Aplastic Anemia

Background

1. Definition
    - rare hemopoietic stem cell disorder that results in bone marrow failure characterized by marrow hypoplasia and peripheral pancytopenia

Pathophysiology

1. Pathology
    - Marrow failure
        - Primary (inherited) disorder of marrow stem cells
        - Secondary (acquired) disorder of marrow stem cells thought most likely from immune-mediated destruction of hematopoietic stem cells.
    - Primary—20% of cases
        - Fanconi's anemia: *(PEPID editor: please create hyperlink to Fanconi Anemia Type C)* Rare autosomal recessive condition characterized by pancytopenia and multiple congenital malformations
        - Other associated congenital conditions include: dyskeratosis congenita, cartilage hair hypoplasia, Pearson syndrome, TAR syndrome (thrombocytopenia with absent radii), Shwachman-Diamond syndrome, Dubowitz syndrome, Diamond-Blackfan syndrome (congenital pure red cell aplasia), and familial aplastic anemia (*PEPID editor: create hyperlinks where able*)
    - Secondary—80% of cases
        - Most thought due to immune mediated destruction: production of cytotoxic T-lymphocytes (CD8 and HLA-DR+) and release of inhibitory cytokines (gamma interferon and tumor necrosis factor) which suppress hematopoiesis
        - Multiple triggers include:
            - Viral Infections—hepatitis, HIV, Parvovirus B19 virus infection—transient aplastic crisis (see Sickle Cell: SS Disease) (*PEPID editor: please create hyperlink to this*)
            - Drug toxicities or reactions (not autoimmune)—chloramphenicol, chemotherapeutic agents, antiepileptic drugs (carbamazepine, valproic acid, phenytoin), sulfonylureas, nifedipine, quinacrine, chloroquine, propylthioruracil, acetazolamide, NSAIDS, cimetidine, chlorpheniramine, sulfonamides
            - Direct toxins: heavy metals (gold, arsenic, mercury, bismuth), radiation, insecticides (DDT, Lindane, Cordane), benzene, kerosene, carbon tetrachloride, chlorophenol
            - Other: collagen-vascular disease, paroxysmal nocturnal hemoglobinemia, graft-versus-host disease, pregnancy, liver transplant, eosinophilic fasciitis

2. Incidence/prevalence
    - Estimated: 0.6-6.1 cases per million (US)
    - Occurs in all age groups
    - Increased incidence
        - Childhood due to clinical appearance of inherited marrow-failure syndromes
        - Ages 20-25 yo
        - > 60 yo
    - Male to female ratio is 1:1
3. Risk factors
    - Family history of marrow defects
    - Exposure to known causative agents
    - mutations in TERT gene, telomerase reverse transcriptase
4. Morbidity/mortality
    - related to infection and bleeding

Diagnostics

1. History
    - Important to obtain history of
        - Solvent/radiation exposure
        - Family occurrences
        - Environmental, travel exposure
        - Infectious diseases
    - Initial symptoms are usually fever or bleeding
    - Pallor, headaches, palpitations, fatigue, or dyspnea (anemia)
    - Mucosal/gingival bleeding and/or petechiae (thrombocytopenia)
    - Infections (neutropenia)
2. Physical exam
    - General
        - Pallor
    - Skin
        - Petechiae, purpura, and/or ecchymoses
        - Jaundice
    - Cardiovascular
        - Tachycardia
    - Associated exam findings from inherited marrow disorders
3. Diagnostic testing
    - Laboratory
        - CBC with reticulocyte count
            - Pancytopenia and low corrected reticulocyte count, occasional macrocytosis
        - Peripheral smear
        - Hemoglobin electrophoresis and blood group testing
            - May show elevated fetal hemoglobin
        - BMP, liver tests, Coombs
        - Serological testing for hepatitis, HIV, CMV, EBV, HSV, and parvovirus B19
        - CD55 and CD59 testing—proteins on the surface of RBCs that prevent against accidental activation of the complement system and subsequent RBC destruction

        - Test for paroxysmal nocturnal hemoglobinuria (PNH)
        - Absence via flow cytometry indicates an increased risk for PNH
    - Diepoxybutane incubation
        - Fanconi anemia—genetic disorder characterized by an inability to repair DNA damage leading to much higher risk for hematologic CA. Is NOT the same as Fanconi syndrome
        - Test looks for chromosomal damage in cells after exposure to diexpoxybutane
    - ANA—collagen vascular or autoimmune disease
- Other studies
    - Bone-marrow aspiration and biopsy
        - Hypocellularity
        - Fatty replacement of marrow and increased non-hematopoietic elements (mast & plasma cells)
    - Histocompatibility testing (for bone-marrow transplantation)
        - Should be conducted early to find potential donors for bone-marrow transplant
    - X-ray
        - Skeletal survey if suspicion of inherited marrow disorder is high
            - Skeletal abnormalities of inherited diseases (skeletal hypoplasia, short stature)
- Diagnostic criteria
    - At least two of the following
        - Absolute neutrophil count < 0.5 x 10^9/L (ANC is most important prognostic factor due to risk of infection with low count)
        - Platelet count < 20 x 10^9/L
        - Anemia with corrected reticulocyte count < 1%
    - And one of the following
        - Bone-marrow cellularity < 25%
        - Bone-marrow cellularity < 50% with fewer than 30% hematopoietic cells

Differential Diagnosis

1. Key differential diagnosis
    - Hematologic (determined by bone-marrow biopsy)
        - Acute lymphoblastic leukemia, acute myelogenous leukemia
        - Agnogenic myeloid metaplasia with myelofibrosis, non-Hodgkin's lymphoma
        - Megaloblastic anemia, myelodysplastic syndrome, myelophthisic anemia
        - B12 deficiency
        - Folate deficiency
    - Rheumatologic
        - Systemic lupus erythematosus (positive ANA), sarcoidosis
    - Infectious
        - Human herpes virus type 6 (positive serology)
        - others, see viral infections above
2. Extensive differential diagnosis
    - Infectious
        - HIV, CMV, Epstein-Barr virus
        - Mycobacterial infection

        - Sepsis
    - Congestive splenomegaly
    - Osteopetrosis

Therapeutics

Acute therapy

1. All unnecessary medication suppressing bone-marrow function should be stopped
2. Transfusion with packed RBCs as needed
3. Transfuse irradiated, leukocyte-filtered blood products
4. Transfuse CMV-negative blood products to all pts. until CMV Ab titers are available
5. Transfuse single-donor platelets if the platelet count is less than 10 x 10^9 or active bleeding
6. Empiric antibiotic therapy with broad-based gram negative and Staph coverage based on local sensitivities as well as anti-fungal agents and anti-pseudomonal agents if pt. is neutropenic and febrile

Chronic/Long-Term Care

1. HLA-matched sibling bone-marrow transplant in pts. with severe disease and young age (<20) (conditioning regimen with anti-thymocyte globulin, cyclosporine, and cyclophosphamide)
2. If no HLA-matched donor, immunosuppressive therapy is recommended
3. Cytokine treatment for treatment of refractory infections (to hasten neutrophil recovery)
    - Sargramostim
    - Filgrastim
4. Limit exposure to infectious agents when able
5. Limit potential trauma during periods of thrombocytopenia

Follow-Up

1. Hematologist and/or bone-marrow transplant specialist management
2. Blood and platelet transfusions as needed with frequent outpatient visits
3. Admit to hospital for infections, bone-marrow transplantation, conditioning treatments

Prognosis

1. Depends on severity of pancytopenia and patient's age
2. 20% of pts. may spontaneously recover with supportive care
3. Estimated 5-year survival rate for pt. receiving immunosuppression is 75%
4. Estimated 5-year survival rate for pt. receiving matched sibling bone-marrow transplant > 90%

Prevention

- In acquired cases, avoidance of toxic exposures

Patient Education

Aplastic Anemia. Mayo Clinic. http://www.mayoclinic.com/health/aplastic-anemia/DS00322 Accessed 6.17.2011

Aplastic Anemia & MDS International Foundation http://www.aamds.org/aplastic/ Accessed 6.17.2011

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