REVIEW

# Hematopoietic Stem Cell Transplantation for Bone Marrow Failure Syndromes in Children

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Bone marrow failure (BMF) syndromes include a broad group of diseases of varying etiologies, in which hematopoeisis is abnormal or completely arrested in one or more cell lines. BMF can be an acquired aplastic anemia (AA) or can be congenital, as part of such syndromes as Fanconi anemia (FA), Diamond Blackfan anemia, and Schwachman Diamond syndrome (SDS). In this review, we first address the evolution and current status of bone marrow transplantation (BMT) in the pediatric population in the most common form of BMF, acquired AA. We then discuss pediatric BMT in some of the more common inherited BMF syndromes, with emphasis on FA, in which experience is greatest. It is important to consider the possibility of a congenital etiology in every child (and adult) with marrow failure, because identification of an associated syndrome provides insight into the likely natural history of the disease, as well as prognosis, treatment options for the patient and family, and long-term sequelae both of the disease itself and its treatment.

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## INTRODUCTION

Bone marrow failure (BMF) syndromes include a broad group of diseases of varying etiologies in which hematopoeisis is abnormal or completely arrested in one or more cell lines. BMF can be an acquired aplastic anemia (AA) or can be congenital, as part of such syndromes as Fanconi anemia (FA), Diamond Blackfan anemia (DBA), and Schwachman Diamond syndrome (SDS). The estimated incidence of BMF is 2 per million in Europe, with higher rates in Asia, perhaps resulting from environmental factors [1]. Acquired AA may occur at any age, and is a serious disease, with a mortality rate of up to 80% reported in 1979, when the only treatment option was supportive care alone [2].

The first successful bone marrow transplantations (BMTs) were performed in children with severe combined immunodeficiency in 1968; soon thereafter came attempts at BMT in patients with AA [3]. In this review, we first address the evolution and current status of BMT in the pediatric population in the most common form of BMF, acquired AA. We then discuss pediatric BMT in some of the more common inherited BMF syndromes, with emphasis on FA, in which experience is greatest. It is important to consider the possibility of a congenital etiology in every child (and adult) with marrow failure, because identification of an associated syndrome provides insight into the likely natural history of the disease, as well as prognosis, treatment options for the patient and family, and long-term sequelae both of the disease itself and its treatment.

## ACQUIRED APLASTIC ANEMIA: SUPPORTIVE CARE AND IMMUNOSUPPRESSION

Initial management of children with marrow failure often requires transfusion for anemia or thrombocytopenia. Granulocyte colony-stimulating factor (G-CSF) may be used to induce a temporary rise in neutrophil counts [4]. These supportive measures do not change the natural history of the disease, however. Acquired severe AA (SAA) is thought to result from immune-mediated destruction of hematopoietic cells, as a result of aberrant immune activation related to genetic risk factors and environmental exposures, such as to infections or drugs [5]. Patients with AA are classified based on the severity of marrow aplasia, with a progressively worse prognosis associated with increasing severity [6]. AA is classified as severe (SAA) when BM cellularity is $< 25\%$ or between 25 and 50% with $< 30\%$ hematopoietic elements and $< 500/mm^3$ granulocytes, $< 20{,}000/mm^3$ platelets, and/or $< 200/mm^3$ reticulocytes.

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Immunosuppressive therapy (IST) with such agents as cyclosporin (CsA) and antithymocyte globulin (ATG) can be effective for children with SAA who do not have a matched sibling donor. Response rates to IST in children are favorable, with survival ranging from 68% in one institution [7] to 80% in another retrospective study at 10 years, with 89% survival if the analysis is confined to responders to IST [8]. There are some concerns regarding immunosuppression, however. Responses often are slow and incomplete, and recurrence is common, with only 40% of patients remaining disease-free at 10 years in one study [9], leading to the need for long-term IST (often for 2 to 3 years), with its associated side effects. In addition, there are data demonstrating the risk for malignant evolution over time with IST therapy, with rates of myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML) ranging from 8% to 25% [10-12].

## ACQUIRED APLASTIC ANEMIA AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

### Matched Sibling Stem Cell Transplantation

The prognosis for children with SAA has improved significantly in recent years. Initial management of a child with SAA who has an HLA-matched related donor generally involves hematopoietic stem cell transplantation (HSCT) [2,13]. Initial attempts at HSCT for SAA began in the early 1970s, using cyclophosphamide (Cy)-based preparative regimens with the goal of maximizing immune suppression with limited myeloablation. Initially, graft rejection occurred in up to 30% to 60% of patients, limiting success [14,15]. High rates of graft rejection were largely from sensitization to donor antigens by multiple previous blood transfusions, because patients were commonly referred for transplantation late in the course of disease [16-18]. Early transplantations also were limited by the use of lower marrow cell doses, which has been associated with increased risk for graft failure [19]. Perhaps as a consequence of these challenges to robust engraftment, 54% of recipients demonstrated mixed donor and host chimerism, putting them at risk for late graft rejection [20].

The most frequently used preparative regimen for pediatric patients with SAA undergoing matched related HSCT is Cy 200 mg/kg, with or without ATG. There remains some debate regarding the role of ATG in sibling donor HSCT for SAA, however. Champlin et al. [21], in a prospective randomized trial of 341 children and adults, found no statistical differences in survival, graft failure, or graft-versus-host disease (GVHD) between patients with SAA undergoing matched related HSCT receiving Cy alone and those whose regimen also included ATG. Irradiation generally does not play a role in preparative regimens for matched related HSCT in SAA. Radiation-based preparative regimes do reduce rejection, but also increase the risk of acute GVHD (aGVHD), interstitial pneumonitis, and malignancy [18]. Current survival rates have improved such that children are now referred for transplantation after minimal exposure to blood products, which has greatly improved (although not completely solved) the problem of graft rejection [22-24]. Children with SAA remain at increased risk for late graft rejection, and immunosuppressive agents used for GVHD prophylaxis posttransplantation should be weaned with great caution.

Adequate control of GVHD is essential for a successful outcome of HSCT for SAA. In a study of patients with SAA undergoing matched sibling donor HSCT, Locatelli et al. [25] reported survival of 98% in recipients with grade 0-I GVHD, compared with 70% in recipients with grade II-IV aGVHD ($P = < .005$). In agreement with these findings, Locatelli et al. [25] also reported a survival advantage for the use of CsA and methotrexate (MTX) compared with MTX alone as GVHD prophylaxis, a finding generally supported by others [20,21].

Pediatric survival rates after matched sibling HSCT for SAA are now excellent, 85% and even higher in some series [9,18,22,23]. Survival is best in the youngest children; a European Group for Blood and Marrow Transplantation (EBMT) study reported 89% survival in children under the age of 10 years. The important impact of age on outcome is clearly shown in Figure 1. Similarly, in a single-institution US study, Kahl et al. [24] reported survival of 88% in a cohort of 81 adults and children with SAA undergoing matched sibling donor HSCT with a preparative regimen of Cy and ATG. An EBMT study of adults and children comparing transplantation and IST for SAA, including recipients of related and unrelated donor stem cells, showed an association between improved survival and younger age, transplantation performed after 1996, a matched sibling donor, a short diagnosis-to-transplantation interval, and no irradiation in the preparative regimen [22].

### Stem Cell Sources: BM and Peripheral Blood Stem Cells (PBSCs)

Recent years have seen an increase in the use of PBSC grafts for allogeneic transplantations. Most studies report faster hematopoietic recovery with the use of PBSCs [26-29]; however, most adult studies also report an increase in chronic GVHD (cGVHD) [28-31]. Some adult studies describe improved survival with PBSCs in adult recipients with high-risk malignancy, although survival generally was no different in those with standard-risk disease [27-29,32]. Pediatric reports of PBSC transplantations also describe rapid