How I treat acquired aplastic anemia

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Symptoms, Signs, and Lab Findings

- Bruising, bleeding, hemorrhage
- Anemia
- Pancytopenia
- Infection – infrequent at presentation
- Prior history of chemical and medical drug exposures
- Prior history of a single lineage cytopenia, usually thrombocytopenia or anemia
- Prior history of seronegative hepatitis in the months before pancytopenia - defines posthepatitis SAA.
- If macrocytosis and mild anemia present – clue that ITP is not the correct diagnosis.
Diagnosis

• Established on blood **AND** bone marrow examination
• Elevated mean corpuscular volume
• “Empty” marrow on histology
• Appearance of the marrow in inherited and acquired cases is identical

Differential diagnosis:

• Marked hemophagocytosis?
• Dysplasia?
• Increased blasts?
• Megakaryocytes are the most reliable lineage to use in distinguishing MDS from SAA.
Spicules are empty and generally devoid of hematopoietic elements.
1. High-power view shows naked nuclei and debris-laden histiocytes
2. Spicules are composed almost entirely of stromal elements
In severe cases, the cellularity is typically <25% of expected for age and predominantly composed of plasma cells and lymphocytes. The biopsy must be of adequate length to ensure that marrow deep to the physiologic subcortical hypocellular region is sampled.

Pathophysiology of acquired aplastic anemia
Treatment (1)

- Moderate cases (lack of blood count criteria for SAA) - observation is appropriate when transfusion is not required
- Transfusion-dependent can be treated according to Fig. 1
- Antibiotics when fever or documented infection occurs in the presence of severe neutropenia (ANC <500/μL)
- Immunosuppressive therapies are widely used due to lack of transplantation
  - ATG-based regimen in combination with cyclosporine
  - 60% of patients are responders at 3 or 6 months after initiation of horse ATG
Algorithm for initial management of SAA. In patients who are not candidates for a matched related HSCT, immunosuppression with horse ATG plus cyclosporine should be the initial therapy.

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Treatment (2)

- Perform ATG skin test if available for hypersensitivity to horse serum and desensitize those by intradermal injection
- Platelets should be maintained at more than 20,000/μL during ATG administration
- Patients need to be free of infection before initiating ATG
- ATG administered at a dose of 40 mg/kg over 4 hours, daily for 4 days
- Prednisone 1 mg/kg is started on day 1 and continued for 2 weeks as prophylaxis for serum sickness
- Acetaminophen and diphenhydramine are conventional premedications for treatment with ATG
Durability of response after horse ATG. (A) Time to first late event among responders.
Responders have better survival prospects than do nonresponders.

Long-term prognosis is predicted by the robustness of the early blood count response:
- Defined as either platelets or reticulocytes > 50 $\times$ 10$^9$/L [50,000/$\mu$L] 3 months after treatment.

Corticosteroids are of unproven benefit, and inferior in efficacy, to conventional immunosuppression regimens.

Should **not** transfuse platelets prophylactically in SAA patients who have a platelet count more than 10,000/$\mu$L and who are not bleeding.
**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

Clonal evolution

- Other abnormal karyotype
  - No
    - Assess for MDS
      - Reassess blood counts and for MDS in follow-up
  - Yes
    - Monosomy 7
      - Consider HSCT or MDS therapies or Experimental protocols

- Consider HSCT from histocompatible donor
- HSCT options
  - Mismatched unrelated
  - Haploidentical
  - Umbilical cord

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Relapse and Long Term Follow-up

- Defined as requirement for additional immunosuppression & not necessarily recurrent pancytopenia
- Does not by itself indicate a poor prognosis
- Major reason for relapse - incomplete eradication by ATG of pathogenic clones
- Second course of ATG therapy can be administered to patients with relapsed or refractory disease
- Cyclophosphamide has been used to treat relapsed/refractory SAA, and is associated with a response rate of about 50%
  - Toxicity of high-dose cyclophosphamide: prolonged neutropenia and susceptibility to infection
  - Higher death rates have been reported with use of cyclophosphamide
References


- ASH Image Bank, www.ashimagebank.org