Aplastic Anemia: Current Thinking on the Disease, Diagnosis, and Non-Transplant Treatment

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Aplastic Anemia

- First described in 1888 by Dr. Paul Ehrlich
  Chauffard (1904): aplastic anemia from the Greek, πλαϑώ απλαστκη (platho aplastike): “shape unformed”
- Incidence: 2 cases per 10^6/year
  - 4-16 per 10^6/year in parts of Asia
- Male:Female 1:1
- Biphasic peak age:
  - 15 – 25 and > 60 years of age

Classification of Aplastic Anemia

Acquired Aplastic Anemia
- Radiation
- Drugs/Chemicals
  - Direct Effect
    - Cytotoxic Agents, Benzene
    - Idiosyncratic
    - Chloramphenicol, anti-inflammatory, anti-epileptic drugs
    - Viruses (5-10%) – EBV, Hepatitis (non-A, B, C, E or G), HIV, other
- Known Immune Disease
  - Eosinophilic faciitis, SLE, Hypogammaglobulinemia, etc.
  - Thymoma

Inherited Bone Marrow Failure Syndromes
- Fanconi anemia
- Dyskeratosis congenita
- Shwachman Diamond syndrome
- Possibly Others

Classification of Aplastic Anemia

- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Myelodysplasia (MDS)

The following disorders must be ruled out prior to the institution of treatment

- Inherited Bone Marrow Failure Syndromes
  - Fanconi anemia
  - Dyskeratosis congenita
  - Shwachman Diamond syndrome
  - Possibly Others
- Clonal Disease – considerable overlap and sometimes difficult to distinguish
  - Paroxysmal Nocturnal Hemoglobinuria (PNH)
  - Myelodyplasia (MDS)
Severe Aplastic Anemia

Definition

- Two of three cytopenias as defined*:
  - Absolute neutrophil count (ANC) ≤ 500/µl*
  - <200/µl - very severe aplastic anemia
  - Platelet count < 20K/µl
  - Reticulocyte count < 40 x 10³/L
  - Bone marrow cellularity <25%
  - Mild to Moderate aplastic anemia: Less precisely defined but refers to less severe cytopenias and marrow hypoplasia

Camitta, Thomas, Nathan et al, Blood 48:63-70, 1976

Key Shared Characteristics of Inherited Bone Marrow Failure Syndromes

Pathophysiology:
Due to a genetic defect: Low apoptotic threshold of mutant cells (these cells are programmed to die)

Clinical Manifestations:
Bone Marrow Failure
Congenital Anomalies (Not Always)
Cancer Predisposition
May present in adulthood

Inherited Bone Marrow Failure Syndromes

Pancytopenia that may mimic acquired aplastic anemia:

- Fanconi Anemia - AR, XLR (16 “DNA repair” genes)
- DNA repair complex
- Dyskeratosis Congenita - XLR, AD, AR (10 “telomere maintenance” genes)
- Telomerase function
- Ribosome synthesis/function
- Severe congenital neutropenia
- AD (ELA2)
- Mitochondrial membrane potential maintenance
- AD (ELA2)
- Misfolded protein response
- Amegakaryocytic Thrombocytopenia - AR (mpl)
- TPO receptor gene
- Thrombocytopenia Absent Radii (TAR) Syndrome – AR (Y14 subunit of EJC)

Inherited Bone Marrow Failure Syndromes

Single Lineage Cytopenia:
- Shwachman-Diamond Syndrome - AR (SBDS)
- Ribosome subunit joining
- Diamond Blackfan Anemia – AD (15 ribosomal protein genes), XLR (GATA2)
- Ribosome synthesis/function
- Severe congenital neutropenia
- AR (NAX1)
- Mitochondrial membrane potential maintenance
- AD (ELA2)
- Misfolded protein response
- Amegakaryocytic Thrombocytopenia - AR (mpl)
- TPO receptor gene
- Thrombocytopenia Absent Radii (TAR) Syndrome – AR (Y14 subunit of EJC)

Fanconi Anemia

- Described in 1927
- Autosomal Recessive Genetic Disorder (>99%):
  - Heterozygote frequency 1 in 300
  - 1 in 100 in Ashkenazi Jews and South African Afrikaners
  - 1 in 60 Gypsies
- X-linked in FANCB (<1%)
- Characterized by:
  - Bone marrow failure
  - Congenital anomalies, including short stature
  - Predisposition to cancer
Dyskeratosis Congenita

- First described in 1906
- Autosomal Dominant, Autosomal Recessive or X-linked Genetic Disorder associated with:
  - Morphologic abnormalities
    - Classic Triad
    - Abnormal skin pigmentation
    - Dystrophic Nails
    - Leukoplakia
  - Characterized by short telomeres

Shwachman Diamond Syndrome

- First described in 1964
- Autosomal Recessive Genetic Disorder associated with:
  - Classic Triad
  - Exocrine pancreatic insufficiency
  - Neutropenia
  - Metaphyseal dysostosis

Minimal Workup According to North American Pediatric Aplastic Anemia Consortium (NAPAAC)

- BM aspirate and Biopsy (100%)
  - Camitta Criteria (60%)
- Cytogenetics (100%)
  - FISH for 5q-, 7 and 8+ (60%)
  - 22q-, 20 and 9 in additional 22%
- PNH by Flow Cytometry (89%)
- Fanconi anemia testing (89%)
- SBDS (Shwachman Diamond) gene sequencing (71%)
- Telomere length (67%)
  - DC genetic testing (43%)
- HEP A, B, C, EBV, CMV, (~80%)
  - HIV, HSV, V2V or HHV6 in additional 33-44%
- Immunologic work-up (55%)
- HLA-typing of patient and sibling (94%)
Pathophysiology of Acquired Aplastic Anemia

- Clues
  - Association with autoimmune disorders
  - Only 50% of syngeneic (identical) twins stem cell transplants engraft without conditioning
  - Response to immunosuppressive therapy
  - HLA – DR2 association
- Inciting event – injury, virus, unknown
- Emergence of CD8 T-cell clones directed against unknown stem cell antigens
  - γ-interferon and other cytokines

Aplastic Anemia

- Immunotherapy Results
  Survival with good to excellent response is approximately 85-90% in children and 60-70% in adults.
  Relapse or clonal evolution usually 2-4 years
  15 – 30% require ongoing Cyclosporine A
  The risk of clonal disease (MDS, AML, or PNH) in survivors is real and justifies HLA-matched SCT as the treatment of choice at this time in patients < 40 years of age. The exact incidence of clonal disease in children is unknown.
  Risk of Clonal Disease in Adults:
  - 10-15% high risk clonal evolution (7-, high grade MDS, complex karyotype, leukemia)
  Survival at 15 years:
  - 95% with no event vs. 65% with an event
  - 75% not high risk event vs. 25% with high risk event

Aplastic Anemia Immunotherapy

- Horse Anti-Thymocyte Globulin (100%) for 4 days (25% for 5 days)
- Methylprednisolone/Prednisone for 4-14 days followed by daily taper
- G-CSF until ANC > 1000/µl (this is controversial – routine (37%), for infection (68.8%)
- Cyclosporine A until G-CSF discontinued and transfusion independent, then taper over 12 months

Aplastic Anemia Treatment

- Mild-Moderate Aplastic Anemia
  - Observation vs. Immunotherapy
- Severe Aplastic Anemia
  Matched Sibling Donor (<40 years of age)
  - Yes
  - HLA-matched transplant
  - Immunosuppression (IST)
  - if no response
  - Repeat Immunotherapy (not preferred in children)
  - Unrelated donor transplant
  - Experimental/Other therapy