Aplastic Anemia is a bone marrow failure disease. The bone marrow is the factory that makes blood.

The 4 major components of blood:

**Red Blood Cells:** Carry oxygen (energy)
- When low called “Anemia”
- Weakness, pale, short of breath, leg swelling
- Usually measured as hemoglobin
  - Normal male 14-16 gm/dl
  - Normal female 12-14 gm/dl

**White Blood Cells:** Immune system (fight infections)
- Neutrophils: primary bacteria fighters
- T-lymphocytes: recognize infections
- B-lymphocytes: make antibodies to prevent repeat infections
- Monocytes: deep penetrating infection fighting and recognition
- Normal WBC 4.5-10 X 10^9/L
- Normal Neutrophil count 1.5-8 X 10^9/L

**Red Blood Cells:**
- Carry oxygen (energy)

**White Blood Cells:**
- Immune system (fight infections)
The 4 major components of blood

- Red Blood Cells: Carry oxygen (energy)
- White Blood Cells: Immune system (fight infections)
- Platelets: clotting (stop bleeding)
  - Normal platelet count 150,000 – 400,000
- Plasma: clotting (stop bleeding)

Too few blood cells leads to

- Weakness
- Shortness of breath
- Pale
- Fevers
- Infections
- Bruising
- Bleeding

In Aplastic Anemia
The bone marrow fails to make enough blood cells

- Severe Aplastic Anemia (SAA)
  - Neutrophils less than 0.5 x 10^9/L
  - Platelets less than 20 x 10^9/L
  - Reticulocytes (early red cells) less than 20 x 10^9/L

- Very Severe Aplastic Anemia (VSAA)
  - Neutrophils less than 0.2 x 10^9/L
  - Platelets less than 20 x 10^9/L
  - Reticulocytes less than 20 x 10^9/L

Making the Diagnosis: The Bone Marrow Biopsy
Making the Diagnosis: The Bone Marrow Biopsy

Healthy bone marrow

Aplastic anemia

The "factories" have disappeared. Thus less blood is made.

Cytogenetic Tests from the Bone Marrow

- Bone marrow cells may be examined for genetic changes
- Some chromosomal changes are more common, and may indicate more of a pre-leukemia (MDS) state with a poorer prognosis
- Genetic alterations, found by Next Generation Sequencing, are common but the implications are unknown
- Fragility studies are important to exclude Fanconi’s anemia (congenital AA) which change treatment
- Telomere length studies are newer, and results are conflicting but potentially patients with shorter telomeres may do worse

Diagnostic procedures in patients with low blood counts

Other tests often performed

- Hemoglobin electrophoresis and blood group testing
  - Elevated fetal hemoglobin and red cell I antigen in stress
- Coombs test
  - Exclude hemolysis (destruction)
- Liver tests and Rheumatology testing
  - Exclude other causes of low counts
- Viral tests
  - May cause low counts (especially hepatitis and HIV)
- PNH testing (paroxysmal nocturnal hemoglobinuria)
- Diepoxybutane incubation (Fanconi’s anemia)
- HLA testing for possible future transplantation
Causes of Aplastic Anemia

• "Damage" to the bone marrow especially the stem cell
  • The stromal cells (supporting cells) are typically normal

• Immune mediated destruction of the blood cell precursors is the major cause of acquired AA
  • Over representation of patients with HLA DR2

• Suppression of hematopoiesis by expanded population CD8+HLA-DR+cytotoxic T lymphocytes. Produce inhibitory cytokines (gamma interferon and tumor necrosis factor). FAS-mediated apoptosis

Causes of Aplastic Anemia

• Increased nitric oxide damage to cells

• Kinectin-derived peptides that suppress growth

• Increased expression of T-bet

• Diminished perforin and SAP proteins

• Decreased TREGs

• Variations in telomere length

Causes of Aplastic Anemia

80% are Acquired

• Idiopathic (unknown)

• Infections – hepatitis, Epstein Barr virus, HIV, parvovirus, mycobacteria

• Exposure to ionizing radiation

• Exposure to toxic chemicals (benzenes, pesticides)

• Transfusional graft vs-host disease

• Orthotopic liver transplantation

• Pregnancy

• Eosinophilic fasciitis

• Anorexia

• Severe nutritional deficiencies (B12, folate)

• Paroxysmal nocturnal hemoglobinuria

• Myelodysplastic syndrome

• Drugs (chloramphenicol, phenylbutazone, gold)

Causes of Aplastic Anemia

20% are inherited / congenital

• Fanconi’s anemia

• Dyskeratosis congenital

• Familial AA

• Cartilage-hair hypoplasia

• Pearson syndrome

• Thrombocytopenia-absent radius syndrome

• Schwachman-Diamond

• Dubowitz syndrome
How common is Aplastic Anemia?

• Very rare: 0.6-6 cases per million US citizens
• More common in Asia

Treatment of Aplastic Anemia

• Treatments depend on the severity of the disease
• For mild cases "supportive care" (occasional transfusions and/or antibiotics) may be sufficient
• For SAA or VSAA emergent treatment is recommended

Blood Transfusions

• May be necessary for symptoms of anemia or thrombocytopenia
  • Fatigue and shortness of breath with very low red blood cells
  • Bleeding with very low platelet counts
• Avoidance of family members as blood donors
  • Sensitization to HLA antigens which could raise risk of future transplant
• Minimize risk of CMV infection
  • A common infection carried in blood cells: pneumonia, diarrhea, vision issues
• Blood products typically irradiated
  • Reduce risk of graft-vs-host disease

Transfusion Related Iron Overload

• Multiple red blood cell transfusions (>20 units lifetime)
  can lead to a build up of excess iron
• Iron is deposited in critical organs
• Chelation therapy may be used to rid excess iron
A strong age effect in patients with aplastic anemia, after transplantation from an HLA identical sibling.

Steps to a transplant
- Find a donor
  - HLA typing matches white cell antigens important for rejection
  - Siblings match 1 in 4 times
  - Unrelated donors can match, but higher complications
    - Cord blood and haplo-identical still uncommon
  - Bone marrow is better than blood stem cells
  - Less graft-vs-host disease
  - Higher stem cell doses better?

Hematopoietic Stem Cell Transplantation
- An aggressive, but potentially curative approach
- Age of the patient and Availability of a Donor are the major determinants of whether a BMT is performed early
- Goal is to "Replace" the defective bone marrow

Treatment strategy in patients with acquired aplastic anemia. Importance of Age and Availability of a Donor

An aggressive, but potentially curative approach
- Age of the patient and Availability of a Donor are the major determinants of whether a BMT is performed early
- Goal is to "Replace" the defective bone marrow
The age effect in UD transplants: best outcome is seen for very young patients, for whom first-line UD BMT may be considered.

Steps of a transplant
- One month hospitalization
- Conditioning chemotherapy (several days)
  - Goal of chemotherapy is to prepare body to accept foreign graft and to suppress the old damaged immune system
  - Cyclophosphamide with ATG most common regimen
  - Addition of fludarabine and/or alemtuzumab and/or radiation in older/unrelated
  - Lower dose regimens in Fanconi’s Anemia
- Infuse the cells
- Support during time of low blood counts
- Recover counts
- Watch for immune rejection (donor against patient and vice versa)

Immunosuppressive Therapy
- There is immune dysregulation in aplastic anemia
- The immune system may attack the bone marrow and slow down blood cell production
- Immunosuppressive therapy seeks to temporarily turn off the immune system to allow the marrow to recover
- “turn off your system and reboot”
- May be effective in 60-80% of cases, but relapses can occur
Immunosuppressive therapy

• Most common regimen consists of two medications
  
  ATG with Cyclosporine

• Potentially a MAJOR change is coming (hold on – wait a couple of slides)

Anti-thymocyte globulin (ATG)

• ATG: Yes, it really is horse serum
  
  • The T-cells in the horse’s blood attack the diseased human immune system – the human immune system temporarily shuts down and cannot attack the bone marrow – then the human immune system regrows
  
  • Given over 4-5 days in the hospital via a large intravenous line
  
  • May cause shaking chills and low blood pressure during administration
  
  • May cause muscle aches and rashes (serum sickness)
  
  • Takes 10-12 weeks to see improvement in counts
  
  • Occasionally a second treatment (course) is given at 3-6 months

Rabbit ATG

• In some parts of the world horse ATG is not available
  
• Rabbit ATG was found to be less effective than horse ATG but can work, used in allergic patients and those failing prior treatment
  
• Higher early complication rate with rabbit ATG

Cyclosporine

• Usually added to ATG to prolong suppression of human T-cells in the original diseased immune system
  
• Pill is taken for a year or more, with slow taper
    • Some patients (a third) require years of cyclosporine
  
• May affect kidney function, so monitored closely

• May cause reversible tremors and hair growth
G-CSF (filgrastim)

- A growth factor ("fertilizer") for white blood cells
- Typically ineffective by itself in AA
- May be added to ATG+Cyclosporine (but benefit questionable)

Eltrombopag

- A pill developed to increase platelet production
- Has broader growth stimulation on the bone marrow
- Used (and now approved) to treat relapsed/refractory AA

A Possible New Standard of Care

Eltrombopag added to ATG+Cyclosporine

The complete response rates were 26-58% and the overall response rates at 6 months were 80%, 87%, and 94%, respectively.

The complete and overall response rates in the combined cohorts were higher than in the NIH historical cohort, in which the rate of complete response was 10% and the overall response rate was 40%.

At a median follow-up of 2 years, the survival rate was 97%; one patient died during the study from a non-hematologic cause.

Marked increases in bone marrow cellularity, CD34+ cell number, and frequency of early hematopoietic precursors

Similar relapse rates to historical cohort

Androgens

- Men have higher blood counts than women, driven in part by androgens such as testosterone
- Androgens may increase blood counts in AA (especially in women)
- Androgens may lengthen telomeres – maybe important in AA
High dose cyclophosphamide

- A chemotherapy drug (intravenous) that markedly suppresses the immune system and a component of most BMTs
- Requires hospitalization and vigorous fluids to prevent bladder damage
- Moderate nausea acutely
- May be effective in relapsed patients, but still mostly experimental

Bodakhy RA et al. Blood. 2010;115:2136-

What not to do

If AA is severe – get definitive treatment

- Growth factors alone (erythropoetin/filgrastim) are ineffective
- Corticosteroids alone are ineffective and raise infectious risks
- Androgens alone as initial therapy is too little and usually ineffective
- Cyclosporine alone as initial therapy is too little

Scheinberg P, Young NS. Blood. 2012;120:1185

Late Complications of Aplastic Anemia

- Relapses of AA
- Clonal evolution to Acute Leukemia (up to 15%)
- Secondary cancers
- Infertility from treatments

- BUT THE MAJORITY OF PATIENTS TODAY CAN EXPECT A LONG HEALTHY LIFE WITH CURRENT THERAPIES

©2012 by American Society of Hematology
Pure Red Cell Aplasia

- A related disease
- Failure to make red cells (energy) but white cells and platelets normal
- Bone marrow often without red cell precursors
- Reticulocytes (early red cells) low
- Causes include congenital (Diamond Blackfan – deletion ribosomal protein RPS19) and acquired (idiopathic, autoimmune, thymoma, SLE, etc)
- Treatment includes immune suppression therapies including steroids, rituximab, cyclosporine, ATG, plasmapheresis

Thank you.
Questions?