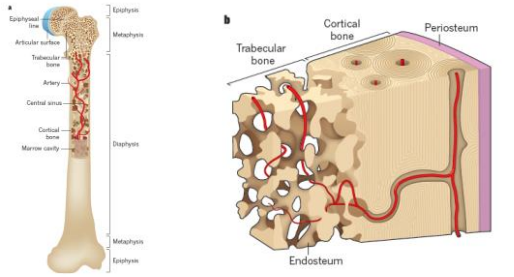
Aplastic Anemia: Understanding your Disease and Treatment Options

Josh Sasine, MD, PhD
Hematopoietic Cell Transplant Program
Division of Hematology-Oncology
University of California, Los Angeles

No financial relationships or commercial interest related to the content of this presentation

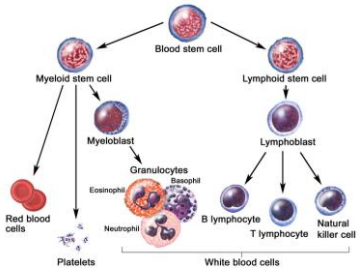
Overview of the Bone Marrow

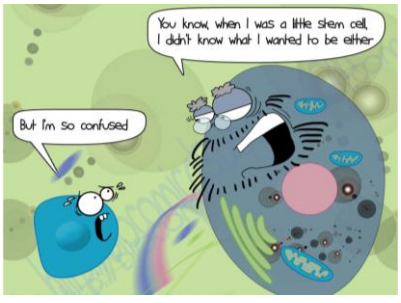


Morrison and Scadden Nature 2014

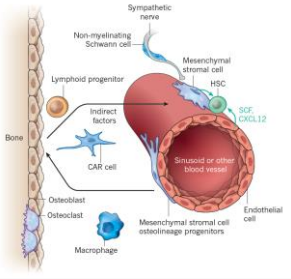
Forming Blood Cells

- **10 billion red blood cells and 1 billion whites are produced per hour**
- **Cell numbers are maintained within narrow limits but can be greatly amplified on demand**
- **No other tissue has this output**



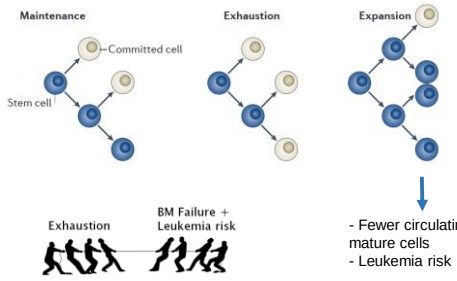


Bone Marrow Niche



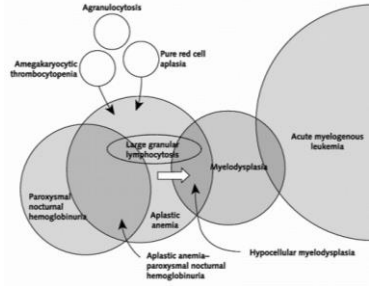
Morrison and Scadden Nature 2014

Stem Cell Biology Crash Course



Ito and Suda. Nat Rev Mol Cell Biol. 2014

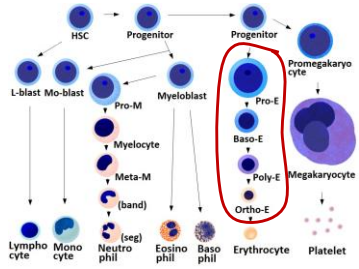
Bone Marrow Failure: Overlapping Diseases



Young. Ann Int Med. 2002

Pure Red Cell Aplasia (PRCA)

- Unable to produce sufficient red blood cells but marrow can make white blood cells and platelets



Pure Red Cell Aplasia (PRCA)

- Generally acquired but can be congenital
- Congenital: often Diamond-Blackfan anemia (DBA)
- Acquired:
  - 60% → no specific associated condition, antibodies against red blood cell precursors, EPO or its receptor
  - Autoimmune disorders (eg. lupus, thymoma)
  - Clonal disorder: LGL, MDS, plasma cell dyscrasia
  - Virus → eg Parvovirus B19
  - ABO-incompatible hematopoietic cell transplantation
  - Medications

Epidemiology of Aplastic Anemia (AA)

- Rare: 2 cases per million people per year
- Higher incidence in Asia
- Male : Female ratio is equal
- Half occur before age 30

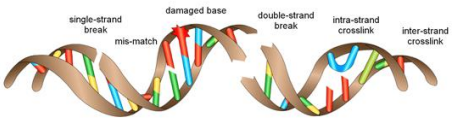
Why Do Some People Get AA?

- Damage to bone marrow cells: radiation, chemotherapy
- Exposure to chemicals → solvents, benzene
- Certain medications or antibiotics (chloramphenicol, carbamazepine, methimazole, etc.)
- Viral infections (hepatitis, EBV, CMV, HIV, parvovirus)
- Congenital → mutations
- Pregnancy
- Paroxysmal Nocturnal Hemoglobinuria
- Immune alterations (lupus, eosinophilic fasciitis, thymoma)

- Idiopathic → unable to identify the cause

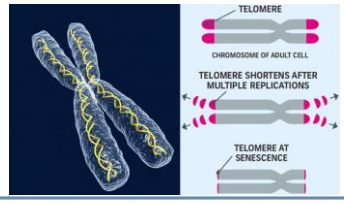
DNA Damage

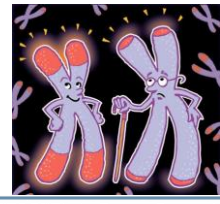
- **DNA damage occurs naturally due to internal and external factors**
- **Internal: reactive oxygen species, normal metabolic byproducts**
- **External: radiation (include UV, though not in the bone marrow), x-rays, plant toxins, chemicals, viruses, etc.**



Telomeres

- **Telomeres are "caps" at the end of each chromosome which serve as a buffer against losing DNA when the cell divides and replicates the DNA**
- **Maintenance of telomeres is an <u>active</u> process**



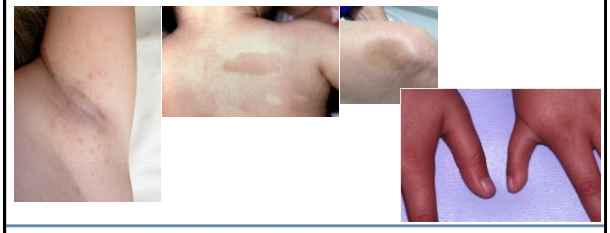


Inherited Conditions

- **<u>Fanconi Anemia</u>**
  - DNA repair problem, most common form of inherited AA
  - Pancytopenia, predisposition to malignancy, and physical abnormalities (eg, short stature, microcephaly, developmental delay, café-au-lait skin lesions)
- **<u>Dyskeratosis Congenita</u>**
  - Mutation in telomere machinery – short telomeres
  - Bone marrow failure, skin and nail findings, pulmonary fibrosis, cancer predisposition, mucosal leukoplakia
- **<u>Shwachman-Diamond syndrome</u>**
  - Usually presents in infancy with bone marrow failure, pancreas dysfunction, skeletal anomalies
  - AA can be seen but intermittent neutropenia (low white blood cells) is most common
- **<u>Congenital Amegakaryocytic Thrombocytopenia (CAMT)</u>**
  - Mutation in thrombopoietin (TPO) or its receptor
  - Low platelets which progress to pancytopenia

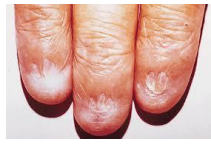
Fanconi Anemia

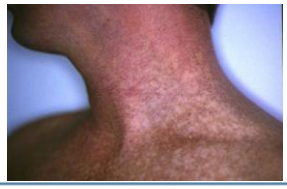
- DNA repair problem, most common form of inherited AA
- Pancytopenia, predisposition to malignancy, and physical abnormalities (eg, short stature, microcephaly, developmental delay, café-au-lait skin lesions)

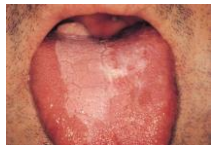


Dyskeratosis Congenita

- Mutation in telomere machinery – short telomeres
- Bone marrow failure, skin and nail findings, pulmonary fibrosis, cancer predisposition, mucosal leukoplakia

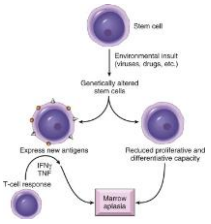






Immunity and AA

- **Autoimmune damage to bone marrow stem cells causes or contributes to most cases of AA, whether another underlying cause is identified or not**

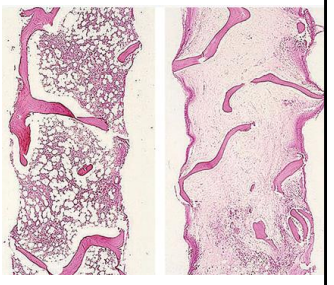


Robbins and Cotrans, Chapter 14, Figure 14-24

Diagnosis

AA = pancytopenia with loss of bone marrow cells and no abnormal infiltrate or fibrosis (scarring)

- **CBC with reticulocyte count**
- **Liver tests**
- **Vitamins: B12 and folate**
- **Viruses: hepatitis, CMV, EBV, HIV, ParvoB19**
- **Autoimmune test**
- **Chromosome breakage tests**
- **Flow cytometry to look for PNH**
- **Bone marrow aspirate and biopsy**
  - **Cytogenetics and karyotype**
  - **Next-generation sequencing for mutations, acquired or inherited**



Anemias Due to Bone Marrow Failure or Infiltration, Bunn H, Aster JC. Pathophysiology of Blood Disorders; 2011.

AA Risk Stratification

Severe aplastic anemia	
Bone marrow cellularity	<30%
Two of three peripheral blood criteria: -absolute neutrophil count -platelet count -reticulocyte count	 500- 200 /mm3 <20.000/mm3 <40.000/mm3
VERY SEVERE APLASTIC ANEMIA -absolute neutrophil count	 <200/mm3
MODERATE APLASTIC ANEMIA Patients with pancytopenia who do not fitfull the criteria of severe disease	

Hematopoietic Cell Transplant

- Early identification of donor
- If age 20 – 50 with SAA and sibling donor → transplant (no IST)
  - Outcomes for matched unrelated donor are also very good
  - Haplo (half-matched) and cord blood donors are also options
- Bone marrow vs. peripheral blood
- Graft failure correlated with number of previous transfusions
- Monitoring for clonal evolution?

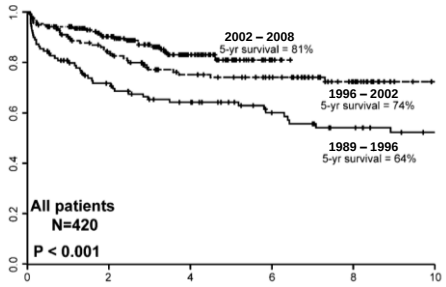
Historical Perspectives

Era	Treatment	Response Rate	Survival
1960s	Corticosteroids	~10%	10 – 20%
1970s	ATG	40 – 50%	40 – 60%
1980s	ATG + cyclosporine	60 – 70%	60 – 70%
2000s	ATG + cyclosporine + eltrombopag	87%	80 – 90%

Outcomes for AA are Improving Over Time - Why?

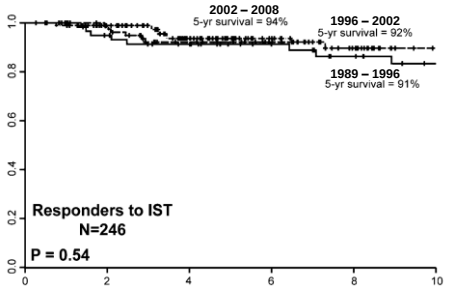
- Better medicines to regenerate bone marrow
- Better supportive care
  - Antibiotics, safer blood transfusions, Chelation for iron overload, etc.
- Improvements in bone marrow transplantation with greater access

All Patients Over Time: Survival



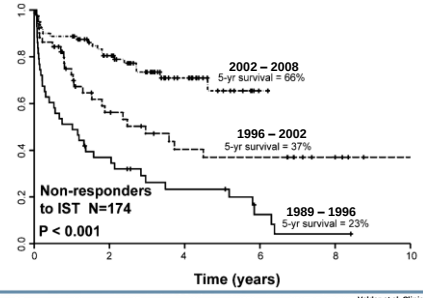
Valdez et al. Clinical Infectious Diseases. 2011

Patients Responding to IST



Valdez et al. Clinical Infectious Diseases. 2011

Patients Not Responding to IST

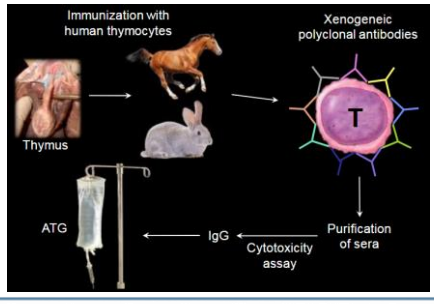


Valdez et al. Clinical Infectious Diseases. 2011

Unsuccessful Attempts to Improve Treatment

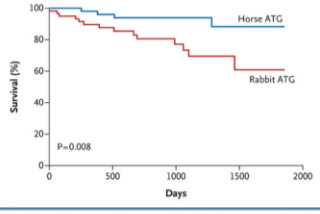
- **Add to or replace ATG with megadose corticosteroids**
  No increase in response; high toxicity (Marmont, Prog Clin Biol Res 1984
- **Replace ATG with high dose cyclophosphamide**
  Toxicity (Tisdale, Lancet 2001; Blood 2002)
- **Replace ATG with moderate dose cyclophosphamide**
  Excessive toxicity from neutropenia (Scheinberg, Blood 2014)
- **Add mycophenolate mofetil to ATG/CsA**
  No improvement in response/survival (Scheinberg, Br J Haematol 2006)
- **Add sirolimus to ATG/CsA**
  No improvement in response/survival (Scheinberg, Haematologica 2009)
- **Add G-CSF to ATG/CsA**
  No improvement in response/survival (Locasciulli, Haematologica 2004)
- **Prolonged CsA (2 years) to prevent relapse**
  Delayed but ultimately equivalent rate (Scheinberg, Am J Hematol 2014)
- **Replace horse with rabbit ATG, or alemtuzumab, frontline**
  No improvement in response/survival (Scheinberg, NEJM 2012)

Production of Anti-Thymocyte Globulin (ATG)



Immunosuppressive Therapy (IST)

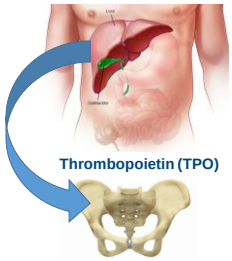
- Horse ATG daily x 4 days vs rabbit ATG daily for 5 days (+ cyclosporine for both)
- Response at 6 months was better with horse ATG (68 vs 37%)
- Overall survival at 3 years was superior in the horse ATG group (96 vs 76%)



Scheinberg et al. N Engl J Med 2011

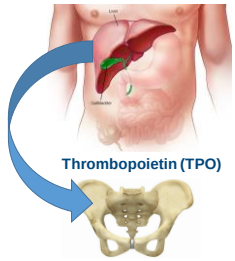
Can We Induce Hematopoietic Stem Cell Growth?

- Hormones produced in the liver (like TPO) can maintain and promote bone marrow stem cells
- Medicines can mimic the effect of TPO in the bone marrow
- Local "hormones" in the bone marrow can also make stem cells grow



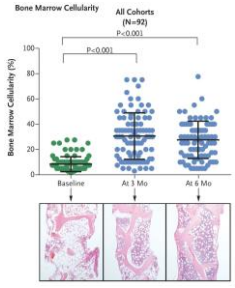
What Do We Know About TPO and Hematopoietic Stem Cells?

- TPO receptor (c-Mpl) is on HSCs and early progenitor cells
- TPO expands HSCs in the lab
- Deleting TPO or c-Mpl in mice reduces HSCs
- Multi-lineage marrow failure occurs in some congenital amegakaryocytic thrombocytopenia



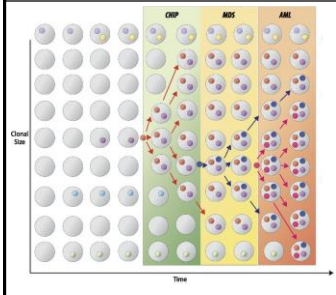
Eltrombobag + IST

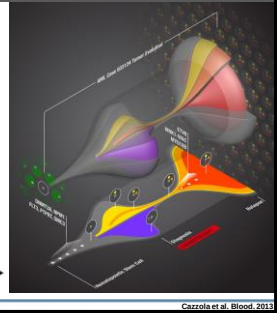
- **Overall response rate** [= no longer meeting criteria for severe AA]: **87%**
  - 66% in historical control patients
- **Complete response** [= ANC >1000 + hg >10 + plts ≥ 100]: **39 %**
  - (58% in high-dose cohort)
  - 10% in historical control patients
- **Survival: 97% at 2 years**



Townsley et al. N Engl J Med 2017

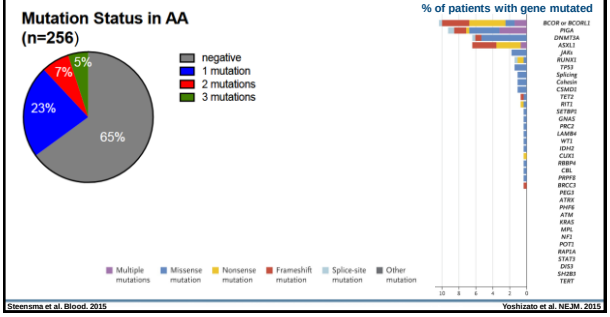
Clonal Evolution





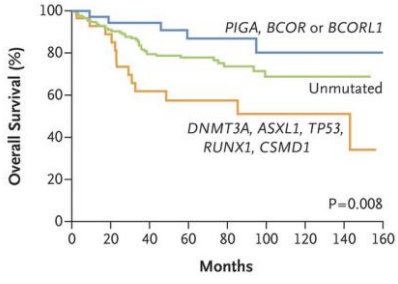
Steensma et al. Blood. 2015 — Cazzola et al. Blood. 2013

Mutations are Non-Random



Steensma et al. Blood. 2015 — Yoshizato et al. NEJM. 2015

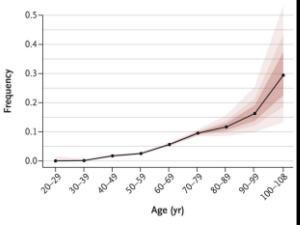
A Subset of Mutations Correlate with Survival



Steensma et al. Blood. 2015 — Yoshizato et al. NEJM. 2015

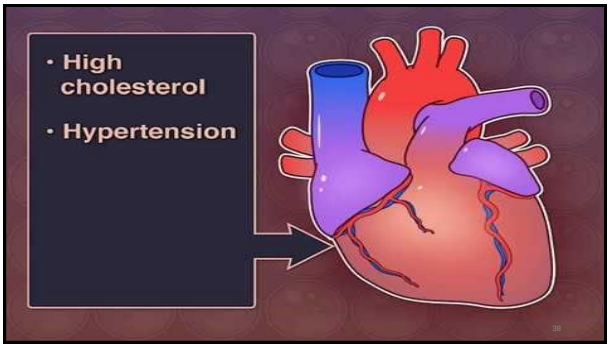
Monitoring → CHIP

- CHIP = clonal hematopoiesis of indeterminate potential
- Form of clonal evolution
- Common with age
- More common in AA
- Predisposition to leukemia and cardiovascular disease



No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Jaiswal et al. NEJM. 2015 and 2017



Important Lab Tests Over Time

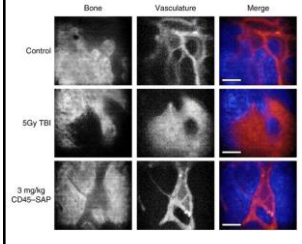
- Ferritin
- Antibody levels
- Kidney function and magnesium if on cyclosporine
- Test for clonal evolution

What About Patients Who Don't Benefit from IST?

- Return of AA occurs in 10 – 35% at 15 years
- No response to initial IST for 10 – 15%
- Options:
  - Repeat IST (horse or rabbit ATG is acceptable)
  - Eltrombopag (+/- ATG +/- cyclosporine)
  - Alemtuzumab (+/- cyclosporine)
  - Transplant
- Must rule out clonal evolution such as MDS
- If not responsive to first IST: ongoing immune attack or persistent stem cell problem?

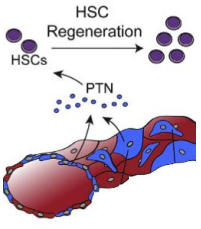
Research

Chemotherapy-free transplantation



Palchaudhuri Nat Biotech. 2016

Growth factors for HSCs



Himburg, Sasine, et al. Cell Stem Cell. 2018

Questions?