Aplastic Anemia: Review Questions
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Aplastic Anemia: Review Questions

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INTRODUCTION

Pancytopenia is a potentially life-threatening problem that places patients at risk for bleeding, cardiopulmonary stress, and infectious complications. Prompt management, including appropriate blood product support with irradiated and filtered products and antimicrobial support, is vital in the early stages. Furthermore, it is important to recognize that these treatments will not impact diagnostic testing results or future management.

The main diagnostic evaluation for the cause of pancytopenia involves a bone marrow biopsy and aspiration, with aspirate and adequate biopsy core obtained for histological testing. Additional key tests on the bone marrow sample include flow cytometry to rule out leukemia and lymphoma and karyotyping and fluorescent in situ hybridization (FISH) studies to evaluate for common abnormalities found in myelodysplasia and acute leukemia. Because many patients with pancytopenia will have a low bone marrow cellularity or low cell numbers on aspiration, collecting an additional core biopsy to make sure adequate sample is present is very important. In patients with pancytopenia who have a marrow cellularity less than 25% of the expected cellularity for their age, and no dysplastic features on marrow examination or karyotypic abnormalities, the diagnosis is aplastic anemia.

The diagnosis of aplastic anemia does not define the cause of the disease, as there is a broad differential of infectious agents, toxins, and inherited disorders that can lead to the development of marrow aplasia. When faced with a patient with aplastic anemia, there are several key considerations in diagnosis and management. First, in young patients with aplastic anemia, congenital disorders leading to aplastic anemia must be ruled out. The 2 most common include Fanconi anemia and dyskeratosis congenita, with a number of other more rare inherited causes of aplastic anemia to be considered. Second, urgent referral to a facility that performs bone marrow transplantation is very important, as transplantation is a treatment consideration for most patients with aplastic anemia. Finally, a thorough history to assess for drug/toxin exposure, viral infections (hepatitis in particular), and pregnancy in women of child bearing potential is necessary (Table 1). A number of diagnostic tests are important to identify a potential cause for the aplastic anemia, define its severity, and evaluate for associated disorders (Table 2).

It is important to remember that aplastic anemia is considered a curable disease. However, the supportive care required for patients with severe and very severe aplastic anemia is intensive. Feverle, neutropenic patients require hospital admission for intravenous antibiotics and investigation for the source of fevers. In a nonfebrile but neutropenic patient, prophylactic antimicrobials are optimal to reduce infectious complications. Blood product support may be required 2 to 3 times a week, with close monitoring for evidence of platelet alloimmunization. In patients who fail to respond to random donor platelets, a platelet refractory workup is necessary to define their alloantibodies and identify specific products for transfusion. Blood product support from family members should be avoided in aplastic anemia patients, as this may increase the risk of rejection in the setting of bone marrow transplantation. Finally, one must continually record the number of units of blood transfused and consider the risk of secondary iron overload. With the current standards of treatment, the 3- to 5-year survival for all patients with aplastic anemia is approximately 80%. Therefore, management of this disease is best done either at a major center experienced in treatment of aplastic anemia or with very good consultative support.

QUESTIONS

Choose the single best answer for each question.

Questions 1 to 3 are based on the following case:

1. A 20-year-old man presents for evaluation of recurrent epistaxis. He reports nose bleeding that
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occurs at least daily, lasting up to 45 minutes at times. This started 1 week ago and has been getting progressively worse. He works in a grocery store, and has noticed the presence of large bruises on his abdomen and thighs from carrying milk crates. He reports being fatigued, but he was able to work up until 2 days ago, at which time he started to note fevers up to 102°F, associated with significant fatigue. He denies sinus congestion, throat pain, cough, shortness of breath, nausea, emesis, melena, hematochezia, or hematuria. He has had headaches and mild gum bleeding with brushing his teeth.

On physical examination, measurement of vital signs shows a temperature of 100.8°F, heart rate of 115 bpm, respiratory rate of 22 breaths/min, and blood pressure of 134/75 mm Hg. In general, this is a pale young man who is fatigued but in no acute distress. On head/eyes/ears/nose/throat examination, pupils are equal, round, and reactive to light; extraocular movements are intact; oropharynx is slightly dry with petechiae on his buccal mucosa and posterior pharynx; and there is no sinus tenderness, no nuchal rigidity, and no neck lymphadenopathy. Cardiac examination reveals regular rhythm, tachycardia, and a 2/6 systolic murmur loudest at the lower left sternal border. Lungs are clear to auscultation bilaterally. Abdomen is soft and nontender with positive bowel sounds and no hepatosplenomegaly. Extremities are warm without edema. Skin examination reveals petechiae present on the lower extremities bilaterally.

Laboratory studies show a white blood cell (WBC) count of 800 cells/μL; hemoglobin, 5.2 g/dL; hematocrit, 14.8%; platelet count, 5000 cells/μL. Automated differential reports 2% segmented neutrophils, 96% lymphocytes, and 2% monocytes.

What is the most appropriate next step in the management of this patient?

(A) Schedule a bone marrow biopsy tomorrow as an outpatient

(B) Admit the patient to the hospital today for intravenous antibiotics, blood and platelet transfusion today, and a bone marrow biopsy

(C) Arrange for a blood and platelet transfusion today, with plans to see him back in clinic the following day for further evaluation

(D) Arrange for a blood and platelet transfusion today, start him on oral levofloxacin, draw blood cultures, and arrange for a bone marrow biopsy tomorrow as an outpatient

<table>
<thead>
<tr>
<th>Table 1. Etiology of Aplastic Anemia</th>
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<tbody>
<tr>
<td><strong>Acquired aplastic anemia</strong></td>
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<tr>
<td>Idiopathic</td>
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<tr>
<td><strong>Secondary</strong></td>
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<tr>
<td>Chemicals</td>
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<tr>
<td>Benzene</td>
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<td>Insecticides</td>
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<td>Glue</td>
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<td>Solvents</td>
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<td>Cytotoxic agents</td>
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<td>Antibiotics</td>
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<td>Nonsteroidal anti-inflammatory drugs</td>
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<td>Anticonvulsive agents</td>
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<td>Gold salts</td>
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<tr>
<td>Radiation</td>
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<tr>
<td>Viruses</td>
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<tr>
<td>Epstein-Barr virus</td>
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<tr>
<td>HIV</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Immune and rheumatologic diseases</td>
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<tr>
<td>Graft-versus-host disease</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
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<tr>
<td>Pregnancy</td>
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| Inherited aplastic anemia          |
| Fanconi anemia                     |
| Dyskeratosis congenita             |
| Schwachman-Diamond syndrome        |


2. A slide from the patient’s bone marrow biopsy specimen is shown in the Figure. What is the diagnosis?

(A) Acute lymphoblastic leukemia

(B) Acute myelogenous leukemia

(C) Aplastic anemia

(D) Myelodysplastic syndrome
3. What is the next best treatment option for this patient?
   (A) A course of rabbit antithymocyte globulin and cyclosporine
   (B) A course of horse antithymocyte globulin and cyclosporine
   (C) Supportive care alone
   (D) Hold any therapy until all of his siblings have been typed to consider an upfront bone marrow transplant

4. An 8-year-old boy with newly discovered pancytopenia is brought by his parents for evaluation. He has a history of recurrent infections and short stature. There is no family history of cancers or blood disorders. Given his young age and history, there is concern about an inherited marrow failure state. What is the most common cause of inherited bone marrow failure?
   (A) Diamond-Blackfan anemia
   (B) Dyskeratosis congenita
   (C) Fanconi anemia
   (D) Schwachman-Diamond syndrome

5. A newly diagnosed 19-year-old with severe aplastic anemia presents for evaluation of bone marrow transplantation. If the patient has an HLA-matched sibling, what is the long-term outcome with bone marrow transplantation for his disease?
   (A) 30% 5-year survival
   (B) 50% 5-year survival
   (C) 60% 5-year survival
   (D) 80% 5-year survival

Questions 6 and 7 are based on the following case:

6. A 62-year-old man with chronic lymphocytic leukemia who completed 4 courses of fludarabine, cyclophosphamide, and rituximab chemotherapy 2 years ago with excellent response is referred for evaluation. Within the last 2 months, he has had a progressive decline in his blood counts and presents now for further workup of his pancytopenia. His examination is notable for scattered petechiae in his mouth, but otherwise there is no adenopathy or hepatosplenomegaly on exam and his cardiopulmonary exam is normal. Laboratory studies show a WBC of 1300 cells/μL, hematocrit of 25.8%, and platelet count of 12,000 cells/μL. Results of renal and liver function tests are normal. A bone marrow biopsy reveals a markedly hypocellular marrow with cellularity of 10% or less. Flow cytometry shows no evidence of chronic lymphocytic leukemia. Cytogenetic studies were unable to be performed due to lack of adequate material. What treatment should be recommended for this patient?
   (A) Azacitidine in standard doses
   (B) Azacitidine with dose reduction due to cytopenia
   (C) Antithymocyte globulin with cyclosporine
   (D) Supportive care alone due to anticipation of count recovery

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Table 2. Diagnostic Workup for Aplastic Anemia

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
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<tr>
<td>Liver function tests</td>
<td>To evaluate for evidence of hepatitis, as hepatitis-associated aplastic anemia is a well-described entity in younger patients, often male (associated with non-A, non-B, non-C viral hepatitis)</td>
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<tr>
<td>Viral hepatitis (including non-A, non-B, non-C) testing</td>
<td>Numerous viral diseases have been associated with aplastic anemia; presence of viral disease can impact treatment</td>
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<tr>
<td>Epstein-Barr virus testing</td>
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<tr>
<td>Cytomegalovirus testing</td>
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<tr>
<td>HIV testing</td>
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<td>Antinuclear antibody</td>
<td></td>
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<tr>
<td>Rheumatoid factor</td>
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<tr>
<td>Peripheral blood flow cytometry for PNH</td>
<td>In approximately half of patients with aplastic anemia, a small PNH clone is found; this is important for follow-up after treatment to assess progression of the PNH</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td></td>
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<tr>
<td>Fanconi anemia testing (peripheral blood breakage analysis)</td>
<td>To assess for inherited disorders associated with aplastic anemia, as patients with aplastic anemia and an inherited disorder require special consideration for treatment and family screening</td>
</tr>
<tr>
<td>Telomere length testing</td>
<td></td>
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<tr>
<td>Dyskeratosis congenita mutation analysis</td>
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</table>

PNH = paroxysmal nocturnal hemoglobinuria.
7. The hematologist prescribes antithymocyte globulin with cyclosporine and the patient has a good partial response. Now 14 months after recovery, his counts have declined again. What is the most likely cause for his declining counts?
(A) Recurrent aplastic anemia
(B) Progressive myelodysplastic syndrome
(C) Secondary myelodysplastic syndrome
(D) Chronic lymphocytic leukemia

8. A 30-year-old woman who has a history of aplastic anemia presents for follow-up. She was diagnosed when she was 22 years old, and was treated with antithymocyte globulin and cyclosporine with a complete response. She underwent a slow cyclosporine taper over 4 years, with her counts remaining stable, and she has been off cyclosporine for the last 3 years.

In the last 6 months she has started to develop new fatigue, associated with intermittent bouts of abdominal pain and recurrent urinary tract infections. Due to count abnormalities, she is referred by her primary care physician to a hematologist for evaluation.

Her complete blood cell count shows a WBC count of 4200 cells/μL; hemoglobin of 8.4 g/dL; hematocrit of 26.4%; and platelet count of 155,000 cells/μL. Automated differential reports 60% segmented neutrophils, 38% lymphocytes, and 2% monocytes. Additional laboratory studies show an absolute reticulocyte count of 125,000 cells/μL, lactate dehydrogenase elevated at 945 U/L, and haptoglobin undetectable. Coombs’ testing is negative. What is the next most appropriate testing in this patient?
(A) Abdominal computed tomography scan to evaluate for lymphoma
(B) Bone marrow biopsy
(C) Peripheral blood flow cytometry for paroxysmal nocturnal hemoglobinuria
(D) Start prednisone for autoimmune hemolysis

9. A 25-year-old man with refractory aplastic anemia is referred for additional treatment recommendations. He was diagnosed with aplastic anemia 7 months ago, and after a search of family members found no appropriate donors he was treated with horse antithymocyte globulin and cyclosporine. Despite this therapy, he has remained platelet and red cell transfusion dependent, with intermittent granulocyte-colony stimulating factor required as well for neutropenia. He is receiving antimicrobials to prevent infections, and has had no major complications to date and remains healthy. He has secondary iron overload as well.

Repeat bone marrow biopsy verifies continued panhypoplasia of the marrow, cytogenetics shows a normal karyotype, and FISH for common abnormalities in myelodysplastic syndrome reveals no abnormalities. What therapy do you recommend at this time?
(A) A course of horse antithymocyte globulin and continued cyclosporine therapy
(B) A course of rabbit antithymocyte globulin and continued cyclosporine therapy
(C) A matched unrelated donor bone marrow transplant
(D) Continued supportive care

10. A previously healthy 62-year-old man with newly discovered pancytopenia presents for evaluation. He has a 1-month history of fatigue and shortness of breath with exertion, and in the last week he has noted easy bruising and bleeding of the gums with brushing. He has had no fevers or infectious symptoms and is taking no medications. He has no family history of blood disorders, and has 5 siblings, all of whom are younger and in good health.

On examination, the patient is a healthy appearing male who appears younger than his stated age and is in no distress. He does have oral petechiae and ecchymoses on his upper and lower extremities, but no other abnormalities are noted on exam.
A p l a s t i c A n e m i a

His complete blood count shows a WBC count of 1800 cells/μL, hemoglobin of 7.2 g/dL, hematocrit of 21.8%, and platelet count of 8000 cells/μL. Automated differential reports 8% segmented neutrophils, 90% lymphocytes, and 2% monocytes.

He is given platelet and red cell transfusion support, and a bone marrow biopsy is performed, revealing a markedly hypocellular marrow, with no findings of dysplasia or leukemia. What is the next best treatment option for this patient?

(A) A course of rabbit antithymocyte globulin and cyclosporine.
(B) A course of horse antithymocyte globulin and cyclosporine
(C) Supportive care alone
(D) Hold any therapy until all of his siblings have been typed to consider an upfront bone marrow transplant

11. A young woman with severe aplastic anemia presents for urgent evaluation of fevers, throat pain and neck adenopathy. She has been treated with 2 courses of antithymocyte globulin and cyclosporine (first horse antithymocyte globulin, then rabbit antithymocyte globulin), and she continues to have poor counts and requires frequent transfusion support. Her last treatment with rabbit antithymocyte globulin took place 2.5 months ago. Efforts to find a bone marrow donor for her have been unsuccessful, and her cord blood options are currently being considered.

On presentation, she reports fevers up to 101°F for the past 2 days, with painful lymphadenopathy noted mainly in the cervical chain. She has had no sick contacts and her indwelling catheter is not tender. She is afebrile in the clinic, with normal vital signs. On exam, she looks uncomfortable but is in no distress. Her oropharynx is moist, with scattered petechiae and left tonsillar erythema and exudate. She has bilateral anterior and posterior cervical chain adenopathy, left greater than right. No other sites of adenopathy are appreciated on exam, and her heart and lung exam are normal, with no hepatosplenomegaly or discomfort on abdominal exam.

The patient is treated with a course of amoxicillin-clavulanate empirically after blood cultures are drawn. Despite being on this agent for 5 days, her fevers persist and her throat pain worsens. In addition, her adenopathy appears worse on exam. What testing should be pursued at this time?

(A) No additional testing is needed; continue her current course of treatment
(B) Perform throat cultures for bacterial infections
(C) Perform throat cultures for fungal infection
(D) Perform polymerase chain reaction blood testing for Epstein-Barr virus

ANSWERS AND EXPLANATIONS

1. (B) Admit the patient to the hospital today for intravenous antibiotics and blood and platelet transfusion today, and a bone marrow biopsy. This patient has 2 potentially life-threatening issues that require urgent management. The first issue that requires inpatient management is neutropenic fevers. Neutropenic fevers require hospitalization and intravenous antibiotics to cover gram-negative bacteria, in particular *Pseudomonas aeruginosa*. The second issue that requires urgent treatment is his severe thrombocytopenia. Spontaneous bleeding can occur with platelet counts less than 10,000 cells/μL, and mucosal bleeding identifies patients at higher risk of severe bleeding. For these reasons, this patient requires a platelet transfusion. While he is hospitalized, review of the peripheral smear, red cell transfusion, and bone marrow biopsy can be performed. The blood products administered to this patient should be irradiated, filtered, and cytomegalovirus-safe to prevent transfusion-associated graft-versus-host disease, given his leukopenia. When performing a bone marrow biopsy to evaluate pancytopenia, it is important to order flow cytometry to rule out both leukemia and lymphoma, and standard cytogenetics to evaluate for myelodysplastic syndrome, with FISH studies to look for common mutations found in myelodysplastic syndrome, in particular abnormalities in chromosomes 5, 7, and 8.

2. (C) Aplastic anemia. The bone marrow sample shown in Figure 1 is devoid of marrow elements, shows no evidence of leukemia or other infiltrative process, and shows no evidence of dysplasia. This patient meets the criteria for very severe aplastic anemia, with profound neutropenia (absolute neutrophil count < 200/µL), thrombocytopenia (platelet count <20,000/µL), and marrow cellularity less than 25% of the normal cellularity for his age. Workup for causes of aplastic anemia, including viral studies (HIV, Epstein-Barr virus, cytomegalovirus, and viral hepatitis), connective tissue disorders, and a thorough review of drugs,
herbal products and chemical/toxin exposures is necessary. Additional common findings in aplastic anemia include the presence of a small paroxysmal nocturnal hemoglobinuria (PNH) clone, and therefore flow cytometry for PNH on peripheral blood is important in the initial workup. Patients with a small clone require continued follow-up of the clone throughout their life.

In younger patients, additional considerations include evaluation for hereditary bone marrow failure syndromes, in particular Fanconi anemia and dyskeratosis congenita. Evaluation for Fanconi anemia is performed by a peripheral blood breakage study, which is done on lymphocytes and can easily be performed despite leukopenia. Dyskeratosis congenita is a disorder of telomere length maintenance, with abnormal shortening of telomeres. In addition to aplastic anemia, patients with dyskeratosis congenita have oral leukoplakia, pigmentation changes in the skin, and nail dystrophy. If examination reveals any findings of dyskeratosis congenita, genetic testing for the common mutations leading to this condition is recommended.

The majority of cases of aplastic anemia are “idiopathic.” However, in idiopathic aplastic anemia, the immune system is implicated in destruction of hematopoietic elements. Cytotoxic T lymphocytes activated against hematopoietic tissue can be identified in some patients with aplastic anemia. Sensitive testing for T cell repertoire in patients with aplastic anemia can identify oligoclonal T cells in some patients; with immune suppression therapy these T cell clones can disappear, heralding response.

(D) Hold any therapy until all of his siblings have been typed to consider an upfront bone marrow transplant. In young patients, the recommended first-line therapy for severe aplastic anemia is a matched sibling bone marrow transplantation. In reviewing outcomes with matched sibling bone marrow transplantation, using a conditioning regimen of cyclophosphamide and horse antithymocyte globulin versus immune suppressive treatment with horse antithymocyte globulin and cyclosporine, the outcomes were superior in the transplanted patients up to the age of 40 years. However, with improvement in transplantation outcomes, the age for considering transplantation has risen into the 50s in most institutions, and individual consideration must be given to each case. Therefore, at our institution, all patients under the age of 60 years in good health have a rapid screen for potential donors in the family before starting any definitive therapy for the aplastic anemia. Supportive care with transfusion support should be utilized while the donor search is underway. In those patients without a matched family member, treatment with immune suppression with horse antithymocyte globulin and cyclosporine is instituted and an unrelated donor search is initiated. Antithymocyte globulin and cyclosporine treatment can take up to 3 months or more to take full effect, but in those patients without a robust response to this treatment the chance of reconstituting hematopoiesis without a bone marrow transplant is low. Therefore, in patients who fail an initial round of antithymocyte globulin and cyclosporine, the next best option for therapy is a matched unrelated donor bone marrow transplant.

(C) Fanconi anemia. Inherited marrow failures must be considered in any patient under the age of 30 years with aplastic anemia or any patient with developmental abnormalities or a family history of aplastic anemia or other cancers. It is very important to identify an inherited cause for marrow failure, because the treatment and outcomes in patients with these diseases is different compared to standard therapy. The most common cause of inherited marrow failure is Fanconi anemia, an autosomal recessive disorder that results from defects in the DNA damage repair pathway. Patients with Fanconi anemia have growth and development anomalies, bone marrow failure and leukemia, and predisposition to cancers of the aerodigestive tract. The second most common cause of inherited marrow failure is dyskeratosis congenita, a disease characterized by bone marrow failure, oral leukoplakia, pigmentation changes in the skin, and nail dystrophy. There are multiple genetic mutations implicated in dyskeratosis congenita, but they all lead to defects in telomere maintenance. Diamond-Blackfan anemia is typically characterized by pure red cell aplasia, but progression to myelodysplastic syndrome or aplastic anemia can occur. Shwachman-Diamond syndrome is a disease characterized by pancreatic exocrine dysfunction, neutropenia, and metaphyseal dysostosis. Progression to aplastic anemia, myelodysplastic syndrome, and acute myelogenous leukemia is not uncommon. The genes implicated in Diamond-Blackfan anemia and Shwachman-Diamond syndrome have recently been identified and defined, and both
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diseases appear to stem from defective ribosomal RNA processing.13,14

5. (D) 80% 5-year survival. Matched sibling allogeneic bone marrow transplants in young patients with aplastic anemia have an excellent outcome, with survival approaching 90% or more with current supportive care.15 The standard conditioning regimen for matched sibling transplantation for aplastic anemia is a combination of cyclophosphamide and horse antithymocyte globulin. This regimen has lower treatment-related toxicity, leading to both excellent survival and quality of life post-transplant. In addition, fertility can be preserved in up to 50% of patients receiving a transplant with this regimen.16 Aplastic anemia is the only indication for urgent bone marrow transplantation when a fully matched relative is identified. The main factor influencing outcomes is graft-versus-host disease,17 and therefore the current research focus is on the reduction of this disease in these transplants.

6. (C) Antithymocyte globulin with cyclosporine. The bone marrow and blood counts are consistent with aplastic anemia. The other main diagnostic consideration in this case is a hypocellular myelodysplastic syndrome,18 and therefore a thorough investigation for dysplasia and chromosomal abnormalities is important, in particular FISH studies for abnormalities in chromosomes 5, 7, and 8. Given the lack of data on karyotype from his initial bone marrow specimen, a repeat bone marrow biopsy with FISH would be warranted. There is some literature describing the development of marrow aplasia after treatment with fludarabine and cyclophosphamide, and although the cause of this is unclear, it may be linked to T cell suppression and emergence of autoreactive lymphocytes.19,20 This patient requires appropriate aggressive management of pancytopenia, with blood product support with irradiated and leukoreduced blood products and antimicrobial prophylaxis. Despite his history of chronic lymphocytic leukemia and treatment, the focus of the therapy is identical to standard aplastic anemia treatment. Given his age, first-line therapy would be a combination of cyclosporine and horse antithymocyte globulin. In estimating his chance of response to this regimen, one would predict an overall response with this therapy at around 50% to 60%, the same as expected for idiopathic aplastic anemia.21 In addition, he should undergo investigation for sibling and/or unrelated donors, as bone marrow transplantation should be considered for management of his aplastic anemia if he fails immune suppression.

7. (A) Recurrent aplastic anemia. Relapse aplastic anemia occurs in approximately 30% of patients treated with antithymocyte globulin and cyclosporine and is defined as a drop in blood counts not otherwise explained by new abnormalities in the marrow. Patients can relapse after they have completed a cyclosporine taper or during their cyclosporine taper. One variable that impacts the risk of relapse is the taper schedule for the cyclosporine, with relapses occurring at a much higher rate in patients who undergo a rapid taper schedule22 compared to a very slow taper schedule. In counseling patients with aplastic anemia treated with antithymocyte globulin and cyclosporine, it is important they understand the long-term need for cyclosporine and the possibility that they will require life-long cyclosporine.22,23 Many relapses can be treated effectively with reinitiation or escalation of immunosuppression (often just cyclosporine alone), with excellent responses. However, bone marrow transplantation must be considered in this patient population that fails immunosuppressive therapy. Another important consideration in this case is secondary myelodysplastic syndrome. Up to 20% of patients with aplastic anemia treated with immunosuppression will develop secondary clonal hematopoietic diseases, including myelodysplastic syndrome, acute leukemia, and PNH.24 Repeating the bone marrow biopsy to rule out a secondary clonal disorder is appropriate in this case.

8. (C) Peripheral blood flow cytometry for paroxysmal nocturnal hemoglobinuria. This patient has the classic presentation for development of PNH as a complication of her previous aplastic anemia. PNH is a disorder of the hematopoietic stem cell, where a mutation in the X-linked gene PIG-A leads to defective production of glycosylphosphatidylinositol (GPI) anchors, leading to defective expression of GPI anchored proteins on the surface of blood cells. The 2 key proteins that are missing on blood cells in PNH are CD55 and CD59, both of which are important to protect red cells from complement-mediated destruction. CD55 and CD59 deficiency renders these red cells highly
susceptible to complement-mediated destruction, and this is the cause of the chronic intravascular hemolysis that is the hallmark of PNH.

At the diagnosis of aplastic anemia, up to 60% of patients will have an identifiable PNH clone in the peripheral blood. These clones are typically small (<10% of cells) or very small (<2% of cells) and not clinically relevant. Patients with aplastic anemia and a small PNH clone do not have the findings of hemolysis found in classic PNH. Over time, however, these small PNH clones can expand and become clinically relevant, with expansion of the PNH clone to become 50% or more of the blood cells. Frank hemolytic PNH is a well-described late complication of aplastic anemia treated with immune suppression.26

In the presented case, the first testing to perform is peripheral blood flow cytometry for PNH, which should include study of both the red cell and white cells. In this patient, one would expect a PNH clone size of over 50% given her history and the extent of hemolysis. For patients who present with significant hemolysis from PNH, treatment directed toward PNH is warranted. The complement blocker eculizumab is the only drug designed to treat the hemolysis from PNH, and treatment with this highly effective agent should be considered in this patient.

9. (C) A matched unrelated donor bone marrow transplant. With improvements in many aspects of bone marrow transplantation in aplastic anemia, the current recommendations for those patients who have failed an initial course of immune suppression is a matched unrelated donor transplant. The improvements in donor identification with the current standard approach of high-resolution typing have minimized the risks of both engraftment failure and graft-versus-host disease. Additional improvements in bone marrow transplantation include the use of reduced-intensity regimens with lower doses of total body irradiation and improvements in supportive care. With the current approach to matched unrelated donor bone marrow transplants for aplastic anemia, the long-term outcomes are well over 50%, with some groups showing 70% or higher 2- and 5-year survival rates.11 These outcomes are far ahead of the response rates in patients who receive a second course of immune suppression (up to 30% response to a second course of immune suppression). In addition, for those patients who fail to respond to therapy, the long-term survival is poor.

10. (B) A course of horse antithymocyte globulin and cyclosporine. The first-line choice of treatment for a 62-year-old patient with aplastic anemia is a course of horse antithymocyte globulin and cyclosporine. While this patient is quite healthy, upfront bone marrow transplant might be considered in some institutions if he had a matched sibling; however, the standard approach would be immune suppression first, followed by transplant if he fails to respond to immune suppression after 3 months.

Around the world the first choice of antithymocyte globulin product has been variable, with some countries using rabbit antithymocyte globulin rather than horse antithymocyte globulin as first-line therapy. There are also variable types of rabbit antithymocyte globulin available across the globe. An abstract presented by the National Institutes of Health group at the American Society of Hematology 2010 meeting described a randomized trial for patients with aplastic anemia that compared first-line treatment with horse antithymocyte globulin and rabbit antithymocyte globulin.27 This study found a stark contrast in response rates and outcomes between the 2 groups. The horse antithymocyte globulin arm had a far superior response rate at 62% compared to the rabbit antithymocyte globulin arm at 35% (P = 0.0017), with an additional increase in deaths in the rabbit antithymocyte globulin arm compared to the horse antithymocyte globulin arm, leading to differences in overall survival between the 2 groups. Given this data, horse antithymocyte globulin should be considered the antithymocyte globulin product of choice in the initial treatment of aplastic anemia.

11. (D) Perform polymerase chain reaction blood testing for Epstein-Barr virus. This question highlights the importance of infectious complications with aplastic anemia and the treatment of this disease. This patient has Epstein-Barr virus reactivation, which if left unmanaged will progress to frank Epstein-Barr virus-associated lymphoma/lymphoproliferative disorder. The management approach at this time includes testing for Epstein-Barr virus by polymerase chain reaction (PCR) to assess viral load, and consideration of lymph node biopsy. Treatment with rituximab is the treatment of choice, with weekly dosing to bring the viral load to an undetectable level and treat the adenopathy. If the adenopathy persists or worsens despite dropping viral loads, then a biopsy is urgently required. Epstein-Barr virus reactivation has been described after immune
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suppression treatment for aplastic anemia. This is seen most commonly in patients who have received alemtuzumab, rabbit antithymocyte globulin or 2 or more courses of any type of antithymocyte globulin. This patient received back-to-back treatments with antithymocyte globulin, which placed her at risk of developing Epstein-Barr virus reactivation. In addition to Epstein-Barr virus reactivation, patients who have received immune suppression therapy are at risk of developing cytomegalovirus reactivation and adenovirus infection. Therefore, monitoring for viral loads by PCR in patients with immune suppressive therapy and fevers is important. In those patients who have been treated with alemtuzumab in particular, routine viral load monitoring is recommended as part of the standard treatment program.

SUMMARY POINTS

- When faced with a patient with profound pancytopenia, providing prompt and aggressive support to reduce infectious and bleeding complications is imperative.
- Aplastic anemia is considered a highly manageable and curable disease, and referral to a center experienced in the care of these patients optimizes their outcome.
- In younger patients with aplastic anemia, inherited disorders leading to aplastic anemia must be ruled out, as this impacts both the management and prognosis in these patients.
- In patients younger than 40 years with severe aplastic anemia and a HLA-matched sibling, the recommended first-line treatment is a bone marrow transplant after conditioning with cyclophosphamide and horse antithymocyte globulin. In many institutions, the age for upfront transplantation may exceed 50 years, and therefore prompt referral to a transplant center in these patients is warranted.
- In patients with severe aplastic anemia without a matched sibling or who are older than the recommended age for upfront transplantation, treatment with a combination of horse antithymocyte globulin and cyclosporine is the recommended therapy.
- The long-term complications for those patients treated with immune suppression include relapse and secondary hematopoietic clonal disorders; therefore life-time follow-up of their blood counts and function is recommended.

REFERENCES

hematopoietic cell transplantation from HLA-identical siblings for severe aplastic anemia in patients over 40 years of age. Biol Blood Marrow Transplant 2010;16:1411–8.


