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-inflammatory, 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.

- **Pancytopenia**
  - BM biopsy
    - Histology: Exclude MDS – leukemia – metastatic cancer
    - Identify marrow hypo/aplasia
  - BM aspirate
    - Cytogenetics/FISH: identify chromosomal abnormalities
    - Cytology: confirm absence of marrow blasts
  - Peripheral blood
    - Neutrophil count: determine severity
    - DEB test: exclude FA
    - Determine proportion of GPI-negative cells
    - Exclude antibody-mediated cytopenias
    - Determine telomere length
- **Acquired aplastic anemia**
  - HLA typing: identify HLA-matched family donors
  - ATG + CSA (androgens/growth factors)
  - CHOOSE TREATMENT
  - BM TRANSPLANTATION

Treatment Algorithms for Patients with Immune Aplastic Anemia.

**Diagnosis and support (days):**
- Control infection
- Transfusions

**Definitive therapy (weeks):**
- Restore blood counts

**Long-term monitoring (months to years):**
- After immunosuppressive therapy:
  - Monitor for relapse and evolution
- After bone marrow transplantation:
  - Manage graft-versus-host disease, infection, and late complications

**A**
- Children (<18 yrs)
- HLA-matched sibling
- Immunosuppressive therapy +/− eltrombopag
  - Response (3–6 mo)
  - Treatment failure
- Alternative donor hematopoietic stem-cell transplantation (matched unrelated donor, umbilical cord blood)
  - Observation
  - Recurrent relapse or evolution to −7, MDS, or AML
- Allogeneic bone marrow transplantation
  - Observation

**B**
- Adults (<40 yrs and HLA-matched sibling)
- Immunosuppressive therapy + eltrombopag
  - Treatment failure
- Allogeneic bone marrow transplantation
  - Observation
- Response
- Relapse
- Evolution to −7, MDS, or AML
  - Matched unrelated donor or haploidentical bone marrow transplantation

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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.

Relapse
- More immunosuppression:
  - Cyclosporine monotherapy (12 wk trial) or
  - Rabbit ATG plus cyclosporine or
  - Alemtuzumab

  - Response
    - Long-term follow-up
  - No response
    - Long-term follow-up

- No response
  - < 40 with matched unrelated donor or > 40 with matched sibling
    - Consider HSCT from histocompatible donor
  - No histocompatible donors
    - HSCT options:
      - Mismatched unrelated
      - Haploidentical
      - Umbilical cord

Clonal evolution
- Other abnormal karyotype
  - Assess for MDS
    - No
      - Reassess blood counts and for MDS in follow-up
    - Yes
      - Consider HSCT or MDS therapies or Experimental protocols

Monosomy 7
- Non-HSCT options:
  - Androgens (12 wk trial)
  - G-CSF + Epo (12 wk trial)
  - Supportive care (transfusions)
  - Experimental protocols (alternative immunosuppressants, eltrombopag)

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