THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

LIVING WITH APLASTIC ANEMIA

Swapna Thota MD

Assistant Professor, Dept of Medicine

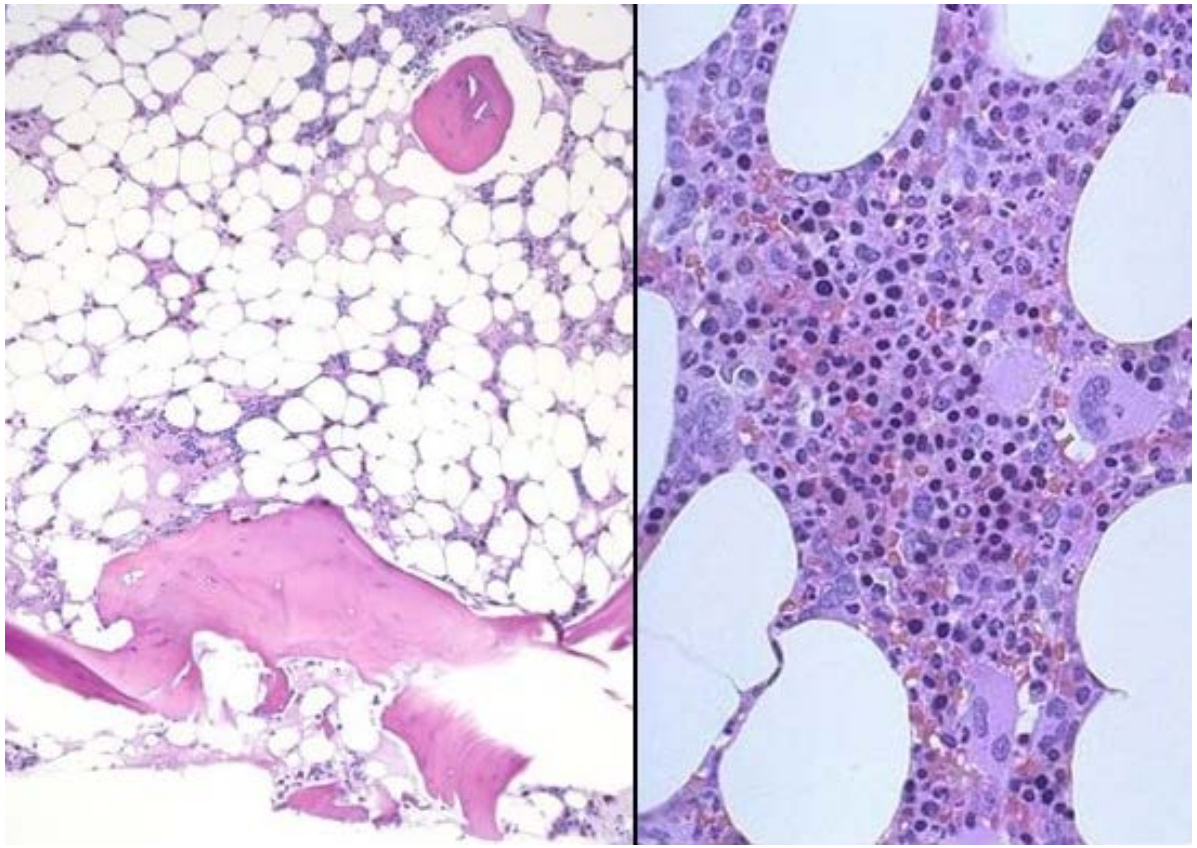
Hematology/Oncology, UTHSC/St Jude

History

Aplastic anemia is a rare bone marrow failure condition that prevents your marrow from producing new blood cells

- 1888, Paul Ehrlich- pathologist
- A young women with high fever anemia and bleeding
- Found an empty bone marrow, later called *aplastique*

BONE MARROW MORPHOLOGY IN AA



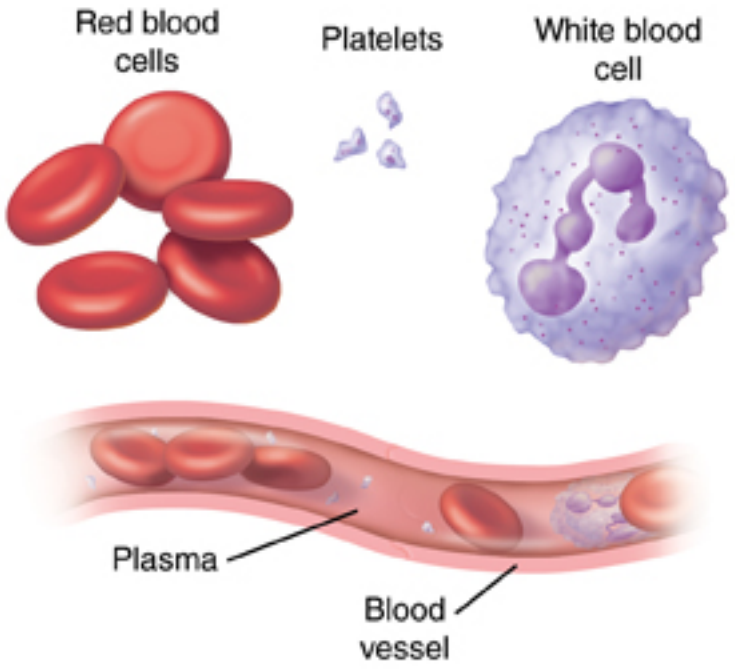
Symptoms of aplastic anemia

Biphasic age distribution with peaks at 10-25 and 55- 60 years of age

This condition leaves you

- pale, fatigued
- short of breath
- lowers immunity levels (fever, rash)
- uncontrolled bleeding

Symptom onset can be sudden or gradual



Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*. 2016;172(2):187–207

Diagnostic work up

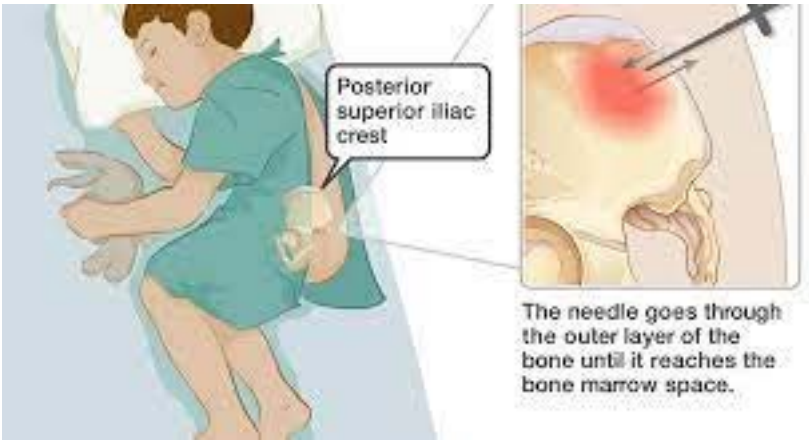
Depending on severity you may be worked up outpatient or while in a hospital.

You may need transfusions to make you feel better and prevent complications from low blood counts

Other medicines are started depending on if there is any infection or risk of infection

You will undergo blood work and a bone marrow biopsy with aspiration.

Especially, others causes of low blood counts are ruled out like leukemia, infections, medications, immune causes etc.



Diagnostic work up

Many tests are done on the tissue

1: Morphology
2: DNA changes in the blood cells (weeks)
3: Genetic tests to identify a cause of AA (1-2 months)

No specific diagnostic blood test

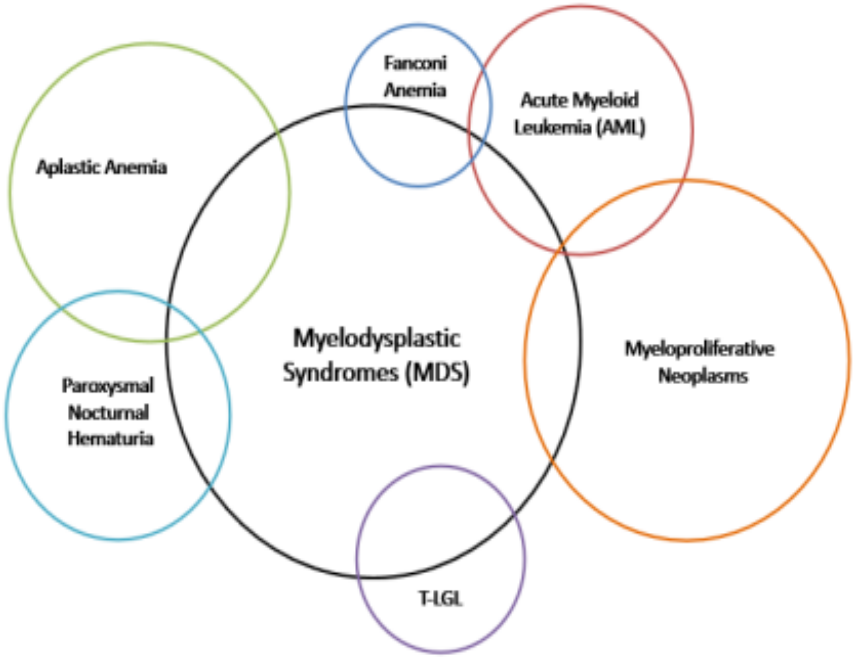
It is a clinical diagnosis made an experienced hematology teams and pathologists.

Diagnostic challenge

Hypoplastic MDS looks the same as AA and presents a great diagnostic dilemma.

AA has overlapping features with other acquired BMF conditions such as PRCA/T-LGL

Identifying subset with inherited disorders is critical.



<u>It takes time to do the accurate tests and establish a diagnosis of AA</u>

Diagnosis of aplastic anemia (AA)

<u>Clues to make diagnosis of AA</u>

Blood **counts are low** – usually atleast two or mostly all three cell lines

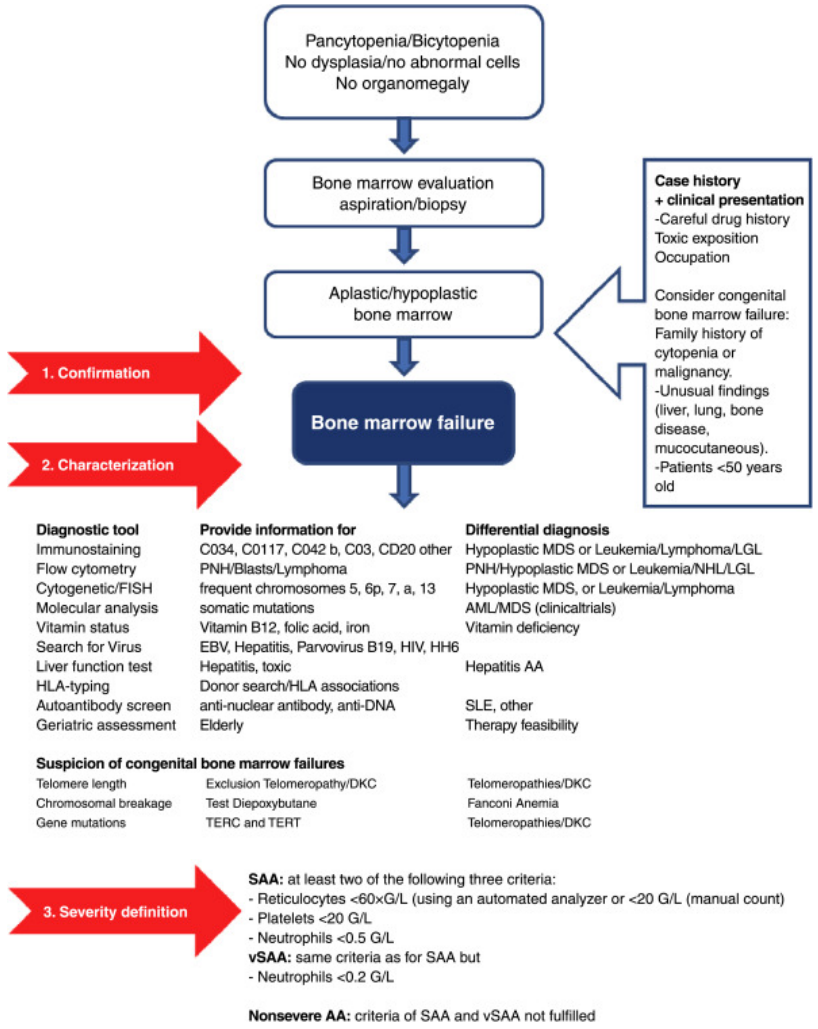
Bone marrow biopsy shows decreased number of cells (**Hypocellular)**

Often **co-exists with another blood disorder** i.e., PNH

Often has **normal chromosomes** in cytogenetics and FISH studies

The cells in marrow look normal and **not dysplastic**

Mutations can be present but rare with exception of **PIG-A, BCOR/BCORL1 mutations**



Diagnosis of Acquired Aplastic Anemia.sciencedirect.com/science/article. 2017, Pages 35-50

Questions to ask after getting AA diagnosed

What kind of aplastic anemia do I have?

Is my family at risk of developing this condition?

Do I need treatment?

How long can I wait to be treated?

If I do require treatment when I do I feel better?

What if I get pregnant?

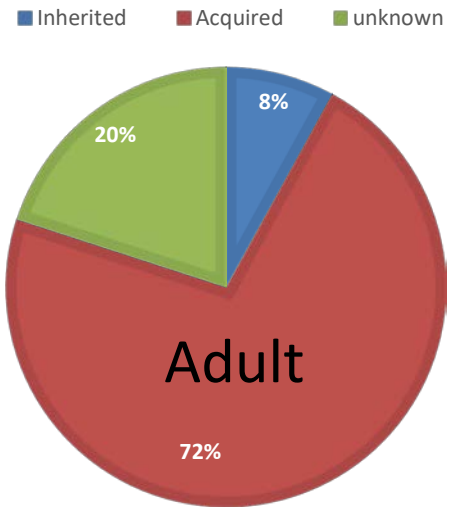
What are the complications or long-term details I need to be aware?

What about food, diet, sports and exercise?

What does survivorship look like?

Severity and types of aplastic anemia

	Very severe AA	Severe AA	Moderate AA
cellularity	< 25%	< 25%	< 25%
Neutrophils ($\times 10^9$/L)	< 200	< 500	> 500
retic count ($\times 10^9$/L)	< 60		
Platelet count ($\times 10^9$/L)	< 10	< 20	> 20



ACQUIRED

- Primary
- Secondary
  - Viral
  - Drug induced
  - Autoimmune
  - Radiation
  - GVHD
  - Pregnancy

INHERITED

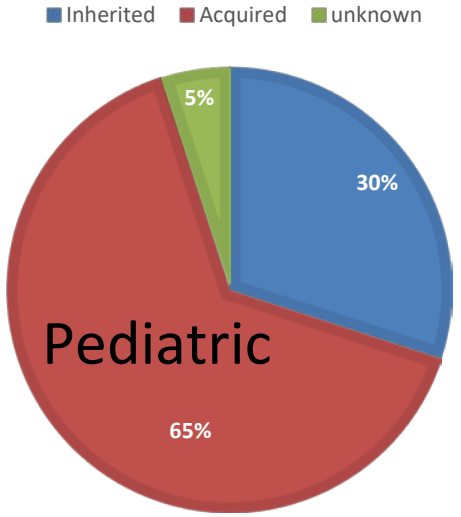
Fanconi Anemia

Shwachman-Diamond syndrome

Dyskeratosis congenita

Diamond-Blackfan anemia

Thrombocytopenia and absent radii syndrome etc.



Family risk

You will learn more about this in Dr. Wlodarski's talk in the next session

Applies to AA patients where a germline cause is detected

Acquired AA is random and families are not higher risk

CONDITION	MODE OF INHERITANCE	WHAT WE OBSERVE
Fanconi Anemia	Autosomal recessive	Skips generations, parents are carrier
Dyskeratosis congenita	X- linked recessive & other patterns	Carrier mother has a 50% chance of having son with DKC
Thrombocytopenia absent radii syndrome	Autosomal recessive	Skips generations, parents are carriers

Do I need treatment

NOT ALWAYS

If you are blood counts are not low enough

- to need transfusion or
- compromisess your immune levels

In other terms a subset of patients with “moderate AA”

We pursue what is called “Expectant management/observation”

A majority of patient require therapy. Let’s review options

How long can I wait to be treated?

When treatment is required, it should not be delayed beyond an average of 4-6 weeks for immunosuppressive therapy.

Delay in time to treatment has been shown in a few studies to lead to suboptimal outcomes (Yoshida N, Haematologica 2011)

If awaiting transplant upto 12-15 weeks is reasonable

Details about common medications used

Immunosuppressive medications

- Cyclosporine (most common)
- Tacrolimus
- Sirolimus

Big tablets, certain formulations have distinct smell and taste.

Levels need to be monitored.

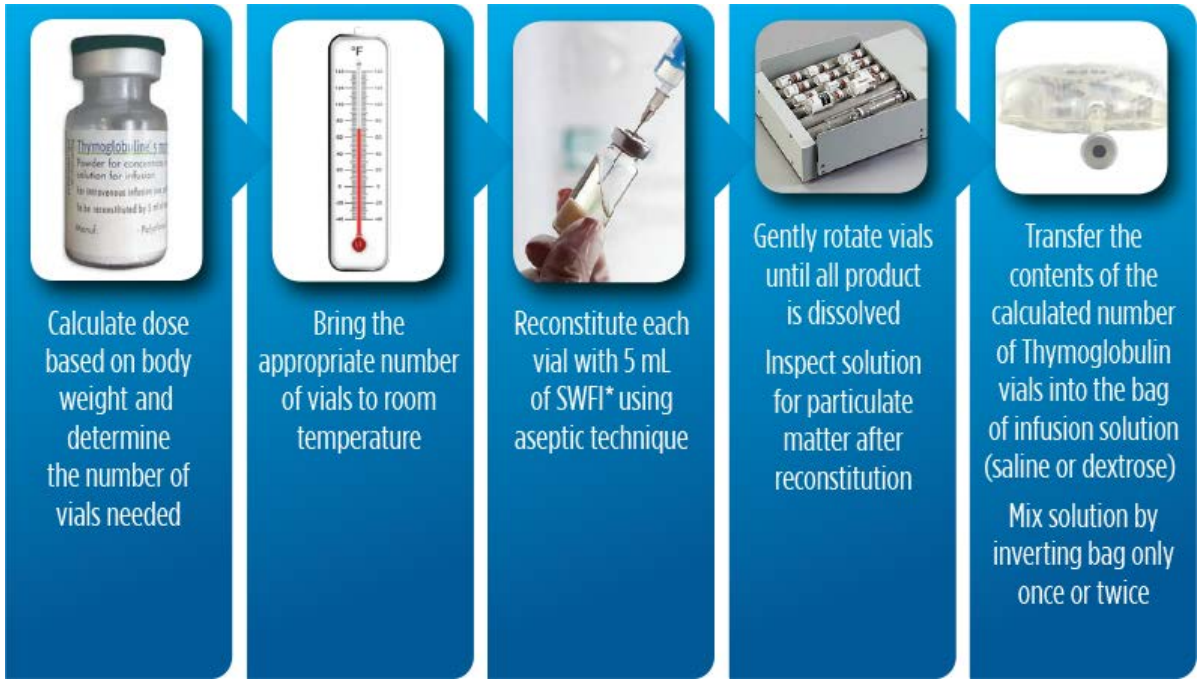
Anti-Thymocyte globulin

Central line is required

Typically given in hospital via a central line

Expected to have infusion reactions, medicines are given to decrease the intensity

Serum sickness: flu type of symptoms+ rash



Details about common medications used

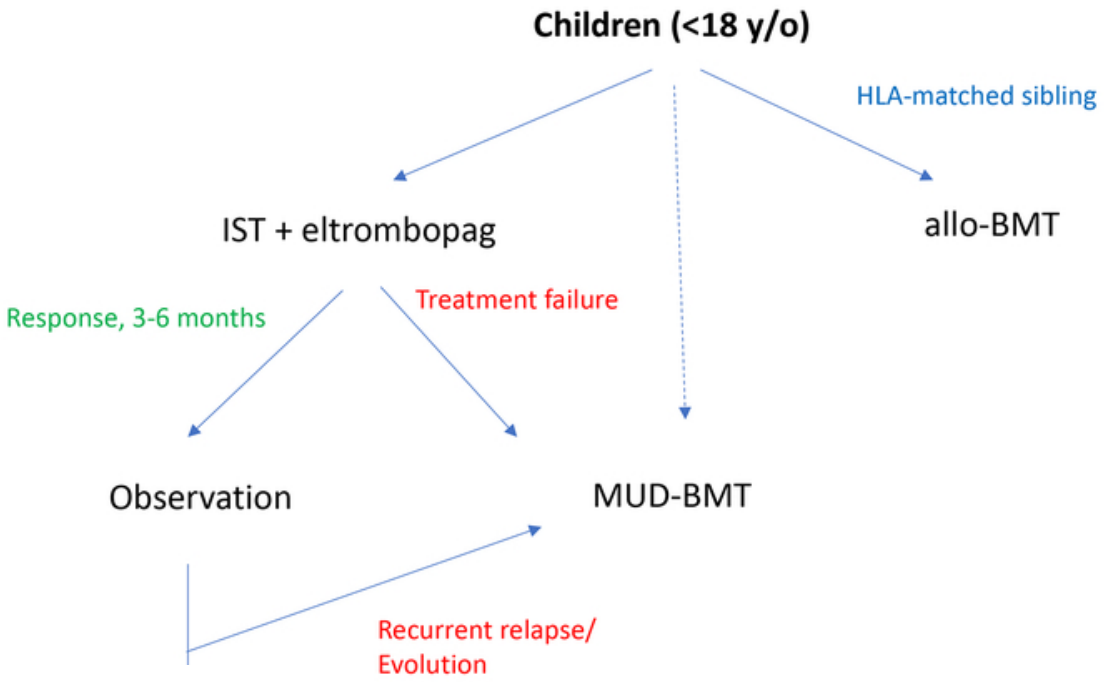
Eltrombopag (promacta)

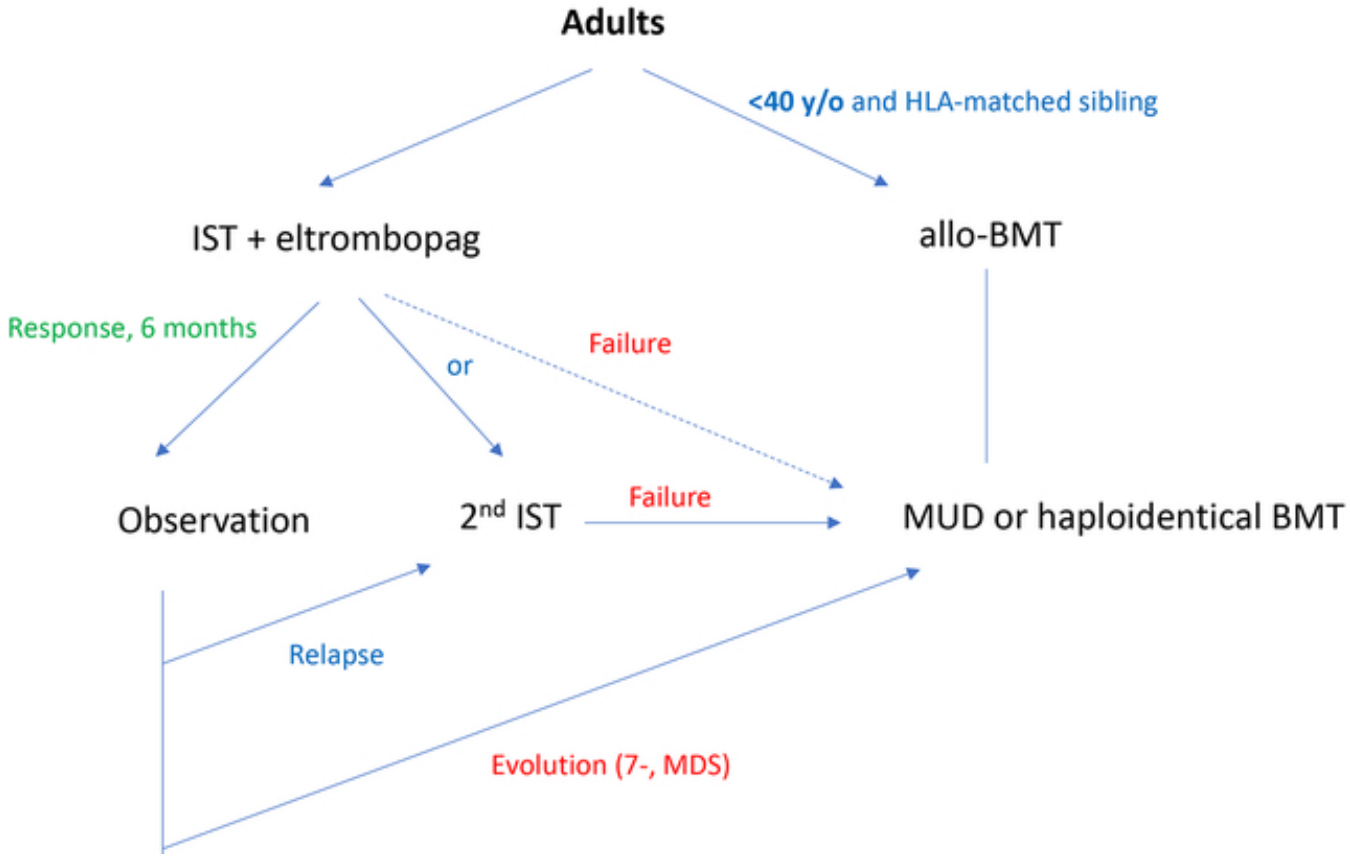
Fasting is required 2 hours before and after.
Blood work is done frequently to keep on eye on liver numbers and blood counts

Alemtuzumab (campath)

Given into vein or under the skin
Used only in relapsed and refractory cases

General Concepts Of SAA Management





Young NS, NEJM 2018

Current standard of care

FACTORS THAT INFLUENCE TRANSPLANT vs. IMMUNESUPPRESSION + EPAG

- Age of the patient
- Donor availability and type of donor
- Duration since diagnosis
- Presence of clonal markers (PNH vs. others)

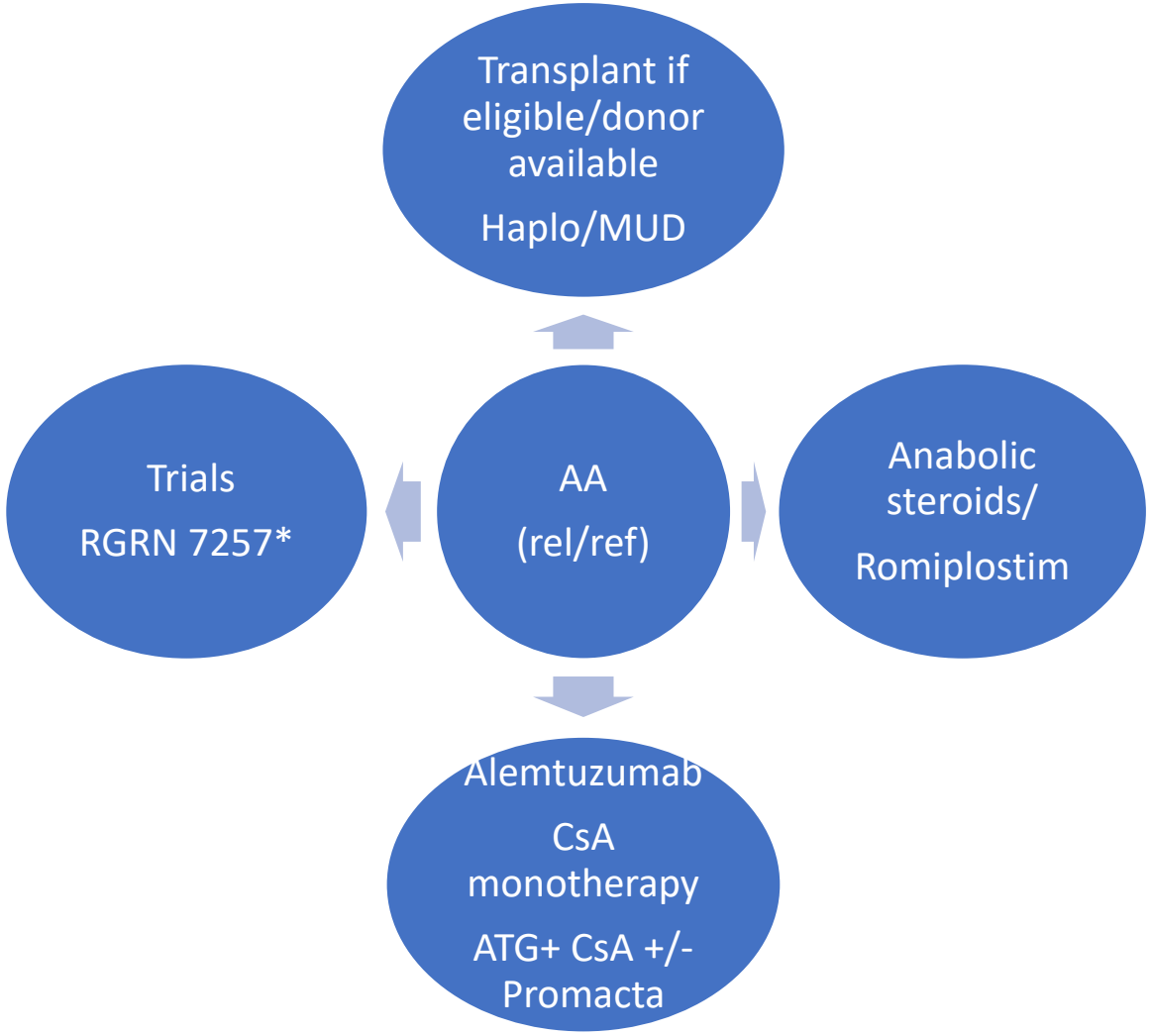
Adults: ATG+ Cyclosporin A+ Eltrombopag
Increases overall response rate but does not impact relapse rate

Children: ATG+ Cyclosporin A +/- Eltrombopag

Over time your medications are tapered when counts are normal or near normal

Relapsed/refractory AA management

- 20-30% patients relapse or have refractory disease.
- Key assessment:
  - R/o progression to cancer
  - R/o Germline causes
  - R/o stem cell exhaustion
  - Consider insufficient immune-suppression
- ?high dose romiplostim in EPAG failures
- Clinical trials



Hoskawa N et al, Leukemia 2021

When can I get back to routine

This depends on your response to therapy

On an average response to therapy takes a minimum of 3 months sometimes upto 6 months.

Response is of a few patterns

Normal counts
Low counts but not needing transfusions

An average of 6 months of frequently seeing doctors, doing labs and then phasing back to routine life activities.

Remember normal distribution is a bell shape curve, your story could fall in any extreme or right in the middle

What if I get pregnant?

Pregnancy is possible for women who have been treated for aplastic anemia.
Supportive care is the mainstay of therapy for pregnant patients with AA
There is a risk relapse of aplastic anemia during pregnancy.

You may have an increased risk of problems during pregnancy if:

- You have a low platelet count.
- You also have PNH

If you have had aplastic anemia and are pregnant or want to get pregnant, find an aplastic anemia specialist and an obstetrician who specializes in high-risk births. (*Blood* (2016) 128 (22): 3909.)

Diet, Sports and Exercise

Safe exercises:
Ongoing fatigue is a major issue
You may want to avoid activities that cause chest pain or shortness of breath

Preventing infection:
Make sure you get a flu shot and other preventive vaccines.
Avoid crowds and sick friends or relatives, especially during cold and flu season.
Wash hands frequently
Regular dental care will help prevent tooth and gum infections

Diet:
Healthy balanced diet. Food hygiene, handling and preparation are just as important.

Pay attention to your inner self and emotional health

Transition of BMF children to adult health care

GENE (% incidence of BMF)	AGE OF ONSET OF CLONAL EVENTS
GATA2 (75%)	Median: 20 years (AML,MPN, MDS, CMML)
ANKRD2 related thrombocytopenia	Diverse outcome, 5th or 6th decade
RUNX1 related Thrombocytopenia (35-40%)	of 33 years (range: 6–76 years) By age 50 (90% incidence)
DKC	Median: 35 years
Fanconi Anemia	MDS/AML: 10-30% Head & neck cancer

Pediatric inspired approaches for AYA leukemia patients has improved outcomes in this population

AA management historically has shared management approach with adult patients; outcomes limited by transplant mortality.

Delayed diagnosis of clonal evolution in BMF conditions leads to poor outcomes.

Surveillance

Patients and families living with or those who are in remission should be aware of long-term risk and need for surveillance.

Aplastic anemia patients could develop overtime:

- PNH (Hemolytic anemia and clots)
- MDS (Blood cancer)
- Acute leukemia (Blood cancer)
- Lower risk clones can exist that do not progress to frank malignancy and need to be monitored especially if you are on EPAG

SURVEILLANCE LEADS TO EARLY DIAGNOSIS
EARLY DIAGNOSIS AVOIDS URGENT THERAPY and BROADENS TREATMENT OPTIONS
BETTER OUTCOMES WITH CONTINUED SURVEILLANCE

SUMMARY & THANK YOU

APLASTIC ANEMIA IS A VERY TREATABLE BLOOD CONDITION WITH GOOD LONG-TERM OUTCOMES

SURVEILLANCE IS KEY TO EARLY RECOGNITION OF LONG-TERM COMPLICATIONS

ITS BEST TO AVOID DELAYS IN CARE WHEN TREATMENT IS INDICATED