Clinical Breakthroughs in the Treatment of Acquired Aplastic Anemia

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Disclosures

- Nothing to disclose

Learning Objectives
At the end of this presentation, you will be able to:

1. Recognize the presenting symptoms, clinical consequences, and pathology of bone marrow failure
2. Discuss treatment modalities for aplastic anemia and the patients for whom each treatment is most appropriate
3. Describe the most common adverse events associated with immunosuppressive treatment for aplastic anemia
4. Recognize relapse and disease progression and determine next line therapy

Severe Aplastic Anemia

- Rare hematological disease
- Affects all age groups
- “Benign” but very ill patients

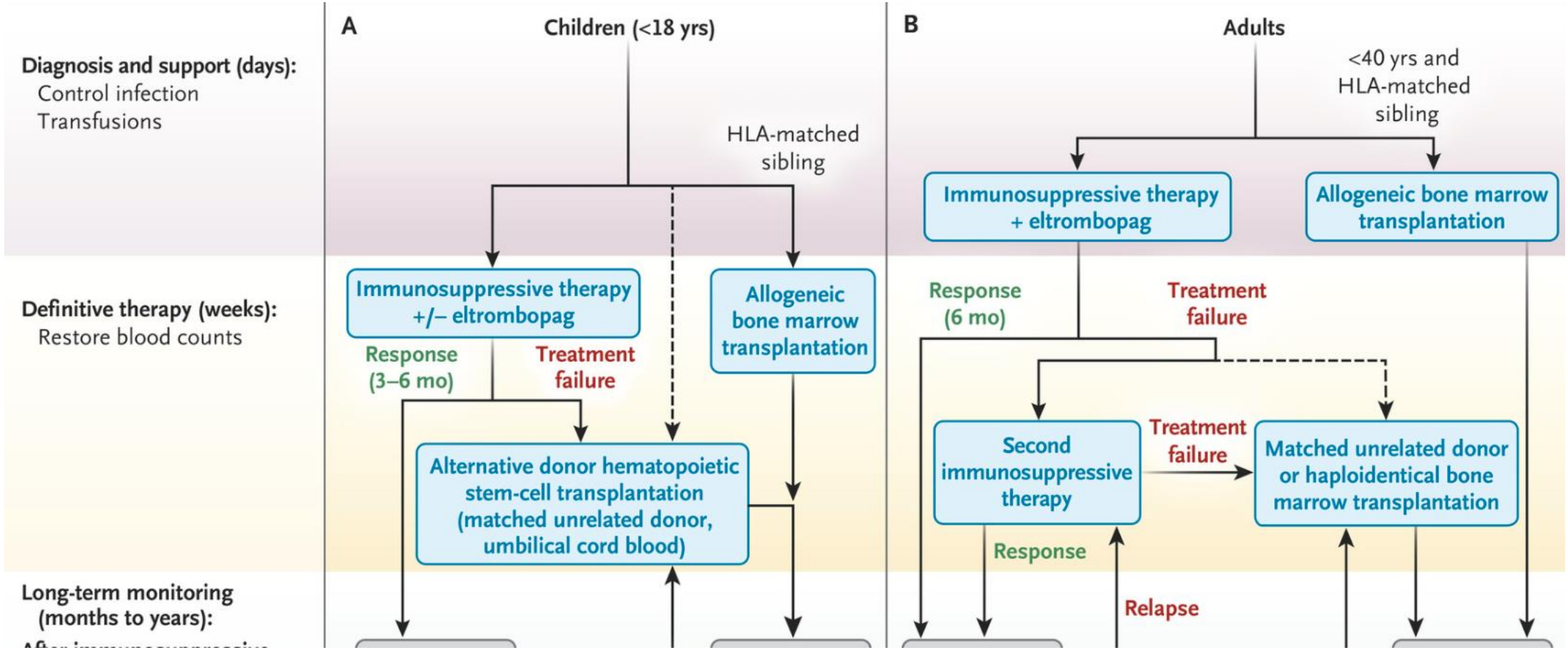
- Defined by hypocellular marrow (<30% cellularity) and cytopenias

- Camitta Criteria (2 out of 3)
  - ANC <500/uL
  - ARC <50/uL (Reticulocytes % - <1%)
  - Plt <20,000 K/dL

  - VSAA – ANC <200/uL

- 1900s – universally fatal, now treatable in most patients

Treatment for newly diagnosed AA patients



Young NS. N Engl J Med.2018

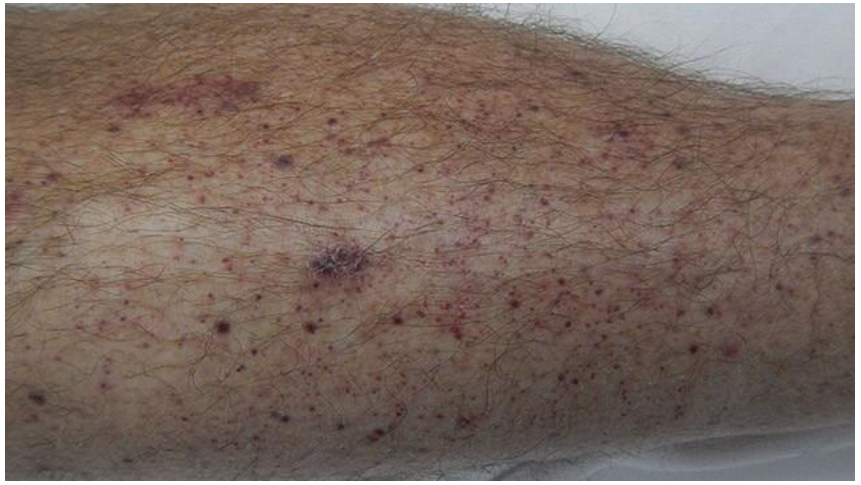
Case presentation

- “Ana” is 39 year old Hispanic female who presented to the ER after fainting at her place of employment.
- She reports fatigue for the past month or so, which she attributed to increased stress. She noticed she was bruising easily on her legs. She is currently day 10 of her period and it is been heavy now for the entire week.
- She is otherwise healthy, not on any medications besides multivitamin, with no significant family history.
- Labs reveal the patient to be pancytopenic with Hgb 5.9, plts 7k ANC 370. She has increased MCV 109 and ARC is low at 22.
- Physical exam shows pallor, LE ecchymoses, petechiae

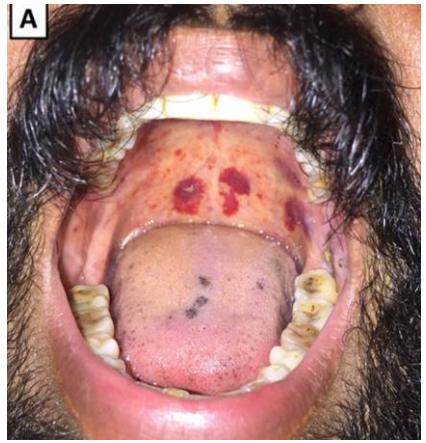
Presenting symptoms

Thrombocytopenia (low platelets)

- Petechiae
- Bleeding
- Bruising
- Wet purpura
- Menorrhagia



https://www.healthline.com/health/petechiae#pictures



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Thrombocytopenia supportive care

- Most bleeding in AA is minor: cutaneous, gingival, nasal
- For prophylaxis maintain platelets >10k
- Leukoreduced and irradiated platelet product
- Platelet transfusion twice per week or more
- For major hemorrhage/surgical intervention >50k
- Platelet refractory - due to HLA antibodies

Anemia (low red cells or hemoglobin)

- Shortness of breath
- Fatigue
- Pallor
- Syncope
- Headaches
- Palpitations

Anemia supportive care

- Transfuse pRBCs for Hgb <7
- Threshold for transfusion may be higher if symptomatic or if cardiac comorbities
- Usually 2 units about every 2 weeks if no active bleeding
- Iron overload - Ferritin will be elevated if heavily transfused pRBCs
  - Stop iron supplementations
  - Consider chelation or therapeutic phlebotomy in in the future after response

Neutropenia (low white cells)

- Infection
- Fever
- If prolonged neutropenia, consider fungal infection

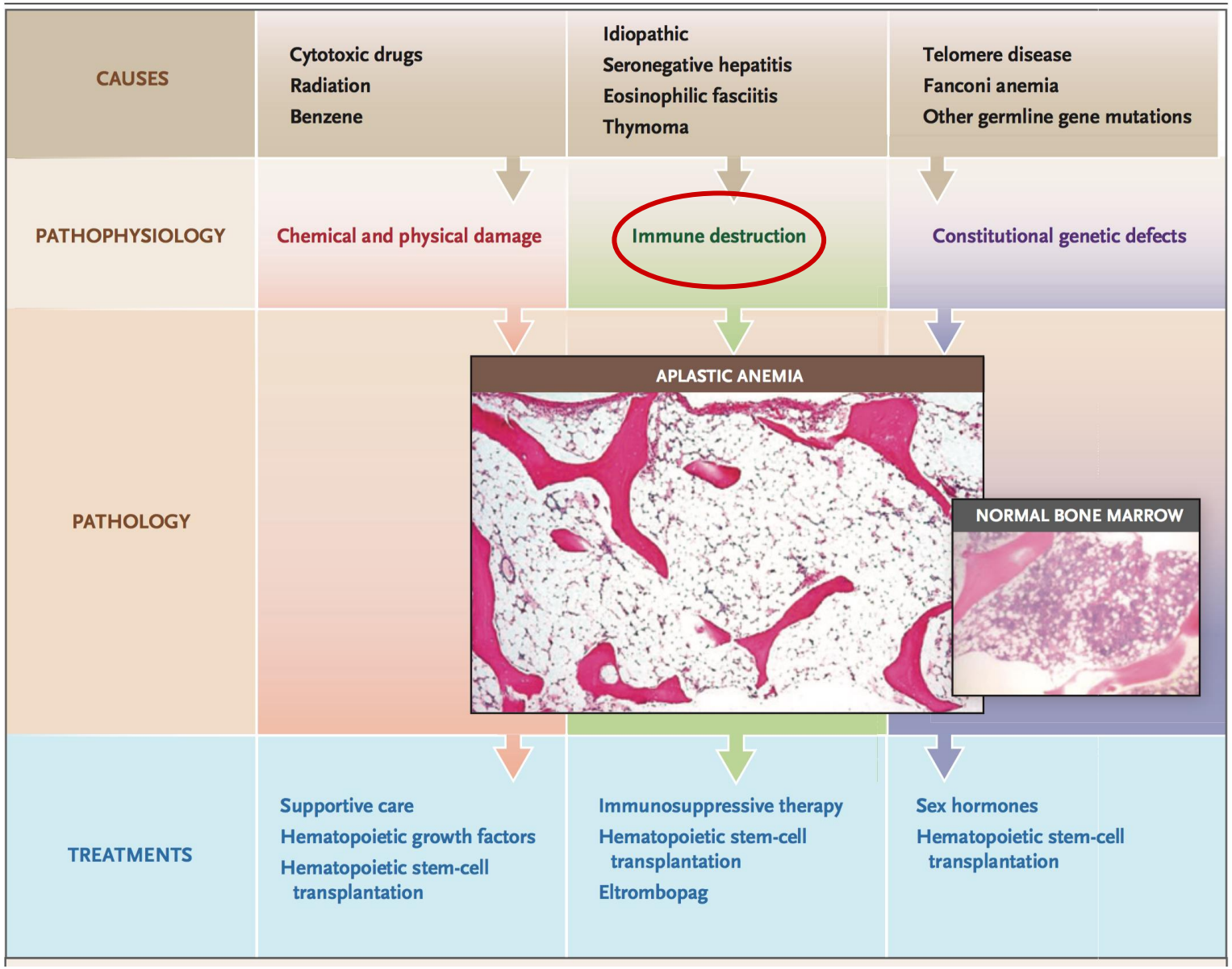
Neutropenia supportive care

- Infection remains major cause of death in AA
- Aggressive, early and broad spectrum treatment
- fever and neutropenia (<500/uL) Admit for IV antibiotics
- Continue therapy for 10-14 days regardless of culture results
- Early introduction of antifungal drugs
  - persistent fever
  - evidence of sinus, lung infection
- G-CSF-mobilized neutrophils
  - in selected circumstances, such as bridge to HSCT

Differential Diagnosis and Workup

- Temporary marrow suppression/peripheral destruction
  - Viral panels – CMV, EBV, Parvo, HIV
  - Exposures/ medications
  - Bone marrow biopsy
- Hypoplastic MDS vs aplastic anemia
  - Bone marrow biopsy
  - Cytogenetics
  - CHIP
  - FISH
- Constitutional vs Acquired
  - Fanconi DEB
  - Bone marrow failure genetic panel
  - Telomere length - DKC
- PNH – may or may not be present in acquired SAA

Treatment different based on the cause



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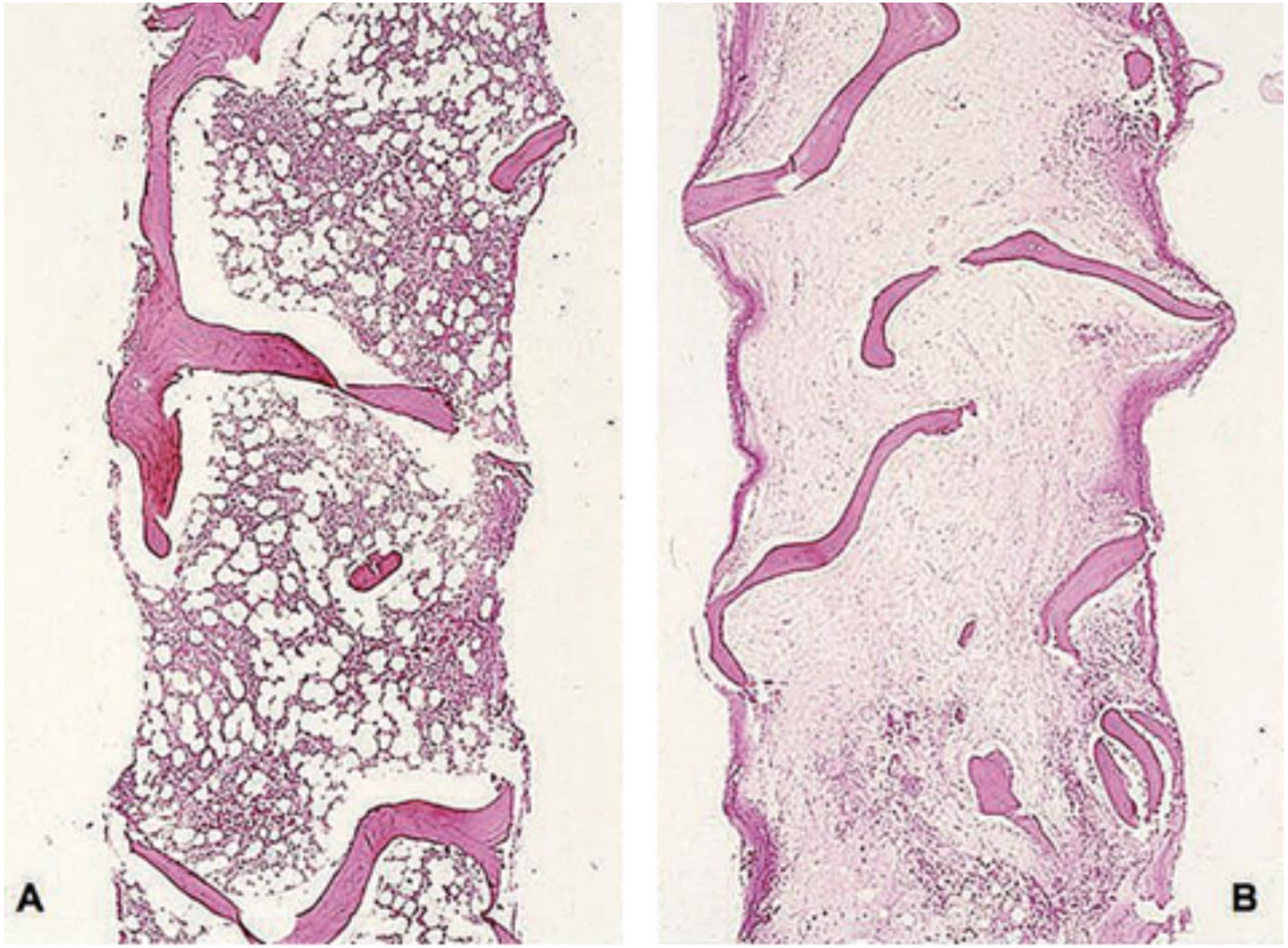
Marrow is “empty”

Normal Marrow



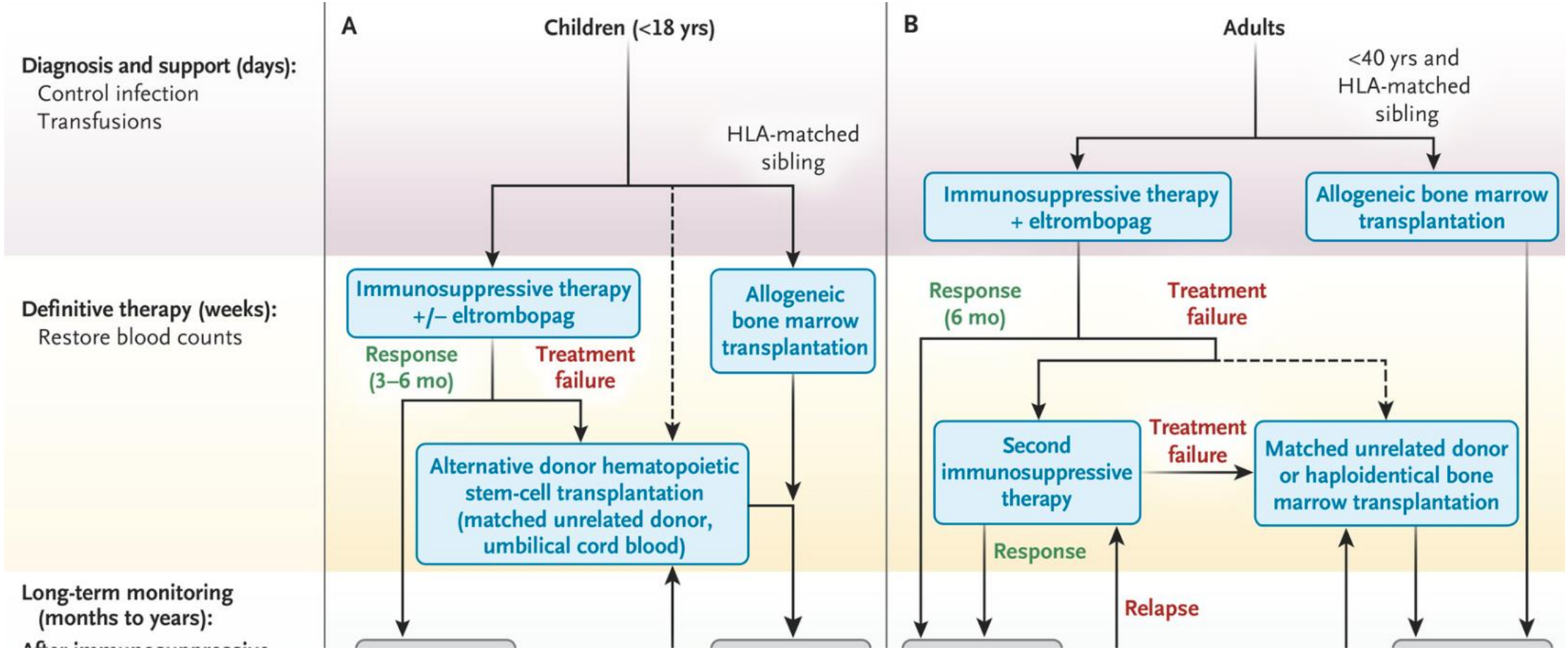
Typical hypocellular SAA Marrow

Courtesy of Dr. Stanley Schreier, American Society of Hematology Image Bank

Ana's results

- Viral studies negative
- Bone marrow biopsy – hypocellular 10% cellularity without dysplasia or increase in blasts
- PNH clone <1%
- Normal cytogenetics 46 XX [20]
- Fanconi DEB negative

Treatment for newly diagnosed AA patients



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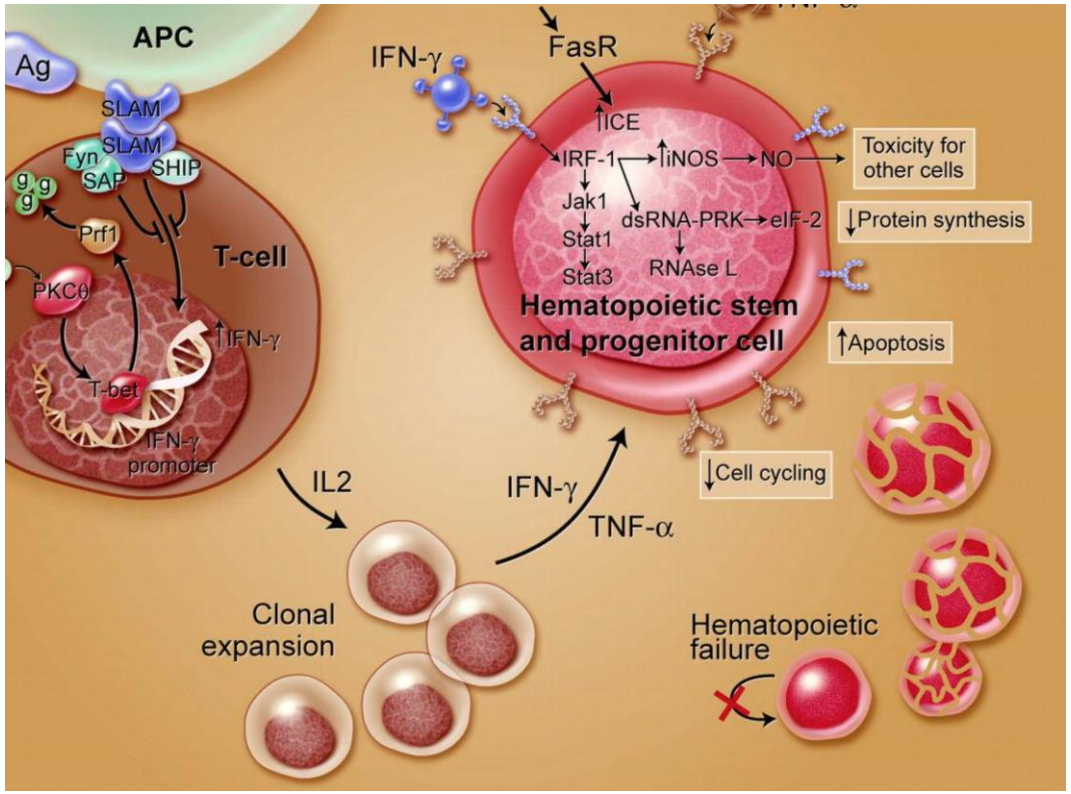
BMT for SAA

- Only curative option
- Limited by donor availability
- Preferred treatment for pediatric patients, but excellent results for patients 40 y/o and younger
- Sibling transplant is standard, but high resolution MUD is also good option
- Haploidentical transplant promising but not standard yet

Immune mediated destruction of progenitor cells



Young, N.S. et al. Blood.2006

Eltrombopag: 2018 Clinical Breakthrough

- November 2018 FDA approves eltrombopag for treatment naïve SAA
- Approval based on large prospective study at NIH
- Now standard of care treatment
- Previously approved for refractory SAA and ITP

Townsley et al. NEJM 2017

Treatment plan – triple therapy

- hATG x 4 days
- Cyclosporine BID dosing for 6 months, then continued at lower dose for 18 months
- Eltrombopag X 6 months
- Total treatment time if no relapse is 2 years
- Results in response in 80-90% of patients at 6 months
- Response can take up to 6 months

Horse anti-thymocyte globulin

- Generally require central venous catheter for administration
- Premedicate before each infusion
- Steroids to prevent serum sickness
- D/c beta blockers to allow for more effective use of agents to support blood pressure in event of anaphylactic reaction
- Dose of 40 mg/kg intravenously over four hours. If infusion reactions are severe, the duration of each daily infusion can be lengthened to 8 or even 24 hours
- If frail or with cardiac comorbities, consider administration in the ICU

Horse ATG side effects

- Serum sickness
- Rigors
- Rash
- hypotension
- Fever

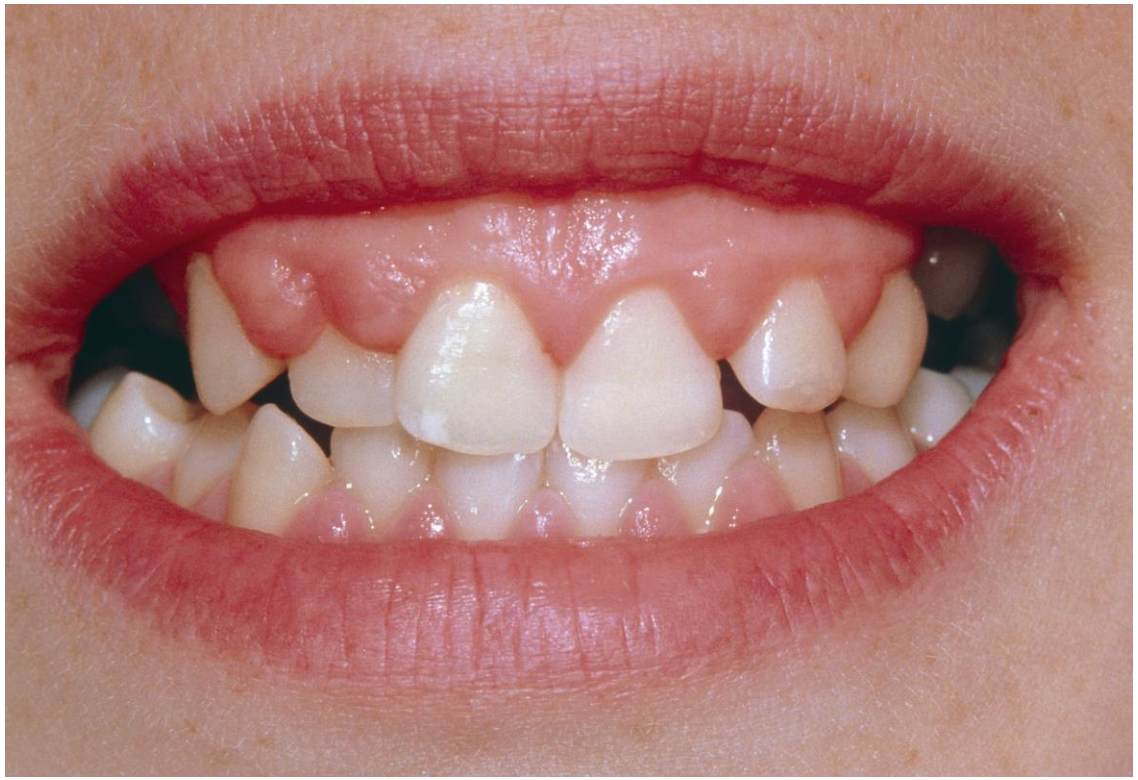
Cyclosporine

- Initiated BID with goal levels 200-400 for the first 6 months
- Trough 12 hours after last dose
- Titrate for side effects
- Hepatic metabolism, CYP3A4

Cyclosporine side effects

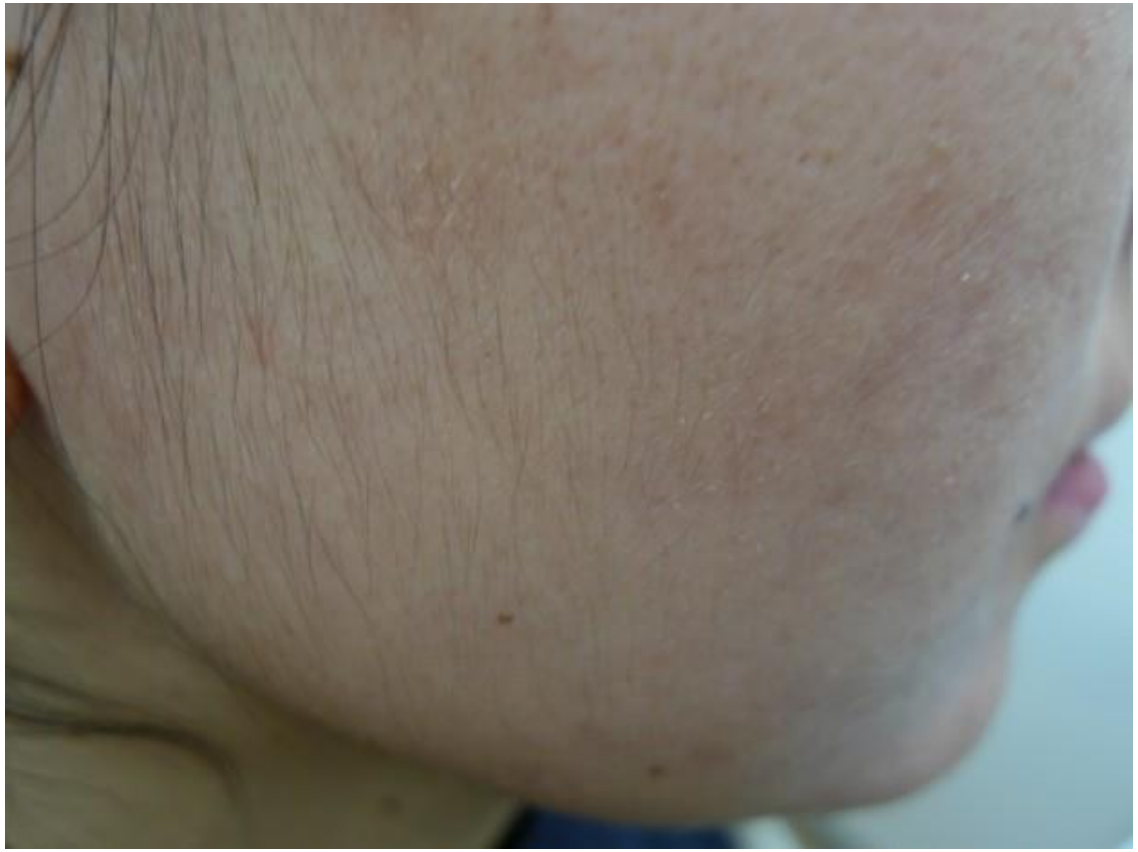
- AKI
- Headache
- Hypertension
- Nausea/vomiting
- Leg cramps
- Hirsutism
- Gum hyperplasia

Gingival hyperplasia



https://www.merckmanuals.com/professional/dental-disorders/periodontal-disorders/gingival-hyperplasia

Hirsutism



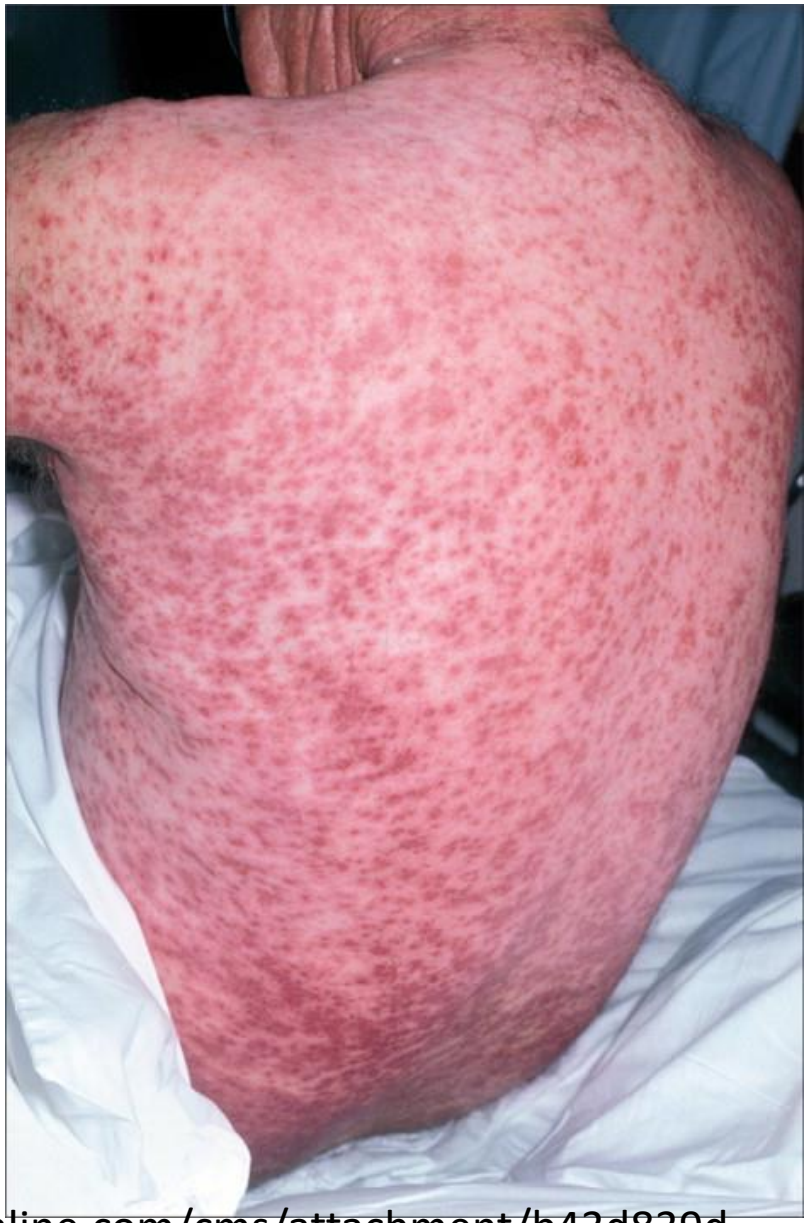
https://www.dermcoll.edu.au/wp-content/uploads/Hirsutism-DavinLim-624x468.jpg

Eltrombopag

- Initiate on Day 1 concurrently with hATG and CSA, continue for 6 months
- Dietary restrictions
- Hepatic metabolism
- If baseline ALT/AST is >6 uln do not start epag until down to <5 uln
- Adult (12 y/o and older) Dose is 150mg once daily for 6 months (75mg daily for Asian ethnicity adult)
- Pediatric dose is weight based for age <6, 75mg from age 6-11 y/o
- Dose reduction based on platelet response
  - Decrease by 25mg every 2 weeks for plts >200k
  - Hold for plts >400k

Eltrombopag

- Rash
- Transaminitis
- Icteric sclera/ ashen pallor



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Prognosis

- Outcomes
  - Predictors of response
- Assessing response
  - Complete response
  - Partial response
  - Refractory
  - Relapse

Back to our case…

- 10 day admission for hATG tolerated well. Taking epag daily at 4am, cyclosporine with magnesium supplement and amlodipine 10mg daily for CSA induced HTN.
- Ana became transfusion independent at 3 months with counts continuing to improve over the first year of treatment.
- She reached a partial response with a Hgb of 11, plts 95, ANC 1.1.
- At two years, when the cyclosporine was discontinued, her platelet counts started to downtrend, 75k, 50k, 30k….
- Now what?

When to call relapse?

- Not as straight forward as initial diagnosis of SAA
- Variable presentation
  - Slow decrease in one of the blood counts
  - Abrupt decrease in one or multiple blood counts
- Many conditions may decrease the cell counts
  - Viral infections, pregnancy, surgery

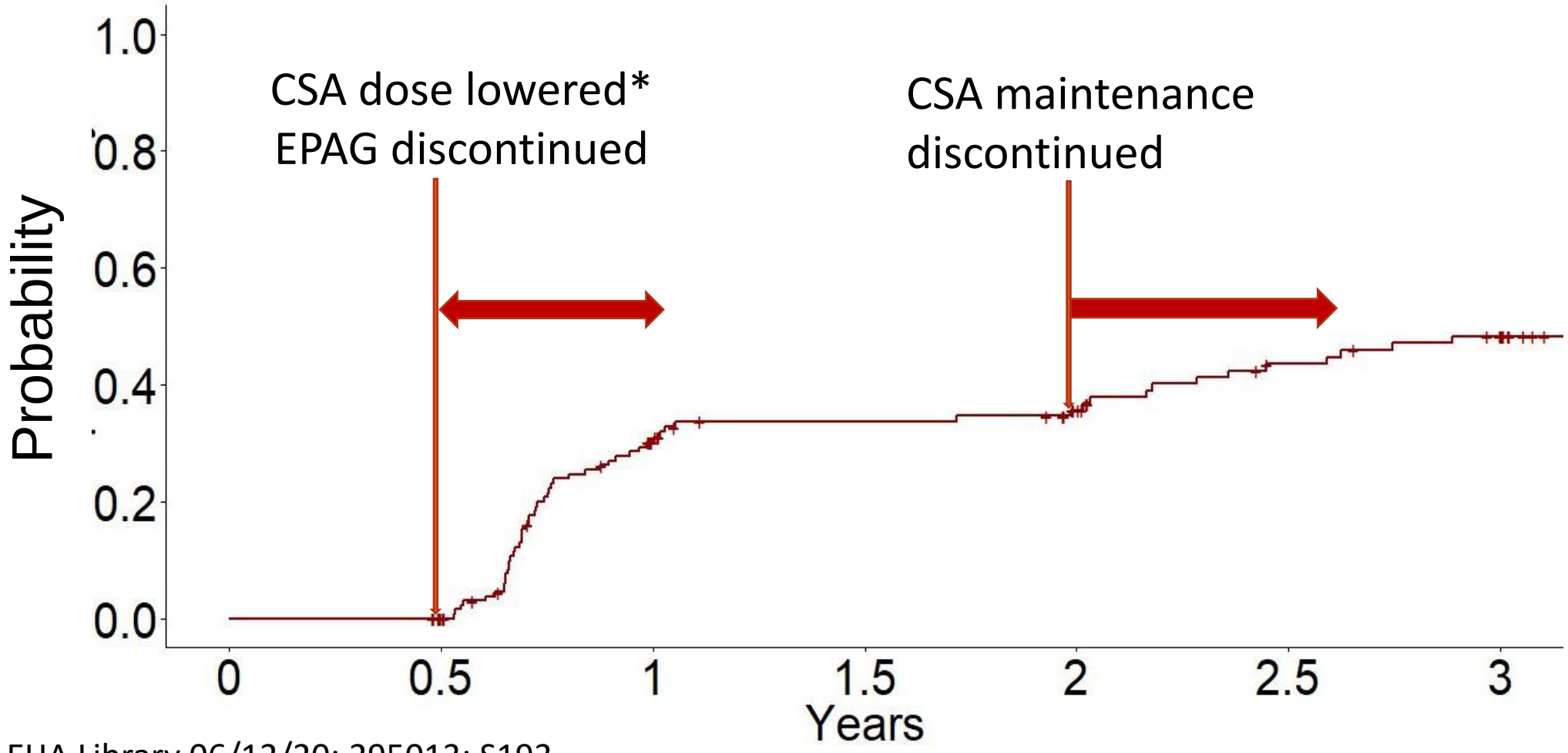
  __Trend important not a single lab value__
  - Can be frustrating/anxiety provoking for patients

Relapse in SAA treated with Immunosuppression and Eltrombopag

- A total of 175 patients from 2012 -2019 were assessed for relapse and clonal evolution.
- Relapse was defined as decline in one or more blood counts requiring reinitiation of treatment.
- Median time of follow up was 2 years

Patel B. EHA Library 06/12/20; 295013; S193

Relapse occurred at 2 distinct timepoints



Patel B. EHA Library 06/12/20; 295013; S193

No. at risk	143	136	82	70	62	48	42

Relapse treatment: Individualized to the patient

- Restart Cyclosporine full dose
- Start or restart Eltrombopag
- Another round of horse ATG or rabbit ATG
- Alemtuzumab
- Bone marrow transplantation if age, co-morbidity, and donor availability allow

Ana

- Became transfusion dependent again for platelets, with Hgb and ANC down trending
- Plts <10k, Hgb 8, ANC <200
- Started on full dose cyclosporine without a response
- Referred Ana to a transplanter to discuss haploidentical transplant, patient elected not to pursue
- Added eltrombopag with count recovery after 8 weeks. Transfusion independent, ANC >1.0.
- Try to taper medications slowly over several months, with close monitoring of blood counts

Practical considerations: Toxicities

Long term side effects

- cyclosporine
  - Kidney problems
- eltrombopag
  - Not entirely known at this time
  - Compared to the patients treated with IST alone, high-risk clonal evolution was not increased with the addition of EPAG (Patel, EHA 2020)
- alemtuzumab
  - extremely immunosuppressive
  - Delayed response

Diagnosis Takeaways

- Important to distinguish inherited vs. acquired BMF
- SAA vs. hypoplastic MDS
- Supportive care and explore transplant options

Treatment Takeaways

- BMT is the only curative option and should be considered as first line for children and young adults
- Immunosuppressive therapy hATG, CSA, eltrombopag is an option for those where transplant may not be available
- IST + eltrombopag well tolerated with response rates better than IST alone

Relapse Takeaways

- Relapse will occur in approximately a third of patients
- The majority of patients (70%) will respond to reinitiation of oral immunosuppression (Patel, EHA 2020)
- IST does not exclude a patient from pursuing transplant if they are refractory/relapse

Future Direction of SAA Treatment

- Optimizing timing of triple therapy
- Preventing and treating relapsed patients

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