Goals for today

- Hematology basics: blood cells, bone marrow, and bone marrow failure
- Diagnosis of aplastic anemia
- Overview of aplastic anemia therapies
  - Transplant
  - Immunosuppressive therapy
- Long-term follow-up
Hematology Basics (1): Blood Cells

- **WBC**: white blood cells, immune cells.
  - **Neutrophils**: immune cells that protect from bacterial and other infections.
  - **ANC**: absolute neutrophil count.
  - **Neutropenia**: low neutrophil count.
  - **Lymphocytes**: immune cells that protect from viral, fungal and other infections.
  - In aplastic anemia, lymphocytes attack bone marrow stem cells.

- **RBC**: red blood cells, carry oxygen.
  - Contain **hemoglobin** (protein that carries oxygen).
  - **Anemia**: low hemoglobin.
  - Low hemoglobin can make you feel tired and short of breath with activity.
  - **Reticulocytes**: baby red blood cells.

- **Plt**: platelets, clotting cells.
  - **Thrombocytopenia**: low platelet count.
  - Low platelets lead to excessive bleeding and bruising.
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Hematology Basics (2): Blood cells are made in the **Bone Marrow**
Symptoms and Presentation of Aplastic Anemia

- Low neutrophils
- Low hemoglobin
- Low platelets
Bone Marrow Biopsy Results in Aplastic Anemia

Normal

Aplastic Anemia

“Hypocellular” (too few cells)

Can be patchy some residual cells
What is Bone Marrow Failure?

Bone marrow failure is a condition when a bone marrow does not make enough blood cells to sustain normal life.

- Low Blood Counts
- Hypocellular Bone Marrow

Bone Marrow Failure
Bone marrow failure can have many different causes, one of which is aplastic anemia.

Possible causes of bone marrow failure include:

- Medications or toxins
- Infections
- Inflammation and autoimmune diseases
- Nutritional deficiencies
- Myelodysplastic syndrome (MDS)
- Other rare causes

A large number of patients with bone marrow failure have no apparent cause. Of these:

- Majority have immune-mediated aplastic anemia (called acquired aplastic anemia, or aplastic anemia)
- Some have congenital bone marrow failure, caused by genetic mutations

Important to identify the cause correctly because treatment can differ for different causes.
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- Important to identify the cause correctly because **treatment can differ for different causes**
Diagnosis of Aplastic Anemia

Low blood counts + hypocellular bone marrow
• Diagnosis of bone marrow failure is made
• Aplastic anemia is suspected
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Exclusion of inherited bone marrow failure syndromes

Exclusion of transient causes of bone marrow failure

Referral to a center with expertise in bone marrow failure and aplastic anemia

Transfusion support

2-4 weeks
Diagnosis of Aplastic Anemia

- Low blood counts + hypocellular bone marrow
  - Diagnosis of bone marrow failure is made
  - Aplastic anemia is suspected

- Exclusion of transient causes of bone marrow failure
- Exclusion of inherited bone marrow failure syndromes
- Referral to a center with expertise in bone marrow failure and aplastic anemia
- Transfusion support

~50% of patients may have laboratory findings specific for immune-mediated aplastic anemia
- PNH clones
- 6p LOH clones allowing for faster diagnosis

2-4 weeks
Aplastic anemia is rare, and can occur in patients of any age, sex, race and ethnicity.

Estimated 600-900 cases of aplastic anemia in the USA per year.
For most patients, no cause or trigger of aplastic anemia can be identified.

However, certain rare associations with aplastic anemia have been described:

- Genetic differences in several immune genes (e.g., Human Leukocyte Antigen genes).
- Rare inflammatory and immune conditions (e.g., non-viral autoimmune hepatitis, eosinophilic fasciitis).
- Cancer immunotherapies.
- Certain medications (some antibiotics (e.g., chloramphenicol), antiepileptics).
- Pregnancy.
- Viral infections.
- Environmental exposures (e.g., benzene, solvents).
- Others.
Aplastic anemia and its therapies at a glance

Lymphocytes attack and destroy stem and progenitor cells in the bone marrow

Aplastic bone marrow with few stem cells

1. Prevent further lymphocyte attack on the bone marrow
   - IST: ATG, cyclosporine
   - BMT: conditioning

2. Make more stem cells
   - IST: eltrombopag, allow time for cells to regrow
   - BMT: replace with donor stem cells
Aplastic anemia and its therapies at a glance

**Lymphocytes** attack and destroy stem and progenitor cells in the bone marrow.

**Stem cells** in aplastic bone marrow with few stem cells.

**Two main approaches**

**IST: immunosuppressive therapy**

1. Prevent further lymphocyte attack on the bone marrow
   - IST: ATG, cyclosporine
   - BMT: conditioning

2. Make more stem cells
   - IST: eltrombopag, allow time for cells to regrow
   - BMT: replace with donor stem cells

**BMT: bone marrow transplant**
Aplastic Anemia Severity Determines Treatment Approach

Very Severe Aplastic Anemia (VSAA)

Severe Aplastic Anemia (SAA)

Non-Severe Aplastic Anemia (NSAA)

NSAA can have varying degrees of low blood counts. Blood counts in one of the lineages may be low enough to require transfusions.
Aplastic Anemia Severity Determines Treatment Approach

**Very Severe Aplastic Anemia (VSAA):** same as SAA but ANC < 200 cells/µL

**Severe Aplastic Anemia (SAA):** 2 of 3 of the following
ANC < 500 cells/µL, reticulocytes < 60*10^3 cells/µL, Plt < 20*10^3 cells/µL

NSAA can have varying degrees of low blood counts
Blood counts in one of the lineages may be low enough to require transfusions

**Non-Severe Aplastic Anemia (NSAA):** not meeting criteria for SAA
Treatment of non-severe aplastic anemia (NSAA) can vary

- Stable, mildly low blood counts, not requiring transfusions:
  - Can be observed with close blood count follow-up without active therapy

- Moderately low blood counts, causing symptoms or progressive blood count decline:
  - Typically managed with medicines (e.g., with immunosuppressive therapy with or without eltrombopag, danazol, etc.)

- Moderate to severe reduction in blood counts, requiring transfusion support
  - Treatment intensity varies, frequently managed similar to Severe Aplastic Anemia (SAA)
### Severe and Very Severe Aplastic Anemia Therapy

**Patient’s age**

<table>
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<tr>
<th>Age &lt;40 (*) years</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>Matched Sibling Donor (MSD) Available*</td>
<td>MSD Bone Marrow Transplant</td>
<td>Immunosuppressive therapy (IST) + eltrombopag</td>
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Severe and Very Severe Aplastic Anemia Therapy

Patient’s age

Age <40 (*) years

Bone Marrow Donor Availability

Matched Sibling Donor (MSD) Available*
Severe and Very Severe Aplastic Anemia Therapy

Patient’s age

- Age <40 (* years

Bone Marrow Donor Availability

- Matched Sibling Donor (MSD) Available?
  - Yes
    - MSD Bone Marrow Transplant
  - No
    - Yes
      - Immunosuppressive therapy (IST) + eltrombopag
    - No
      - No

Recommended Therapy
Severe and Very Severe Aplastic Anemia Therapy (*)

Patient’s age

Bone Marrow Donor Availability

Recommended Therapy

Improving transplant outcomes in adults allow for transplant consideration in select middle-aged adults: ~ 40-50 years

Improving outcomes with matched unrelated donors (MUD) can make MUD transplant feasible in some pediatric patients based on donor availability, rapidity of transplant and center experience

Bone Marrow Transplant

Immunosuppressive therapy (IST) + eltrombopag*

Immunosuppressive therapy (IST) + eltrombopag

* Ertrombopag is usually added to IST in adults, and may be added in children as a part of upfront IST
Transplantation for Aplastic Anemia: Overview

Hospitalization (~ 4 weeks)
- Conditioning: Chemotherapy +/- radiation
- Infusion of donor bone marrow cells
- Blood count recovery
- Discharge from the hospital
  - Taking medications to prevent GVHD, infection, rejection
  - In most cases do not need transfusions on discharge
- Taper of immunosuppressive medications
- Long-term survival free of aplastic anemia

Possible complications, some of which can be life-threatening, include: allergic reactions to ATG, serum sickness, organ toxicity from chemotherapy and medications, infections, graft failure/graft rejection, graft-versus-host disease, infertility
Younger Aplastic Anemia Patients Benefit the Most from Transplant

Probability of survival after matched sibling donor transplant for aplastic anemia adjusted for performance score, time to transplant and conditioning regimen

Gupta et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. Haematologica 2010;95(12):2119-2125
Transplant Outcomes Have Improved Over Time

Survival of Aplastic Anemia Patients Receiving Stem Cell Transplant

**Age < 18 years old**

- 2016-2018 (n=355)
- 2011-2015 (n=486)
- 2006-2010 (n=441)
- 2001-2005 (n=278)

**Age 18 years and older**

- 2016-2018 (n=490)
- 2011-2015 (n=714)
- 2006-2010 (n=533)
- 2001-2005 (n=338)

Transplant from Matched Related Donors Has Better Outcomes than from Unrelated Donors

Survival of Aplastic Anemia Patients Receiving Stem Cell Transplant

Age < 18 years old

Age 18 years and older

Transplants for patients older than 40 years still carry significant risk of mortality

The 5-year overall survival of patients aged:
- 40 to 49 years: 67%
- 50 to 59 years: 58%
- >60 years: 45%

Graft failure: 10-15%
Acute GVHD grade II-IV: 11-15%
Chronic GVHD: 25-31%

EBMT Severe Aplastic Anemia Working Party, Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved?, Blood, 2018, Figure 1.
Patient outcomes are better in centers with more experience in treating aplastic anemia patients

Survival of patients >40 years old receiving transplant for aplastic anemia

Bacigalupo and Benintende, Bone marrow transplantation for acquired aplastic anemia: What’s new, Best Practice & Research Clinical Haematology, Volume 34, Issue 2, June 2021, 101284
Immunosuppressive Therapy (IST) for Aplastic Anemia: Overview

**IST**
- Horse ATG (intravenous)
- Cyclosporine (oral)
- + Eltrombopag (oral)

**Hospitalization (~ 7 days)**
- Transfusion support
- Blood count improvement takes 3-6 months

**Discharge from the hospital**
- Taking medications: cyclosporine + eltrombopag
- Steroids to prevent serum sickness
- Medicines to prevent infections

**Eltrombopag stopped at ~6 mo.**
- Cyclosporine continued for about 2 years

Possible complications, some of which can be life-threatening, include:
- allergic reactions to ATG, serum sickness, side-effects of medications, infections, prolonged time to recover blood counts,
- refractory disease, risk of relapse, risk of long-term clonal evolution (PNH, MDS)
Response to immunosuppression + eltrombopag is \(~80\%\) at 3 months
(horse ATG + cyclosporine)

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<th>Responses</th>
<th>After 3 months</th>
<th>After 6 months</th>
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<tr>
<td>Partial</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>Complete</td>
<td>30%</td>
<td>39%</td>
</tr>
<tr>
<td>Total Response</td>
<td>80%</td>
<td>87%</td>
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Townsley et al. Eltrombopag added to standard immunosuppression for aplastic anemia, NEJM 2017: 376: 1540-50
IST with eltrombopag leads to bone marrow recovery

Townsley et al. Eltrombopag added to standard immunosuppression for aplastic anemia, NEJM 2017: 376: 1540-50
Response to immunosuppression without eltrombopag is ~62% at 3 months (horse ATG + cyclosporine)

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<tr>
<td>Horse ATG + cyclosporine</td>
<td>62%</td>
<td>68%</td>
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<tr>
<td>Rabbit ATG + cyclosporine</td>
<td>33%</td>
<td>37%</td>
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Scheinberg et al. Horse versus rabbit ATG in acquired aplastic anemia, NEJM 2011 365(5):430-8
Cyclosporine is essential to maintain durability of remission

Probability of relapse was higher when cyclosporine was stopped early in the course of therapy

For most patients, second remission can be achieved by resuming cyclosporine and/or eltrombopag

Townsley et al. Eltrombopag added to standard immunosuppression for aplastic anemia, NEJM 2017: 376: 1540-50
Long-term follow-up of aplastic anemia patients

- **Post-IST:**
  - blood count follow-up
  - monitor for relapse or disease evolution
    - PNH
    - MDS (10-15%)

- **Post-BMT:**
  - follow-up by a survivorship program at a transplant center