**Bone Marrow Failure**

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1. A 16-year-old girl with dyskeratosis congenita (DC) has had a rapid, progressive decline in her blood counts, which are currently a hemoglobin of 6.8 g/dL, ANC of 380/µL, and platelets of 22,000/µL. Her last annual surveillance bone marrow examination showed no evidence of myelodysplastic syndrome, and cytogenetics including fluorescent in situ hybridization were normal. She has had no invasive infections or bleeding. She is taking no medications. She has no full siblings.

What is the best long-term treatment for this child at this time?

A. Antithymocyte globulin (ATG) and cyclosporine

B. Monitoring blood counts and observing clinical status

C. Granulocyte colony-stimulating factor (G-CSF)

D. Oxymetholone

E. Unrelated donor transplant with reduced-intensity conditioning

**Explanation**

Although the usual therapy for a patient with DC in childhood is quarterly monitoring of blood counts and consideration of bone marrow examination, including cytogenetics periodically when the counts start to decline, this patient with DC has very low blood counts, at the level where transfusions likely will soon be necessary. Thus, continued observation is insufficient. ATG and cyclosporine, the immunosuppressive therapy recommended in severe idiopathic aplastic anemia, has no role in the treatment of DC. Although G-CSF and oxymetholone therapy alone or in combination may increase granulocyte numbers and perhaps all blood counts for several years, their use, particularly together, has been associated with splenic peliosis and splenic rupture in DC. This teenage patient is young enough, with low enough blood counts, that curative therapy with unrelated donor hematopoietic stem cell transplant should be pursued at this time.

Patients with inherited bone marrow failure syndromes (IBMFSs) that involve DNA repair defects, such as Fanconi anemia and DC, have increased sensitivity of other body tissues to alkylating agents and radiation, increasing the risk of transplant morbidity and mortality with standard transplant regimens. Conditioning regimens with lower dosages of cyclophosphamide, lower-dose or no radiation, substitution of fludarabine, and, in some circumstances, T-cell depletion, have resulted in improved transplant outcomes for patients with an IMBFS. However, patients with an IBMFS have a higher risk of malignancy in tissues outside the marrow after transplant. Patients with DC who undergo transplant also are at particular risk for late pulmonary toxicity and pulmonary fibrosis, which are a known complication of the untransplanted disease. Despite the risks, the best long-term therapy for this patient with DC and progressively falling blood counts is an unrelated donor transplant with appropriately reduced-intensity conditioning.

2. A 6-year-old boy presents with a 1-week history of bruising all over his body, fatigue, and fever. His CBC shows pancytopenia. A bone marrow biopsy has 20% cellularity.

Which of the following values would be most diagnostic of severe aplastic anemia?

A. Absolute phagocyte count of 980/µL

B. Hemoglobin of 7.9 g/dL

C. Mean cell volume of 90 fL

D. Platelet count of 10,000/µL

E. Total leukocyte count of 900/µL

**Explanation**

Severe aplastic anemia is classically defined as a bone marrow cellularity of less than 25%, or 25% to 50% with less than 30% hematopoietic cells, and two of the following: ANC less than 500/µL, absolute reticulocyte count less than 40,000/µL, or platelet count less than 20,000/µL.

Hemoglobin, total leukocyte, and absolute lymphocyte or phagocyte counts are not criteria for severe aplastic anemia. Similarly, increased mean cell volume (with a normal red cell distribution width) and percentage of fetal hemoglobin and little-i antigen, which are features commonly associated with aplastic anemia, also are not diagnostic criteria.

3. A 3-year-old boy was just diagnosed with medulloblastoma and has a lifelong history of mild blood count abnormalities. His present blood counts are a hemoglobin of 9.8 g/dL, mean corpuscular volume of 100 fL, total WBC count of 5,280/µL, ANC of 1,056/µL, and platelet count of 140,000/µL.

Which of the following is most likely to be the cause of his low blood counts?

A. He has Diamond-Blackfan anemia (DBA).

B. He has common variable immunodeficiency.

C. He has Fanconi anemia.

D. He has metastatic medulloblastoma, which is suppressing his bone marrow.

E. There is no relationship between his medulloblastoma and the low blood counts.

**Explanation**

This patient with medulloblastoma has macrocytic anemia, leukopenia, and thrombocytopenia before therapy. In the setting of long-standing cytopenias, a relationship with the malignancy should carefully be assessed before therapy starts. Although Fanconi anemia, and indeed all bone marrow failure syndromes, are most commonly associated with the development of myelodysplastic syndrome and acute myeloid leukemia, there is an association with nonmarrow malignancies, as well. Specifically, Fanconi anemia complementation groups D1 and N are associated with the development of medulloblastoma and Wilms tumor. DBA has been associated with the development of osteosarcoma, Hodgkin disease, non-Hodgkin lymphoma, and hepatocellular and breast carcinomas, among other malignancies. Patients with common variable immunodeficiencies have recurrent infections and may develop cytopenias, particularly autoimmune ones, and extranodal B-cell lymphomas as well as lymphadenopathy, splenomegaly, enteropathy, and granulomatous disease. They usually are not at risk for medulloblastoma. It is unlikely that metastatic medulloblastoma has been a factor in his cytopenias for the patient’s entire life. The best answer is C—this child with lifelong cytopenias and medulloblastoma probably has Fanconi anemia.

4. An 8-week-old girl is being evaluated for neonatal anemia. She has a hemoglobin of 5.4 g/dL, MCV of 98 fL, reticulocyte count 0.9%, WBC count of 5,890/µL, ANC of 1,020/µL, and platelet count of 170,000/µL. She was born at 35 weeks’ gestation after an uncomplicated pregnancy. There were no neonatal problems, and jaundice was not present. She has gained weight and grown well since birth, and is in the third percentile for age. No blood loss has been noted. She is the first child for both parents. The father was transfused multiple times for anemia as a small child. The mother has well-controlled hypertension.

What is the most likely diagnosis for this patient?

A. Diamond-Blackfan anemia (DBA)

B. Dyskeratosis congenita

C. Fanconi anemia

D. Shwachman-Diamond syndrome

E. Transient erythroblastopenia of childhood (TEC)

**Explanation**

The presentation of a severe macrocytic anemia, particularly in association with mild neutropenia, in the first few months of life should raise concern for an inherited bone marrow failure syndrome. The differential diagnosis would be unrecognized feto-maternal (or neonate-placental) bleeding and undetected ABO, RH, or other blood group incompatibility causing hemolytic disease of the newborn. By this age there should be some reticulocytosis to suggest these diagnoses. The anemia is too severe for a usual physiologic nadir in a late preterm infant who has been well. Dyskeratosis congenita usually presents in adulthood, so it is unlikely. Fanconi anemia can present in the newborn period, but thrombocytopenia and neutropenia are more common than marked macrocytic anemia in the newborn. This patient has only mild neutropenia and no pancreatic malabsorption symptoms to suggest Shwachman-Diamond syndrome. Patients with both DBA and TEC may also have thrombocytopenia and neutropenia, but these associated cytopenias are at least twice as common in DBA. Furthermore, TEC does not usually present so early in life. However, in this patient the history of transfusion-requiring anemia in the father suggests that perhaps he had DBA and, like 20% to 25% of patients, experienced a remission by age 25. The lack of congenital anomalies does not decrease the likelihood of an inherited marrow failure syndrome. The marked macrocytic anemia, reticulocytopenia, and suggestive family history make answer A, DBA, the best answer.

5. An 8-year-old boy presents with a platelet count of 84,000/mm3, hemoglobin 10.4 g/dL, MCV 101, reticulocytes 1%, and WBC count of 1,100/mm3 with 25% neutrophils. His physical exam is unremarkable. Serum chemistries, including LDH, bilirubin, and uric acid, are normal. The bone marrow aspirate shows a cellularity of 40% with decreased megakaryocytes.

What is the most important test to perform to establish a diagnosis?

A. Antiplatelet antibody test

B. Bone marrow cytogenetics

C. Direct antiglobulin test

D. Erythropoietin level

E. Thrombopoietin level

**Explanation**

The patient has pancytopenia with macrocytosis and a blunted reticulocyte count. The marrow is hypocellular for age. This may be due to aplastic anemia, an inherited bone marrow failure syndrome (IBMFS), or myelodysplastic syndrome (MDS). Cytogenetics usually are normal at diagnosis in aplastic anemia, and clonal cytogenetic abnormalities are commonly seen with IBMFSs or MDS. Antiplatelet antibody testing is neither sensitive nor specific for the diagnosis of immune thrombocytopenic purpura (ITP), a diagnosis that would be associated with increased, not decreased, marrow megakaryocytes (as in the vignette). A direct antiglobulin or Coombs test would be positive in autoimmune hemolytic anemia, a diagnosis that should have an increased reticulocyte count and increased marrow erythroid cellularity. Although the erythropoietin level should be elevated in aplastic anemia, it is not diagnostic. Thrombopoietin levels would not distinguish between aplastic anemia, IBMFS, and MDS. Thus, bone marrow cytogenetics is the most useful test to differentiate the possible diagnoses.

6. A 12-year-old girl with severe aplastic anemia was treated with antithymocyte globulin (ATG) and cyclosporine. One week after completion of treatment with ATG, she developed a fever to 38.6 °C and an erythematous maculopapular serpiginous rash along the borders of her palms and soles. She also complained of pain in her knees, hips, and back. Blood cultures are negative.

What is the most likely cause of her symptoms?

A. Graft-versus-host disease (GVHD)

B. Reaction to antibiotics

C. Serum sickness

D. Transfusion reaction

E. Viral infection

**Explanation**

Serum sickness is caused by the formation and deposition of immune complexes and complement fixation in response to the foreign protein. Symptoms usually develop 5 to 11 days after the first dose of ATG. The pattern of distribution for this rash on the borders of palms and soles is classic. Other symptoms include fever, myalgias, arthralgias, and joint swelling. Gastrointestinal and neurologic symptoms, as well as transient renal dysfunction, also may occur. Infectious causes must be promptly evaluated and ruled out because the patient is very immunocompromised at this stage. Transfusion-associated GVHD may result from the transfusion of nonirradiated blood products into an immunocompromised host but would present as profound pancytopenia. Although viral infection or a reaction to antibiotics or blood products is possible, they do not present with fever and this type of rash.

7. A 2-year-old boy presents with failure to thrive and neutropenia. His parents report frequent, runny, malodorous stools. His exam is otherwise unremarkable. His blood counts are notable for a WBC of 5,000/ mm3, ANC of 500/mm3, hemoglobin of 11.1 g/dL, MCV of 100 fL, and platelet count of 200,000/mm3. His serum B12 and folate levels are normal. PT is slightly prolonged, but PTT and fibrinogen are normal. Liver enzyme levels and bilirubin levels are normal. A sweat test for cystic fibrosis and workup for celiac disease are negative. No intestinal pathology is noted by upper or lower endoscopy.

A mutation in which of the following genes is most likely to account for the constellation of symptoms in this child?

A. *c-Mpl*

B. *ELA2*

C. *HAX1*

D. *RPS19*

E. *SBDS*

**Explanation**

Failure to thrive, steatorrhea, and the elevated PT suggestive of vitamin K deficiency are consistent with fat malabsorption. The combination of exocrine pancreatic insufficiency and otherwise idiopathic neutropenia is diagnostic of Shwachman-Diamond syndrome, which is associated with mutations in the *SBDS* gene in most cases. Mutations in *c-Mpl* are associated with congenital amegakaryocytic thrombocytopenia and clinical thrombocytopenia. *ELA2* mutations are associated with severe congenital neutropenia (SCN) or cyclic neutropenia (CN). *HAX1* mutations also are associated with SCN. Exocrine pancreatic insufficiency is not characteristic of either SCN or CN. *RPS19* mutations are associated with Diamond-Blackfan anemia, which is characterized by red cell aplasia.

8. An 18-year-old patient presents with acute myeloid leukemia (AML). He had severe neutropenia first noted in infancy and had a history of recurrent bacterial infections and oral aphthous ulcers. The neutrophil counts rose to normal and the infections resolved after the initiation of G-CSF. Analysis of the leukemic clone revealed an acquired mutation in the cytoplasmic domain of the G-CSF receptor.

Which gene mutation would probably be constitutionally present in this patient?

A. *c-Mpl*

B. *ELA2*

C. *FANCA*

D. FLT3

E. *RPS19*

**Explanation**

This is a typical case of severe congenital neutropenia (SCN or CN). Of the answers given, only *ELA2* mutations are associated with SCN or CN. Mutations in the G-CSF receptor often arise in patients with SCN and result in constitutive activation of the G-CSF receptor. The clinical significance of these mutations is not clear because some mutant G-CSF clones progress to leukemia, whereas others remain stable for many years. However, development of AML after prolonged G-CSF therapy is a commonly observed event in patients with SCN with the acquired mutation indicated. *RPS19* mutations are associated with Diamond-Blackfan anemia. *C-Mpl* mutations are associated with congenital amegakaryocytic thrombocytopenia. *FANCA* mutations are present in Fanconi anemia group A. *FLT3* is the most commonly mutated gene in acute myeloid leukemia but would not usually be a constitutional mutation.

9. A 15-month-old boy is referred to you for neutropenia, malabsorption, and intermittent severe acidosis. The bone marrow examination shows vacuolated erythroid precursors and ringed sideroblasts. Cytogenetics are normal.

Which of the following tests is most likely to result in a diagnosis?

A. Mitochondrial DNA sequencing

B. MMC/DEB chromosomal breakage study

C. *RPL35A* genetic testing

D. *SBDS* genetic testing

E. Telomere length assay

**Explanation**

This patient’s symptoms and bone marrow morphologic findings are classic for Pearson syndrome resulting from a mitochondrial DNA deletion. Shwachman-Diamond syndrome is caused by mutations in the *SBDS* gene. Although Shwachman-Diamond syndrome and Pearson syndrome both present with marrow failure and exocrine pancreatic dysfunction, Shwachman-Diamond syndrome lacks the vacuolated erythroid precursors in the marrow. An MMC/DEB chromosomal breakage study is the diagnostic test for Fanconi anemia. *RPL35A* mutations are associated with Diamond-Blackfan anemia. Very short telomere lengths are associated with dyskeratosis congenita.

10. You are called to the nursery to see a newborn baby with cutaneous and mucosal bleeding. The platelet count is 20,000/mm3. The other blood counts are normal. Labor and delivery were uncomplicated, and maternal platelet counts are normal. The mother was not taking any medications that would affect the platelet count. There are no signs of infection. On exam, the baby’s lower arms appear abnormal, but normal thumbs are present bilaterally.

Which of the following is the most likely diagnosis?

A. Acquired aplastic anemia

B. Amegakaryocytic thrombocytopenia

C. Diamond-Blackfan anemia

D. Shwachman-Diamond syndrome

E. Thrombocytopenia absent radii (TAR) syndrome

**Explanation**

Both Fanconi anemia and TAR syndrome are autosomal recessive disorders that may present with radial ray (forearm) anomalies and low platelets in infancy. In TAR syndrome, the defect is intercalary, with missing radii and normal thumbs. In Fanconi anemia the defect is terminal; if the patient has an absent radius, the thumb on that side will also be abnormal or absent. Amegakaryocytic thrombocytopenia may present with thrombocytopenia early but not absent radii or thumb anomalies. Shwachman-Diamond syndrome may present with cytopenias early in life, but radial ray anomalies have not been commonly reported. Diamond-Blackfan anemia presents with red cell aplasia and present radii, although the thumbs may be digitalized (look like a finger). Acquired aplastic anemia is not typically associated with congenital anomalies.

11. A 7-year-old girl with Diamond-Blackfan anemia undergoes stem cell transplantation from her 2-year-old HLA-identical brother. At day 100 neutrophils and platelets are fully reconstituted, but the patient remains red cell transfusion dependent. The marrow reveals red cell aplasia. Genetic analysis reveals 100% donor status.

Of the following, what is the most likely cause of this failure of erythroid engraftment?

A. Anti–red cell antibodies

B. Donor with Diamond-Blackfan mutations

C. Graft-versus-host disease (GVHD)

D. Inadequate conditioning

E. Inadequate cell dose

**Explanation**

In matched sibling donor transplants for all forms of inherited bone marrow failure syndromes (IBMFSs), it is essential to critically evaluate the donor for evidence of the same IBMFS. Differences in clinical expression of these disorders may lead to siblings with identical genetic constitutional abnormalities and completely normal or very abnormal blood counts. This requires that the donor be genetically tested for the mutation present in the recipient (if known). In Diamond-Blackfan anemia, evaluation of an erythrocyte adenosine deaminase also may be helpful because mutations are known for only about 60% to 75% of clinically diagnosed patients. Anti–red cell antibodies should lead to anemia and hemolysis, not failure of erythroid engraftment. GVHD or inadequate conditioning or cell dose could lead to failure to engraft all cell lines but should not lead to selective erythroid nonengraftment, particularly with a marrow that is 100% donor. The most likely explanation is that the donor also carried the same disease-causing Diamond-Blackfan anemia mutations as the patient, despite the presumably normal pretransplant evaluation including blood counts, which was not apparent to the transplant team, leading to red cell failure to engraft in the recipient.

12. You are evaluating an 8-year-old boy for thrombocytopenia. Previous blood counts demonstrate a progressive macrocytic anemia as well. The child is in the 5th percentile for height and weight, has no problems with malabsorption, but has five café au lait spots, including one in the axilla. The bone marrow biopsy is 10% to 15% cellular without dysplasia. Cytogenetics are pending.

Which of the following tests is most important to help you clarify the diagnosis and plan therapy?

A. Erythrocyte adenosine deaminase activity (eADA) level

B. Mitochondrial DNA deletion analysis

C. DEB/MMC chromosomal breakage assay

D. *NF1* gene mutation analysis

E. Paroxysmal nocturnal hemoglobinuria (PNH) clone analysis

**Explanation**

This patient has aplastic anemia, but you do not know whether it is congenital or acquired. It is imperative that you screen for the presence of increased chromosomal breakage (suggesting a diagnosis of Fanconi anemia [FA] or other DNA repair syndrome), which would necessitate alternative therapy—reduced conditioning for a hematopoietic stem cell transplant or androgen instead of immunosuppressive therapy. The short stature and café au lait spots suggest a diagnosis of FA, but increased chromosomal breakage in response to di-epoxy butane (DEB) or mitomycin C (MMC) is necessary to support the diagnosis. If the screen were positive, chromosomal evaluation for known mutations (previously known as complementation groups) would be sought to confirm the diagnosis and allow evaluation of siblings and potential donors for disease. If the DEB/MMC testing were negative and you still strongly suspected FA, a skin biopsy could be obtained and the fibroblasts grown to confluence and tested for FA mosaicism. The extent of the evaluation for inherited bone marrow failure syndrome is guided by clinical suspicion. For example, a history of malabsorption would suggest screening for Shwachman-Diamond syndrome with either the gene test or serum trypsinogen and fecal elastase. However, most experts recommend screening peripheral blood for chromosomal breakage in all patients with newly diagnosed aplastic anemia.

Elevated eADA levels are seen with Diamond-Blackfan anemia (DBA), which typically presents with macrocytic pure red cell aplasia. Although some patients with DBA may also have some degree of thrombocytopenia or neutropenia, it is rare at diagnosis. An increased proportion of cells missing glycophosphatidylinositol-linked protein are seen with paroxysmal nocturnal hemoglobinuria (PNH). Screening for a PNH clone is recommended at presentation of aplastic anemia but is not critical to direct therapy. Mitochondrial DNA deletions are associated with Pearson syndrome, and vacuolated precursors should have been present in the marrow. Café au lait spots are also seen in neurofibromatosis, but marrow failure and thumb abnormalities are not typical for this disorder.

13. A 15-year-old girl returns for routine follow-up 8 years after immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporine for severe aplastic anemia. She had a good response to IST, with normalization of her peripheral blood counts. Annual paroxysmal nocturnal hemoglobinuria (PNH) clone testing has shown no loss of glycophosphatidylinositol (GPI)-linked proteins. She does not have any full siblings. Her blood counts show recurrent pancytopenia with a hemoglobin of 8.5 g/dL, MCV of 108 fL, WBC of 1,200/µL with 10% neutrophils, and platelets of 15,000/µL.

What is the most important next step in management?

A. DNA breakage analysis with DEB/MMC

B. Evaluation of bone marrow cytogenetics

C. Flow cytometry for PNH clone size

D. HLA typing

E. Telomere length testing

**Explanation**

Relapse of aplastic anemia after IST with ATG and cyclosporine is common (occurring in up to 30% of patients in some series). Patients treated with IST are at increased risk for developing clonal cytogenetic abnormalities, including monosomy 7, as well as leukemic transformation. Thus, a bone marrow aspirate and biopsy with cytogenetics would be the next step to evaluate the etiology of her recurrent pancytopenia and guide treatment. If morphologic evidence of myelodysplastic syndrome, cytogenetic abnormalities, or leukemia is present, therapy should include hematopoietic stem cell transplantation if an appropriate donor can be found. If none of these is present, and the patient and family did not want to pursue transplantation, then repeat treatment with ATG and cyclosporine, possibly with the addition of eltrombopag, should occur.

Although reevaluation at relapse should include reassessment of the size of the population of GPI-deficient cells (PNH clone), this is not the most important test to be evaluated. DEB or MMC testing for DNA breakage should have been done with the first presentation, and a patient with Fanconi anemia or another breakage syndrome would have been unlikely to respond to IST and maintained normal counts for years. Patients who experience a relapse of their aplastic anemia soon after immunosuppression is withdrawn may be re-treated with cyclosporine alone or with combined agent IST. HLA typing for an unrelated donor should have been done at initial presentation, even without a sibling, in order to be aware of options for transplantation in case of a poor response to IST. Telomere length testing may be of interest, but it may have been done with initial presentation and does not influence the care of a patient who had a long initial response to IST. At this time, the most important diagnostic evaluation is to reexamine the bone marrow with morphology and cytogenetics to rule out the acquisition of (pre)-malignant changes.

14. You are evaluating a 17-year-old boy with a 5-year history of mild but stable thrombocytopenia (platelet count 105,000 to 120,000/mL, MPV normal). Today his WBC count is 6,000/mL with 38% neutrophils, hemoglobin 13.2 g/dL, MCV 110 fL, and platelet count 115,000/mm3. Bone marrow examination is hypocellular, with no dysplasia and normal cytogenetics. DEB/MMC testing shows no increased breakage. B12 and folate levels are normal. Family history is remarkable for oral squamous cell carcinoma in his father (who does not smoke or drink) at the age of 25. Paternal grandmother (who also does not smoke) is on oxygen therapy. Mother is healthy. The patient’s physical examination was previously noted as normal, and today he has a new white patch on the right side of his tongue.

Of the following, which test will be most helpful in establishing a diagnosis?

A. *c-Mpl* sequence analysis

B. Fanconi anemia (FA) genetic testing

C. Platelet antibody testing

D. Telomere length analysis

E. *WAS* gene testing

**Explanation**

Longstanding cytopenias with macrocytosis are common features of inherited bone marrow failure syndrome. In this patient the father’s history is most concerning, suggesting that the white patch on the patient’s tongue may represent oral leukoplakia. Leukoplakia with an increased risk of squamous cell carcinoma is associated with dyskeratosis congenita (DC) and FA. In patients with both of these syndromes, suspicious oral lesions should be biopsied promptly.

The family history is consistent with an autosomal dominant pattern of inheritance, with a father with oral squamous cell carcinoma and a paternal grandmother with lung disease that could be pulmonary fibrosis. This is seen more commonly in DC than FA, where inheritance of all genotypes is autosomal recessive except *FANCB,* which is X-linked. The inheritance patterns of DC vary, depending on the mutated gene, and may be autosomal dominant, autosomal recessive, or X-linked. Telomeres will almost always be very short in multiple hematopoietic cell lineages in DC, and assessment of 6-panel telomere length in total leukocytes and leukocyte subsets (granulocytes, total lymphocytes, naive T cells, memory T cells, B cells, and natural killer cells) is the recommended screening test for this disorder. A positive finding should be followed up by sequential genetic testing for mutations in telomerase or shelterin complex.

Although thrombocytopenia may be seen with *c-Mpl* mutations, which occur in congenital amegakaryocytic thrombocytopenia, the platelet counts are lower and disease more quickly progressive than in this patient. The MCV is normal, arguing against *WAS* mutations, which would be associated with small platelets. Platelet antibody testing is not standardized, is of unclear utility in chronic thrombocytopenia, and would be of most help with immune thrombocytopenia with large platelets and would not be related to the marrow hypocellularity or macrocytosis. None of these other syndromes is associated with an increased risk of leukoplakia or squamous cell carcinomas. This patient had negative DEB/MMC testing previously. If the test is convincing that there is no increase in breakage, then FA genetic testing is not generally advised.

15. An 8-year-old girl with severe aplastic anemia is transfusion dependent for red cells and platelets and has an ANC of 450/µL. Workups for Fanconi anemia and infectious causes of bone marrow failure are negative. She is here today with her parents and two siblings, one of whom is HLA compatible.

What would you suggest as the next step in management of this patient?

A. Acyclovir therapy of viral marrow suppression

B. G-CSF at the lowest dosage and frequency possible

C. Hematopoietic stem cell transplant (HSCT) from sibling donor

D. Immunosuppressive therapy

E. Oral androgen therapy

**Explanation**

The treatment of choice for severe aplastic anemia (SAA) in childhood is an HLA-matched sibling donor HSCT. All patients with SAA should be HLA typed at diagnosis and all full siblings also evaluated. If a compatible sibling donor is available, then transplant should proceed as soon as possible. If no sibling donor is available, then registries should be queried to determine whether an acceptable unrelated donor might be available, but current recommendations are to promptly proceed to immunosuppressive therapy (IST) as first treatment. If there is not an adequate response to IST within 3 to 6 months (generally transfusion independence at a minimum), then unrelated or other donor transplantation should be considered. If the patient or family wants to avoid transplantation, then repeat treatment with antithymocyte globulin and cyclosporine, possibly with the addition of eltrombopag, should occur.

After IST, blood counts often remain abnormal but improved to levels of transfusion independence; however, there is an ongoing risk of relapse or clonal evolution. Short-term survival with sibling donor HSCT and IST are comparable, but long-term outcomes and the quality of count recovery are superior with sibling donor HSCT. Current research trials are investigating the feasibility of progressing to unrelated donor HSCT as initial therapy and comparing it with IST for patients without an upfront sibling donor.

This patient has no evidence of a viral cause of her aplastic anemia, so acyclovir therapy is not indicated and may be marrow suppressive. Randomized trials with G-CSF did not show an improvement in outcome for patients with SAA, and indeed it may promote the development of myelodysplasia. Oral androgen therapy is used in the management of Fanconi anemia for patients without acceptable donors and does not have a role in SAA.