What you need to know about

Aplastic Anemia

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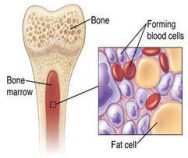
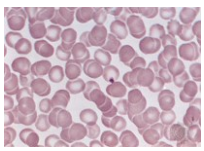
Aplastic Anemia is a bone marrow failure disease



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**

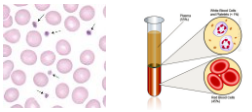


The 4 major components of blood

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

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

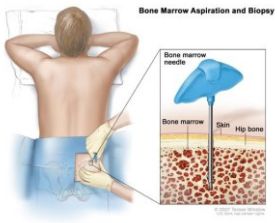
- **Severe Aplastic Anemia (SAA)**
  - Neutrophils less than 0.5 X 10^9/L
  - Platelets less than 20 X 10^9/L
  - Reticulocytes (early red cells) less than 20 X 10^9/L

  At least 2

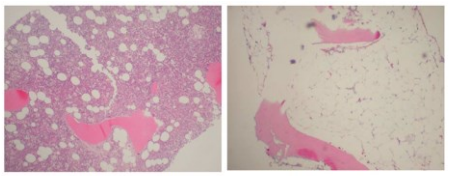
- **Very Severe Aplastic Anemia (VSAA)**
  - Neutrophils less than 0.2 X 10^9/L
  - Platelets less than 20 X 10^9/L
  - Reticulocytes less than 20 X 10^9/L

  At least 2

Making the Diagnosis: The Bone Marrow Biopsy



Making the Diagnosis: The Bone Marrow Biopsy



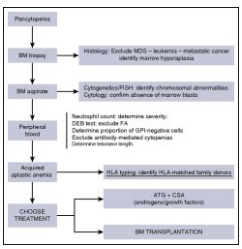
Healthy bone marrow | Aplastic anemia

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



Andrea Bacigalupo Blood 2017;129:1428-1436

blood

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

(The Biology Slides)

- "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

Biology II

- 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

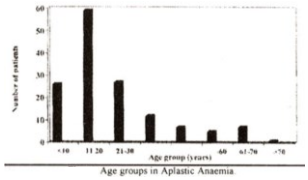
- Idiopathic (unknown)
- Infections – hepatitis, Epstein Barr virus, HIV, parvovirus, mycobacteria
- Exposure to ionizing radiation
- Exposure to toxic chemicals (benzenes, pesticides)
- Transfusional graft-vs-host disease
- Orthotropic liver transplantation
- Pregnancy
- Eosinophillic fasciitis
- Anorexia
- 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

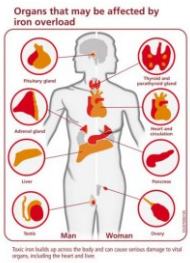
- Treatments depend on the severity of the disease
- For mild cases "supportive care" (occasional transfusions and/or antibiotics) may be sufficient
- For SAA or VSAA emergent treatment is recommended

Blood Transfusions

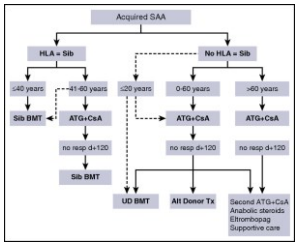
- May be necessary for symptoms of anemia or thrombocytopenia
  - Fatigue and shortness of breath with very low red blood cells
  - Bleeding with very low platelet counts
- Avoidance of family members as blood donors
  - Sensitization to HLA antigens which could raise risk of future transplant
- Minimize 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



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



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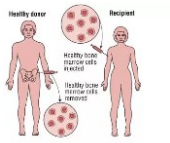
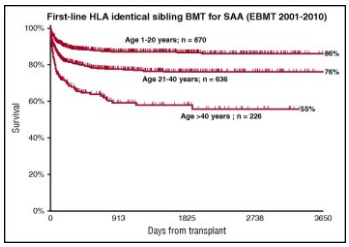
Hematopoeitic Stem Cell Transplantation

- 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



A strong age effect in patients with aplastic anemia, after transplantation from an HLA identical sibling.



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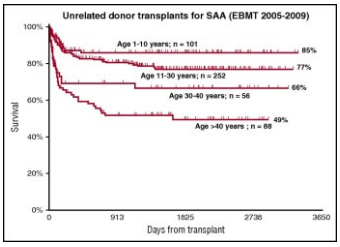
Steps to a transplant

- **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?**

The age effect in UD transplants: best outcome is seen for very young patients, for whom first-line UD BMT may be considered.



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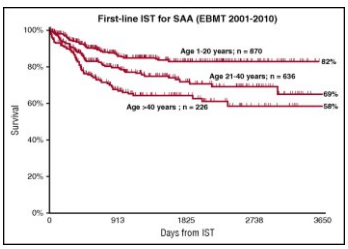
Steps of a transplant

- 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**

The age effect in patients receiving first-line Immunosuppressive Therapy



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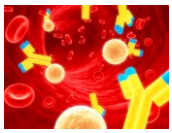
blood

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

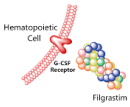
- In some parts of the world horse ATG is not available
- Rabbit ATG was found to be less effective than horse ATG but can work, used in allergic patients and those failing prior treatment
- Higher early complication rate with rabbit ATG

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

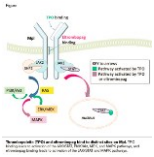
G-CSF (filgrastim)

- 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

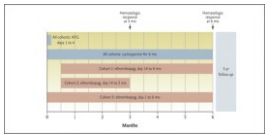
The complete response rates were 26-58% and **the overall response rates at 6 months were 80%, 87%, and 94%, respectively.**

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 66%.

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

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

Similar relapse rates to historical cohort



Townsley D et al: N Engl J Med 2017; 376:1540

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

Calado RT et al. Blood. 2009;114:2236-

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

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

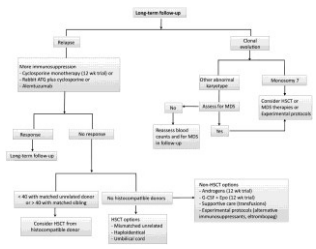
What not to do

If AA is severe – get definitive treatment

- Growth factors alone (erythopoeitin/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

Long-term follow-up after immunosuppression.



Philip Scheinberg, and Neal S. Young Blood 2012;120:1185-1196

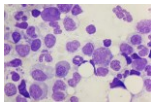
blood

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

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?