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Aplastic Anemia in Adolescents and Young Adults

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Abstract

Adolescent and young adult patient presentations of aplastic anemia require a particular perspective on both diagnosis and treatment. This unique age group necessitates a thorough diagnostic evaluation to ensure the etiology, acquired or inherited, is sufficiently determined. The treatment options include human leukocyte antigen-identical sibling hematopoietic cell transplantation or immunosuppressive therapy, and both require attention to the specific medical and social needs of these adolescents and young adults. Longitudinal surveillance throughout life for the development of late complications of the disease and treatment is mandatory.

Keywords

Aplastic anemia; Bone marrow failure; Adolescent; Hematopoietic cell transplant; Immunosuppressive therapy

Introduction

Aplastic anemia (AA) is a diagnosis that can present in any age group. Adolescent and young adult patients (up to the age of 30 years) with severe aplastic anemia (SAA) can have unique presentations of marrow failure in comparison to older adults. As a younger cohort may exhibit different proportions of inherited and acquired conditions, the differential diagnosis is broad and requires a more comprehensive workup. Accurate diagnosis is critical, as etiology and age at diagnosis may dictate therapeutic decisions.

Once alternative diagnoses have been eliminated, appropriate therapy for SAA should be initiated promptly. Although considerable debate continues over the upper age limit at which either hematopoietic cell transplantation (HCT) or immunosuppressive therapy (IST) should be used as the first-line approach for idiopathic SAA, the definitive treatment for a younger patient with a human leukocyte antigen (HLA)-identical sibling is an HCT. The cure rate for this younger cohort now approaches 90%, primarily due to advances in supportive care and standardization of conditioning regimens. In the absence of an HLA-identical sibling, IST is the most common alternative first-line approach to treatment.

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Irrespective of the treatment method, longitudinal surveillance throughout life for development of late complications of marrow failure and its treatment is mandatory in these adolescents and young adults. This review serves to cover the presentation, treatment options and survivorship care in this unique age range.

Pathophysiology

AA can be inherited or acquired. Inherited forms may result from DNA repair defects (Fanconi anemia, FA), abnormal telomere physiology (dyskeratosis congenita, DKC) or abnormalities of ribosomal biogenesis (Shwachman-Diamond syndrome). With rare exceptions, the pathophysiology of acquired AA in adolescents and young adults is not distinct from that of other populations. Acquired forms of AA are believed to be the result of an autoimmune attack directed at hematopoietic progenitor cells. The immune attack is primarily directed by cytotoxic T cells that target hematopoietic stem cells and cause apoptosis leading to hematopoietic failure. It remains unclear which antigens the T cells are targeting.

Presentation and Diagnosis

AA is defined as a clinical syndrome characterized by pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltration or increased reticulin [1] . The clinical presentation is directly linked to the severity of the underlying cytopenias as well as the etiology. In this physically active age group, diagnosis may be delayed as fatigue, infection or bruising can be attributed to other causes. Cardiac reserve in younger patients may also delay appreciation of anemia as the cause of systemic symptoms. It is also possible that young adults suffer delays in diagnosis due to less frequent interactions with the medical system, related to overall good health or to social issues such as lack of insurance or increased geographic mobility.

The considerations applied to any patient with pancytopenia pertain equally to this age group. However, additional considerations may have more weight. For example, particular attention should be paid to history and findings suggestive of an inherited bone marrow failure syndrome (IBMFS). Some patients may have overt manifestations (e.g. short stature, hyperpigmentation, triphalangeal thumbs) that had been overlooked previously whereas the findings in some disorders (e.g. hair graying and reticulate pigmentation in DKC, premature meno-pause in FA) can become more obvious with age. Previous reports have suggested that a significant number of patients present with FA (9%) or DKC (46%) over the age of 16 [2] . With improved testing and a higher index of suspicion, it is becoming evident that these numbers are likely an underestimate. Table 1 reviews the differential diagnosis in this age group. Other etiologies of marrow failure, while in and of themselves infrequent, may also be more common in this age group. Aplasia secondary to anorexia nervosa is a pertinent example.

As in any age group, a thorough history and physical examination are imperative for diagnosis. For adolescents, it may be difficult for the patient to be forthcoming in the presence of parents. It may be easier to get an adequate history of relevant issues such as eating disorders, recreational drug use or an unplanned pregnancy without parents present.

Family history may contribute significantly to the diagnosis of IBMFS (e.g. short stature, abnormal pigmentation, pulmonary failure). Physical examination should include a search for subtle findings associated with IBMFS. The etiology of any surgical scars should be determined with certainty as adolescents and young adults may not know why they have a scar, yet a history of orthopedic, cardiac, renal or gastrointestinal repairs may raise suspicion of an IBMFS. For young adults, we suggest special attention to the items in table 2 .

The diagnostic workup must be thorough. Bone marrow evaluations including an aspirate and a biopsy are obligatory. Traditionally, in older adults conscious sedation is not necessary for the procedure but should be considered (as it is in pediatrics) in this age group. Once diagnosed with marrow hypocellularity, table 3 reviews how to classify AA severity [3] . The natural history of SAA is continued progression of the cytopenias, with minimal chance of spontaneous remission. Clinical outcomes do correlate with severity at presentation – with a worse prognosis for very SAA [4] . Moderate AA may spontaneously remit and may not require treatment [5] .

It is important to realize that cytogenetic studies, including fluorescence in situ hybridization for common abnormalities, are an essential component of testing for any patient with SAA regardless of age. Myelodysplasia (MDS) can occur in younger as well as older patients. As hypocellular MDS can be exceedingly difficult to differentiate from SAA, chromosomal studies may be critical to diagnosing MDS. Clinical paroxysmal nocturnal hemoglobinuria (PNH, e.g. accompanied by hemolysis) is less frequent in younger patients but not unknown. Moreover, evidence of a PNH clone may suggest both acquired AA and greater responsiveness to IST [6] . While not every patient requires an extensive laboratory evaluation for IBMFS, chromosomal breakage studies are almost always warranted to exclude FA as FA patients may present without any obvious physical manifestations of the disease. Given that they would be unlikely to respond to IST, can respond to androgens and would require a reduced intensity conditioning regimen for HCT, making this diagnosis is critical [7] . Likewise, in a patient with a family history (pulmonary fibrosis, early graying, liver disease) or physical findings (nail dystrophy, mucosal leukoplakia) suggestive of DKC, telomere length studies or gene mutation testing should be considered as these patients are also often androgen responsive and extremely sensitive to myeloablative conditioning regimens [8] . The ramifications of making an IBMFS diagnosis extend beyond the patient to the family – from ascertaining appropriate HCT donors to providing genetic counseling.

Treatment

Hematopoietic Cell Transplantation

Adolescents and young adults (age of <30 years) with SAA who have an HLA-matched sibling donor should proceed directly to HCT as this is potentially curative (fig. 1). Results of HCT for SAA have improved over the last few decades, particularly in regard to use of donors other than matched family members. A report from the European Group for Blood and Marrow Transplantation (EBMT) of over 1,500 patients transplanted from 1991 to 2002 confirmed that predictors of survival following HCT included matched sibling donor, recipient age of less than 16 years, early HCT (time from diagnosis to HCT of less than 83 days) and a nonradiation conditioning regimen [9] . An advantage of HCT over standard IST

is a marked reduction in the risk of relapse and abrogation of the risk for late clonal disorders such as MDS and PNH. The risks of acute and chronic graft-versus-host disease (GVHD) remain a challenge after HCT. The EBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR) reviewed outcomes in nearly 700 patients with SAA receiving transplants from HLA-matched siblings. Their results showed that day-100 probabilities of acute grade 2–4 GVHD in younger patients were 10 and 14%, after bone marrow (BM) and peripheral blood progenitor cell (PBPC) HCT, respectively. Chronic GVHD rates were higher after PBPC (27%) than after BM HCT (12%) in patients less than 20 years old [10] .

Graft rejection rates have fallen in past decades, but early and late graft failures with persistent or recurrent pancytopenia may occur. In the context of immunosuppression for GVHD prophylaxis, most patients achieve full donor chimerism after HCT. It is imperative to have detailed and regular conversations with the younger patients, who may be in more fluid and less regimented social settings, to ensure compliance with the full HCT immunosuppressive regimen. Failure to adhere to regular medication dosing may predispose to graft rejection. Patients with the greatest risk of late graft failure are those with a progressive increase in recipient cells (>5%), especially around the time of withdrawal of IST [11] .

Improving HCT outcomes in adolescents and young adults is an area of active research, including choice of donor as well as source of stem cells. As above from the EBMT and CIBMTR, in patients younger than 20 years of age, rates of chronic GVHD (relative risk 2.82; $p = 0.002$) and overall mortality (relative risk 2.04; $p = 0.024$) were higher after transplantation of PBPC grafts than after BM HCT. In younger patients, the 5-year survival was 85% after BM HCT but only 73% after PBPC HCT. These data suggest that BM grafts are preferable in this age group [10] . Further development of alternative donor options is under evaluation. None have moved to first-line therapy as of yet given historically poor survival rates, but there are promising results in haploidentical, [12, 13] unrelated donor, and cord blood HCT [14, 15] . These options are currently considered in the relapsed and refractory settings only.

Frontline IST

Another highly effective therapy for SAA is antithymocyte globulin (ATG) and cyclosporine (CsA) IST. This is generally the first-line therapy for adolescent and young adult SAA patients who lack matched sibling donors [16] . The hematopoietic response rate after ATG/CsA is 60– 70%, and the probability of survival at 5 years ranges from 60 to 85% [9] . However, up to 40% of patients eventually relapse, a significant concern in this age group with long life expectancy. In a recent meta-analysis outcomes study from the EBMT of 2,479 patients with SAA, actuarial survival analyses were performed according to whether the patient's first-line treatment was HCT or IST. At 10 years, the survival was 73% in HCT recipients and 68% in those treated with IST ($p = 0.002$). The rates of secondary malignancy were tenfold higher in the patients who received IST alone (1.2%) compared with those who received HCT (0.1%) [17] .

Other Immunosuppressive Options

Considering the rates of relapse and secondary clonal disease following ATG/CsA, a need for better nontrans-plant approaches persists, perhaps even more so in the young adult patient population. In hopes of decreasing rates of relapse and progression to secondary clonal conditions, additional IST, including mycophenolate, tacrolimus and alemtuzumab, have been added to the ATG/ CsA platform, but no improvement in outcome has been observed [18–20] . While excess relative toxicity has been reported [21] , high-dose cyclophosphamide has been utilized in younger populations with durable complete remissions [22] and may provide an alternative for some adolescent and young adult patients without a matched sibling donor.

Late Effects after Treatment

Clonal outgrowth with secondary hematological malignancies and impaired fertility are among the most profound late effects of IST and HCT, respectively, for adolescents and young adults treated for AA. Patients treated with IST should be told that there is a 1–5% chance of secondary hematological malignancies with clonal evolution to MDS or clinical PNH [17, 23] . Routine monitoring (generally annual) should be performed. Fear of infertility should not be considered a reason to withhold an HCT in a young patient. Both female and male survivors of matched sibling HCT for SAA have demonstrated fertility. The majority with successful reproduction after HCT received nonmyeloablative matched-sibling HCT with ATG/cyclophosphamide [24] . While transient ovarian and testicular dysfunction are common after cyclophosphamide-based HCT preparative regimens for SAA, fertility can return over the longer term [25] . In those who receive myeloablative preparatory regimens, preserved fertility is much less likely [23] . Fertility preservation techniques such as semen, egg or embryo cryopreservation should be attempted where possible and desired. Such attempts must weigh the planned conditioning regimen, the rapidity with which the move to HCT is anticipated and any procedural complications due to risks of infection or bleeding. While they may or may not be at an age where this is a current concern, fertility issues should be discussed at length as limited options could later have significant social consequences. Monitoring for fertility after transplantation can be done as part of a survivorship program in consultation with reproductive endocrinologists.

Finally bone health and overall endocrine function must also be monitored over the long term [26] . After IST or HCT, hip or other persistent joint pain should prompt imaging to evaluate for avascular necrosis and appropriate orthopedic or physical therapy referral. Monitoring for osteopenia may be appropriate if steroid use and/or inactivity have been prolonged or if there is endocrine dysfunction. Serial thyroid monitoring should be implemented because as many as 10% of patients may have hypothyroidism after HCT.

Plans for long-term monitoring should also reflect other regimen-related toxicities. Rates of both melanoma and nonmelanoma skin cancer are increased after IST and HCT. Renal dysfunction and hypertension have also emerged as treatment-related issues. Evaluation for metabolic syndrome, which can be considered as a late treatment effect, is often not part of routine medical screening in this age group and may be missed. To this end, additional guidance from the National Comprehensive Cancer Network guidelines for adolescent and

young adult oncology patient long-term follow-up after HCT can be reviewed and applied to the AA survivor population.

Supportive Care

Vascular Access

Placement of a central venous catheter should be strongly considered for all patients with AA, given the frequency of phlebotomy, transfusions and administration of therapeutic medications. Adolescents and young adults may need coaxing to agree to this as it is an obvious manifestation of illness that may be socially undesirable to them. The specific type of catheter (peripherally inserted central catheter, central insertion or subcutaneously located port) should be selected after discussion with the patient to ensure they will respect its physical limitations and maintain the device's care. While peripherally inserted central catheters may limit arm mobility and be more obvious, their weekly flush schedule could be an advantage to a young adult who does not want to come to the clinic more frequently or is unwilling to flush a catheter daily at home.

Blood Transfusions

Patients with severe cytopenias require frequent and sometimes urgent support with blood products. Blood products should be irradiated to prevent transfusion-associated GVHD [27] and leukofiltered to reduce the incidence of viral infections and prevent alloimmunization [28] . Parents and other family members often offer to be the source of transfusions, but this should be avoided to decrease sensitization to potential HCT donors. The initial goal of transfusion therapy for anemia should be to correct or avoid cardiopulmonary complications. Most adolescent and young adult patients without significant comorbidities should be transfused with packed red blood cells when symptomatic. A restrictive transfusion policy may be judiciously applied as long as a hemoglobin ≥ 6 g/dl is maintained. The goal of platelet transfusion is to maintain a high enough platelet count to prevent spontaneous bleeding. For most patients, platelet transfusions are indicated when platelet levels are below 10,000/μl or if the patient is experiencing bleeding. The young patient who feels well enough to continue day-to-day activities should be cautioned that there is an increased risk for bleeding with activities such as contact sports. Granulocyte transfusions remain controversial in SAA and should be used judiciously. Granulocyte transfusions may have an adjunctive role in patients with SAA and severe infections such as invasive bacterial and fungal infections unresponsive to maximal antibiotic and/or antifungal therapy [29] .

Growth Factors

Hematopoietic growth factors (HGFs) may provide clinical benefit in some circumstances but do not induce disease remissions. The use of HGFs to support blood counts is of limited value in SAA, as predicted by both in vitro studies and the markedly elevated endogenous serum levels of HGFs. There may be a limited role for granulocyte colony-stimulating factor administration in an attempt to stimulate a neutrophil response to a severe infection, although there have been no prospective randomized studies in SAA that show a survival benefit with granulocyte colony-stimulating factor [30, 31] . These data suggest that granulocyte colony-stimulating factor support with IST might be used for patients with SAA

as it may enhance neutrophil recovery, but it must be recognized that it does not modify the overall response and survival [32] . There are also some data suggesting that HGFs may be linked to earlier presentations of MDS or leukemia [33] .

Infections

Fungal and bacterial infections are a major cause of death in patients with SAA. Data from children suggest that mortality from fungal infections is higher in patients with SAA than in patients with acute myelogenous or lymphoblastic leukemia [34] . However, an active fungal infection should not delay a more definitive therapy such as IST or HCT [35] . It has been recognized that there may be a possible role for tobacco and/or marijuana smoking in increased risk for aspergillus exposure and infection [36] . Thus, young patients should be discouraged from these activities, especially in the setting of SAA.

There is no standardized approach to antibiotic therapy in AA at any age group. Vigilance and proactive prescription of prophylactic antibiotics (when deemed clinically appropriate), antivirals and antifungals in this patient population is imperative [37] . Where possible, it is prudent to avoid agents associated with high rates of marrow suppression, but therapy should be directed as dictated by the requirements of supportive care or as indicated by positive cultures. IST may render patients susceptible to viral infections, particularly community-acquired respiratory viruses and members of the Herpes-viridae family. There is also an association between the viral hepatitides and SAA, such that patients may have ongoing or resolving hepatitis at the time of diagnosis.

Iron Overload

Iron overload may result from prolonged red blood cell transfusion support which is a reason to target lower hemoglobin levels in this population if tolerated. If ignored, iron overload can potentially produce irreversible organ damage, in particular to the liver and heart but also to endocrine organs, which may be of particular importance in younger patients. Chelation schedules vary significantly, but most often chelation therapy with deferoxamine is instituted if the patient's serum ferritin level is greater than 1,000–2,000 μg/l [16] . Data on alternative chelating agents in SAA is increasingly available [38, 39] .

Menstrual Suppression/Pregnancy/Contraceptive Options

This is an area of importance in this age group, who may have irregular cycles (postmenarchal) or are premenarchal. Menstrual bleeding can be a source of significant blood loss, especially with profound thrombocytopenia and can be difficult to stop. Increased platelet transfusion goals to greater than 30,000 may be required until bleeding ceases. The method of menstrual suppression with the greatest likelihood of inducing amenorrhea should be chosen to protect against blood loss as well as possible gonadal and fertility protection. The most frequently reported method in females in HCT is a gonadotropin-releasing hormone agonist such as leuprolide. Given the bleeding and potential infection concerns of injection in neutropenic, thrombocytopenic patients, hormonal contraceptive pills are a reasonable alternative. This can be difficult to discuss with adolescents if parents are present, particularly as family members may be unaware or

unrealistic about the current sexual activities or the fertility goals of the patient. Patients should be strongly discouraged from conception during this time period.

Rarely, AA can develop in pregnancy. Spontaneous remission can occur in 25–30% of patients, often upon birth or termination of the pregnancy. If termination is either not desired or medically appropriate, patients can be followed with stringent supportive care. CsA may be a safe drug antenatally in such patients. Complications appear to be more likely in pregnant patients with low platelet counts and associated PNH [40] .

Social Issues and Survivorship

Patients in this age category have unique health issues and health care insurance coverage requirements. Efforts to address these issues are critical to assure support for a smooth transition into adulthood with a disease such as AA. There is an unfortunate lack of social, financial and standardized health care delivery to young adults. Individuals aged 19–29 are the group most likely to be uninsured in the USA. The same concerns extend to their social milieu. They may be living in communal settings, such as dormitories or military barracks, which make adherence to medical requirements very difficult. They may also be alone with minimal social support and nascent careers, making it difficult for them to care for themselves in times of increased medical need. As their peer cohort is equivalently likely to have less command of resources, including workplace flexibility, their peer community may be particularly limited in its ability for support and practical assistance.

At diagnosis, careful consideration should be given to topics that may be ambiguous yet critical for individuals of this age with significant illness. Such issues range from autonomy, support structure, information sharing, alternative decision makers (for advanced directives, for example) to the primary holder of insurance coverage. As AA is a rare disease, a detailed discussion at the time of diagnosis surrounding the nature of the disease, treatment, prognostic and social impact is imperative for the patients as well as their families. The treating doctor should provide a comprehensive explanation regarding all possible situations that may occur during the treatment, with emphasis on the chronic nature and the potentially slow response of the disease. Younger patients may have life plans, such as secondary education or employment endeavors, that make being tolerant with the pace of recovery challenging. As cytopenias will persist in a significant proportion of patients, it is useful to address quality of life with treatment as well as the goal of curing the disease. For young individuals, just starting life out on their own, overt discussion of guidelines for maintaining their social life are helpful – especially in patients with persistent neutropenia. The goal is to avoid excessive limitations on acceptable social outlets. Similarly, direct discussions about sexual function in relation to cytopenias and their treatment are essential. A life, as normal as possible, in most patients is a vital adjunct for psychological health. As the diagnosis of AA is a life-changing experience, some patients, especially in this age group, may want to consider professional psychological support. As their physicians, we should be proactive in destigmatizing this need and make referrals early. For some individuals, it may be helpful to contact other patients through marrow failure organizations. Details of patient support groups should be provided and encouraged.

Transition to Adult Care Providers

When a diagnosis of this magnitude is made in adolescence and even in young adults, the parents and other family members may be involved in treatment discussions. Once the treatments have been provided and outcomes completed, a longitudinal follow-up with adult providers is important. With adolescents, it is important to address why they may not want to leave their current pediatric provider, and review why medically this will be of benefit to them [41, 42] . Even after HCT when cure may be assumed, the patient will benefit from long-term follow-up with appropriate physicians, either in a defined survivorship program or with adult hematologists to follow for late effects and potential relapse. Survivor-ship clinics after HCT are often available at larger institutions.

Conclusions

Adolescent and young adult patients diagnosed with AA are a unique patient population that requires added attention to both diagnosis and treatment. The treatment of choice remains an HLA-identical sibling HCT if available. IST is an option in those patients who do not have an HLA-identical sibling. Regardless of the treatment method in these adolescents and young adults, long-term follow-up for the development of late complications of the disease and treatment is mandatory.

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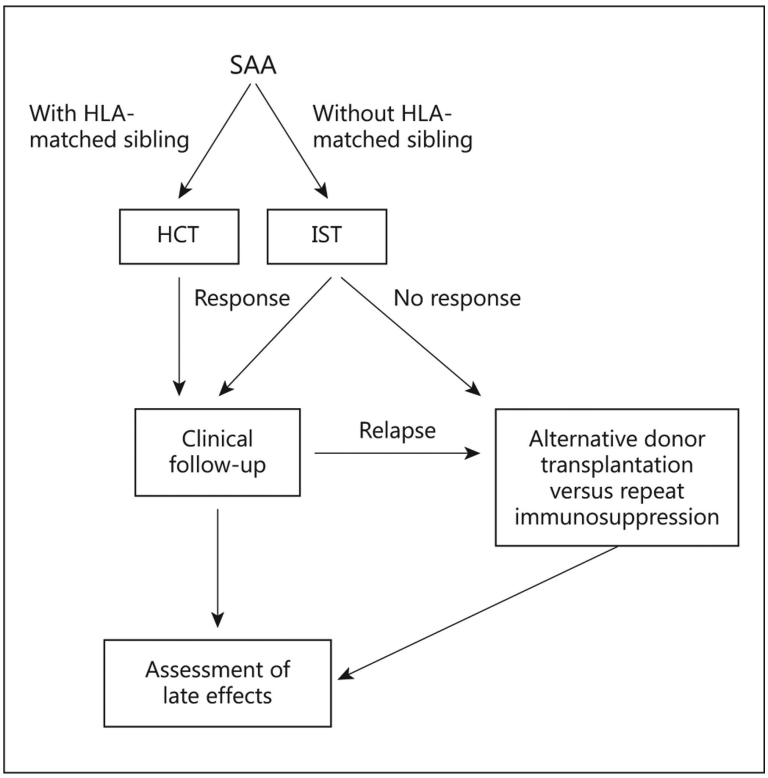

Fig. 1.
Treatment schema for SAA.

Table 1

Differential diagnosis of pancytopenia in young adults

	Diagnosis
Infection	Epstein-Barr virus, cytomegalovirus, human herpesvirus 6 Hepatitis B, C Human immunodeficiency virus Parvovirus
Environmental exposures	Recreational drugs Prescription drugs Toxic exposures
Clonal disorders	Leukemia Paroxysmal nocturnal hemoglobinuria Histiocytic disorders
Bone marrow failure syndromes	DKC FA Shwachman-Diamond syndrome Diamond-Blackfan anemia
Other	Pregnancy

Table 2

Initial evaluation of adolescents and young adults presenting with cytopenias

Patient history	Duration of cytopenias (are pediatric records available?)
	Medications (prescribed and over-the-counter supplements)
	Immunization records
	Exposures
	Transfusions
Family history	Constitutional abnormalities
	Malignancies
Physical examination	Height (in context of mean parental height)
	Limb abnormalities
	Skin and nail abnormalities (café-au-lait spots, nail dystrophy, pale patches)
Laboratory	Peripheral blood
	β-Human chorionic gonadotropin (consider even if intercourse is not explicitly stated)
	Complete blood count with differential
	Reticulocyte counts
	Chemistries
	Transaminases and bilirubin
	Hepatitis serologies
	Fluorescent aerolysin assay for paroxysmal nocturnal hemoglobinuria
	Chromosome breakage tests
	Telomere length and mutational analysis (if DKC suspected)
	Bone marrow
	Aspirate and biopsy
	Flow cytometry (including quantitative CD34)
	Cytogenetics

Table 3

Diagnostic criteria for the classification of AA

Peripheral blood cytopenias	Nonsevere (moderate) AA (not meeting criteria for severe disease)	SAA (any 2 of 3)	Very SAA (meeting criteria for severe disease and absolute neutrophils <200)
Bone marrow cellularity	<25%	<25%	<25%
Absolute neutrophil count		<500/μl	<200/μl
Platelet count		<20,000/μl	
Reticulocyte count		<1.0% corrected or <60,000/μl	