Penn Medicine
Abramson Cancer Center

# Understanding Aplastic Anemia

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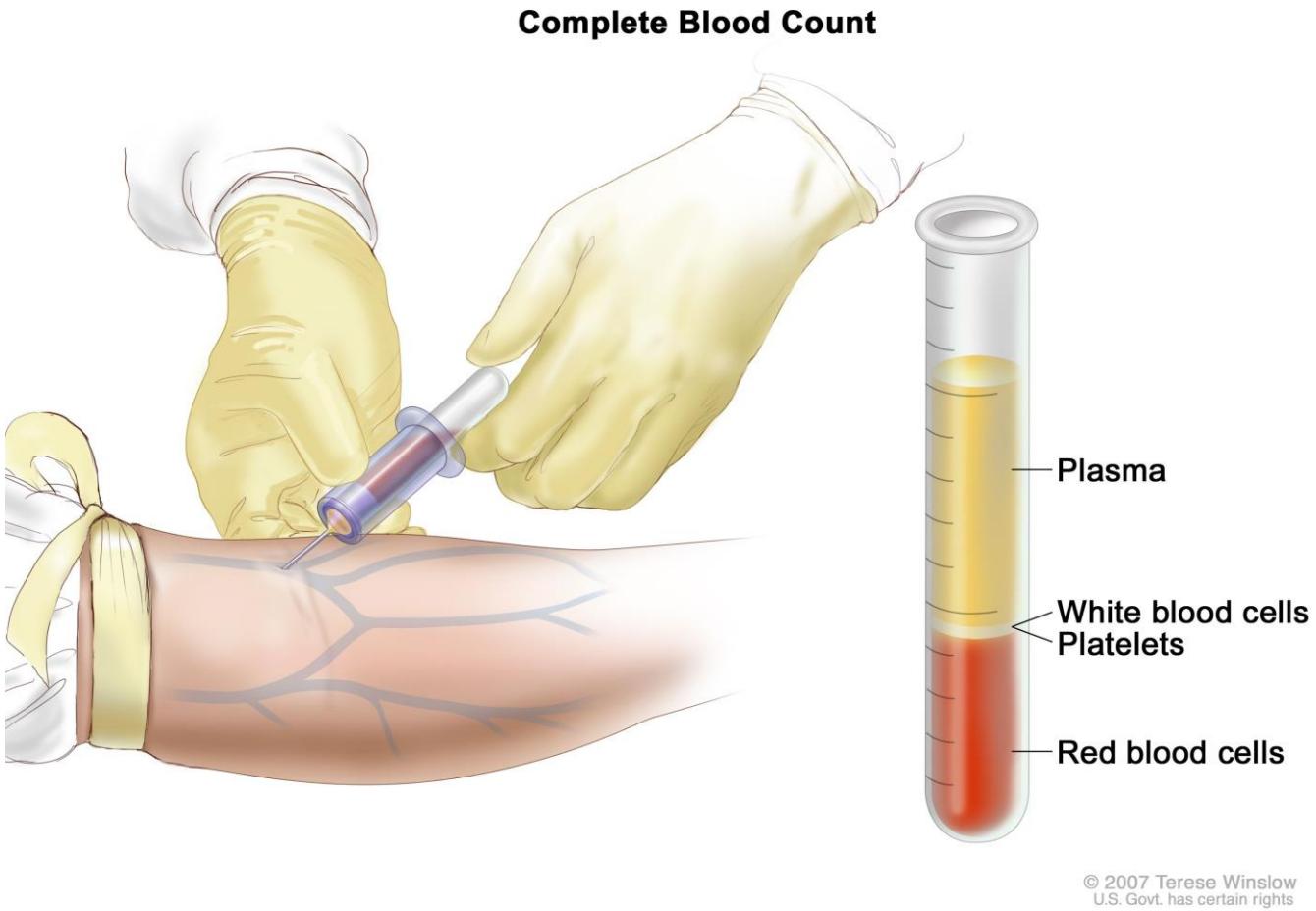
# Goals for today

- 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.

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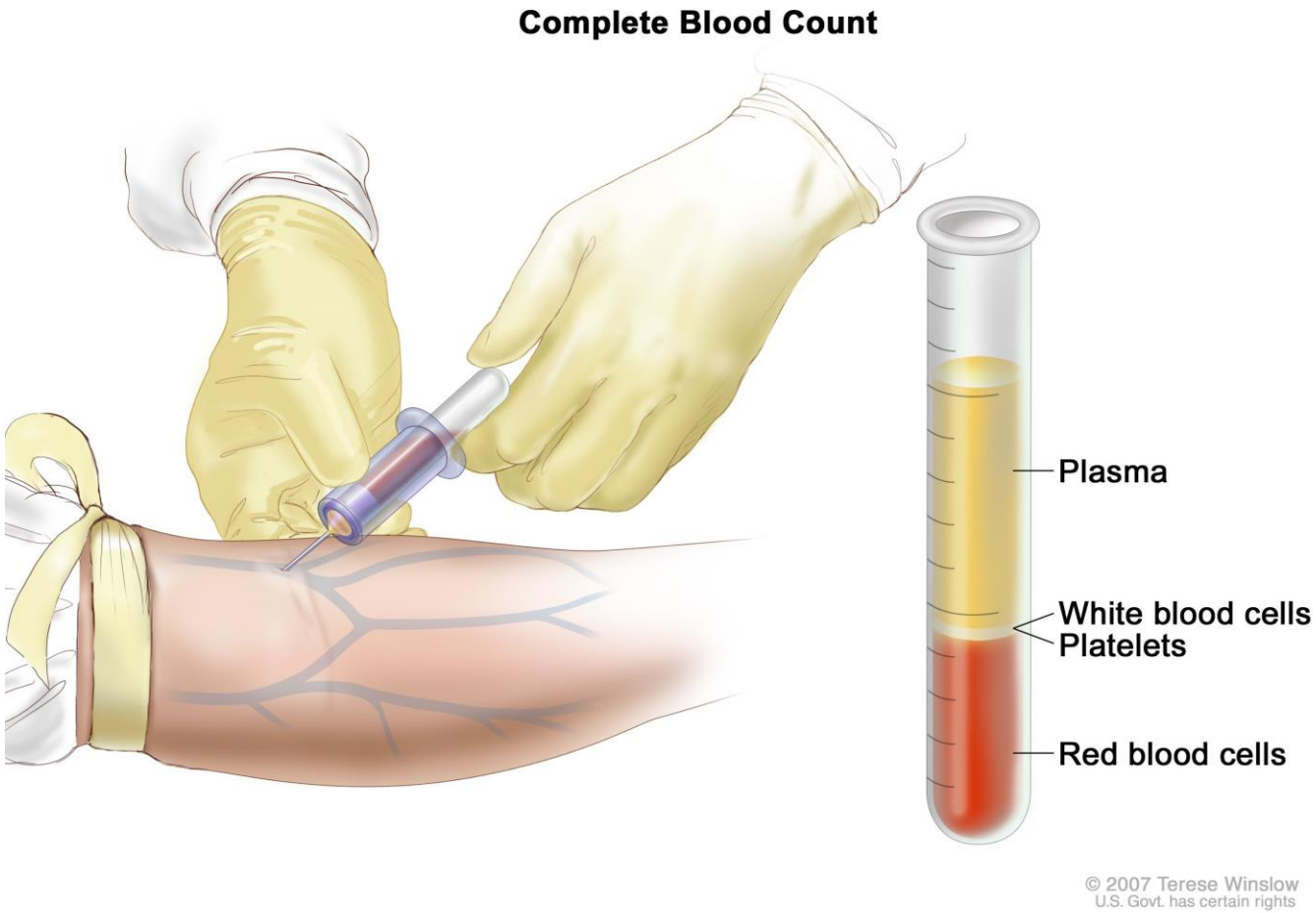


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- **RBC**: **red blood cells**, carry oxygen.
  - Contain **hemoglobin** (protein that carries oxygen).
  - **Anemia**: low hemoglobin.
  - Low hemoglobin can make you feel tired and short of breath with activity.
  - **Reticulocytes:** baby red blood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

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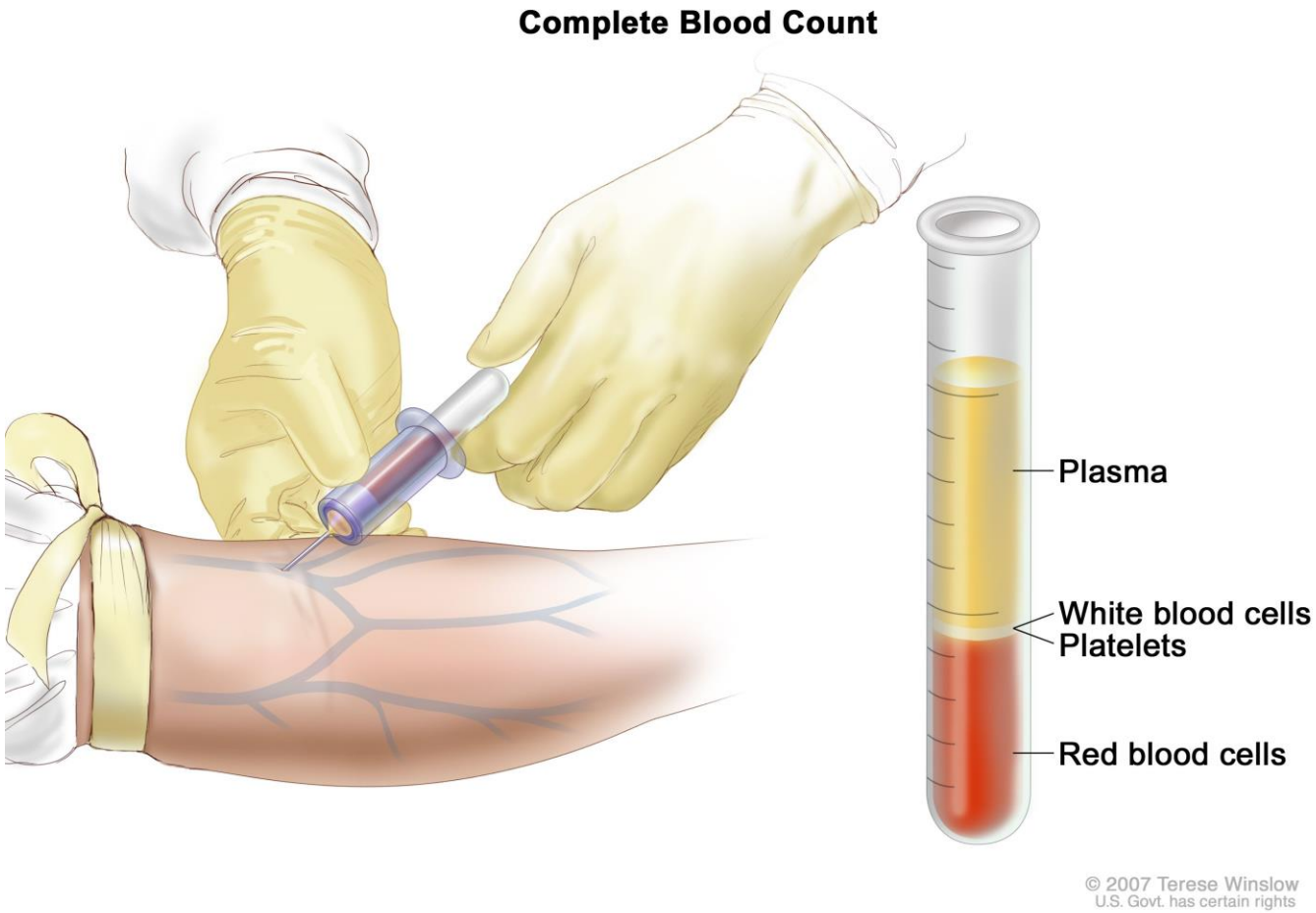


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  - **Reticulocytes:** baby red blood cells
- **Plt**: **platelets**, clotting cells
  - **Thrombocytopenia**: low platelet count
  - Low platelets lead to excessive bleeding and bruising.

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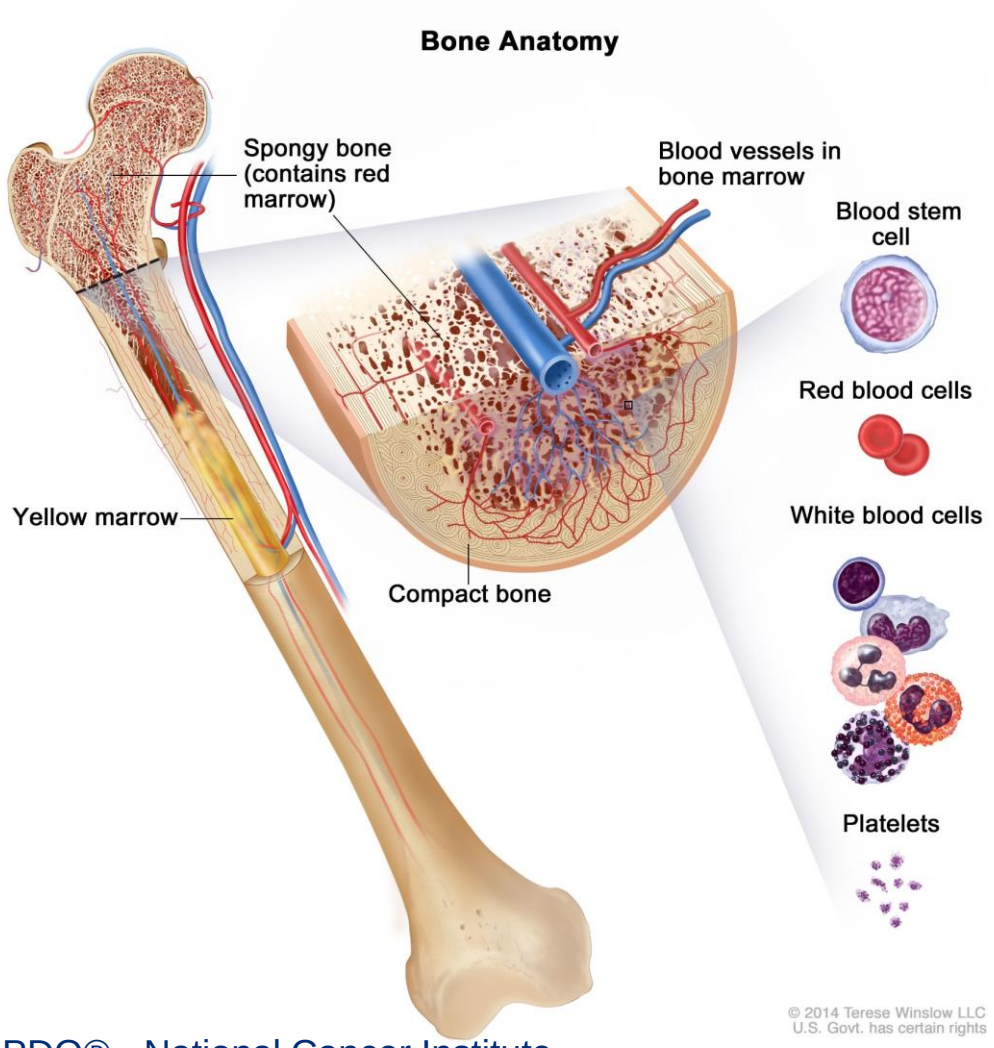
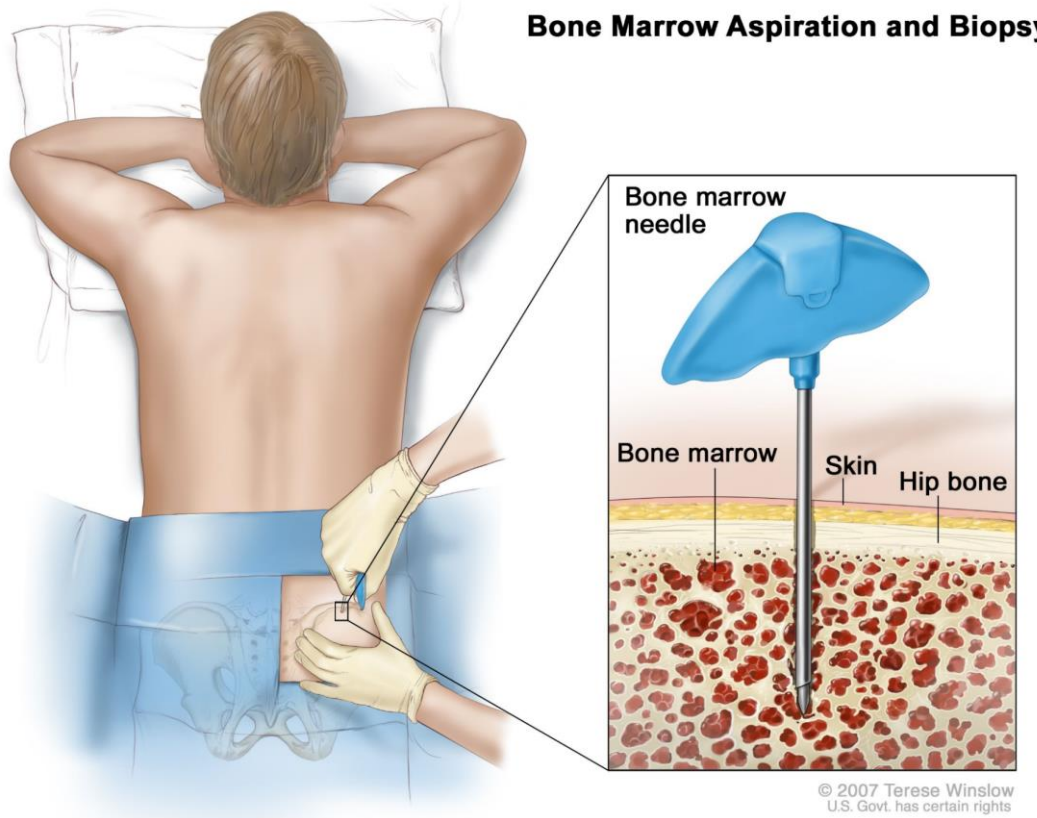
# Hematology Basics (2): Blood cells are made in the **Bone Marrow**

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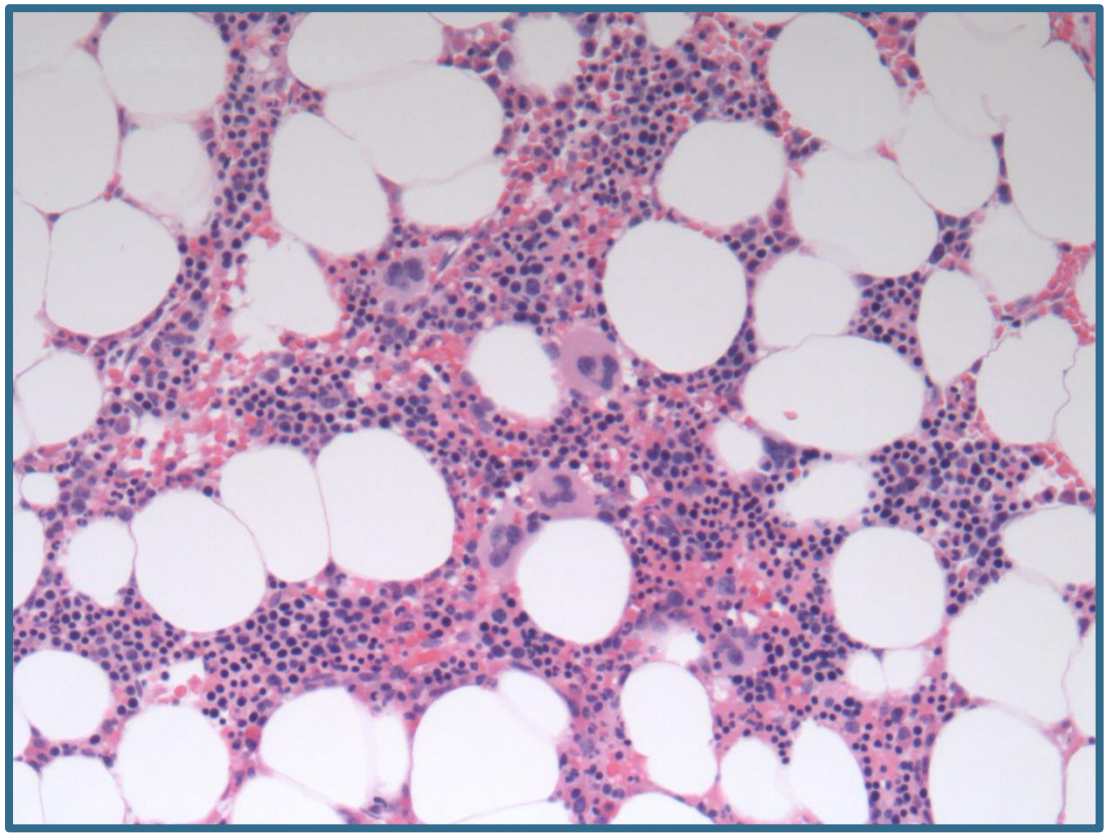
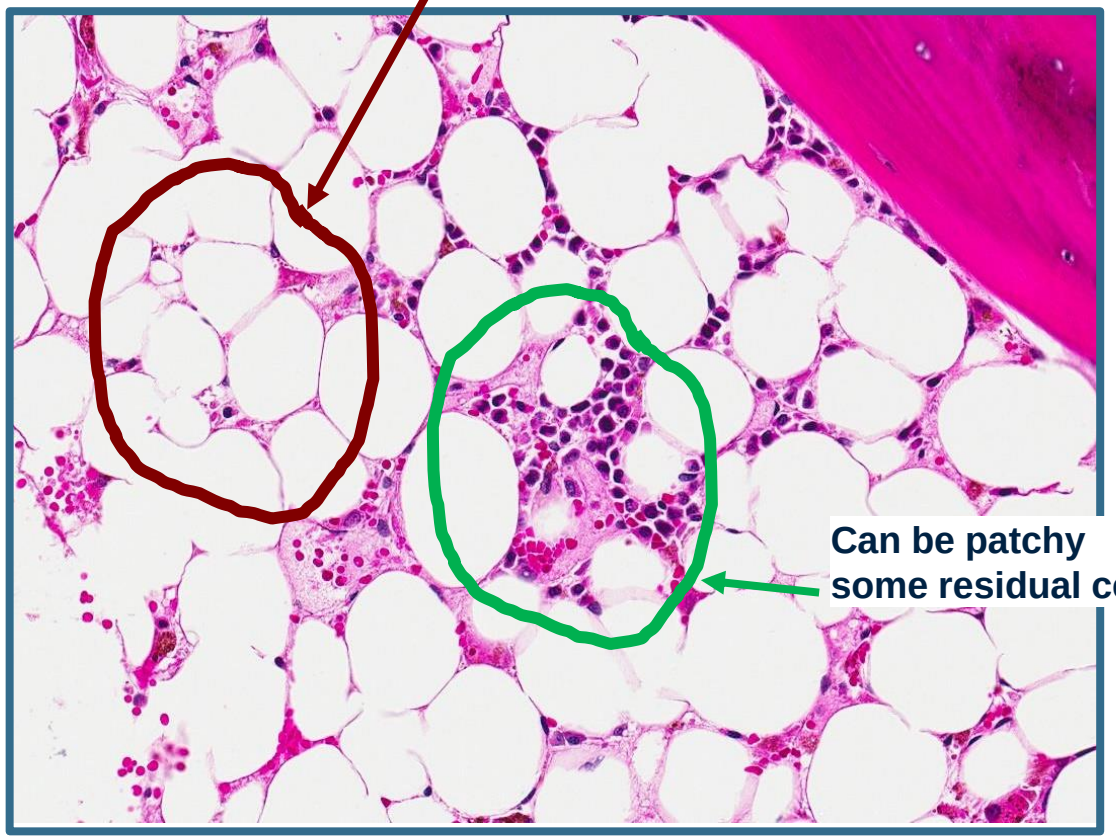
# Symptoms and Presentation of Aplastic Anemia


- Low neutrophils
- Low hemoglobin
- Low platelets

# Bone Marrow Biopsy Results in Aplastic Anemia

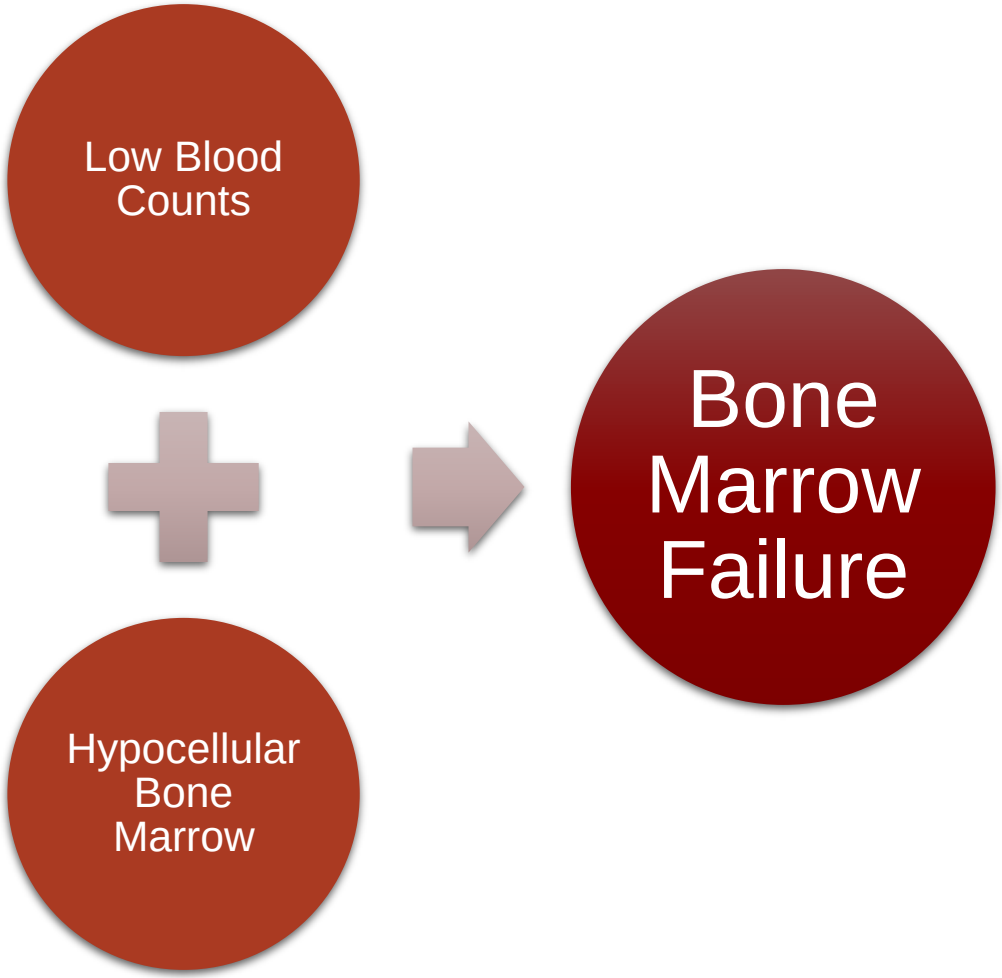


Normal




Aplastic Anemia

# 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

# Bone marrow failure can have many different causes, one of which is aplastic anemia

# 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

# Bone marrow failure can have many different causes, one of which is aplastic anemia

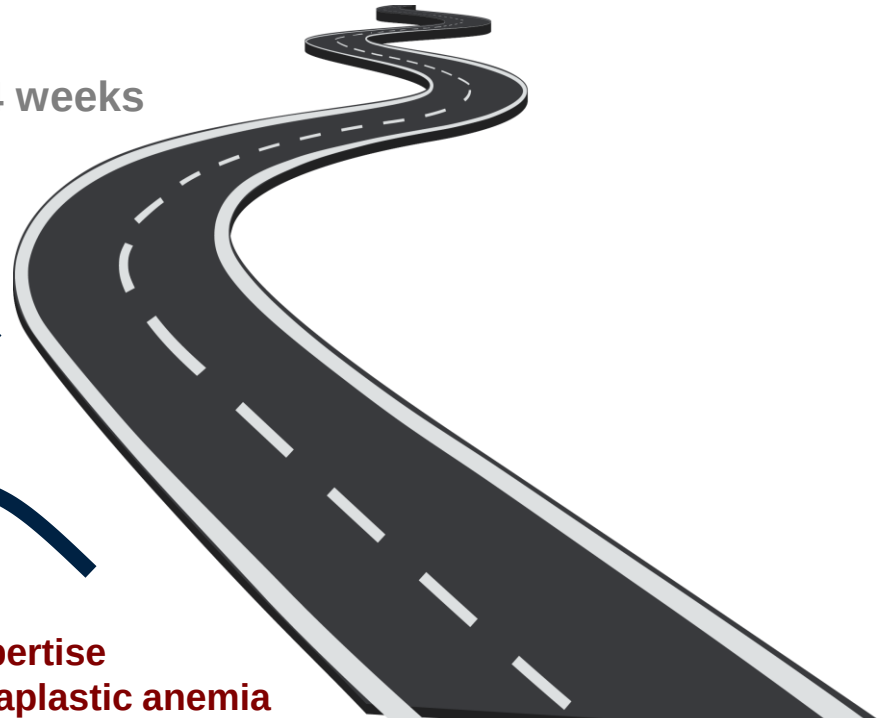
- Possible causes of bone marrow failure include:
  - Medications or toxins
  - Infections
  - Inflammation and autoimmune diseases
  - Nutritional deficiencies
  - Myelodysplastic syndrome (MDS)
  - Other rare causes
- A large number of patients with bone marrow failure have no apparent cause. Of these:
  - 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

# Diagnosis of Aplastic Anemia

Low blood counts + hypocellular bone marrow

- Diagnosis of bone marrow failure is made
- Aplastic anemia is suspected

# Diagnosis of Aplastic Anemia

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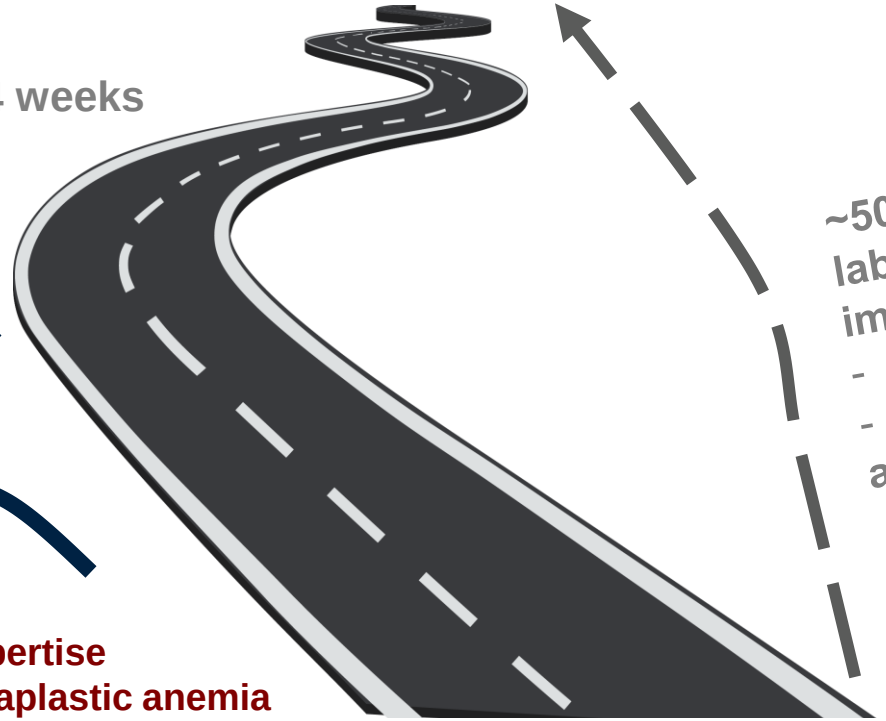



**Exclusion of inherited bone marrow failure syndromes**

**Exclusion of transient causes of bone marrow failure**

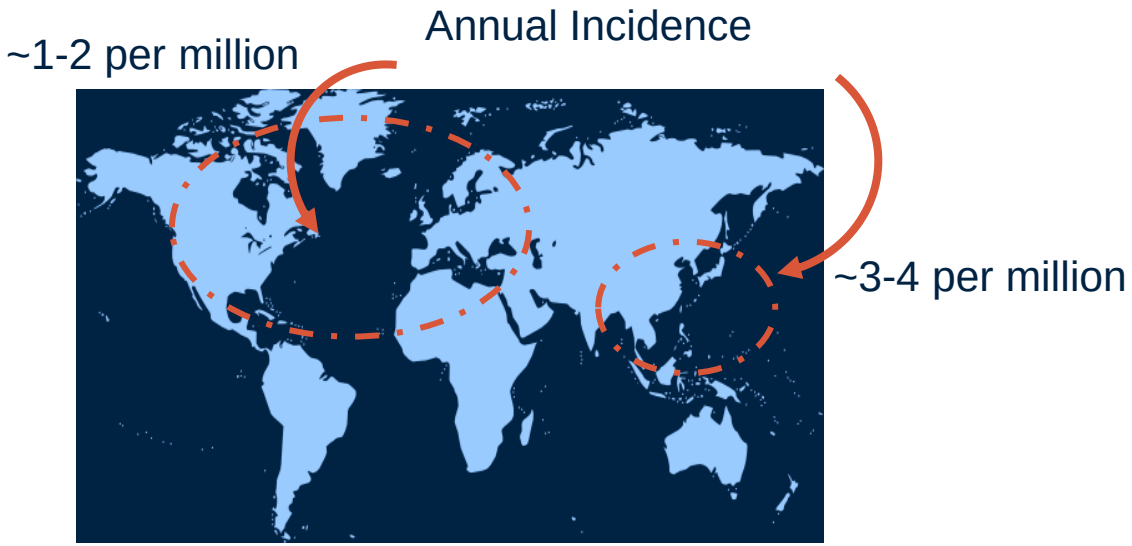
**Referral to a center with expertise In bone marrow failure and aplastic anemia**

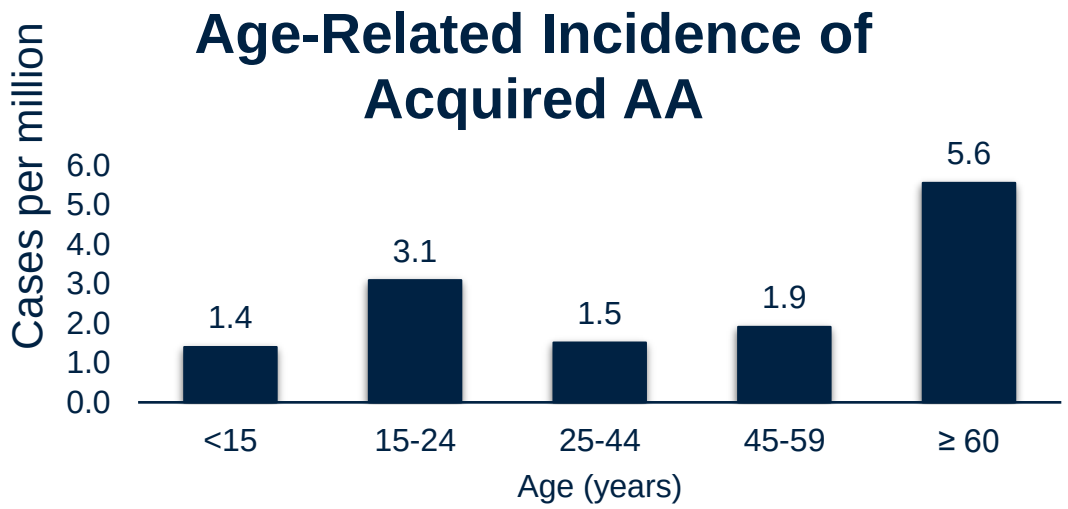
**Transfusion support**

Low blood counts + hypocellular bone marrow

- Diagnosis of bone marrow failure is made
- Aplastic anemia is suspected

# 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**

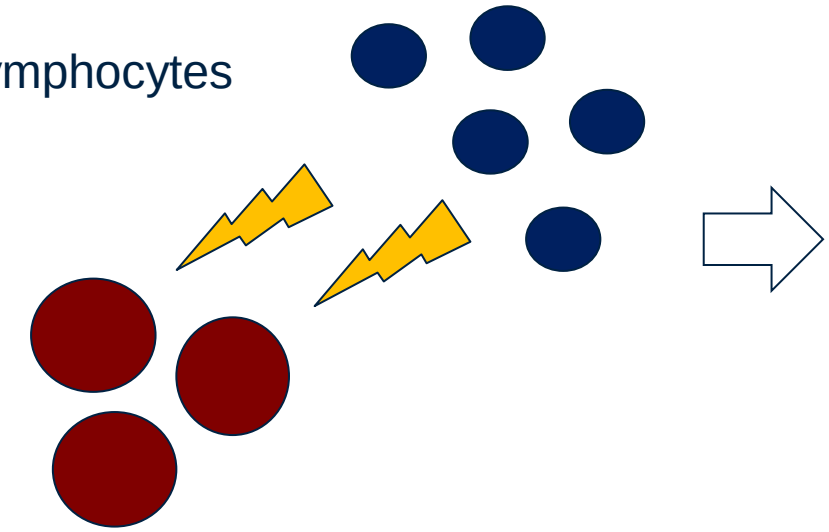
# For most patients, no cause or trigger of aplastic anemia can be identified

- 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

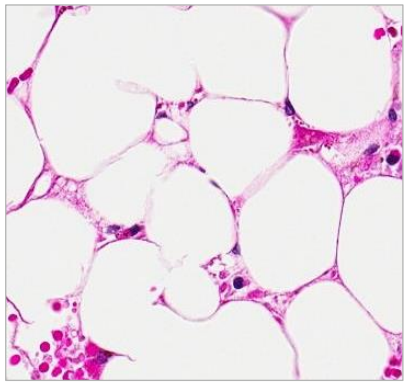
Lymphocytes attack and destroy stem and progenitor cells in the bone marrow

Lymphocytes



Stem cells

Aplastic bone marrow with few stem cells



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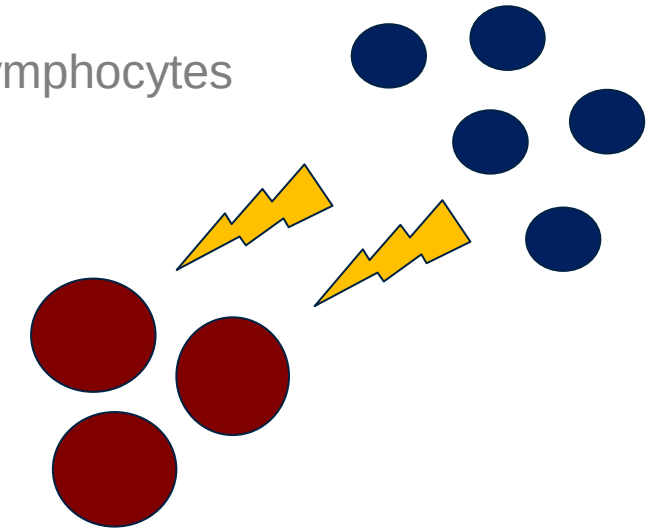
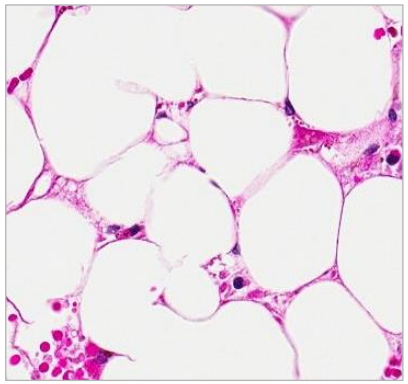


Stem cells

Aplastic bone marrow with few stem cells



<u>Two main approaches</u>

IST: immunosuppressive therapy
BMT: bone marrow transplant

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 Severity Determines Treatment Approach

**Very Severe Aplastic Anemia (VSAA)**

**Severe Aplastic Anemia (SAA)**

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)**

# 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)

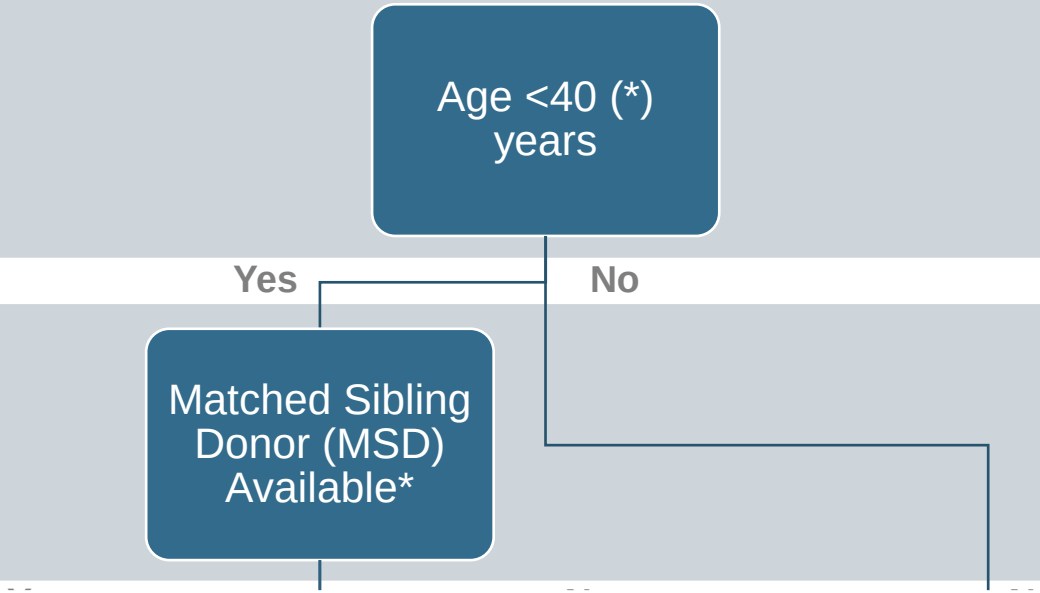
# Severe and Very Severe Aplastic Anemia Therapy

## Patient's age

# Severe and Very Severe Aplastic Anemia Therapy

Patient's age

Bone Marrow Donor Availability

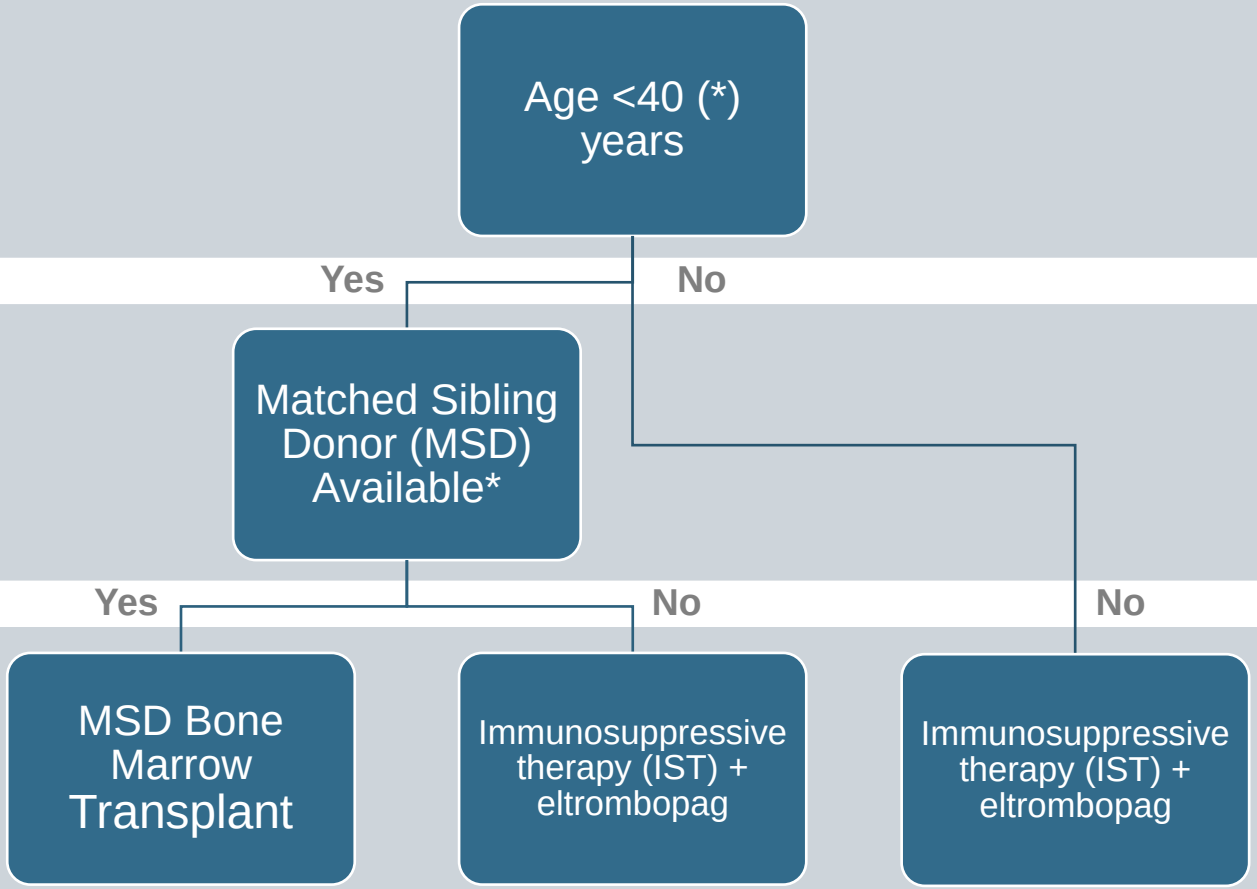


# Severe and Very Severe Aplastic Anemia Therapy

Patient's age

Bone Marrow Donor Availability

Recommended Therapy



# Severe and Very Severe Aplastic Anemia Therapy (*)

## Patient's age

Age <40* years

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

Yes

No

## Bone Marrow Donor Availability

**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**

Matched Sibling Donor (MSD) Available*

Yes

No

No

## Recommended Therapy

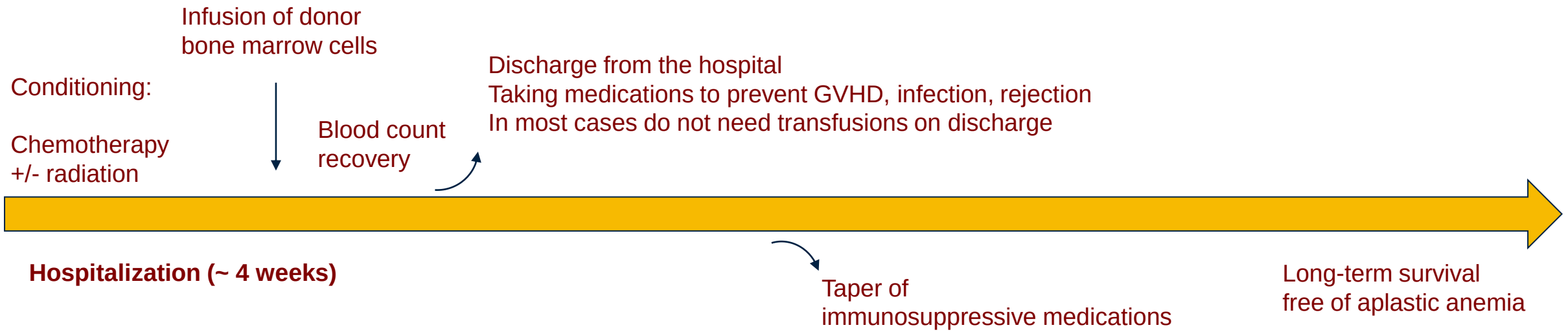
Bone Marrow Transplant

Immunosuppressive therapy (IST) + eltrombopag*

Immunosuppressive therapy (IST) + eltrombopag

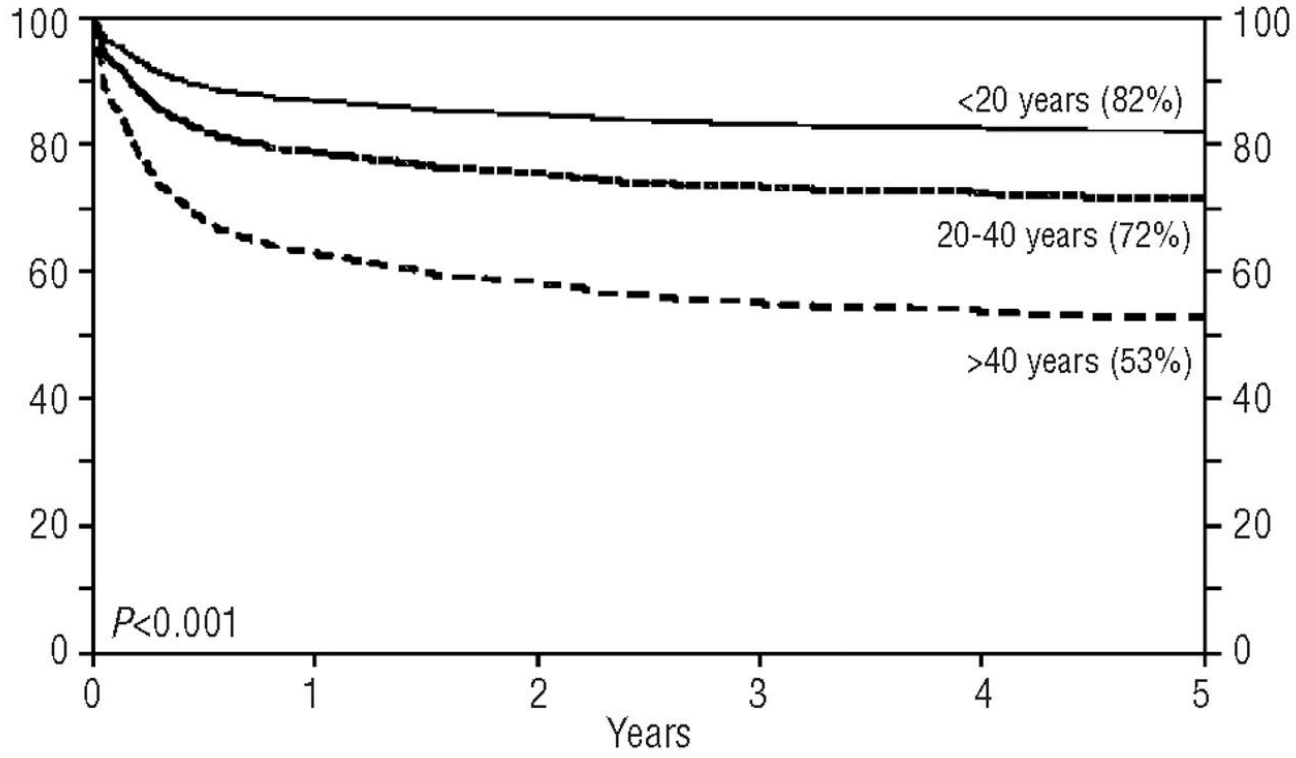
*** Eltrombopag is usually added to IST in adults, and may be added in children as a part of upfront IST**

# Transplantation for Aplastic Anemia: Overview




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



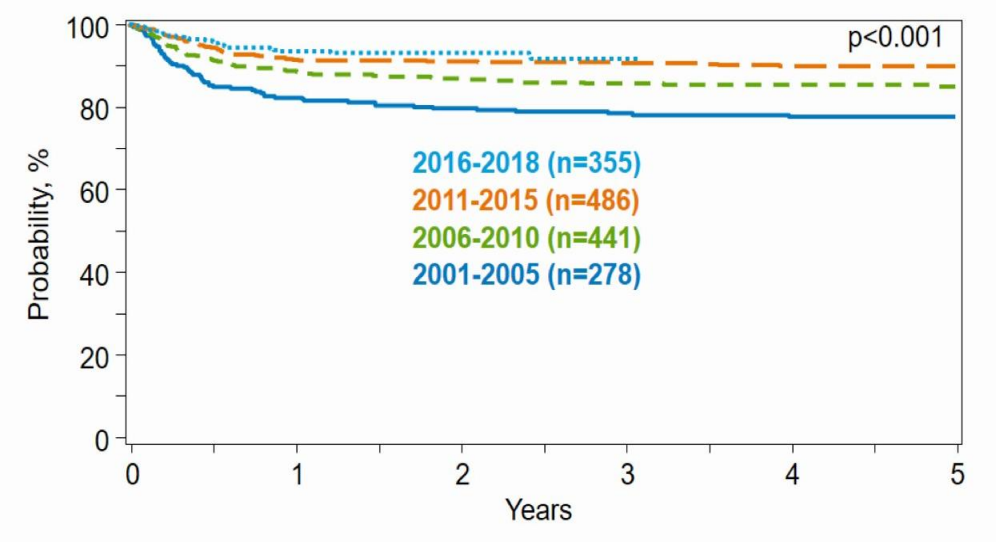

**Probability of survival after matched sibling donor transplant for aplastic anemia adjusted for performance score, time to transplant and conditioning regimen**

**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**)**

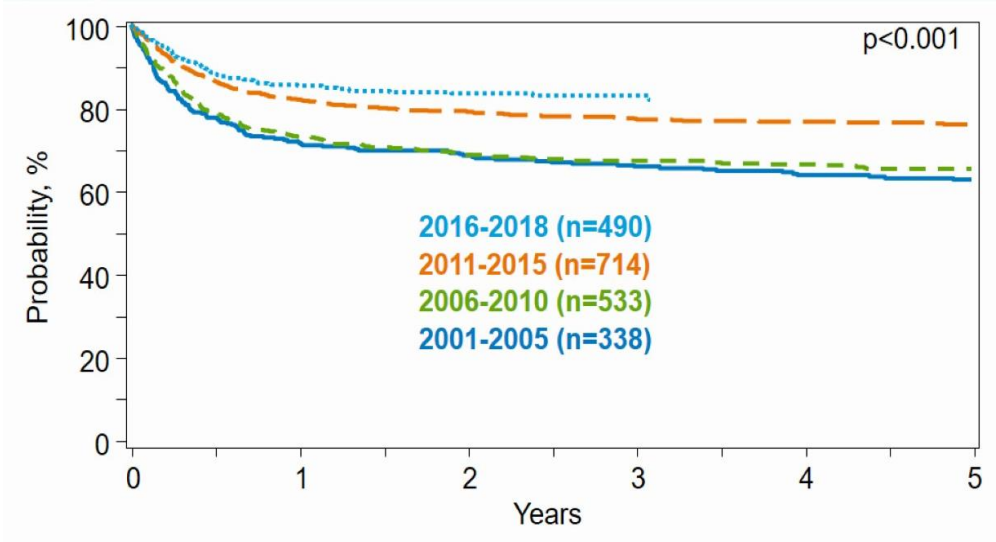
# Transplant Outcomes Have Improved Overtime

**Survival of Aplastic Anemia Patients Receiving Stem Cell Transplant**

**Age < 18 years old**




**Age 18 years and older**




Phelan, R., Arora, M., Chen, M. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2020.

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

**Survival of Aplastic Anemia Patients Receiving Stem Cell Transplant**

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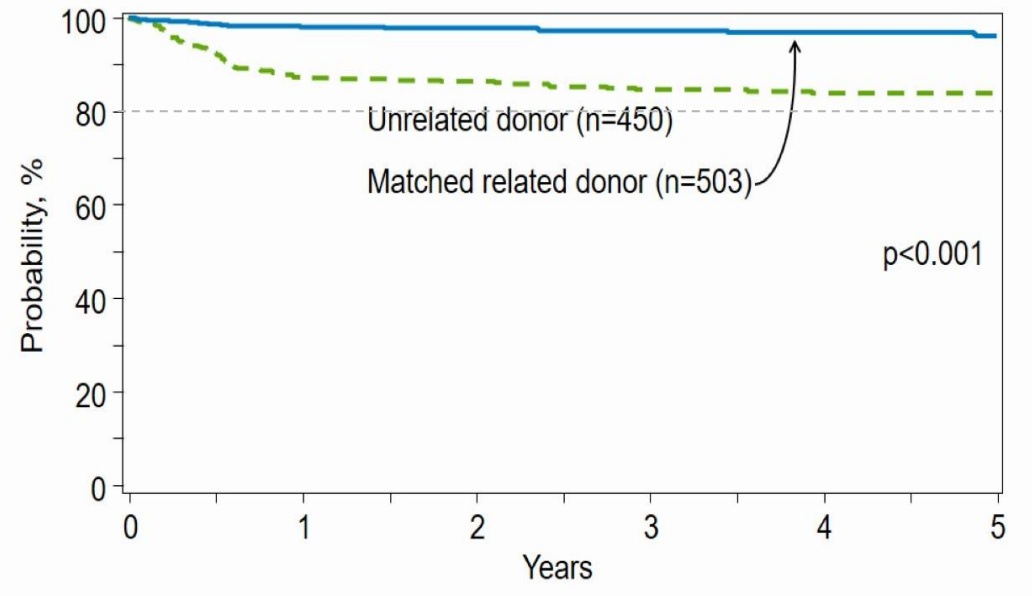


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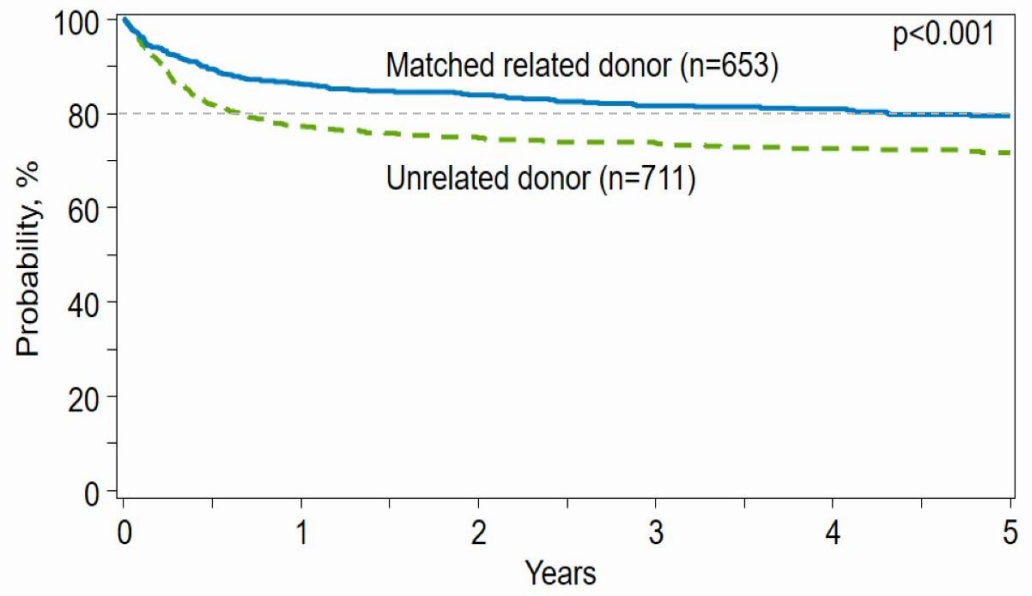
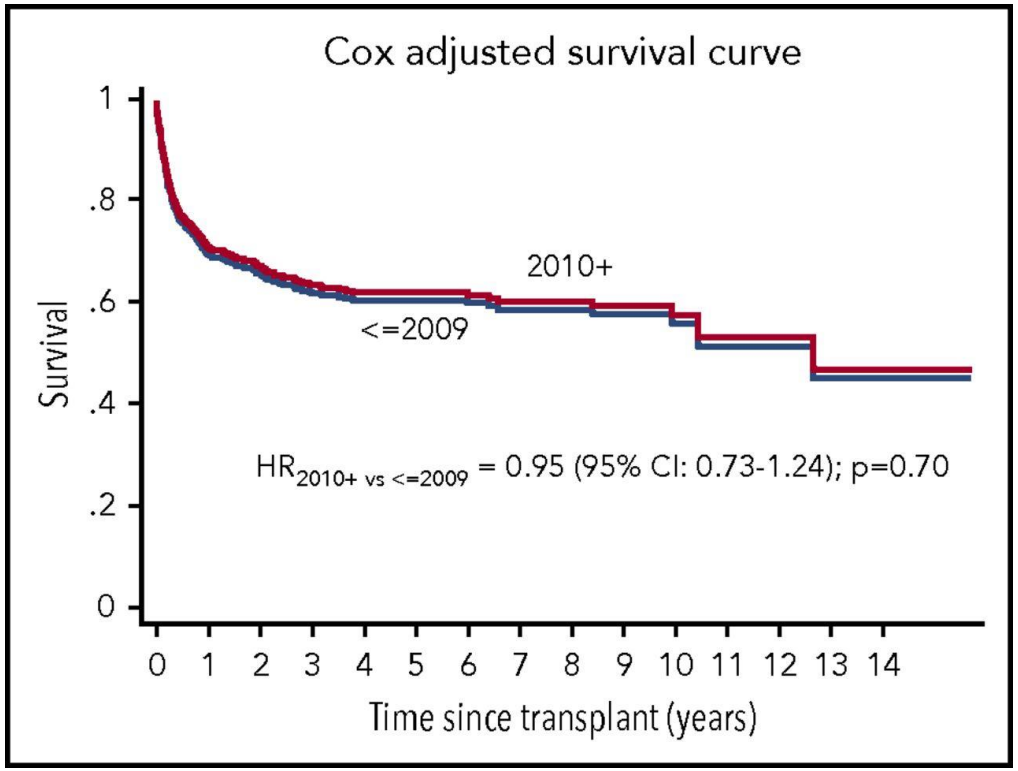



Phelan, R., Arora, M., Chen, M. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2020.

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



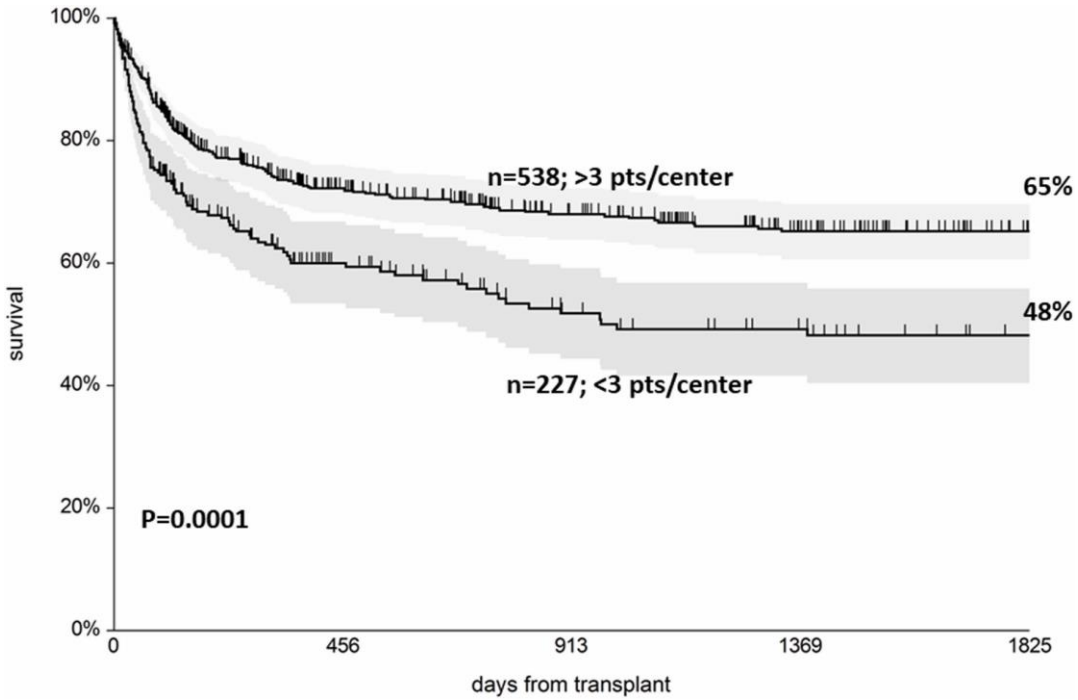

The 5-year overall survival of patients aged:
40 to 49 years: 67%
50 to 59 years: 58%
>60 years: 45%

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.

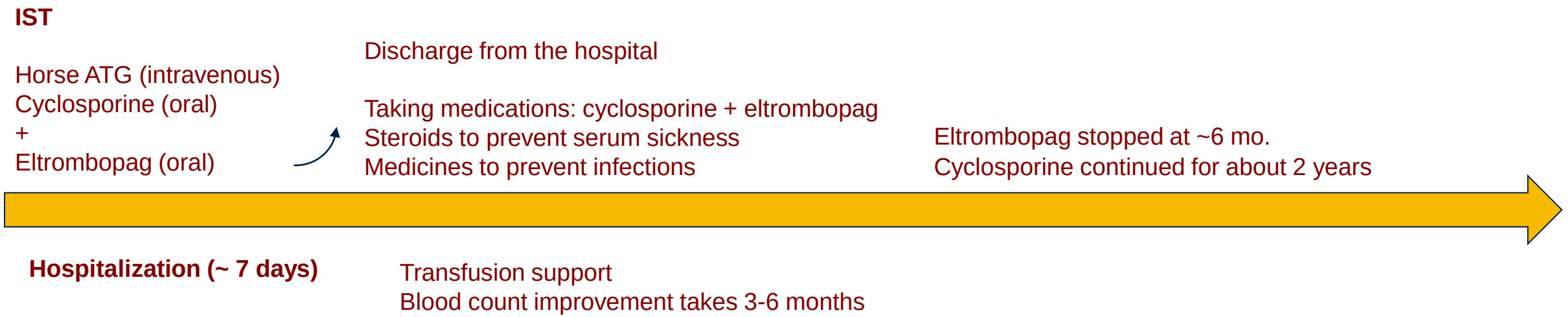
# Patient outcomes are better in centers with more experience in treating aplastic anemia patients

**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




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)**

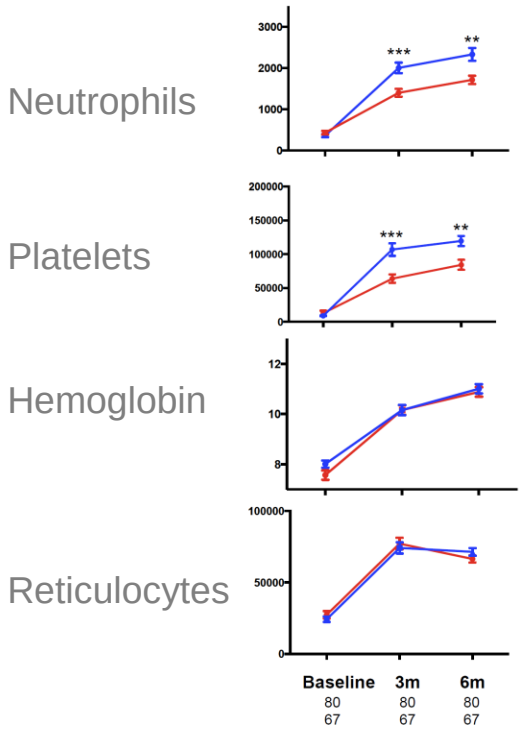
| Responses | After 3 months | After 6 months |
|---|---|---|
| Partial | 50% | 48% |
| Complete | 30% | 39% |
| Total Response | 80% | 87% |

Table 2. Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.*

| Cohort and Response | Rate at 3 Mo | Rate at 6 Mo | P Value |
|---|---|---|---|
| All cohorts | | | |
| No. of patients | 92 | 92 | |
| Response — no. (% [95% CI]) | | | |
| Overall response | 74 (80 [72–89]) | 80 (87 [80–94]) | <0.001† |
| Partial response | 46 (50 [40–60]) | 44 (48 [37–58]) | |
| Complete response | 28 (30 [21–40]) | 36 (39 [29–49]) | <0.001 |

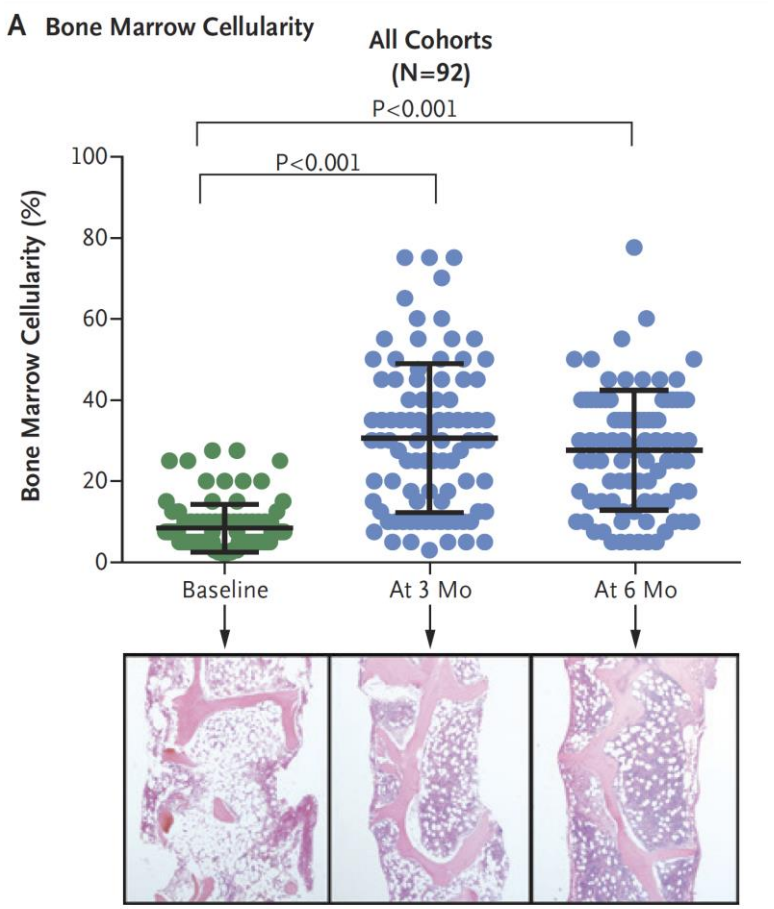
**Total Responses at 6 months**

**IST + Eltrombopag**
**IST alone**




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)

| Total Responses | After 3 months | After 6 months |
|---|---|---|
| **Horse** ATG + cyclosporine | 62% | 68% |
| **Rabbit** ATG + cyclosporine | 33% | 37% |

**Table 2. Hematologic Response at 3 and 6 Months to Horse ATG and Rabbit ATG.**

| Response | Horse ATG (N=60) | 95% CI | Rabbit ATG (N=60) | 95% CI | P Value |
|---|---|---|---|---|---|
| | *no. (%)* | | *no. (%)* | | |
| At 3 mo | 37 (62) | 49–74 | 20 (33) | 21–46 | 0.002 |
| At 6 mo | 41 (68) | 56–80 | 22 (37) | 24–49 | <0.001 |

Survival

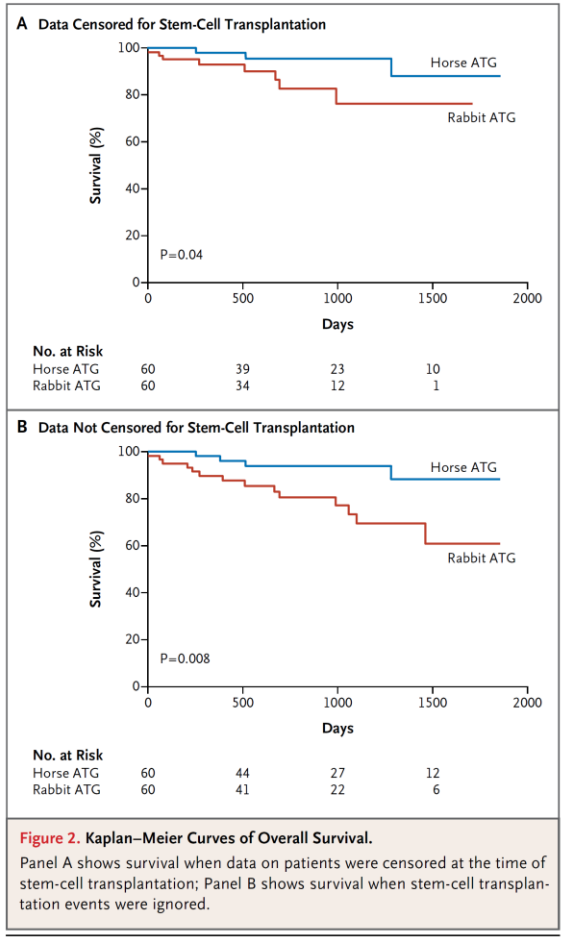
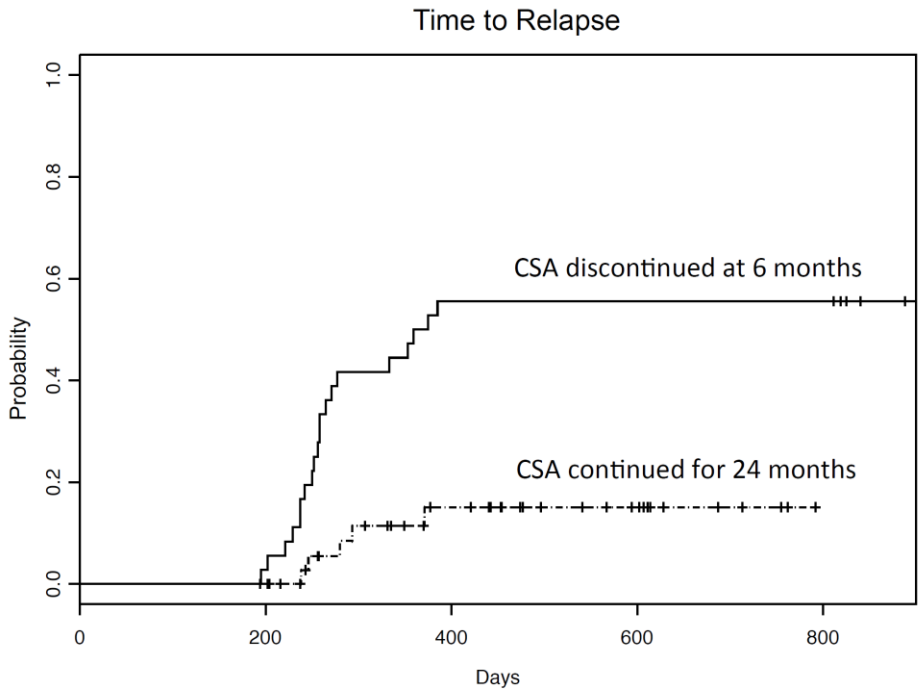



**Figure 2. Kaplan–Meier Curves of Overall Survival.**
Panel A shows survival when data on patients were censored at the time of stem-cell transplantation; Panel B shows survival when stem-cell transplantation events were ignored.

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**




| No. at risk: | | | | | |
|---|---|---|---|---|---|
| CSA discontinued | 92 | 35 | 17 | 16 | 16 |
| CSA continued | 92 | 43 | 24 | 11 | 1 |

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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