropathy</td>
</tr>
</tbody>
</table>
Severe Congenital Neutropenia (SCN)

- Patients present with severe persistent neutropenia in infancy (ANC <200) & infections

- Rest of CBC generally normal
  - May have peripheral monocytosis & eosinophilia

- Severe infections in first month of life, die by 3 years of age unless treated with G-CSF or bone marrow transplant
  - Note on G-CSF therapy: risk of MDS & AML with prolonged use, increases with duration of use
Bone Marrow Morphology in SCN

- Normal to slightly decreased cellularity
- Decreased myeloid precursors with maturation arrest – few precursors that mature beyond promyelocyte or myelocyte stage
- May have enlarged multinucleated myeloid precursors
- Promyelocytes often vacuolated
- Increased monocytes, eosinophils, macrophages, plasma cells common
Schwachman-Diamond Syndrome

- Very rare
- Autosomal recessive
- 50% with short stature, metaphyseal dysostosis, exocrine pancreas insufficiency
- Mutations in SBDS gene on 7q11 in 95% of patients
- Presents in infancy with progressive neutropenia
  - 40% have other cytopenias as well
<table>
<thead>
<tr>
<th>Patient number</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 37)</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>1</td>
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<tr>
<td>1</td>
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<tr>
<td>1</td>
</tr>
</tbody>
</table>
Box 1
Clinical and molecular diagnostic features of Shwachman–Diamond syndrome

Biallelic mutations in SBDS or clinical Shwachman–Diamond syndrome: one criteria from Category I and II

Category I
Low levels of trypsinogen (age <3 years) or low pancreatic isoamylase levels (age >3 years)
Low levels of fecal elastase
Supportive features:
  Pancreatic lipomatosis
  Elevated 72-hour fecal fat excretion and absence of intestinal pathologic condition

Category II
Hypoprotective cytopenias
  Neutropenia (absolute neutrophil count <1500)
  Anemia or idiopathic macrocytosis
  Thrombocytopenia (<150,000)
Bone marrow examination with any of the following:
  Myelodysplasia
  Leukemia
  Myelodysplasia syndrome
  Hypoactivity for age
  Cytogenetic abnormalities

Supporting features
First-degree or second-degree blood relative with Shwachman–Diamond syndrome
Personal history of
  Congenital skeletal abnormalities consistent with chondrodysplasia or a congenital thoracic dystrophy
  Height 3% or less, of unclear cause
  Deficiency in 2 or more fat-soluble vitamins (A, 25-OHD, and E).
Schwachman-Diamond Syndrome

- Bone marrow findings
  - Myeloid hypoplasia with left shift & “maturation arrest”
  - 40% progress to have other lineages also affected, although total marrow aplasia unusual
- Treated with androgens, G-CSF, bone marrow transplant
- Median survival 35 years
- Increased risk of MDS and AML
Case #4

5 week old boy with persistent thrombocytopenia
Diagnosis

Marked megakaryocytic hypoplasia
Congenital Amegakaryocytic Thrombocytopenia (CAMT)

- Autosomal recessive (rare X-linked)
- 30% with associated malformations
  - Microcephaly, micrognathia, intracranial malformations, low birth weight, congenital heart disease, failure to thrive
- \textit{C-mpl} mutations (TPO receptor) at 1q34 in majority
  - In those without associated malformations
- Neonatal thrombocytopenia
  - <20 K
  - Normal platelet morphology
- May have macrocytic anemia, increased Hgb F
Congenital Amegakaryocytic Thrombocytopenia (CAMT)

- Bone marrow – normal cellularity with absent or markedly reduced megakaryocytes
  - Megs are small and atypical
- 50% develop pancytopenia and trilineage hypoplasia with complete marrow failure
- Treated with growth factors, BMT
- Progression to pancytopenia & multilineage bone marrow failure by 2\textsuperscript{nd} decade
- Median survival <10 years
Thrombocytopenia with Absent Radii (TAR)

- Rare DNA repair disorder (radiation sensitive)
  - Gene not identified as of yet, but normal \textit{c-MPL}
  - 1q21.1 appears to be the chromosomal region involved
- Autosomal recessive
- Neonatal thrombocytopenia
  - 10-30K range
- Bone abnormalities
  - Congenital absence or extreme hypoplasia of radial bones (thumbs are present), commonly bilateral
  - Absent, short, or malformed ulnae
  - Variety of other skeletal abnormalities also described
- Cardiac lesions in a subset
Thrombocytopenia with Absent Radii (TAR)

- High incidence transient leukemoid reactions (can be >100,000)
- Bone marrow with normal cellularity but absent or markedly decreased megakaryocytes in infancy
  - If present, megs are small and immature
  - Myeloids & erythroids are normal
- Spontaneous recovery common with normalization of platelet count and more normal numbers of megakaryocytes
Radial Abnormalities in TAR vs FA

Normal thumb and fingers, just absent radius

Fig. 13. Comparison of radial ray anomalies in TAR and FA. Left, TAR. Right, FA. TAR patient has absent radii, but thumbs are present, albeit not normal in shape or position. FA patient has an absent radius, but the thumb is also absent, and the fingers are abnormal.64,153

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance Pattern</th>
<th>Genes</th>
<th>Physical Findings</th>
<th>Laboratory Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>AR, XLR</td>
<td>FA-A—FA-P, Breast cancer genes</td>
<td>Short stature, radial limb, thumb</td>
<td>DEB chromosome breakage, Mitomycin C breakage assay</td>
</tr>
<tr>
<td>DC</td>
<td>AR, AD, XLR</td>
<td>TERT, TERC, DKC, TINF2, NOP10, TCAB1, NHP2</td>
<td>Nails, skin, leukoplakia</td>
<td>Telomere lengths, lymph subsets, Gene testing</td>
</tr>
<tr>
<td>Shwachman-Diamond</td>
<td>AR</td>
<td>SBDS</td>
<td>Pancreatic insufficiency, skeletal abnormalities</td>
<td>Serum trypsinogen, isoamylase, fecal elastase, pancreatic imaging, Gene testing</td>
</tr>
<tr>
<td>DBA</td>
<td>AD</td>
<td>RPS7, RPS17, RPS19, RPS24, RPS26</td>
<td>Short stature, head, upper limbs, urogenital</td>
<td>Erythrocyte adenosine deaminase, Gene testing</td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
<td>AR</td>
<td>C-MPL</td>
<td>—</td>
<td>Gene testing</td>
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</tbody>
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