Overview of Aplastic Anemia

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Overview of Aplastic Anemia
- Epidemiology
- Normal hematopoiesis
- Causes of bone marrow failure
- Presentation of aplastic anemia
- Evaluation
- Treatment

Epidemiology of aplastic anemia
- Incidence ~2 cases per million
- ~600 US cases annually
- 1:1 male:female incidence
- 50% cases in first 3 decades

Normal hematopoiesis
- Bone marrow-derived hematopoietic stem cells are self-renewing and are responsible for production of normal blood cells ("hematopoiesis"):
  - White blood cells fight infection
  - Red blood cells carry oxygen to tissues
  - Platelets clot blood to prevent bleeding
Normal and aplastic bone marrow

Normal bone marrow 30-70% cellularity
Aplastic anemia <10% cellularity

Differential diagnosis of bone marrow failure

Inherited causes of bone marrow failure

- Fanconi anemia
- Dyskeratosis anemia
- Schwachman-Diamond anemia
- Amegakaryocytic thrombocytopenia
- Often associated with physical findings
- Typically (not always) diagnosed in childhood

Acquired causes of bone marrow failure

- Toxic insults
  - Chemotherapy, radiation, chemicals
  - Idiosyncratic drug reactions
    - Antibiotics, anti-epileptics, non-steroidals
- Infections
  - Viral (HIV/EBV/HBV/CMV), sepsis
- Nutritional deficiencies
  - B12/folate/copper/iron
- Malignant
  - MDS/MPD/AML/LGL
Autoimmunity as a cause of acquired bone marrow failure

- Failure of the immune system (T cells) to discern normal HSC’s as “self”
- May be precipitated by drugs, viruses, chemicals
- Association with autoimmune disorders
  - Lupus
  - Rheumatoid arthritis
  - Felty’s syndrome
  - “Idiopathic” aplastic anemia

Acquired pure red cell aplasia

- Profound anemia with otherwise normal blood counts
- Bone marrow shows absent red blood cell precursors with sparing of other lineages
- Many cases have serum inhibitory antibodies of erythropoiesis
- May be transient or chronic

Causes of pure red cell aplasia

- Autoimmune disorders
- Indolent hematologic malignancies (eg, LGL, CLL)
- Thymoma
- Drugs
- Viral infection (HIV/hepatitis/EBV/CMV)
- Parvovirus

Clinical presentation of aplastic anemia

- Fatigue
- Easy bruisability/bleeding
- Infection
- Pancytopenia (decreased blood cell numbers)
- Markedly hypoplastic (“empty”) marrow
- 30-40% clonal hematopoiesis of uncertain significance (“CCUS”)
Aplastic anemia clinical spectrum

- Moderate
  - 2/3 cytopenias, <30% marrow cellularity
- Severe
  - ANC <500, plts <20K, retics <40K
- Very severe
  - ANC <200
- Significant mortality without effective treatment

Evaluation of bone marrow failure

- Bone marrow biopsy, cytogenetics, PNH marker, ? MDS gene mutation screening
- Careful history:
  - Drugs, infections, family history…
- Physical exam:
  - Short stature, skin/nail changes, hypogonadism, developmental delay…
- PNH marker, genetic testing as appropriate for congenital syndromes

Treatment of aplastic anemia

- Supportive care
  - Transfusions (limit to minimize alloimmunization)
  - Prophylaxis/treatment of infection
  - Iron chelation?
- Immunosuppressive therapy (IST)
- Eltrombopag
- Allogeneic transplantation

Immunosuppressive therapy (IST) for aplastic anemia

- Equine anti-thymocyte globulin (ATG) 40 mg/kg IV daily d1-4
- Cyclosporine (CSA) 5-6 mg/kg twice daily (titrated to target trough levels)
- Corticosteroids 1 mg/kg daily for 2 weeks with rapid taper
- Common toxicities:
  - Infusional fever, chills, hypoxia
  - Delayed “serum sickness”

Frickhofen et al. NEJM (1991) 324: 1297-1304
Majority of patients respond to IST
- ~65% overall response rate observed
- Majority incomplete
- Time to response often delayed
- Relapses not uncommon after tapering CSA
- Responses observed after retreatment

Eltrombopag following IST failure
- Phase 2 study of oral eltrombopag for patients with SAA refractory to standard IST
  - 84% had 2 or more prior therapies
  - 40% had hematologic response by 3-4 mo
  - 5 of 43 had normalization of counts
  - 8 of 43 had clonal evolution (acquisition of new cytogenetic abnormalities)

Eltrombopag added to IST for previously untreated AA
- Phase 1-2 study of IST plus eltrombopag (150 mg) in 92 previously untreated patients with severe AA
- Three eltrombopag schedules analyzed individually and in composite
- Primary endpoint: complete hematological response at 6 months
- Secondary endpoints: ORR, survival, relapse, clonal evolution

Improved response rate compared with historical controls
- Responses of the combined cohort superior to historical control:
  - ORR 80% vs 66%
  - CR 36% vs 10%
  - 2 yr OS 97%
  - 6 pts had no response; 12 patients received a transplant
  - Relapse requiring resumption of CsA occurred in 32% after 6 months
  - Clonal evolution occurred in 8% patients at 2 years
  - Adverse events ≥ grade 3: rash (2%), ↑LFTs (18%)
Donor transplant considerations
- Suitably matched donor availability
- Treatment-related toxicity
- Relapse risk (30-40% with IST)
- Late risk of clonal hematopoietic disorders (10-20% with IST)
- Improved upfront transplant outcome
- Increased transplant mortality with age

Factors impacting outcome after allogeneic transplant for AA
- Patient age
- Matched sibling donor
- Donor gender
- Bone marrow stem cell source
- Early transplant
- CSA/FK GVHD prophylaxis

Graft failure following allogeneic transplant for aplastic anemia
- Increased risk compared with other transplant indications (10-20%)
- Transfusion burden increases risk through alloimmunization
- Avoid transfusion of products from family members
- Leukoreduction of blood products
Strategies to reduce graft rejection
- Limit transfusions
- Early transplant
- Leukoreduced blood products
- Single donor platelets
- Increased immunoablative conditioning
  - Radiation, ATG, purine analogs

Alternative donor transplant for aplastic anemia
- 20-80% of transplant candidates lack a matched sibling or unrelated donor
- Inferior outcomes with mismatched unrelated donors
- Umbilical cord blood and haploidentical related donors provide alternative stem cell sources for transplant
- Ongoing BMT Clinical Trials Network (CTN) study of haplo vs cord donors

Summary
- Aplastic anemia is a serious but potentially treatable disorder
- Outcomes with both non-transplant and transplant approaches have improved
- Transplant candidates without suitably matched donors may benefit from alternative donor sources