Aplastic Anemia

IT IS JUST NOT ANEMIA

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Criteria for aplastic anemia (AA)

- Decrease in blood counts involving > /= to two cell lineage
  - Hb (retic count <60 x 10 9 /L)
  - Platelet (< 20)
  - WBC (Absolute neutrophil count <0.5 x 10 9 /l)
- Bone marrow cellularity of <25% (normal approx. >50%) , most of BM is fat
  - CD 34 (immature cells : momma cells) marker of stem cells near absent

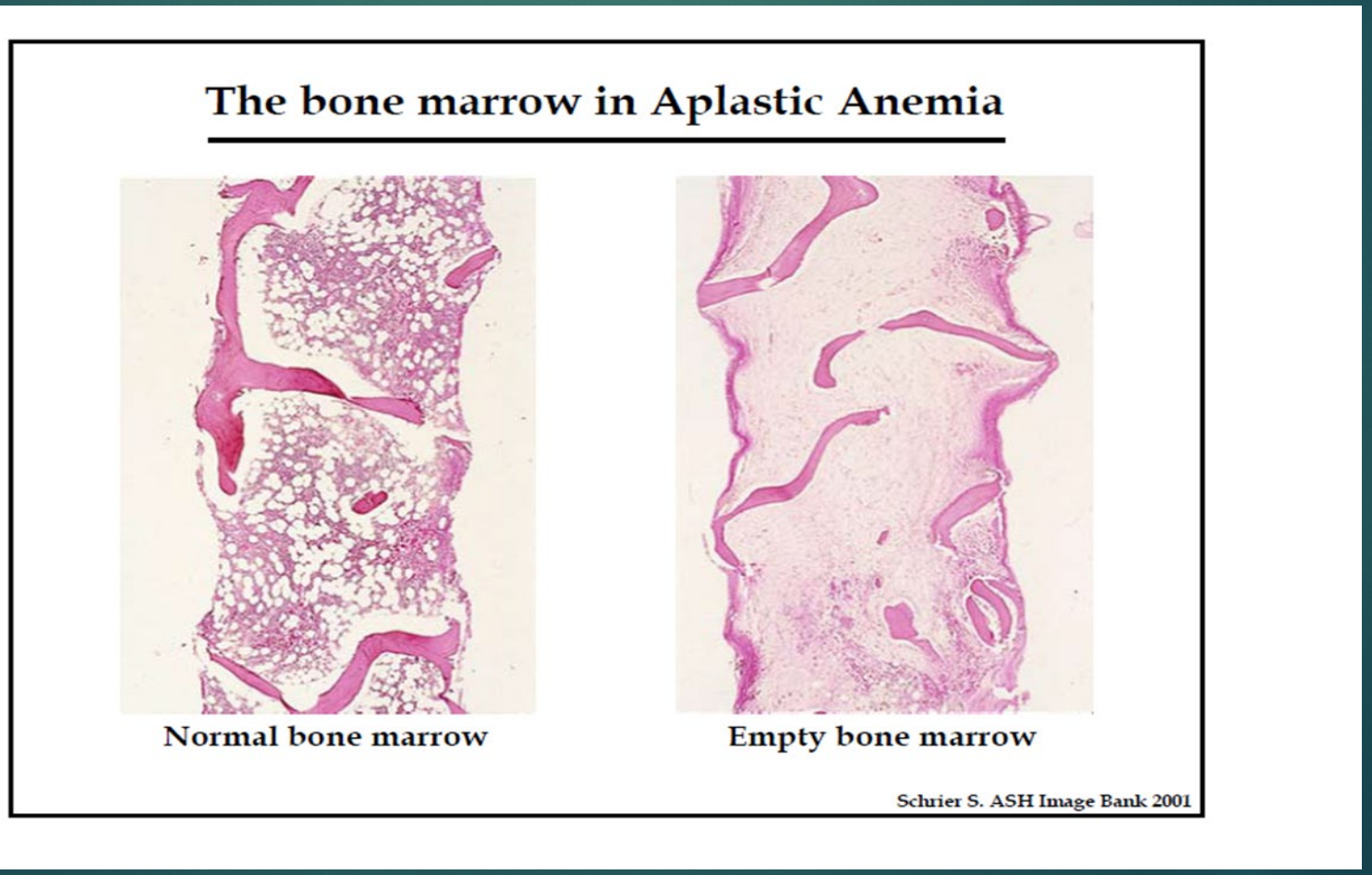
- Severe AA ANC < 0.2

Criteria for AA

Severity of Aplastic Anemia	
Nonsevere aplastic anemia (NSAA)	<30% cellularity ≥2 cytopenias not meeting SAA criteria
Severe aplastic anemia (SAA)	<25% cellularity ≥2 of: ANC <500/uL, PLT <20,000/uL, ARC <60,000/uL
Very severe aplastic anemia (VSAA)	Criteria for SAA plus ANC <200

ANC indicates absolute neutrophil count; ARC, absolute reticulocyte count; PLT, platelet.

Bone marrow in AA



Aplastic anemia : pathophysiology

- Constitutional syndromes: inherited . Genetic lesions lead to diminished capacity for blood cells to repair DNA or interfere with self – renewal or differentiation ; Childhood

- Immune aplastic anemia : associated with sero negative hepatitis , eosinophilic fasciitis , thymoma but most idiopathic
  - Associated with loss chromosome 6 (HLA complex) in 10% patients , expansion of PNH clones

Aplastic anemia

- 70% of cases are idiopathic (no know cause)
- Two peaks young adults and elderly
- Incidence is 2 pr million western countries and 4-6 /million Asia
- Can present with 1 or 2 cell lineage (WBC/Hb /platelets) low but ultimately all three become low

Pancytopenia (multiple other causes)

- Infiltration of bone marrow by tumor, infections , storage diseases
- Chemotherapy, medication or radiation induced bone marrow damage/depletion
- B12, folate, copper , zinc deficiency
- Infections that can suppress blood making capabilities , viral infections (CMV , hepatitis , EBV , HIV covid 19, paro virus etc)
- Enlarged spleen (filter of blood) can cause sequestration of blood and lower blood counts
- Hematologic diseases that involve bone morrow
  - Hairy cell leukemia , myelodysplasia , acute leukemia , paroxysmal nocturnal hemoglobinuria

Aplastic anemia (types)

- Congenital
  - Fanconi anemia
  - Congenital keratosis
  - Shwachman - Diamond

- Acquired AA
  - Thought related to damage to hematopoietic stem cells (HSCs) which are cells in BM they are pleuripotent : they are "mother " cells that give birth to new blood , RBC, WBC , platelet
  - External factors such as viruses , radiation ,chemotherapy affect HSC
  - Increased programmed cell death of HSC also occurs
  - Autoimmune :destruction mediated via activated T cells

Congenital AA : associated features (family or personal)

- Short statue : skeletal abnormalities
- Pancreatic insufficiency
- Pulmonary fibrosis and /or early onset COPD
- Early onset GI cancers
- Neurologic dysfunction
- Grey hair prior to 25, nail dysplasia

- Screening test is chromosome breakage and lymphocyte telomere length measurement from peripheral blood
- Why know congenital vs acquired: IST does not work, choice of conditioning regimen for transplant

Aplastic anemia : the imposters and musical chairs : do the BM

- Hypo-plastic myelodysplasia (MDS) : abnormal maturation of blood
  - Normally MDS normal or hypercellular
  - morphology of dysplasia (blood cells look odd) Chromosome findings
- Paroxysmal nocturnal hemoglobinuria
  - Absence of certain surface proteins on blood cells (PIG proteins) which make RBC susceptible to hemolysis (destruction) , leads to anemia associated with high LDH and low haptglobin .
  - Can have pancytopenia (all cell lines are low)
  - Simple test to measure the absence of therse proteins on cell surface , usually minimally threshold is 10% but small % common with AA
- Hemophagocytic lymphohistiocytois (HLH) : cannibals

work up for AA

- Viral screen hepatitis , parvo, EBV, CMV , HIV , covid 19
- B 12 and folate
- LDH , bilirubin, haptoglobin (hemolysis : destruction of RBC)
- Screen for PNH : small clones in 70% cases of AA
- If under 40 and have AA screen for Fanconi anemia

- Bone marrow biopsy
  - Chromosomal evaluation and FISH for MDS
  - Myeloid mutations : overlap between MDS and AA

Why is AA "bad"

- Major risk if infection and this is related to absolute neutrophil count
  - Risk of infection increases significantly if ANC < 0.5
  - Risk of infection becomes very high if ANC < 0.2
  - Risk of infection with low WBC count related to other factors too
    - length of time patient has low WBC count
    - If they have received recent chemotherapy where may have mucositis : thinning of GI barrier
    - Underlying immune function aside from low WBC count (example low immunoglobins , poor T lymphocyte function etc,
    - Local environmental issues (work you did , infections of those around you)
- Thrombocytopenia : bleeding risk (high when <10)
- Anemia : weakness and fatigue

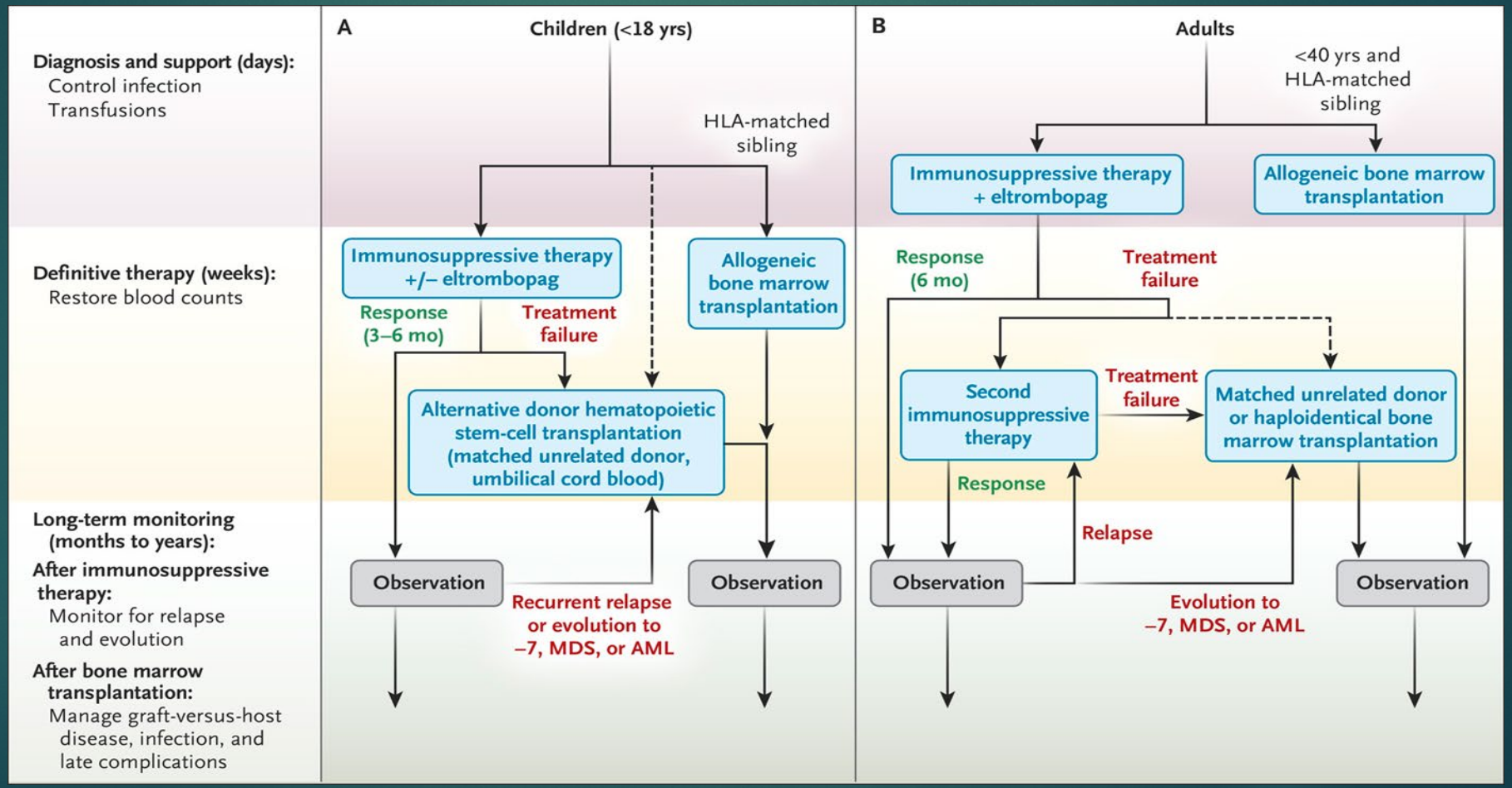
AA : things to help you stay safe

- Minimize blood transfusions : avoid allo-immunizations (refractory)
- Avoid Aspirin and NSAID (poison platelets)
- All blood should be irradiated (prevent transfusion GVH) and leuko-depleted (prevent allo- immunizations : platelet antibodies)
- Medications to minimize infections
  - Levofloxin (bacterial) , fluconazole/posoconozole (fungal) , acyclovir (viral) , Bactrim (PCP)
- Prudent isolation from environment risks : no cleaning house , gardening , wear mask ,Strick hand washing
- Iron chelation therapy : remove iron from body
- Low bacterial diet probable no value but avoid uncooked food , restaurant salads etc

Therapy for Aplastic leukemia

- Supportive care : transfusions : important to minimize transfusion to avoid allo –immunizations (develop antibodies against transfused platelets and against proteins of any donor stem cells which may be considered later)
- If not severe : consider measured short observation as sometimes environmental toxic injury (virus , medication , etc) may resolve on own .
- Therapy : two types if acquired AA (congenital AA : only effective therapy is transplant)
  - Immunosuppressive therapy (IST)
  - Bone marrow /stem cell transplant .

Therapy for AA



Immunosuppressive therapy of AA

- Cyclosporin
- ATG (anti thymycyte globulin) : Horse vs rabbit
- Eltrombopag (Promacta)

- Adjuvant therapy
  - Danazol (androgen ; sometimes helpful to increase Hb)
  - G-CSF (neupogen): used to increase WBC> rarely helpful

ATG : infusion

- Given as in patient
- Given with steroids/antihistamines to prevent serum sickness
  - Fever, chills , rash , muscle and joint pains,
  - Low BP and shortness of breath on occasion
- Often require infusion to pause , and slow due to infusion reactions
- Short term worsening of low blood counts
- Can get late serum sickness 10-14 days after ATG
  - Therapy steroids , prednisone or hydrocortisone

Cyclosporin

- Early discontinuation high relapse rate
- Maintenance delays relapse
- Full dose cyclosporin trough 200-300 mcg/liter for 12 months
- Slow taper over I year
- Commonly associated side effects
  - Rise in creatine (kidney function)
  - Hypertension
  - Loss of magnesium
  - Risk of ongoing infection

Immunosuppressive therapy for AA

- Eltrobopag (promacta) added to cyclosporin and ATGAM
  - 92 patients (NEJM 2017 page 1540)
  - For those receiving promacta day 1-180
    - At 6 months Overall response 94% with complete response 58%
    - At median follow up 2 years , 97% overall survival
    - For those with severe neutropenia ANC < 0.2 median time to ANC>0.5 was 48 days , median time to transfusion independence was 32 days platelets and 39 days RBC
    - Beginning day 1 and extending therapy to at least 6 months improves outcome

Eltrombopag (promacta) for AA

- 25 patient study refractory to IST (immunosuppressive therapy)
- Promacta previous approved for disease call ITP , this is thrombopoietin drug but discovered also can improved other cell lineages
- 44% 11/25 had hematologic response at 3 months with 9/25 patients no longer needing platelet transfusions , 6/25 improved Hb ,9/25 improved WBC count , 7/11 responders continued fro median of 16 months
- For those responding at 12 weeks , more robust response seen after continuation of the promacta (late responses can occur)

Problem with IST

- Delayed blood count recovery
- Relapse 25-40% at 5 year
- Refractory 10-20 % (with promacta/IST :5% refractory)
- Clonal evolution to PNH
- Clonal evolution to MDS/AML
- Not curative

Transplant for AA

- Traditionally consider front line therapy for all those under 20 years (with HLA match) and
- Not considered for those over 40 (as front line therapy: but considered for those whom fail IST)
- between 20-40 grey area but less grey now : **transplant** vs IST
  - This is evolving concept, and more is based on availability of donor , co morbid conditions , severity of cytopenias , patient preference

Transplant for AA

- Need to find donor : full sibling 25% chance of match
- Even if have sibling match can take few weeks to organize and get approval for transplant
  - HLA Type patient and donor (where do they live)
  - Get insurance approval for typing and transplant
  - Patient and donor need medical evaluation
  - Harvest of donor
- Matched unrelated donor (registry) commonly takes 2-3 months (donor may not be available)
- Donor on registry can be found for most , but more so for Caucasians
- Donor search in registry ethnic minorities lesser chance of match's due to under representation of minorities on bone marrow registry

Transplant for AA

- Newer approaches to AA with modifications of conditioning regimen (therapy given before patient gets their stem cells /bone morrow donor cells) to eradicate native immune system
- In past conditioning regimen high dose Cytoxan and ATG
- More recent modifications reduced doses of Cytoxan and add fludarabine : for sibling
- MUD low dose Cytoxan /fludarabine/ low dose TBI (radiation therapy : those with mismatch)
- Median time from diagnosis to transplant European study 10 months
- Strongest negative predicator pf survival using PBSCs, interval of >180 days to transplant , age > 20 , CMV status(donor /patient)

Transplant AA: continued

- Newer conditioning regimens (lancet haematology 2015)
  - MMUD : 97.4% 1 year survival , longer follow up 3 deaths (8%)
  - Risk of GVH acute 23% , chronic GVH 22%
  - OS for 10/10 matched siblings and MUD same but risk for GVH double for those having MUD donor
  - Graft vs host disease
    - Donor immune system attacks patient' body : acute GI , skin , liver , chronic after day 180 any organ can be affected
    - Can be treated but small population long term problem can affect QOL (swap one problem (AA) for another problem GVH

Medical therapy (ISI) vs transplant

- Transplant
  - Need donor : ideal sibling but donor pool expanding for even those with mismatch
    - Need to delay therapy to identify donor
  - Cure high with low relapse rate
  - Upfront 5-10% death rate
  - Risk of graft vs host disease
  - No significant risk for secondary MDS or PNH emerging
- Immunosuppressive therapy
  - Can start therapy immediately and look for donor if ISI does not work
  - Those treated first for ISI may have more complications if transplant later done
  - Response high but cure less Approx ?? 50% , on going relapses even years after Rx
  - No risk of GVH , late complications uncommon , QOL good post therapy
  - Risk to develop MDS or PNH later

Treatment of refractory AA

- Rabbit ATG vs re-treatment horse ATG
- High dose Cytoxan (without stem cell or bone marrow rescue): for treatment naïve high response rate but in randomized study by NIH terminated early due to excess deaths related to fungal infections
- Campath : +/- cyclosporin 35-50% response : no large studies 3 year OS 83% lin NIH study , frequent relapses
- Danozol : only help Hb response

Prognosis with AA

- 5-10 Year overall survival is 80-90% with modern therapy
- Untreated SAA 1 years mortality (death) is 70%
  - …So get treatment