Aplastic Anemia: Diagnosis and Treatment

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Aplastic Anemia

- Bone marrow failure disorder characterized by diminished or absent hematopoietic precursor cells in the bone marrow
- Low blood counts with hypocellular bone marrow
- Can be congenital or acquired

Epidemiology of Aplastic Anemia

- Estimated to occur in 2-4 individuals per million population per year
- No racial predisposition in the United States
- More prevalent in the Orient/Far East
- Male: female distribution is approximately 1:1
- Bimodal age distribution
  - Majority in younger age
  - Peak incidence ages 20-25 and another peak >60

Congenital Aplastic Anemia

- Approximately 20% of cases
- Patients usually have physical abnormalities but abnormal blood counts may be presenting feature
- Diseases include
  - Fanconi Anemia
  - Dyskeratosis congenita
  - Shwachman-Diamond syndrome
  - Familial aplastic anemia

Acquired Aplastic Anemia

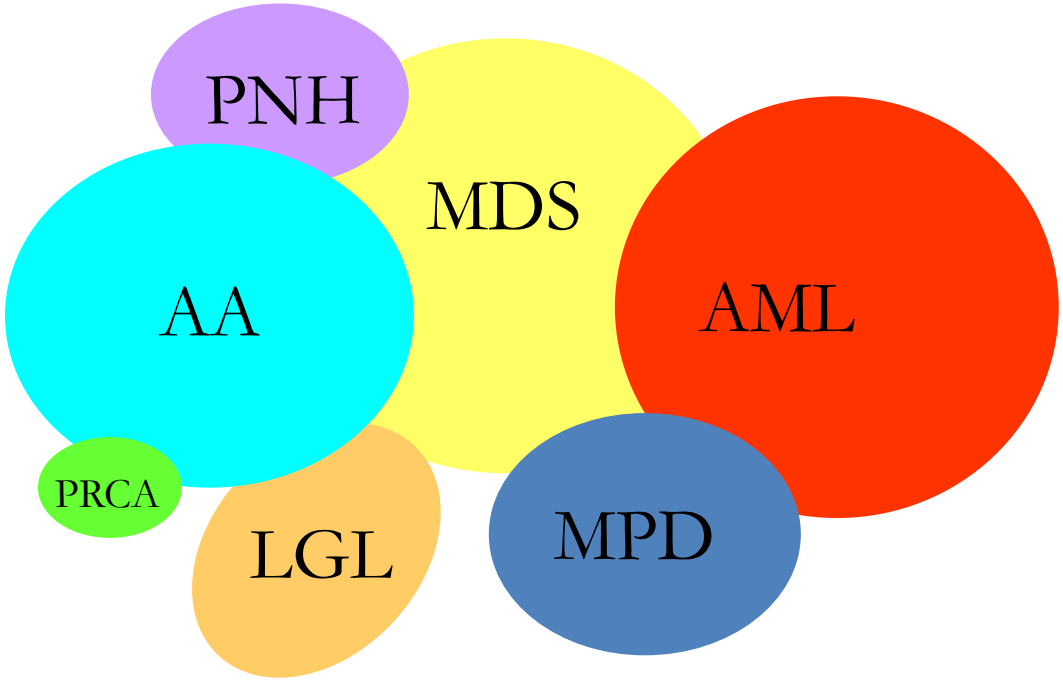
- Idiopathic – majority of cases
  - Autoimmune, stem cell defect
- Infections
  - Typically viral
  - Hepatitis, Herpes, Parvovirus
- Toxins
  - Radiation exposure
  - Chemicals (benzene, toluene, glues)

Acquired Aplastic Anemia

- Medications
  - Chemotherapy
  - Chloramphenicol
  - Antibiotics, Anti-inflammatories, Anti-convulsants
- Pregnancy
- Paroxysmal nocturnal hemoglobinuria
- Immune diseases
  - Lupus, Rheumatoid arthritis

Clinical Overlap / Associations

- **Bone marrow failure disorders**
- **Many overlapping disorders:**
  - **Myelodysplastic Syndromes**
  - **Acute Myeloid Leukemia**
  - **Myeloproliferative Disorders**
  - **Paroxysmal Nocturnal Hemoglobinuria**
  - **Autoimmune diseases:**
    - **Aplastic Anemia**
    - **LGL leukemia**
    - **Pure Red Cell Aplasia**



J Maciejewski, M.D. Taussig Cancer Center/ Cleveland Clinic Foundation
American College of Physicians from Young NS. Ann Intern Med. 2002 Apr 2;136(7):534-46

Aplastic Anemia: Presenting Symptoms

- Anemia
  - Fatigue, shortness of breath, dizziness
- Neutropenia
  - Frequent or recurrent infections
- Thrombocytopenia
  - Bleeding or easy bruising

Classification

- Moderate aplastic anemia
  - Marrow cellularity < 30%
  - Depression of at least two of three blood elements
  - Absence of severe pancytopenia
- Severe aplastic anemia
  - Marrow cellularity < 25% or <50% with 2 of the following criteria
    - ANC < 500/microL
    - Platelets < 20,000/microL
    - Absolute reticulocyte count < 20,000/microL
- Very severe aplastic anemia – ANC < 200/microL

Supportive Care

- Withdrawal of offending agent
- Sometimes spontaneous recovery can occur
- Generally do not wait longer than 2-3 months to initiate treatment

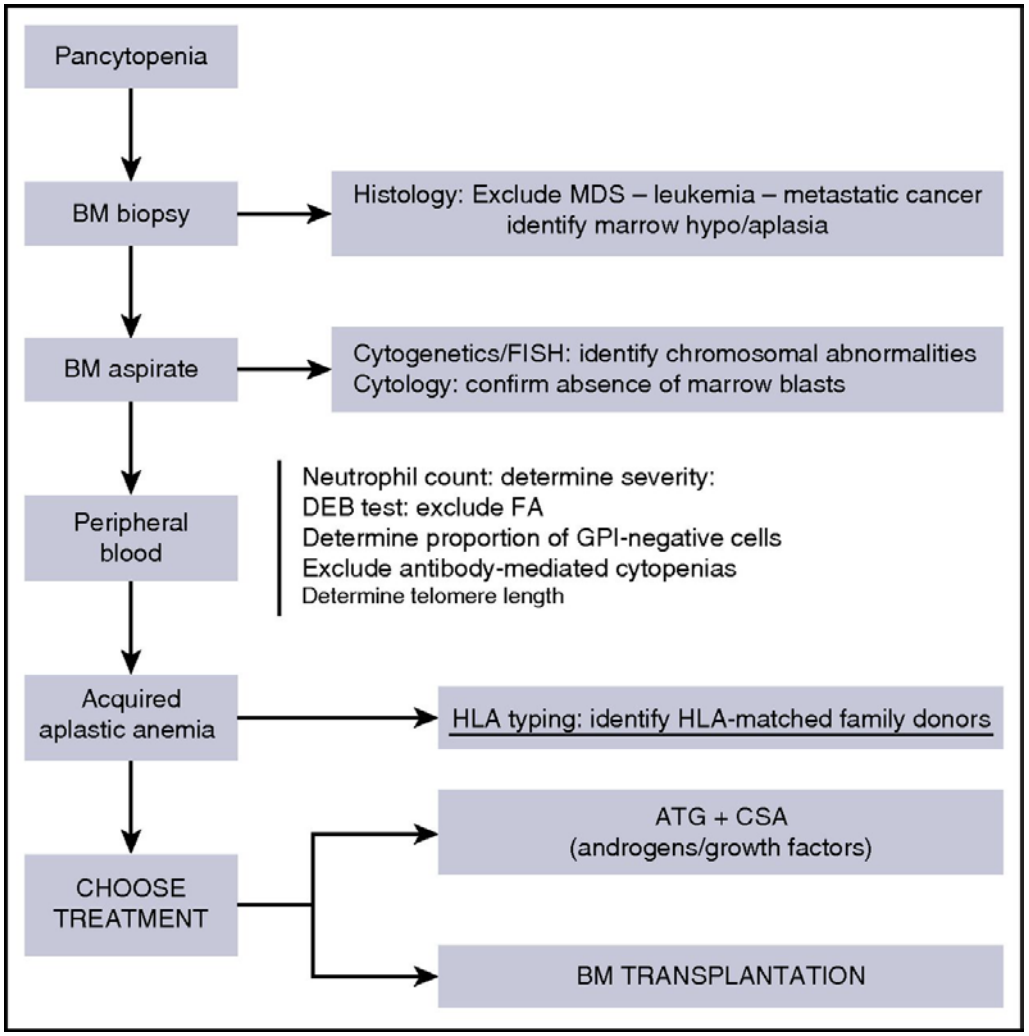
Supportive Care - AA

- Blood product transfusions - leukoreduced
  - Red blood cells
  - Platelets
- Antibiotics
  - Intravenous if febrile with low neutrophil count
  - Prophylactic antifungal – voriconazole or posaconazole for severe AA
- Growth Factors – not typically used in first line
- Corticosteroids – avoid in first line therapy

Moderate Aplastic Anemia

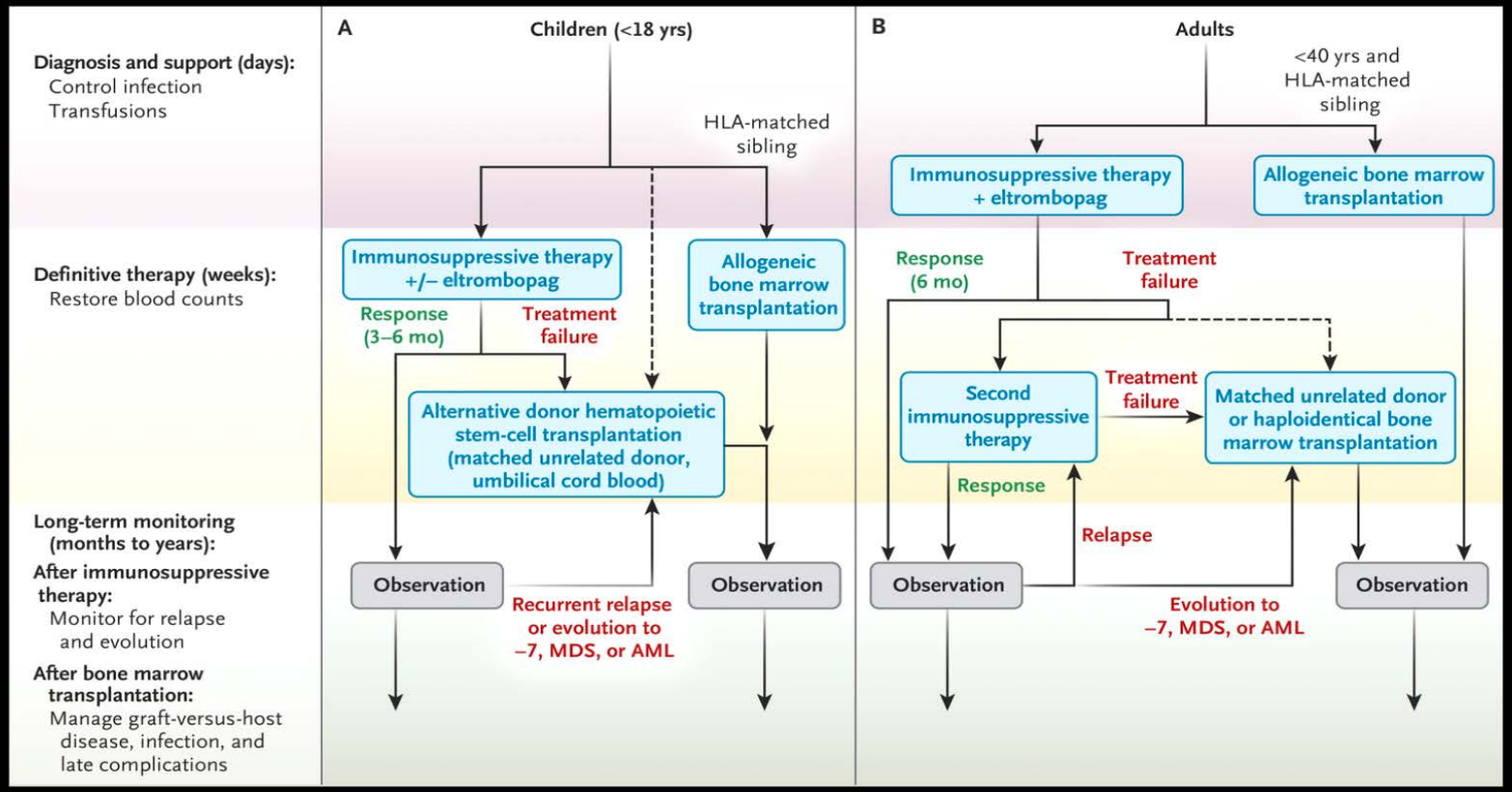
- Observation is often appropriate
  - Especially if transfusion independent
- Many patients have stable blood counts for years
- Elderly or frail patients with significant comorbidities may also benefit from a supportive approach

Diagnostic procedures in patients with pancytopenia.



Bacigalupo A et al. Blood 2017;129:1428-1436

Treatment Algorithms for Patients with Immune Aplastic Anemia.



NS Young. N Engl J Med 2018;379:1643-1656.

The NEW ENGLAND JOURNAL of MEDICINE

Bone Marrow Transplant

- Recommended as first line therapy for adults up through age 50 with appropriate donors (matched sibling preferred)
- Outcomes have improved with unrelated donors
- Bone marrow is preferred as the source of stem cells for severe aplastic anemia
  - Less rates of chronic GVHD

Treatment

- Bone Marrow Transplantation
  - High rate of graft rejection has become less problematic
    - Avoidance of heavy transfusion burden
    - Better conditioning regimens (Fludarabine/Campath)
  - Rates of GVHD increase with age
  - Outcomes in the most favorable age group (children with matched sibling donor) result in long-term survival of 80%

Treatment

- Immunosuppression
  - Standard is horse anti-thymocyte globulin (ATG) + cyclosporine + eltrombopag
  - Produces hematologic recovery in 60-80% of cases
  - Does not prevent clonal evolution
  - Ongoing trials using eltrombopag in upfront therapy
    - Duration of response, selection of patients for drug discontinuation, safety in clonal evolution

Immunosuppression

- Rabbit ATG
  - Successful in refractory or relapsed SAA patients after initial horse ATG
  - Attempted as first-line therapy
  - However, hematologic response first line was 37% compared to 68% with standard horse ATG

Immunosuppression

- Anti-thymocyte globulin
  - Administered at a dose of 40 mg/kg over 4 hours daily over 4 days
  - Prednisone 1 mg/kg is started on the first day and continued for 2 weeks, followed by rapid taper
  - Premedication with tylenol and benadryl
  - Must be monitored carefully for infusion reactions

Immunosuppression

- Cyclosporine initiated on day 1 starting at a dose of 5-6 mg/kg/day
- Target level of 200 – 400 ng/mL
- Kidney function must be monitored
- Hypertension can develop
- Eltrombopag is given at 150 mg orally daily for 6 months

Management after ATG

- Response is defined as improvement in blood counts
  - Might take 2-3 months; if no response after 3 months, may want to consider alternative strategies
  - Cyclosporine taper occurs around 6 months

Refractory SAA

- Blood counts still fulfilling severe criteria 6 months after immunosuppressive therapy
  - Younger patients should undergo unrelated transplant if available
  - Second course of immunosuppression with rabbit ATG/CSA is an option
  - Alemtuzumab – humanized monoclonal antibody against CD52
    - Hematologic response in 30-40% of patients

Eltrombopag

- Approved by FDA for patients with severe aplastic anemia who fail to respond adequately to immunosuppressive therapy
- Oral thrombopoietin receptor agonist
  - Induces proliferation and differentiation of bone marrow stem cells to increase production of blood cells

Eltrombopag

- Initial dose of 50 mg, can be titrated up to 150 mg
- 40% of patients experienced a response in 12 weeks
- Most common side effects are nausea, fatigue, cough, diarrhea, headache, liver function abnormalities

Eltrombopag

- Can produce tri-lineage hematopoiesis in severe aplastic anemia patients refractory to immunosuppressive therapies
  - 44% clinical response rate
  - Transfusion Independence
  - Well-tolerated
- Addition of eltrombopag early in SAA may increase response rate and decrease time to response

Long-Term Follow-up

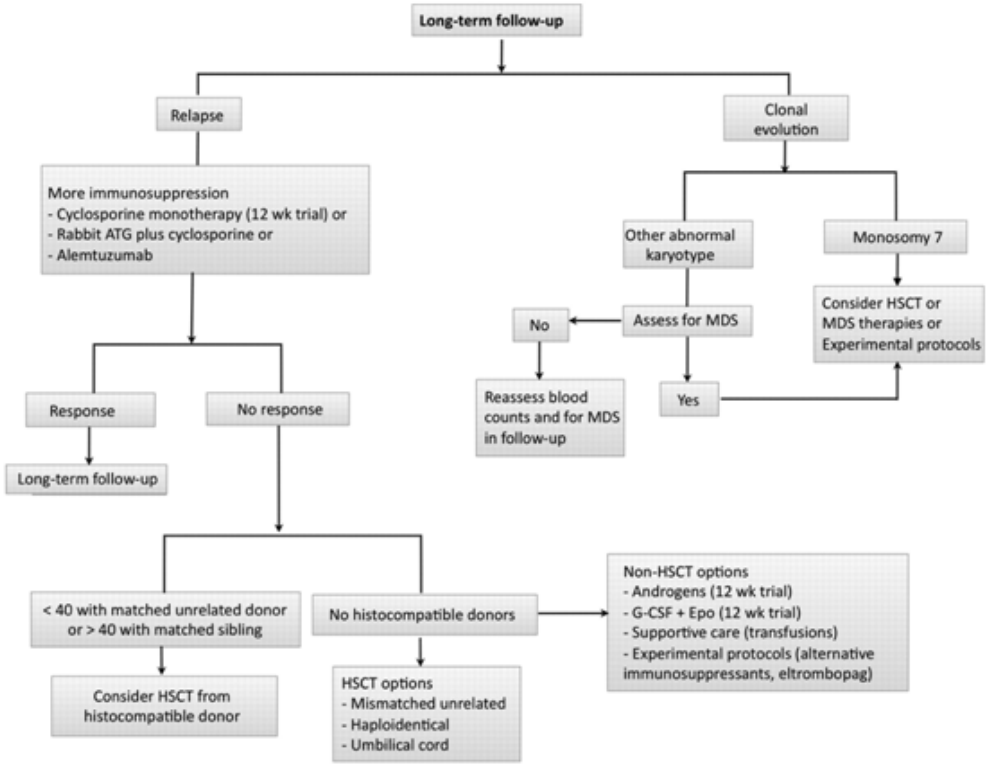
- Assess bone marrow morphology and cytogenetics of responders at 6 and 12 months and then yearly
- Blood counts should guide management
- Monitor for clonal evolution to MDS and AML
- Many patients who relapse can get further immunosuppression or stem cell transplant

Clonal Evolution

- 10 to 15 percent of patients can develop myelodysplastic syndromes or leukemia
- Manifestations:
  - Worsening blood counts unresponsive to immunosuppression
  - Dysplasia in the bone marrow
  - Abnormal chromosomes

Long-Term Follow-up

Long-term follow-up after immunosuppression.



Phillip Scheinberg, and Neal S. Young Blood 2012;120:1185-1196

COVID-19 Pandemic

- Definitive therapies remain transplant or immunosuppression for severe aplastic anemia
- ATG and cyclosporine are not profoundly immunosuppressive
- Hospitalization for ATG may be problematic in some centers – consider expectant care with oral cyclosporine and eltrombopag

ASH Guidelines COVID-19 and Aplastic Anemia

Aplastic Anemia

- Bone marrow failure disorder
- Immunosuppression and stem cell transplant are the mainstays of treatment
- Eltrombopag is approved for refractory disease and also upfront with IST
- Patients must be monitored for relapse or clonal evolution