Aplastic Anemia

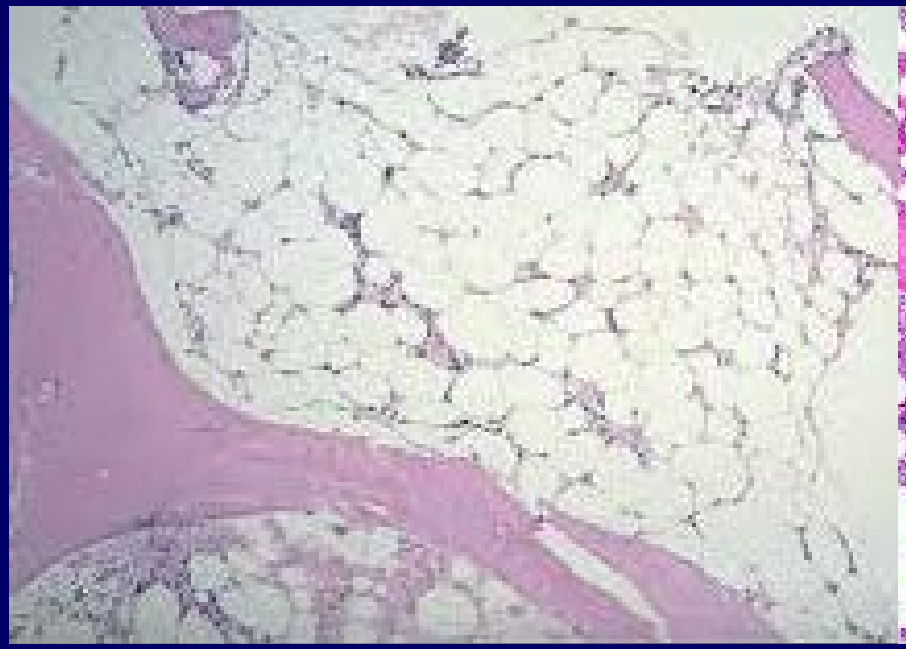
Ron Paquette, MD

Cedars-Sinai
Division of Hematology/Oncology

Aplastic Anemia

- Disease of bone marrow stem cells
  - Low number of cells in bone marrow without myelodysplasia, leukemia cells, or chromosome abnormalities
  - Low blood counts affecting at least 2: WBC, RBC, platelets
- Immune attack against bone marrow stem cells
  - Some people are predisposed based on tissue type
  - Killer T cells are observed in the bone marrow
  - Response to immunosuppression

Bone Marrow Biopsy



What Causes AA?

- Abnormal immune response in most patients
- Rarely, inherited bone marrow disease (Fanconi's anemia, others)
- Inherited mutations of telomerase genes (TERT, TERC) in <5%
- Acquired gene mutations affecting one or more genes in 30-50%
- Medications in about 25% of cases
  - Anti-inflammatory drugs (Indocin, Motrin)
  - Sulfa drugs (antibiotics, diabetes drugs, diuretics)
  - Anti-seizure drugs (Dilantin, Tegretol)
  - Rheumatologic drugs (gold, allopurinol)
- Hepatitis (not viral) in 2% of cases

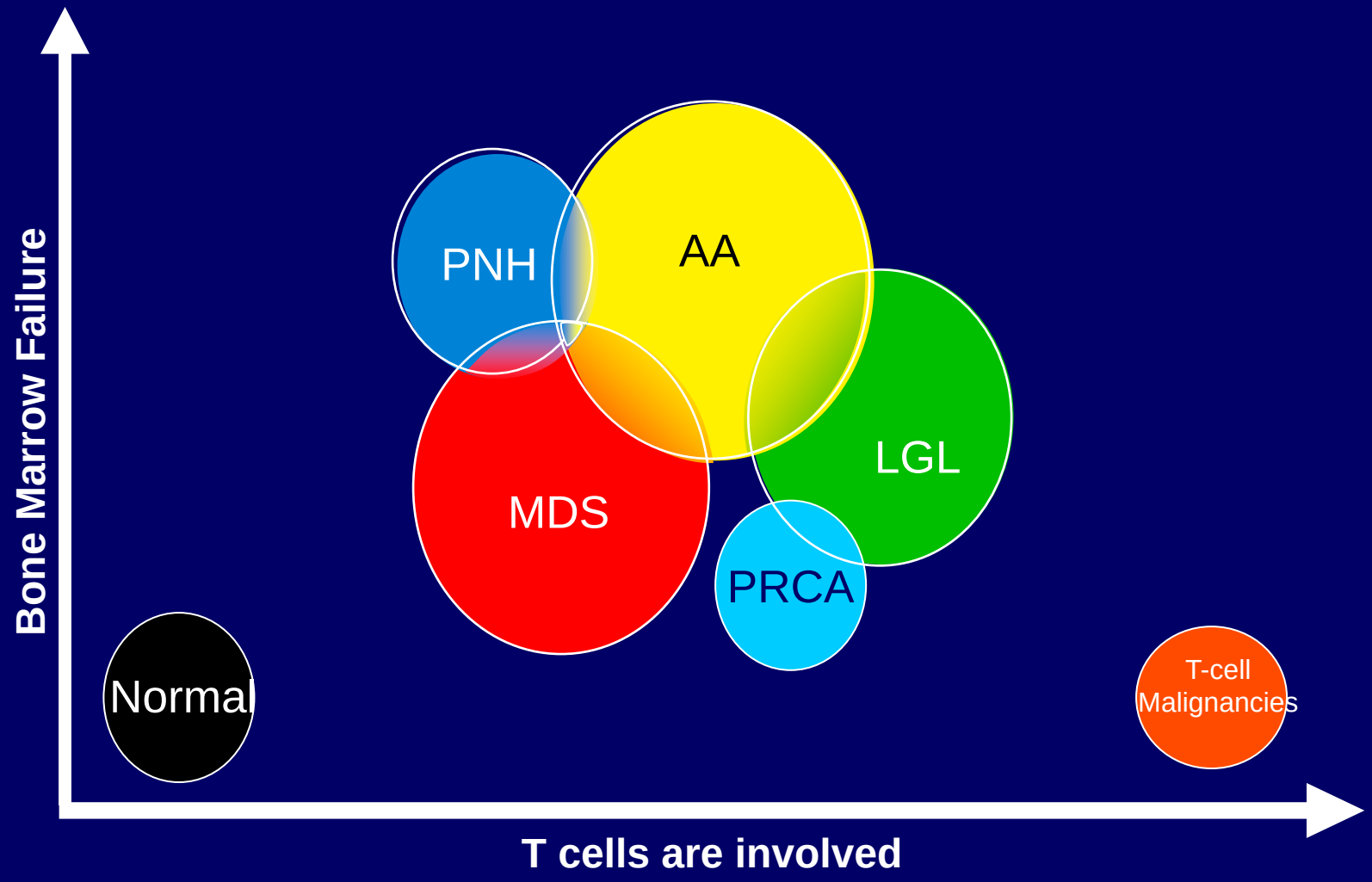
Gene Mutations

- Inherited
  - Mutations of FANC genes that encode DNA repair proteins (FANC A>C>G)
  - Dyskeratosis congenita (telomere gene mutation: shelterin)
  - Other telomere gene mutations (TERC, TERT) in 3% of adult patients
- Acquired up to half of adults with AA have one or more myeloid gene mutations
  - BCOR or BCORL1 – better response to therapy
  - PIGA - better response to therapy
  - DNMT3
  - ASXL1 – tends to progress
  - RUNX1 – tends to progress
  - Splicesome genes
  - TP53
  - TET2

Bone Marrow Failure Disorders

- Blood forming stem cells are affected
  - Aplastic anemia (AA)
  - Pure red cell aplasia (PRCA)
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Large granular lymphocyte leukemia (LGL)
  - Myelodysplastic syndrome (MDS)

Relationships Between Idiopathic Bone Marrow Failure States



J Maciejewski, 2004

Aplastic Anemia: Classification

- Severe AA: any two criteria
  - absolute neutrophil count <500/μL
  - absolute reticulocyte count <20,000/μL
  - platelet count <20,000/μL
- Very severe AA: neutrophil count <200/μL
- Moderate AA: any two criteria
  - absolute neutrophil count <1200/μL
  - hemoglobin <8 g/dL with corrected reticulocyte count <1%
  - platelet count <60,000/μL

Aplastic Anemia: Treatment Options

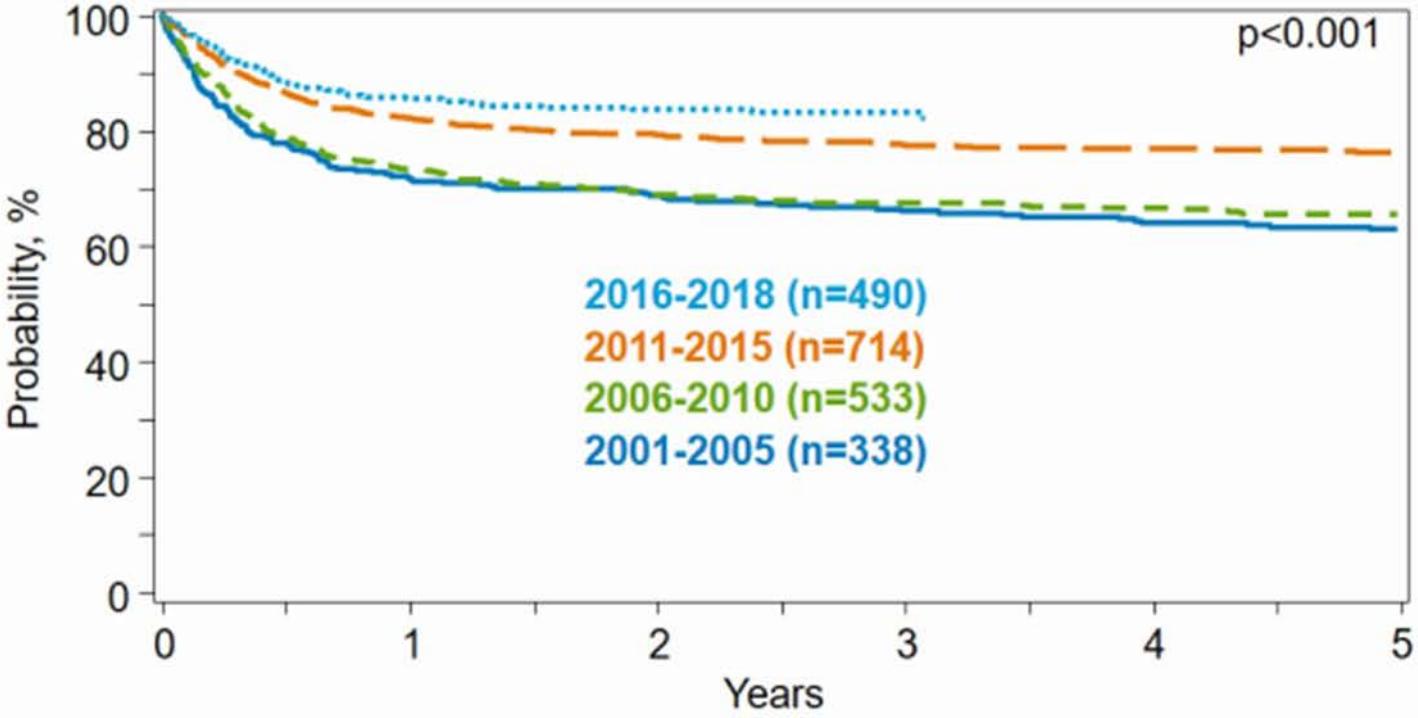
- Allogeneic stem cell transplantation
- Immunosuppressive therapy
- Hematopoietic growth factors

Bone Marrow Transplantation in Aplastic Anemia

- Indicated for severe or very severe AA in “younger patients”
- Conditioning: Flu/Cy/ATG. TBI is added for unrelated or haplo related
- Bone marrow associated with superior survival compared to PBSC
- GVHD prophylaxis: CsA, MTX for matched transplants, CTX for haplo
- Survival approximately 80% at 10 years
  - Outcomes are best if transplant done within 2 years of diagnosis
  - Age <40 significantly better than age $\geq$40
- Risks
  - graft failure: 10-15%
  - acute graft vs host disease: 20% grade 3/4
  - fatal infection or organ failure: 10-20%
  - chronic graft vs host disease: 20%–40%
  - late solid tumors: 10%

Transplant Outcomes for Aplastic Anemia

Trends in Survival after Allogeneic HCT for Severe Aplastic Anemia (SAA), Age ≥18 Years, in the US, 2001-2018



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Immunosuppressive Therapy in Aplastic Anemia

- Antithymocyte globulin 40 mg/kg/d x 4 doses better than ALG
- Cyclosporine 5 mg/kg/d for >6 months
- Eltrombopag 150 mg/d (75 mg/d for Asians)
- Response: 80%–94% (CR 26-58%) at 6 mos
- Survival 97% at 2 years
- Risks
  - fatal infection/bleeding
  - AML or MDS: 10%–15% at 10 years
  - PNH: 10%
  - relapse: 32% at 6 mos (54% if CsA stopped at 6 mos, 14% if CsA continued)

Townsley DM, et al. N Engl J Med 2017; 376:1540

White Blood Cell Growth Factors

- Granulocyte colony stimulating factor (Neupogen) can increase production of white blood cells by the bone marrow
- GCSF can increase the neutrophil counts of some AA patients, but the likelihood of response is inversely proportional to the baseline neutrophil count
- They do not improve the response rates or survival of patients receiving immunosuppressive therapy
- They should not be used as the only treatment for patients
- They may benefit patients with active/recurrent infection
- Neupogen may increase the risk of MDS or AML when given over a prolonged period of time

Incomplete Response

- Approximately half of patients receiving ATG/CsA/Promacta ultimately achieve a complete response
- The remaining patients must continue to live with blood counts that are lower than normal
- This should not cause chronic anxiety: the survival of patients experiencing a partial response is not different from that of patients who have a complete response
- What is the minimal acceptable level of blood counts?
  - Platelet count >20,000/mcL without bleeding
  - Neutrophil count >500/mcL without recurrent infections
  - Hemoglobin ?

What to Do if ATG Doesn't Work

- Unrelated donor bone marrow transplantation
- Haploidentical related BMT
- Umbilical cord blood transplantation
- Second course of horse ATG
- Rabbit antithymocyte globulin (Thymoglobulin)
- Prolonged cyclosporine alone
- Promacta or Romiplostim
- Experimental trials

Unrelated Donor Bone Marrow Transplantation in Severe Aplastic Anemia

- Indication: SAA that failed to respond to IST
- Median age: 27 years (range 7-53 years)
- Conditioning: TBI 200 cGy/ATG/Flu/Cy 50 mg/kg
- GVHD prophylaxis: CsA, MTX
- Graft failure 17%
- Acute GVHD II-IV 18%, III-IV 7%; chronic GVHD 50%
- Survival: 79% at 2 years
- Prognostic variables
  - age <27 yrs (78%) vs ≥27 yrs (79%)
  - disease duration <2 yr (87%), ≥2 yrs (55%)

Bacigalupo A, et al. *Haematologica.* 2010;95:976.

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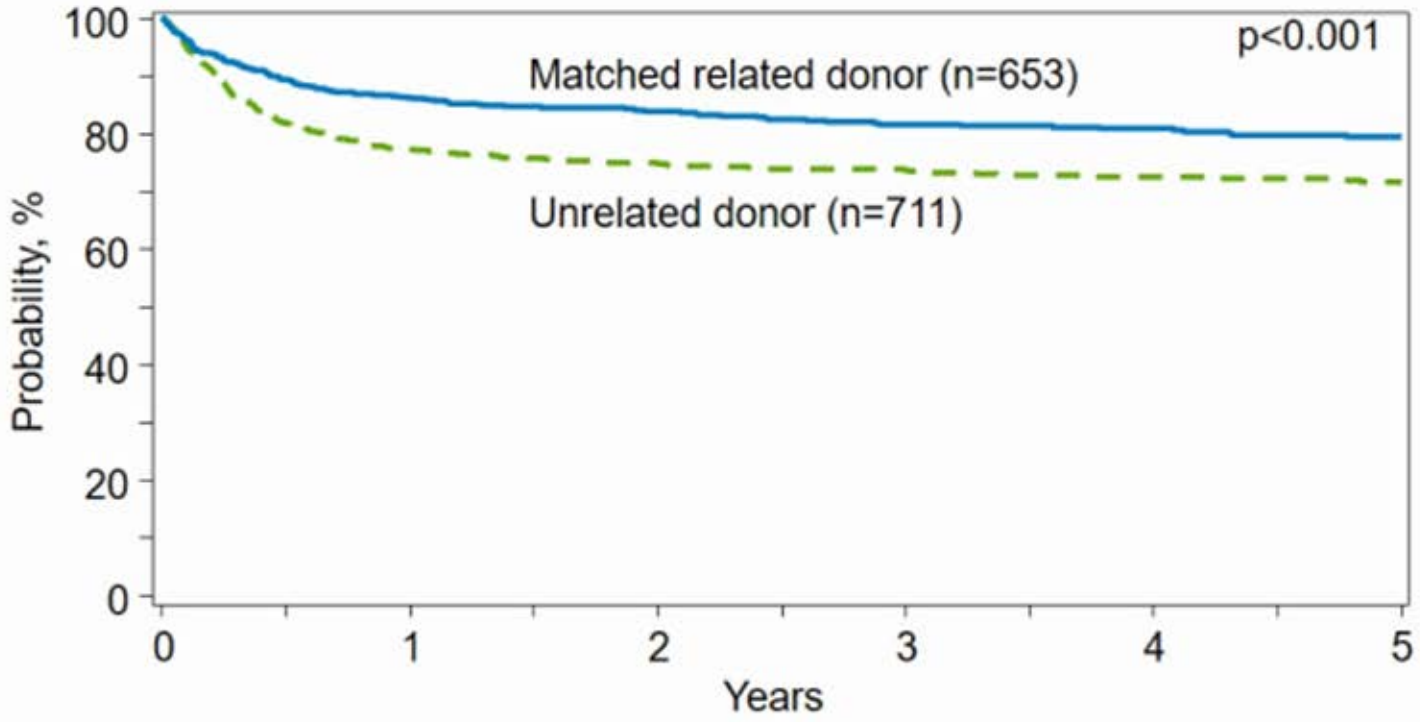

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Eltrombopag for Aplastic Anemia

- 40 patients had 50% response rate after 6 mos
- Two cell types improved in 22% and all three improved in 18% of patients
- Among responding patients who discontinued treatment, one third had to restart drug due to relapse
- 18% of patients developed MDS-like chromosomal abnormalities or MDS/AML within 6 months (mostly loss of chromosome 7/7q)

Winkler T, et al. Blood 2019;133:2575-2585

Romiplostim for Aplastic Anemia

- 31 patients were treated with up to 20 mcg/kg SQ weekly for up to 12 months
- At least one cell type improved in 84% of patients
- All three cell types improved in 39% of patients
- Two patients developed MDS-like chromosomal abnormalities

Jang JH, et al. Br J Haematol 2021;192:190-199.

Falling Counts!

- What is causing it?
  - Relapse: 35-45% risk at 10 years
  - MDS or AML: 10-15% at 10 years
  - PNH: 10% risk at 10 years
- How much of a drop is important?
  - Traditionally 50% decrease from best response is used to define relapse, but I would take notice sooner
- What to do?
  - Bone marrow biopsy with cytogenetics
  - Myeloid gene sequencing
  - Flow cytometry for CD55/59 (FLAER)

Risk Factors for Late Hematologic Complications

- Relapse of AA
  - Cyclosporine withdrawl
  - Pregnancy (19% risk)
- MDS/AML
  - MDS gene mutations (ASXL1, RUNX1, others) at diagnosis
  - Older age
  - Lack of response to immunosuppression
  - Prolonged use of G-CSF or eltrombopag (esp developing deletion chromosome 7 or 7q)

Treatment of Relapsed Aplastic Anemia

- Second course of ATG/cyclosporine/eltrombopag
  - consider for more severe disease
  - response: 50%–70%
- Restart cyclosporine if it was discontinued, or increase the dose
  - reasonable for early or partial relapse
- Stem cell transplantation
  - appropriate for severe disease
  - consider if high risk mutations on BM biopsy, suboptimal initial response to ATG, or intolerance of immunosuppression

Kidney Insufficiency Due to Cyclosporine

- Prolonged cyclosporine administration is frequently required to optimize response, maintain response (25% of pts are CsA dependent), and prevent relapse
- Chronic cyclosporine causes progressive deterioration of kidney function in most patients
- Kidney insufficiency frequently necessitates CsA dose reduction that can increase relapse risk
- Therefore, the minimum effective dose of CsA should be used
- However, there are minimal data regarding the optimal therapeutic dose or blood level of CsA for aplastic anemia
- Doses from 2 to 5 mg/kg/day appear to be active
- Careful attention to blood pressure control may help to minimize kidney toxicity

Avascular Necrosis

- AVN is caused by high dose steroids used to prevent and treat serum sickness from ATG
- Incidence is approximately 10%
- Most commonly affects hips (head of femur), but can also affect shoulders or knees
- Progressive joint pains occur months or years after ATG
- Plain X-rays can detect advanced AVN
- MRI is most sensitive test
- Joint replacement is only effective treatment, but is reserved for advanced disease

Iron Overload

- Transfusions (>20–30 units) are associated with iron overload
- Iron overload can eventually (over years) cause cirrhosis, heart failure, diabetes or other hormone deficiencies
- Survival in low risk MDS patients may be adversely affected by a high burden of iron; this is likely to be true for aplastic anemia as well
- Iron chelation therapy is initiated after the ferritin is over 1000 mg/dL
- Treatment continues until the ferritin is less than 1000 mg/dL
- Three drugs are available:
  - Deferoxamine (Desferal) given by SQ infusion

    Side effects: nausea, diarrhea, decreased vision, decreased hearing
  - Deferasirox (Exjade, Jadenu) by mouth

    Side effects: increased creatinine, nausea, diarrhea
  - Deferiprone (Ferriprox) by mouth

    Side effects: neutropenia, liver function abnormalities, joint pain

Conclusions

- Aplastic anemia patients can be treated successfully with several options
- Careful selection of initial and salvage therapies is important – risks and benefits of available options should be fully discussed
- Awareness of potential complications of treatment will often help to minimize toxicities
- Consulting a physician familiar with aplastic anemia can be beneficial
- Patient education is important in achieving a favorable outcome of aplastic anemia therapy

COVID-19 and Aplastic Anemia

- There is very little information about the outcome of COVID-19 infection in patients with AA
- Patient care (e.g. frequency of laboratory testing or transfusion support) should be modified, when possible, to limit patient visits to clinics and hospitals (ASH, EBMT)
- Patients should be tested for COVID-19 infection before administering ATG or transplant conditioning and treatment should be delayed until infection has cleared

ASH = American Society of Hematology

ESBMT = European Society for Blood and Marrow Transplantation

COVID-19 and Immunosuppression

- The effect of immunosuppression on the outcome of COVID-19 infection in AA patients is unknown, but it is expected to adversely affect the outcome of patients who subsequently become infected (EBMT)
- Treatment should not be delayed in patients with very severe AA (ASH)
- Use of ATG therapy should be limited to patients with severe cytopenias and immediate risk of death (EBMT)
- In AA patients who cannot receive ATG for logistical or other reasons, treatment with cyclosporine and eltrombopag (ASH) or eltrombopag alone (EBMT) represents a potentially beneficial alternative
- Cyclosporine doses should not be decreased in patients already receiving maintenance therapy (EBMT)

COVID-19 and BMT

- BMT should be postponed whenever possible (according to severity), especially unrelated donor (EBMT)
- Transplant donors should be tested for COVID-19 infection before collecting cell products. These should be collected and stored in advance of starting conditioning therapy on the transplant recipient

COVID-19 Vaccine and Aplastic Anemia

- Risk versus benefit of vaccination favors vaccine administration, especially in patients with risk factors for severe COVID-19 infection (ASH)
- Patients within 6 months of receiving ATG would not be expected to have a good response to a vaccine, so they should be considered for antibody therapy if they become infected with COVID-19 (ASH)
- Patients receiving maintenance cyclosporine more than 6 months after ATG may respond to vaccination, but there is no information about it safety of effectiveness (ASH)
- BMT patients would be unlikely to respond to vaccination before 6 months post-transplant, or later if they are receiving immunosuppression for graft versus host disease (ASH)