1. Aplastic anemia is a disorder of production of the major hematopoietic lineages, with decreased bone marrow cellularity, and no malignancy or underlying myeloproliferative disorder.

2. Leukemia and aplastic anemia are the two most common causes of severe pancytopenia. Leukemia is about 20 times more common than aplastic anemia. Aplastic anemia is more likely when the patient lacks symptoms of bone pain, lymphadenopathy, and organomegaly.

3. A bone marrow biopsy is necessary to make a diagnosis of aplastic anemia. This allows a measurement of the overall cellularity of the bone marrow. A bone marrow aspirate (drawing out the liquid part of the marrow) is adequate for diagnosing leukemia.

4. Mild and moderate aplastic anemia may improve with time. Severe aplastic anemia is defined by a bone marrow cellularity of less than 25% and two of the following; the actual neutrophil count being less than 500, platelets less than 20,000/microliter, and reticulocyte count less than 1%. Patients with severe aplastic anemia almost never get better on their own, and require treatment.

5. Patients with aplastic anemia have a high risk of dying from opportunistic infection, and bleeding if not transfused. Because of this, we move rapidly to treat them.

6. Most commonly, aplastic anemia is caused by an autoimmune phenomenon, mediated by T-cells, where hematopoietic stem cells are the target. Aplastic anemia can be also caused by infections such as hepatitis B and C, Dengue, EBV and CMV, HIV and parvovirus. A number of medications can cause aplastic anemia; antibiotics such as chloramphenicol, sulfá drugs, antihistamines, antiseizure medications, and chemotherapy. Environmental exposures to benzene and radiation can cause aplastic anemia. Aplastic anemia rarely can be secondary to an underlying bone marrow failure disorder such as Fanconi’s anemia, amegakaryocytic thrombocytopenia, or Shwachmann/Diamond syndrome. Paroxysmal nocturnal hemoglobinuria (PNH) can present with aplastic anemia.

7. The treatment of choice for a child is an HLA matched sibling bone marrow transplant. The treatment of choice for an adult is immunosuppression. The reason for this difference is that adults have a higher risk of dying from graft-versus-host disease from a matched sibling transplant. Most patients do not have HLA matched siblings.

8. Laboratory workup once diagnosis of aplastic anemia has been made includes performing a HLA typing of the patient and their sibs, marrow karyotype, screening for infections listed above, a PNH screen, and chromosomal fragility testing for Fanconi’s anemia. Fanconi’s patients are handled differently, as they are less likely to respond to immunosuppression and can have lifethreatening reactions (organ failure because of their...
fragile chromosomes) to chemotherapy or radiation that might be given to condition them for transplant.

9. If patient does not have a matched sibling, they receive immunosuppression consisting of prednisone, antithymocyte globulin for 5 days, and cyclosporine for 6 months. The prednisone is given to prevent reactions to the ATG, but the main target of the immunosuppression is T-cells. 70% of patients with aplastic anemia will eventually respond to immunotherapy. However, of the responders, 30% eventually recur, develop myelodysplasia, PNH, or leukemia.

10. Some patients lacking a response to immunotherapy or who develop a secondary problem (myelodysplasia, PNH, leukemia) will get a matched unrelated bone marrow transplant.

11. Congenital bone marrow failure syndromes should be considered in any patient with the combination of a cytopenia and short stature and/or a birth defect.

12. Macrocytosis (high MCV) is often present in bone marrow failure syndromes.

13. Bone marrow failure syndromes should be thought of in terms of the cell lines that are depressed
   a. Leukocytes
      1. Congenital neutropenia (Kostmann’s syndrome)
      2. Shwachmann-Diamond syndrome (Neutropenia with pancreatic dysfunction, Metaphyseal dysostosis).
   b. Erythrocytes
      Diamond-Blackfan Anemia
   c. Platelets
      Thromocytopenia-Absent Radii syndrome (TAR syndrome)
      Amegakaryocytic thrombocytopenia
   d. Pancytopenia
      Fanconi Anemia
      Dyskeratosis Congenita
      Aplastic Anemia


15. Congenital neutropenia is a disorder that typically presents in the neonatal period with serious life-threatening infections. Actual neutrophil counts are usually < 500. Nine out of ten patient respond to granulocyte colony stimulating factor (G-CSF, neupogen), and this has been a life-saving therapy for these patients. 30% of patients with congenital neutropenia eventually develop leukemia. Leukemia is often preceded
by cytogenetic changes in the bone marrow (myelodysplasia), and so these patients have yearly bone marrow aspirations with cytogenetics.

16. Shwachmann-Diamond syndrome presents like cystic fibrosis, only with neutropenia. These patients tend to be small (< 5th percentile), and have diarrhea. X-rays of the wrist may show the metaphyseal dysostosis. These patients can have a number of other birth defects. Many of these patients also respond to Neupogen. SDS is also a preleukemic syndrome.

17. Diamond-Blackfan Anemia. These patients tend to have short-stature and anemia. In contrast to transient erythroblastopenia of childhood (TEC) which presents classically in toddlers, DBA patients present during the first year of life with profound anemia. Some patients with this disorder respond to prednisone. Non-responders are typically managed with transfusion and chelation. Bone marrow transplant is curative, but not often performed because of risks of transplant related mortality. DBA is less associated with leukemia than the disorders noted above, though it has been reported.

18. Thrombocytopenia absent radii syndrome. Patients are born with absent radii, thrombocytopenia and normal thumbs (Fanconi’s anemia typically have small thumbs). Mortality is mainly associated with the trauma of birth, and the thrombocytopenia in these patients improves with time for unknown reasons. This disorder is not associated with leukemia.

19. Amegakaryocytic thrombocytopenia. Patients are born with thrombocytopenia, but go on to develop aplastic anemia.

20. Fanconi’s anemia. Fanconi’s anemia is classically associated with short stature and thumb abnormalities. However, 30% of patients have a completely normal phenotype. In addition, the VACTERL associations are seen in Fanconi anemia, and patients with these (Vertebral, Cardiac, Tracheo-esophageal fistula, Renal, and Limb anomalies) and cytopenias should be worked up for Fanconi Anemia. These patients present at an average age of 7, and usually begin with thrombocytopenia but progress to pancytopenia. Patients with Fanconi Anemia have increased chromosomal breakage, leading to mutations that predispose to cancer. These patients develop leukemia as well as cancers of the head and neck, liver and cervix.

Cases.

1. A 2 month old presents to you with diarrhea, failure to thrive, and a perianal abcess. The perianal abcess should make you think about neutropenia. The diarrhea should make you think about Shwachmann Diamond syndrome.

2. A 15 month old presents with the sudden onset of pallor and lethargy. The child growing normally. CBC shows a Hgb of 5 with reticulocyte count of 0.7. MCV is 74.
This patient has a normocytic anemia and probably has transient erythroblastopenia of childhood, which is usually associated with a parvovirus infection. The onset of anemia late (after 1 year of age) and the normocytic nature of the anemia argue against Diamond Blackfan anemia. As patients recover from TEC, their MCV rises as the reticulocytes tend to be larger cells. This picky little fact tends to show up as a board question from time to time.

References: