

# Aplastic Anemia: Review of Etiology and Treatment

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**A**plastic anemia is defined as the failure of bone marrow to produce blood cell components. The hallmarks of the disease are pancytopenia and a hypocellular bone marrow. Aplastic anemia is a rare disease, and approximately 2000 patients are diagnosed in the United States every year.<sup>1</sup> The estimated incidence is approximately two cases per million in Europe, and the incidence in Asia is two to three times higher.<sup>2</sup> This geographic variation is more likely caused by environmental rather than genetic elements, although individual susceptibility is an important factor.

## ETIOLOGY

The most common causes of aplastic anemia are listed in **Table 1**. Inherited forms of the disorder are rare and consist of Fanconi's anemia, dyskeratosis congenita, and Schwachman syndrome. Among patients with the acquired disorder, idiopathic aplastic anemia, in which no cause is apparent, accounts for approximately 65% of all cases of aplastic anemia.

### Secondary Aplastic Anemia

Secondary aplastic anemia occurs after exposure to environmental factors and in certain disorders. The following factors have been implicated as causes of secondary aplastic anemia: chemicals, drugs, infectious agents, radiation, rheumatic disease, and pregnancy.

**Chemicals.** A definitive linkage between benzene and aplastic anemia has been established from clinical and epidemiologic data, as well as from animal and in vitro studies.<sup>3,4</sup> Despite this association, benzene is still widely used as a solvent and in the manufacture of other chemicals, drugs, dyes, explosives, leather goods, and rubber. Chemicals used in insecticides (chlorophenothane), glue (toluene), and Stoddard solvent (petroleum distillates) have also been associated with aplastic anemia.

**Drugs.** Chloramphenicol was, at one point, the most common cause of drug-induced aplastic anemia in the

United States. Anticonvulsant medications, in particular carbamazepine and hydantoins, are also associated with the development of aplastic anemia. The toxic metabolic intermediate of carbamazepine has been implicated in fatal cases of aplastic anemia.<sup>5</sup> Treatment with anti-neoplastic cytotoxic agents carries a high risk of aplastic anemia, and drugs such as gold salts, D-penicillamine, phenylbutazone, quinacrine, and acetazolamide have also been implicated. Commonly used drugs such as penicillin, furosemide, allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs) are linked to a lesser degree with aplastic anemia.

**Infectious agents.** Some viral infections, notably infectious mononucleosis caused by Epstein-Barr virus, have been associated with aplastic anemia. Whether anemia results from a direct effect by the virus on the bone marrow or from a host immunologic response is unclear. The association between hepatitis and aplastic anemia is also strong, but anemia does not appear to be related to infection with hepatitis viruses A, B, or C, and may be caused by an unknown virus.<sup>6</sup> Human parvovirus B19, the virus that causes fifth disease, has been linked with pure red cell aplasia but not with severe aplastic anemia. Although some cases of aplastic anemia have been reported with human immunodeficiency virus (HIV) infections, most patients with HIV infection have a cellular bone marrow, despite varying degrees of peripheral cytopenia.

**Radiation.** Repeated exposure to low doses of radiation has been associated with aplastic anemia. Single exposure to high doses of radiation (such as after a nuclear explosion) is more likely to lead to leukemia rather than aplastic anemia.

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**Rheumatic diseases.** Connective tissue disorders such as rheumatoid arthritis and systemic lupus erythematosus have been associated with aplastic anemia. However, it is not certain whether the drugs used to treat these disorders (NSAIDs, gold salts, allopurinol, D-penicillamine) cause the anemia or whether the activated immune system, which is a feature of these diseases, is the responsible factor.

**Pregnancy.** Many cases of aplastic anemia have also been found in association with pregnancy. However, because these cases showed variable clinical courses, the relationship between pregnancy and aplastic anemia is yet to be defined.

#### **PATHOPHYSIOLOGY**

The pancytopenia in aplastic anemia reflects failure of the hematopoietic process manifested as a severe decrease in the numbers of all hematopoietic progenitor cells. Two mechanisms have been suggested for bone marrow failure. The first mechanism is direct hematopoietic injury by chemicals (eg, benzene), drugs, or radiation to both proliferating and quiescent hematopoietic cells. The second mechanism, supported by clinical observations and laboratory studies, is immune-mediated suppression of marrow cells;<sup>7</sup> examples of this mechanism are bone marrow failure after graft-versus-host-disease (GVHD), eosinophilic fasciitis, and hepatitis. The mechanism for idiopathic, pregnancy-associated, and some cases of drug-associated aplastic anemia is not clear but may involve immunologic processes as well. Cytotoxic T cells are thought to mediate the suppressive effect on hematopoietic cells through the production of hematopoiesis-inhibiting cytokines such as interferon- $\gamma$  and tumor necrosis factor- $\alpha$ .<sup>8</sup> An immune-mediated suppressive effect on hematopoiesis may explain why most patients with acquired aplastic anemia respond to treatment with immunosuppressive therapy.

At presentation, patients with aplastic anemia usually do not have more than 10% of the normal number of stem cells. However, laboratory studies show that stromal cells from patients with aplastic anemia can support growth and development of normal hematopoietic stem cells and can also produce normal or increased quantities of hematopoietic growth factors. Although the success of bone marrow transplantation depends on adequately functioning stromal elements, clinical and in vitro data do not support the use of hematopoietic growth factors alone in the treatment of aplastic anemia.

The pathophysiology of aplastic anemia, therefore, suggests two major approaches for treatment: replacement of deficient stem cells by bone marrow transplan-

**Table 1.** Etiologic Classification of Aplastic Anemia

#### **Acquired aplastic anemia**

- Idiopathic
- Secondary
  - Chemicals
    - Benzene
    - Insecticides
    - Glue
    - Solvents
  - Drugs
    - Cytotoxic agents
    - Antibiotics
    - Nonsteroidal anti-inflammatory drugs
    - Anticonvulsive agents
    - Gold salts
  - Radiation
  - Viruses
    - Epstein-Barr virus
    - Non-A, non-B, non-C hepatitis viral agent (?)
    - Human immunodeficiency virus
  - Immune and rheumatologic diseases
    - Graft-versus-host disease
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
  - Paroxysmal nocturnal hemoglobinuria
  - Pregnancy

#### **Inherited aplastic anemia**

- Fanconi's anemia
- Dyskeratosis congenita
- Schwachman syndrome

tion and suppression of a destructive immunologic process.

#### **CLINICAL PRESENTATION**

The signs and symptoms of patients presenting with aplastic anemia are typically related to the decrease or absence of peripheral blood cellular components.<sup>9</sup> The clinical presentation ranges from insidious to dramatic. Because platelets are depleted early in the process of the disease, dependent petechiae, bruising, gum bleeding, buccal hemorrhage, epistaxis, or retinal hemorrhage may be among the first presentations. Because of anemia, patients may complain of shortness

**Table 2.** Diagnostic Criteria for Severe Aplastic Anemia\*

**At least two of the following:**

Absolute neutrophil count  $<0.5 \times 10^9/L$

Platelet count  $< 20 \times 10^9/L$

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

\*According to the International Aplastic Anemia Study Group

Data from Camitta et al: A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood* 1979;53:504.

of breath, fatigue, or chest pain. Neutropenia or leukopenia may result in fever, chills, or infections. Hepatosplenomegaly, lymphadenopathy, or bone pain are less common in patients with aplastic anemia, but these findings should alert the physician to other diagnoses, such as infection, leukemia, or lymphoma.

## DIAGNOSIS

### Differential Diagnosis

Pancytopenia is a common feature of many illnesses. Although the medical history, physical examination, and basic laboratory studies can often exclude aplastic anemia, the distinction is more difficult in certain hematologic diseases, and further testing is required.

Causes of pancytopenia that need to be considered in the differential diagnosis include Fanconi's anemia, paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS), myelofibrosis, aleukemic leukemia, agranulocytosis, and pure red cell aplasia. Each of these conditions is briefly reviewed in the following discussion.

**Fanconi's anemia.** This congenital form of aplastic anemia is an autosomal recessive inherited condition in which 10% of patients present beyond childhood.<sup>10,11</sup> Typical physical stigmata include short stature, skin hyperpigmentation, microcephaly, thumb or radius hypoplasia, urogenital abnormalities, and mental retardation. Fanconi's anemia is confirmed by cytogenetic analysis of peripheral blood lymphocytes, which show chromosome breaks after culture with substances that promote chromosome stress (eg, diepoxybutane or mitomycin C).

**Paroxysmal nocturnal hemoglobinuria.** PNH is an

acquired disorder that is characterized by anemia caused by intravascular hemolysis and manifested by transient episodes of hemoglobinuria and life-threatening venous thromboses.<sup>12</sup> A deficiency of CD59, an erythrocyte surface antigen that inhibits reactive lysis, is largely responsible for the hemolysis.<sup>13</sup> Approximately 10% to 30% of patients with aplastic anemia develop PNH later in the clinical course.<sup>14</sup> It is possible that the majority of patients with PNH have an underlying aplastic process.<sup>15</sup> The diagnosis of PNH is currently made by demonstrating decreased expression of the cell surface antigen CD59 by flow cytometry, replacing previously used screening tests such as the sucrose hemolysis test and examination of the urine for hemosiderin.<sup>16</sup>

**Myelodysplastic syndromes.** The MDSs are a group of clonal hematopoietic stem cell disorders that are characterized by abnormal bone marrow differentiation and maturation, which leads to bone marrow failure with peripheral cytopenias, dysfunctional blood elements, and probability of leukemic conversion. The bone marrow in MDS is typically hypercellular or normocellular, although hypocellularity may also be detected. It is important to distinguish hypocellular MDS from aplastic anemia because the diagnosis dictates clinical management and prognosis. A critical feature that identifies hypocellular MDS is an associated clonal cytogenetic abnormality (such as deletions in chromosome arms 5q and 7q).<sup>17</sup>

**Idiopathic myelofibrosis.** The two major features of idiopathic myelofibrosis are extramedullary hematopoiesis (in spleen, liver, and other organs) and bone marrow fibrosis. The extramedullary hematopoiesis causes hepatosplenomegaly in the majority of patients. Bone marrow biopsy specimens show varying degrees of reticulin or collagen fibrosis, with prominent megakaryocytes.

**Aleukemic leukemia.** Aleukemic leukemia, a rare condition characterized by the absence of blast cells in the peripheral blood of patients with leukemia, occurs in fewer than 10% of all leukemic patients and is generally seen in very young children or in elderly patients. Bone marrow aspirate and biopsy demonstrate the blast cells.

**Pure red cell aplasia.** This rare disorder that involves only erythrocyte production is characterized by severe anemia, a reticulocyte count of less than 1%, and a normocellular bone marrow containing less than 0.5% mature erythroblasts.

**Agranulocytosis.** Agranulocytosis is an immune disorder that affects the production of blood granulocytes but not that of platelets or erythrocytes.

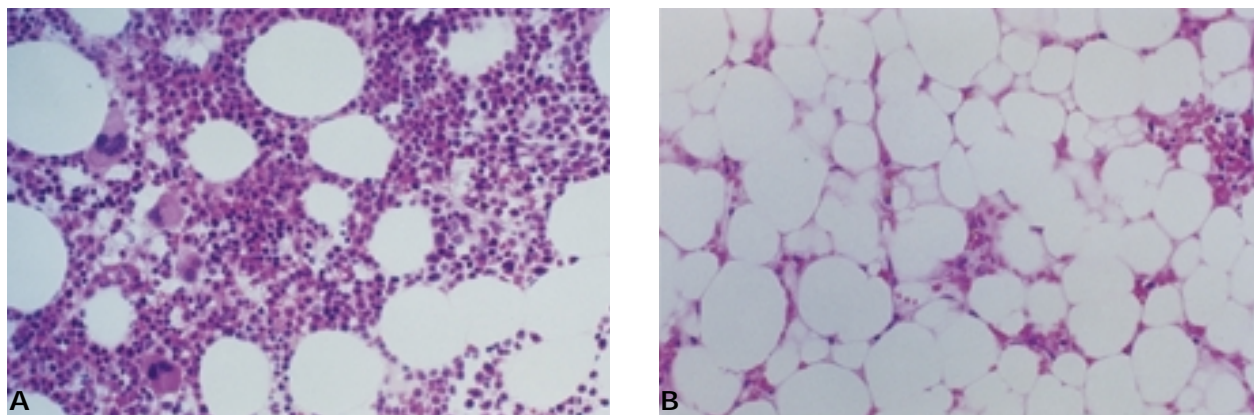


Figure 1. Bone marrow biopsy specimens from A) a healthy patient and B) a patient with aplastic anemia.

### Diagnostic Evaluation

The hallmark of aplastic anemia is pancytopenia and a hypocellular bone marrow.<sup>2</sup> A complete blood count is the initial diagnostic study, and this study reveals varying degrees of anemia, thrombocytopenia, and leukopenia. Because of the hypoproliferative marrow, the reticulocyte response is low or absent despite the anemia.

Aplastic anemia is classified as mild, moderate, or severe on the basis of the severity of the pancytopenia. Criteria for classifying aplastic anemia as severe are listed in **Table 2**. The most important prognostic factor is the absolute neutrophil count (ANC). Patients with an ANC less than  $0.5 \times 10^9/L$  have a high risk of developing infection and patients with an ANC less than  $0.2 \times 10^9/L$  have a poor prognosis.

Bone marrow aspiration and biopsy must be performed to rule out other possible causes for pancytopenia, such as MDS or leukemia. In normal bone marrow, 40% to 60% of the marrow space is typically occupied with hematopoietic cells (depending on the age of the person) (**Figure 1A**); by contrast, the bone marrow in patients with aplastic anemia typically contains very few hematopoietic cells and consists primarily of fatty space and stromal cells (**Figure 1B**).

Human leukocyte antigen (HLA) typing should be performed on all patients as soon as the diagnosis of aplastic anemia is entertained. Tests for exposure to viruses, especially cytomegalovirus, should also be performed early because these tests assist in the choice of blood products for transfusion.

**Table 3** lists the relevant diagnostic studies that must be undertaken in patients with aplastic anemia.

### TREATMENT

#### Treatment Considerations and Supportive Care

The severity of aplastic anemia and the age of the pa-

tient are, in general, the two major considerations that guide treatment.<sup>18</sup> As an initial treatment strategy, all unnecessary medications that could be suppressing bone marrow function should be discontinued. Occasionally, patients with mild to moderate aplastic anemia respond to treatment with androgens, which act by stimulating erythropoiesis.<sup>19</sup>

Some patients with aplastic anemia may have decreased production of cytokines that are required in hematopoiesis. Administration of hematopoietic growth factors (such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) as the sole treatment for aplastic anemia, however, has not been very successful.<sup>18</sup> Growth factor administration as an adjunct to immunosuppressive treatment or after bone marrow transplantation has been useful in decreasing periods of absolute neutropenia.

While diagnostic testing for aplastic anemia is being undertaken and treatment options are being contemplated, patients may require transfusions of blood products. It is important that patients, particularly potential candidates for bone marrow transplantation, receive as few blood products as possible in order to decrease the risk of sensitization. Also, blood donations from a family member should be avoided during this time period. Younger patients may tolerate hemoglobin levels of 7 to 8 g/dL; older patients or patients with a history of coronary artery disease may require hemoglobin levels to be maintained at more than 8 g/dL. Platelet transfusions should be given when the patient has an active bleeding episode or when the platelet count is severely depressed (less than  $10 \times 10^9/L$ ). Blood transfusion guidelines for patients with aplastic anemia are presented in **Table 4**.

Precautions for neutropenia should be followed in patients with aplastic anemia. These patients should

**Table 3.** Diagnostic Studies and Additional Laboratory Tests for Aplastic Anemia

**Diagnostic studies**

- Complete blood count with differential
- Platelet count
- Reticulocyte count
- Bone marrow aspirate and biopsy (cytogenetic analysis and flow cytometry studies)

**Additional laboratory tests**

- Human leukocyte antigen typing
- Viral titers
  - Cytomegalovirus
  - Hepatitis A, B, and C viruses
  - Herpes simplex virus 1 and 2
  - Human immunodeficiency virus
  - Human parvovirus B19 viral antibody titers
- Flow cytometric evaluation of CD59

**Table 4.** Blood Transfusion Guidelines for Patients with Aplastic Anemia

- Transfuse irradiated, leukocyte-filtered blood products
- Transfuse cytomegalovirus-negative blood products to all patients until cytomegalovirus antibody titers are available
- For cytomegalovirus-negative patients, administer cytomegalovirus-negative units only
- Transfuse packed erythrocytes for severe or symptomatic anemia
- Transfuse single-donor platelets if the platelet count is  $< 10 \times 10^9/L$  or for active bleeding

avoid fresh fruits and vegetables, focus on careful mouth and dental care, wash hands frequently and thoroughly, minimize invasive procedures, and use a stool softener. In patients with febrile neutropenia, a broad-spectrum antibiotic should be administered after cultures have been obtained from blood, urine, and any anatomic location in which infection is suspected.

In patients with severe aplastic anemia, supportive care alone carries a poor prognosis. Hematologic recovery occurs in only 20% of patients, and approximately 50% of patients die within 6 months of diagnosis from complications such as bleeding or infections.<sup>20</sup>

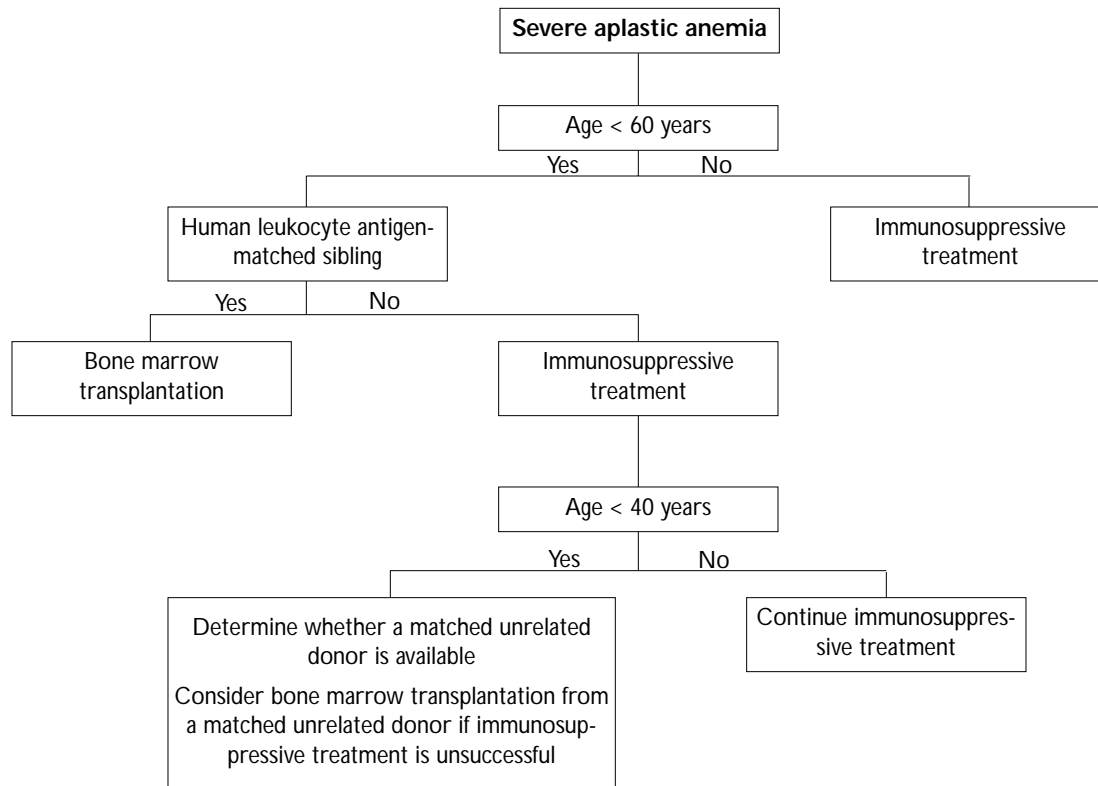
**Bone Marrow Transplantation**

Bone marrow transplantation (BMT) from an HLA-matched sibling is the treatment of choice for severe aplastic anemia in patients age 60 years or younger (**Figure 2**). HLA typing of the patient and any potential sibling donor(s) should be performed as soon as BMT has been identified as a treatment option. Survival rates of 70% to 90% after BMT have been reported in a number of studies, with higher survival rates in patients younger than 40 years who receive HLA-identical BMT.<sup>2</sup> The benefit of concomitant immunosuppressive treatment was reported for a series of 40 patients with severe aplastic anemia who received a BMT from their genetically identical twins between 1964 and 1992.<sup>21</sup> Patients who received initial treatment with immunosuppressive agents (such as cyclo-

phosphamide or total body irradiation) had improved rates of hematologic recovery (12 of 17), compared with patients who received genetically identical marrow without preceding immunosuppressive treatment (seven of 23). Of the latter group, 13 of 15 patients who received two to five additional transplants after immunosuppressive treatment subsequently recovered their marrow function.<sup>21</sup> Thus, clinical findings from patients receiving genetically identical BMT show that aplasia can result not only from a stem cell defect but also from immunologically mediated suppression of marrow function.

Despite the excellent survival after HLA-matched allogeneic BMT, the procedure carries potential risks. To prevent GVHD, treatment regimens include high-dose cyclophosphamide with or without antithymocyte globulin (ATG), which leads to prolonged periods of immunosuppression and places the patient at high risk for opportunistic infections. Other potential problems are graft failure, in which the donor bone marrow either fails to “take” (primary graft failure), or graft loss, in which the graft is rejected weeks or even months after the BMT (delayed graft failure).<sup>1</sup> The risk of graft failure increases with the number of blood transfusions before BMT. Intensive immunosuppressive therapy must be administered to prevent primary and delayed graft failure.

Increasingly, matched unrelated donor (MUD) transplants have been performed in patients younger than age 40 years who do not have a matching sibling donor, and response rates of 25% to 35% have been obtained. MUD transplants for patients with aplastic anemia carry a high risk of GVHD or graft rejection, which can result in early death of the patient. In patients who are younger than age 40 years and who lack an HLA-identical related donor, immunosuppressive treatment should be started without awaiting the



**Figure 2.** Treatment guidelines for patients with severe aplastic anemia.

result from a search for an unrelated donor because this process typically takes approximately 6 months.

**Immunosuppressive Therapy**

The risk of morbidity and mortality after BMT increases with age. Hence, immunosuppressive treatment is considered first-line treatment for older patients and for younger patients for whom a matched sibling donor is not available.

Immunosuppressive therapy, which typically consists of ATG, cyclosporine, and corticosteroids, is aimed at suppressing T-cell subsets that might exert a suppressive effect on bone marrow function. ATG, which is prepared from horse serum, can lead to allergic reactions or serum sickness, with patients developing fever, arthralgia, and skin rash.<sup>22</sup> Steroid treatment can reduce or eliminate many of these symptoms. Cyclosporine inhibits interleukin-2 (IL-2) production by T cells and also inhibits proliferation of T cells in response to IL-2.<sup>19</sup> Patients treated with cyclosporine require close monitoring because the drug may cause renal dysfunction or hypertension and also leads to interactions with other drugs.

Intense immunosuppression with simultaneous ad-

ministration of ATG and cyclosporine has resulted in hematologic recovery in 70% to 80% of patients.<sup>22,23</sup> In a series of 51 patients, 67% of patients showed a response to treatment within 3 months, and this number increased to 78% by 1 year.<sup>22</sup> A patient was considered a responder if the patient's peripheral blood count no longer met the criteria for severe disease. In a series of 227 patients with severe aplastic anemia who were treated with immunosuppressive therapy at a single center over a period of 23 years (1978 to 1991), 78 patients (34%) achieved a complete or partial response, 23 patients (10%) had a minimal response, 122 patients (54%) did not respond, and four patients (2%) were not evaluable. Of the 122 nonresponders, 29 died within 3 months of the start of treatment.<sup>24</sup>

**PROGNOSIS**

Before the advent of BMT and intensive immunosuppressive therapy, the prognosis for patients with severe aplastic anemia was dismal—more than 25% of patients died within 4 months of diagnosis and 50% died within 1 year.<sup>19</sup> In previously untransfused patients, BMT has a cure rate of 75% to 85%; in patients who receive multiple transfusions before BMT, the cure

rates are 55% to 65%.<sup>19</sup> However, 20% to 30% of all patients undergoing BMT may suffer from severe GVHD. Approximately 15% of patients suffer a relapse of aplastic anemia. Older immunosuppressive regimens led to a significant improvement in blood counts in 50% of patients,<sup>19</sup> but with the recent intensive regimens, response rates as high as 78% by 1 year have been reported.<sup>22</sup> Although 36% of the patients responding to intense immunosuppressive treatment had a risk of relapse at 2 years, most of these patients responded to additional courses of immunosuppression.<sup>22</sup> As many as 40% of patients who initially respond to immunosuppressive agents progress over a 10-year period to PNH, acute myeloid leukemia, or MDS because of the underlying stem cell disorder.<sup>19</sup>

#### SUMMARY

Severe aplastic anemia is a rare disease, but this disease must be included in the differential diagnosis of patients presenting with pancytopenia. With prompt diagnostic evaluation and appropriate initial supportive care, the majority of patients respond to aggressive treatment with immunosuppressive agents or to BMT. HP

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