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Evolving Hematopoietic Stem Cell Transplantation Strategies in Severe Aplastic Anemia

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Abstract

Purpose of Review—Significant improvements in unrelated donor hematopoietic stem cell transplantation (HSCT) in recent years has solidified its therapeutic role in severe aplastic anemia (SAA) and led to evolution of treatment algorithms, particularly for children.

Recent Findings—Advances in understanding genetics of inherited bone marrow failure syndromes (IBMFS) have allowed more confidence in accurately diagnosing SAA and avoiding treatments that could be dangerous and ineffective in individuals with IBMFS, which can be diagnosed in 10–20% of children presenting with a picture of SAA. Additionally long-term survival after matched sibling donor (MSD) and matched unrelated donor (MUD) HSCT now exceed 90% in children. Late effects after HSCT for SAA are minimal with current strategies and compare favorably to late effects after up-front immunosuppressive therapy (IST), except for patients with chronic graft versus host disease (GVHD).

Summary—1) Careful assessment for signs or symptoms of IBMFS along with genetic screening for these disorders is of major importance. 2) MSD HSCT is already considered standard of care for up-front therapy and some groups are evaluating MUD HSCT as primary therapy. 3) Ongoing studies will continue to challenge treatment algorithms and may lead to an even more expanded role for HSCT in SAA.

Keywords

severe aplastic anemia (SAA); transplantation

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Introduction

Severe aplastic anemia (SAA), a rare multi-lineage bone marrow failure disorder, has an estimated annual incidence of 2 cases per million in the United States (US) and Europe and 4 per million in parts of Asia.[1, 2] There is a biphasic distribution of onset with peaks between 10 to 25 years of age and over 60 years of age.[3] The large majority of SAA diagnoses (over 80%) are termed “acquired” SAA and thought to be caused by autoimmune destruction of hematopoietic stem cells; accordingly the disease can be treated and often cured by immunosuppressive therapy (IST) or marrow replacement through hematopoietic stem cell transplantation (HSCT).[3, 4] HSCT from a human leukocyte antigen (HLA) matched sibling donor (MSD) has become standard initial therapy for younger, newly diagnosed patients [3, 4, 5] with long-term survival up to 95–100% in patients under 20.[6, 7, 8]

IST with horse anti-thymocyte globulin (ATG) and cyclosporine (CSA) is generally recommended for SAA patients who lack a MSD or are not good candidates for HSCT.[3, 9, 10] It takes an average of 3–4 months to see hematologic response with approximately 70–80% of patients having a full or partial response and achieving transfusion independence.[3, 4] However, up to 30% of patients eventually relapse [3, 11] and up to an additional 20% develop secondary clonal hematopoiesis.[3, 10, 12, 13] Patients with relapsed or refractory disease or clonal evolution may be considered for a matched unrelated donor (MUD) HSCT. Improvements in survival after MUD HSCT for SAA have been noted using reduced doses of total body irradiation (TBI),[14] the substitution of some cyclophosphamide dosing with fludarabine,[15, 16] and selection of donors who are fully HLA-matched to patients at the allele level. These approaches have helped lower graft failure, graft versus host disease (GVHD), and mortality, the major early barriers to MUD HSCT success in SAA.[3] Historically, umbilical cord blood (UCB) HSCT in SAA has led to poor outcomes.[17, 18] Haploidentical HSCT in SAA has only more recently been attempted and accordingly there are limited published data regarding outcomes with this approach.[19*, 20*, 21*] Studies are underway to improve outcomes using alternative donors as some patients will not have an available MSD or MUD and yet still require HSCT for cure. Additionally, in cases where first HSCT results in graft failure, it is important to note good success reported with second HSCT for salvage.[22*, 23*, 24*]

Presentation and Diagnostic Evaluation

Patients present with bruising, bleeding, pallor, infections and/or fatigue; the diagnosis of SAA includes at least 2 of 3 cytopenias defined by 1) neutrophil count $<0.5 \times 10^9/L$, 2) platelet count $<20 \times 10^9/L$, and/or 3) anemia with reticulocyte count $<20 \times 10^9/L$. Very SAA occurs in patients who otherwise meet criteria but also have a neutrophil count $<0.2 \times 10^9/L$. [3, 25] Differential diagnosis for SAA includes conditions such as reversible toxic or infectious exposure, malignancy, myelodysplasia (MDS), and genetic syndromes. Bone marrow examination including both aspiration and biopsy must be performed to look for diagnostic hypocellularity $<25\%$ (or 25–50% but with $<30\%$ residual hematopoietic cells) and rule out other conditions such as malignancy with infiltrating cells or MDS with cytogenetics and fluorescent in situ hybridization (FISH) looking at minimum at

chromosomes 5, 7 and 8. Figure 1 outlines a diagnostic algorithm. Given the need for different treatment approaches, it is essential to rule out IBMFS with at minimum screening for Fanconi Anemia and paroxysmal nocturnal hemoglobinuria (PNH). We also suggest screening for Dyskeratosis Congenita and Schwachman Diamond Syndrome. Although some IBMFS present without any phenotypic features, patients with history and exam features listed in Table 1 should be considered for more extensive genetic evaluation with available focused screens (e.g. marrowSeq [26**]) or whole genome sequencing.

Matched Sibling Donor Transplantation: Indications, Results, Stem Cell Source, and Conditioning Regimens

MSD HSCT is the treatment of choice for patients diagnosed with SAA <40 years old. This standard of care has been adopted internationally and is recommended by different national treatment algorithms including one adopted by the United Kingdom Paediatric Blood and Marrow Transplant Group (Figure 2), leading to cure rates above 80% with higher rates (>90%) in pediatric series.[8, 27*, 28**, 29*] IST leads to worse overall outcomes compared to MSD HSCT,[30, 31, 32*] given higher risk of clonal evolution and relapse.[33**, 34*] Additionally, MSD HSCT results are worse after preceding IST.[35, 36]

Older age is a risk factor for worse outcome with MSD HSCT for SAA,[37*] and even among children in one report, survival appears better for patients aged 0–11 years versus 12–18 years;[33**, 34*, 38*) with three year overall survival (OS) of 91% and 86% respectively, and event-free survival (EFS) of 87% and 83% respectively. Another important risk factor for survival is stem cell source, with bone marrow favored over peripheral stem cells due to less GVHD.[39, 40, 41, 42]

MSD HSCT conditioning regimen

The original “Seattle protocol” for SAA included cyclophosphamide 200 mg/kg and ATG.[43] This approach yielded consistently good results with survival up to 95% in younger patients. To reduce the dose of cyclophosphamide and its associated side effects, fludarabine was incorporated by some groups. Using fludarabine 120 mg/m², cyclophosphamide 1200 mg/m² and ATG,[44, 45, 46, 47, 48] patients over age 30 had an OS of 80% versus 60% (p=0.04) for those conditioned with conventional cyclophosphamide dosing,[49] with no primary engraftment failures and acceptable rates of acute and extensive chronic GVHD (10% and 13% respectively). With these excellent results using chemotherapy based regimens, especially in children, there is no current role for the use of TBI in MSD HSCT for pediatric SAA.

Serotherapy in preparative regimens improves outcomes

Very early data reported improved survival with the addition of ATG to cyclophosphamide in the preparative regimen.[43] A retrospective study from the European Society for Blood and Marrow Transplantation (EBMT) with 1886 MSD HSCT between 1999 and 2009 showed that the omission of ATG resulted in significantly lower survival.[42] Alemtuzumab was tested in a retrospective study with 50 pediatric and adult patients [50] showing a low incidence of chronic GVHD (4%), hinting at a significant role of alemtuzumab in GVHD

prevention. A second retrospective study compared outcomes in 155 patients receiving ATG or alemtuzumab during conditioning with no difference between groups in engraftment, time to count recovery, full chimerism achievement and acute GVHD, but less chronic GVHD with alemtuzumab (11 vs 26%, $p=0.031$).[51*]

Matched Unrelated Donor Transplantation: Indications, Results, Stem Cell Source, and Conditioning Regimens

The role of MUD HSCT for SAA is currently being reshaped. Traditionally, MUD HSCT was only indicated for patients failing upfront IST. In the last 20 years, however, results of MUD HSCT have dramatically improved with better HLA matching, supportive care and reduced intensity regimens. On the other hand, long term follow up of SAA patients treated with IST revealed that quality of remission is often suboptimal, with subsets of patients requiring second line IST up to 50% of the time.[34*, 38*] Moreover, experience has shown that clonal evolution is more common after IST (up to 20% of cases).[52] For these reasons, the role of MUD HSCT in the SAA population is being re-evaluated.

The EBMT explored fludarabine based conditioning in this setting without TBI,[48] whereas American and Japanese groups de-escalated the TBI dose to 200–300 cGy, and still achieved survival in the range of 60–65%.[53, 54] More recent results report even better outcomes. In 2015, Dufour and colleagues described 2 years OS for MUD recipients of 96%. More significantly, front-line MUD recipients had better EFS compared to IST recipients (92% vs 40%, $p=0.0001$). In this paper 29 patients undergoing MUD HSCT received a fludarabine, alemtuzumab, and cyclophosphamide conditioning regimen. GVHD was low with 10% acute grade II–IV GVHD and 19% chronic GVHD (all cases limited). One patient experienced graft failure after 1-antigen mismatched transplant and there was one case of transplant related mortality reported. Cumulative incidence of rejection at 2 years was 4%. Moreover, time from diagnosis to neutrophil recovery was superimposable in a recent comparison between MSD and MUD recipients, as well as compared to patients receiving IST, thus ruling out increased risks for severe infections while awaiting count recovery in MUD recipients.[33**]

Bacigalupo et al, presented the outcome of 508 HSCT from MUD in children and adults. Engraftment was 91%, acute GVHD grade III was 10%, and extensive chronic GVHD 11%. OS was 76% at 3 years, with children doing better than adults (HR for improved OS with age <20 was 1.45, 95% CI 1.01–2.10).[28**] These data still show increased GVHD with MUD compared to MSD HSCT, but no difference in OS. Stem cell source and age remain strong predictors of survival in the MUD setting, mirroring the experience of MSD HSCT. Other specific donor factors, like telomere length, have been examined as prognostic factors. Their role is still not completely understood and requires further study.[55**]

MUD HSCT conditioning regimen

A retrospective comparison between conditioning with or without low dose TBI in a fludarabine-cyclophosphamide-ATG regimen was performed.[56] The two groups were different as most patients below age 14 did not receive TBI. OS, EFS and rejection rates

were similar, but there was a higher incidence of chronic GVHD with TBI (50% vs 27%, $p=0.06$). The study suggested that young recipients with well-matched donors may not require low dose TBI, potentially avoiding some long-term complications.

The EBMT SAA working party currently recommends fludarabine 120 mg/m², cyclophosphamide 120 mg/kg and ATG (or alemtuzumab based on some positive experiences with this substitution)[50, 57*, 58*] as a preparative regimen for MUD HSCT. TBI 200 cGy can be added for patients above 14 years of age in case of mismatched grafts and may be considered for younger children if previously sensitized (transfusion refractory), to reduce the risk of graft rejection.[59] A BMT CTN study explored cyclophosphamide dose reduction in the context of fludarabine (120 mg/m²), ATG (9 mg/kg) and 200 cGy TBI. Both 100 and 50 mg/kg cyclophosphamide doses led to good outcomes, but superior early survival was noted in the 50 mg/kg cohort (97.4% at 1-year) with 11.7% graft failure, 23.7% grades II-IV acute GVHD and 22.5% chronic GVHD, suggesting this approach is also reasonable [60*].

Groups from Europe and America are studying the approach of MUD search at diagnosis in SAA patients lacking a MSD. If a suitable MUD is identified and available to donate bone marrow within 3–4 months from diagnosis, upfront MUD transplantation can be considered. If the choice is upfront IST, patients can be reassured that rescue rates with MUD HSCT after failed IST remain good with 74% EFS and OS at 2 years post-transplant.

Mismatched Donor, Cord Blood, and Haploidentical Transplantation

International guidelines suggest SAA patients lacking a matched donor should be considered for alternative donor HSCT after multiple IST failures.[59] Experience with alternative donors is limited, however, studies in Europe and a BMT CTN trial in the US are addressing this need with innovative approaches.

Umbilical cord blood (UCB) HSCT

Small reports from Japanese and European groups show poor outcomes after UCB with 2 year OS of 38–41%.[17, 18] Of note, these data suggest that myeloablative conditioning and lower total nucleated cell dose ($<3.9 \times 10^7$ /kg) are associated with reduced survival.[17] More recent reduced intensity approaches with fludarabine, low dose cyclophosphamide, low dose TBI, and ATG are more encouraging.[18, 61]

Haploidentical HSCT

Transplants from mismatched family donor had been reported in the past by different groups for refractory patients, generally with suboptimal outcomes.[62] Recently both T-cell depleted and T-cell replete haploidentical strategies have been reported for multiply relapsed SAA patients lacking a matched donor.[63*, 64*, 65*] Im and colleagues describe 21 patients who underwent fludarabine, cyclophosphamide, 400 cGy TBI and ATG conditioning followed by either CD3/19 or CD3 α beta/CD19 depleted grafts. OS was reported as 94% at 3 years, without cases of chronic GVHD.[66*] T-replete haploidentical approaches have been taken by Wang (17 children, full intensity conditioning and 4 agent GVHD prophylaxis: OS 71% at 1 year, 20% chronic GVHD)[20*] and Gao (26 adults, RIC

conditioning with 3 agent GVHD prophylaxis: OS 82% at 2 years, GVHD 40%).[21*]
Limited data are available for a reduced intensity approach followed by T-replete haploidentical transplant and post infusion cyclophosphamide GVHD prophylaxis. Overall 24 patients have been reported in 2 different series with OS approaching 70% and low GVHD rates.[19*, 67*]

Mismatched HSCT in SAA is improving, but with published outcomes lagging behind MUD and MSD survival, until studies demonstrate improvements, this approach should be restricted to refractory or multiply relapsed patients.

Late Effects

Previously discussed, up to 20% of patients treated with IST in childhood go on to develop secondary clonal hematopoiesis. A seminal study on occurrence of malignant tumors after treatment of SAA with IST (n=860) or HSCT (n=748) showed 10-year cumulative incidence of 18.8% after IST compared to 3.1% after HSCT. After IST patients primarily develop hematologic malignancy compared to solid tumors after HSCT. In the same study, the risk of solid tumors after HSCT was primarily driven by the use of radiation in the conditioning regimen.[68] Subsequent studies of malignancy after HSCT for SAA have shown rates up to 13%, but in each case driven by high rates of chronic GVHD and use of >400 cGy TBI,[35, 69, 70] which no longer applies to more recent reduced intensity regimens and their excellent outcomes. Many post-HSCT malignancies are skin or thyroid in origin and easily treated,[71] while others are head and neck tumors in the field of radiation exposure in patients with chronic GVHD.[35, 68] The most contemporary studies of late effects after reduced intensity approaches to HSCT for SAA show much lower rates of secondary malignancy down to 2% or less.[72, 73]

Aside from malignancy, additional side effects of IST and HSCT need to be considered. Medications like CSA, used long-term for IST, can lead to renal dysfunction and persistent hypertension in up to 15% of patients, even after discontinuation. Overall very little is reported about other late effects after IST.[74] Late effects after reduced intensity HSCT for SAA show that these regimens are very well tolerated.[71, 72, 73] Table 2 shows most commonly reported late effects including bone and endocrine issues, which are largely driven by steroid exposure in the treatment of chronic GVHD. Most patients, however, will go on to live healthy lives without impact on educational attainment or fertility and only very minimal risk of late complications.[71, 73]

Conclusion

Improved HSCT strategies that have led to excellent survival with low rates of GVHD and low rates of late effects are helping to change the pediatric acquired SAA treatment algorithm. MSD HSCT is standard of care up-front therapy. MUD HSCT is being evaluated for the same purpose. Alternative donor HSCT is being optimized to help capture patients who do not have a MSD or MUD. These evolving strategies may lead to an even more expanded role for HSCT in pediatric acquired SAA.

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None

References

1. Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia. *Haematologica*. 2008; 93(4):489–492. [PubMed: 18379007]
2. Issaragrisil S, Sriratanasatavorn C, Piankijagum A, et al. Incidence of aplastic anemia in Bangkok. The Aplastic Anemia Study Group. 1991
3. Samarasinghe S, Webb DK. How I manage aplastic anaemia in children. *British journal of haematology*. 2012; 157(1):26–40. [PubMed: 22348483]
4. Scheinberg P, Young NS. How I treat acquired aplastic anemia. *Blood*. 2012; 120(6):1185–1196. [PubMed: 22517900]
5. Eapen M, Horowitz MM. Alternative donor transplantation for aplastic anemia. *Hematology Am Soc Hematol Educ Program*. 2010; 2010:43–46. [PubMed: 21239769]
6. Storb R, Blume KG, O'Donnell MR, et al. Cyclophosphamide and antithymocyte globulin to condition patients with aplastic anemia for allogeneic marrow transplantations: the experience in four centers. *Biol Blood Marrow Transplant*. 2001; 7(1):39–44. [PubMed: 11215697]
7. Pasquini, Wang. Current use and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides. 2013
8. Burroughs LM, Woolfrey AE, Storer BE, et al. Success of allogeneic marrow transplantation for children with severe aplastic anaemia. *British journal of haematology*. 2012; 158(1):120–128. [PubMed: 22533862]
9. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. *N Engl J Med*. 2011; 365(5):430–438. [PubMed: 21812672]
10. Saracco P, Quarello P, Iori AP, et al. Cyclosporin A response and dependence in children with acquired aplastic anaemia: a multicentre retrospective study with long-term observation follow-up. *British journal of haematology*. 140. England. 2008:197–205.
11. Schrezenmeier H, Marin P, Raghavachar A, et al. Relapse of aplastic anaemia after immunosuppressive treatment: a report from the European Bone Marrow Transplantation Group SAA Working Party. *British journal of haematology*. 1993; 85(2):371–377. [PubMed: 8280610]
12. Socie G, Rosenfeld S, Frickhofen N, et al. Late clonal diseases of treated aplastic anemia. *Seminars in hematology*. 2000; 37(1):91–101. [PubMed: 10676914]
13. Kojima S, Horibe K, Inaba J, et al. Long-term outcome of acquired aplastic anaemia in children: comparison between immunosuppressive therapy and bone marrow transplantation. *British journal of haematology*. 2000; 111(1):321–328. [PubMed: 11091219]
14. Deeg HJ, O'Donnell M, Tolar J, et al. Optimization of conditioning for marrow transplantation from unrelated donors for patients with aplastic anemia after failure of immunosuppressive therapy. *Blood*. 2006; 108(5):1485–1491. [PubMed: 16684959]
15. Tolar J, Deeg HJ, Arai S, et al. Fludarabine-based conditioning for marrow transplantation from unrelated donors in severe aplastic anemia: early results of a cyclophosphamide dose deescalation study show life-threatening adverse events at predefined cyclophosphamide dose levels. *Biol Blood Marrow Transplant*. 2012; 18(7):1007–1011. [PubMed: 22546497]
16. Samarasinghe S, Steward C, Hiwarkar P, et al. Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience. *British journal of haematology*. 2012; 157(3):339–346. [PubMed: 22372373]

17. Peffault de Latour R, Purtill D, Ruggeri A, et al. Influence of nucleated cell dose on overall survival of unrelated cord blood transplantation for patients with severe acquired aplastic anemia: a study by eurocord and the aplastic anemia working party of the European group for blood and marrow transplantation. *Biol Blood Marrow Transplant*. 2011; 17(1):78–85. [PubMed: 20561593]
18. Yoshimi A, Kojima S, Taniguchi S, et al. Unrelated cord blood transplantation for severe aplastic anemia. *Biol Blood Marrow Transplant*. 2008; 14(9):1057–1063. [PubMed: 18721769]
19. Clay J, Kulasekararaj AG, Potter V, et al. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. *Biol Blood Marrow Transplant*. 2014; 20(11):1711–1716. [PubMed: 25016195] This pilot study of 8 patients showed the feasibility of a novel protocol for haploidentical HSCT for SAA in patients with refractory disease who lacked other donors.
20. Wang Z, Zheng X, Yan H, et al. Good outcome of haploidentical hematopoietic SCT as a salvage therapy in children and adolescents with acquired severe aplastic anemia. *Bone Marrow Transplant*. 2014; 49(12):1481–1485. [PubMed: 25133891] This pilot study of 17 patients showed the feasibility of a haploidentical approach to HSCT for SAA as salvage therapy for refractory disease.
21. Gao L, Li Y, Zhang Y, et al. Long-term outcome of HLA-haploidentical hematopoietic SCT without in vitro T-cell depletion for adult severe aplastic anemia after modified conditioning and supportive therapy. *Bone Marrow Transplant*. 2014; 49(4):519–524. [PubMed: 24464145] This retrospective analysis of 26 adult patients treated at five centers in China show encouraging results of haploidentical HSCT for SAA when other donors were not available.
22. Cesaro S, de Latour RP, Tridello G, et al. Second allogeneic stem cell transplant for aplastic anaemia: a retrospective study by the severe aplastic anaemia working party of the European society for blood and marrow transplantation. *British journal of haematology*. 2015 This report from the EBMT showed feasibility of second allogeneic HSCT as a rescue for graft failure in 162 SAA patients.
23. Kudo K, Muramatsu H, Yoshida N, et al. Second allogeneic hematopoietic stem cell transplantation in children with severe aplastic anemia. *Bone Marrow Transplant*. 2015 This report from the Japanese Society for HSCT showed justification for the recommendation of second allogeneic HSCT in 55 children after graft failure.
24. Zhu F, Chen HR, Guo Z, et al. [Therapeutic efficacy of second allo-HSCT for aplastic anemia after failure of first allo-HSCT]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology*. 2014; 22(5): 1348–1353. This retrospective study of 10 SAA patients showed that second allogeneic HSCT is an effective therapy for first HSCT implant failure.
25. Camitta BM, Thomas ED, Nathan DG, et al. A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood*. 1979; 53(3):504–514. [PubMed: 32941]
26. Zhang MY, Keel SB, Walsh T, et al. Genomic analysis of bone marrow failure and myelodysplastic syndromes reveals phenotypic and diagnostic complexity. *Haematologica*. 2015; 100(1):42–48.

[PubMed: 25239263] This study introduced the use of marrowSeq as a method of broad unbiased genetic screening in the diagnostic workup for children and young adults with bone marrow failure and myelodysplastic syndromes.

27.

Barone A, Lucarelli A, Onofrillo D, et al. Diagnosis and management of acquired aplastic anemia in childhood. Guidelines from the Marrow Failure Study Group of the Pediatric Haemato-Oncology Italian Association (AIEOP). *Blood cells, molecules & diseases*. 2015; 55(1):40–47. This publication outlined the important advances and changes in treatment algorithms for the diagnosis and management of childhood SAA in Italy.

28.

Bacigalupo A, Socie G, Hamladji RM, et al. Current outcome of HLA identical sibling vs. unrelated donor transplants in severe aplastic anemia: an EBMT analysis. *Haematologica*. 2015; 100:696–702. [PubMed: 25616576] This study showed the important equivalence of MSD and MUD HSCT in SAA that has been helping to change the treatment algorithms for SAA.

29.

Xue HM, Xu HG, Huang K, et al. Allogeneic hematopoietic stem cell transplantation in children with aplastic anemia. *Genetics and molecular research. GMR*. 2015; 14(2):5234–5245. [PubMed: 26125718] This study confirmed the upfront use of MSD HSCT for children with SAA in China.

30. Bacigalupo A, Brand R, Oneto R, et al. Treatment of acquired severe aplastic anemia: bone marrow transplantation compared with immunosuppressive therapy--The European Group for Blood and Marrow Transplantation experience. *Seminars in hematology*. 2000; 37(1):69–80. [PubMed: 10676912]

31. Peinemann F, Grouven U, Kroger N, et al. First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia. *PLoS One*. 2011; 6(4):e18572. [PubMed: 21541024]

32.

Yoshida N, Kobayashi R, Yabe H, et al. First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor versus immunosuppressive therapy. *Haematologica*. 2014; 99(12):1784–1791. [PubMed: 25193958] This study confirmed the upfront use of MSD HSCT for children with SAA in Japan.

33.

Dufour C, Veys P, Carraro E, et al. Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT. *British journal of haematology*. 2015 [Epub ahead of print]. This study showed the improved outcome of MUD HSCT for SAA as upfront therapy, such that it is comparable to MSD HSCT upfront therapy, and superior to MUD HSCT after failed IST, paving the way for changes in the current treatment algorithm.

34.

Dufour C, Pillon M, Passweg J, et al. Outcome of aplastic anemia in adolescence: a survey of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2014; 99(10):1574–1581. [PubMed: 25085353] This study documented the superiority of upfront MSD HSCT to IST in adolescents with SAA in Europe, examining event free survival as the primary endpoint.

35. Ades L, Mary JY, Robin M, et al. Long-term outcome after bone marrow transplantation for severe aplastic anemia. *Blood*. 2004; 103(7):2490–2497. [PubMed: 14656884]

36. Kobayashi R, Yabe H, Hara J, et al. Preceding immunosuppressive therapy with antithymocyte globulin and ciclosporin increases the incidence of graft rejection in children with aplastic anaemia who underwent allogeneic bone marrow transplantation from HLA-identical siblings. *British journal of haematology*. 2006; 135(5):693–696. [PubMed: 17038001]
37. Bacigalupo A. Bone marrow transplantation for acquired severe aplastic anemia. *Hematology/oncology clinics of North America*. 2014; 28(6):1145–1155. [PubMed: 25459184] This is an important review of HSCT strategies in SAA that has helped lead the debates about changes to treatment algorithms.
38. Dufour C, Pilon M, Sociè G, et al. Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. *British journal of haematology*. 2015; 169:565–573. [PubMed: 25683884] This study documented the superiority of upfront MSD HSCT to IST in children with SAA in Europe, examining event free survival as the primary endpoint.
39. Eapen M, Le Rademacher J, Antin JH, et al. Effect of stem cell source on outcomes after unrelated donor transplantation in severe aplastic anemia. *Blood*. 2011; 118(9):2618–2621. [PubMed: 21677312]
40. Schrezenmeier H, Passweg JR, Marsh JC, et al. Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia. *Blood*. 2007; 110(4):1397–1400. [PubMed: 17475907]
41. Chu R, Brazauskas R, Kan F, et al. Comparison of outcomes after transplantation of G-CSF-stimulated bone marrow grafts versus bone marrow or peripheral blood grafts from HLA-matched sibling donors for patients with severe aplastic anemia. *Biol Blood Marrow Transplant*. 2011; 17(7):1018–1024. [PubMed: 21034842]
42. Bacigalupo A, Sociè G, Schrezenmeier H, et al. Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. *Haematologica*. 2012; 97(8):1142–1148. [PubMed: 22315497]
43. Storb R, Leisenring W, Anasetti C, et al. Long-term follow-up of allogeneic marrow transplants in patients with aplastic anemia conditioned by cyclophosphamide combined with antithymocyte globulin. *Blood*. 1997; 89(10):3890–3891. [PubMed: 9160700]
44. Kumar R, Prem S, Mahapatra M, et al. Fludarabine, cyclophosphamide and horse antithymocyte globulin conditioning regimen for allogeneic peripheral blood stem cell transplantation performed in non-HEPA filter rooms for multiply transfused patients with severe aplastic anemia. *Bone Marrow Transplant*. 2006; 37(8):745–749. [PubMed: 16518427]
45. Itala M, Aho H, Remes K. Reduced-intensity conditioning and blood stem cell transplantation from an HLA-identical sibling for severe aplastic anaemia: two patients with successful engraftment but a fatal post-transplant lymphoproliferative disorder in the other. *The hematology journal : the official journal of the European Haematology Association / EHA*. 2004; 5(5):440–443. [PubMed: 15448671]
46. Srinivasan R, Takahashi Y, McCoy JP, et al. Overcoming graft rejection in heavily transfused and allo-immunised patients with bone marrow failure syndromes using fludarabine-based haematopoietic cell transplantation. *British journal of haematology*. 2006; 133(3):305–314. [PubMed: 16643433]
47. Resnick IB, Aker M, Shapira MY, et al. Allogeneic stem cell transplantation for severe acquired aplastic anaemia using a fludarabine-based preparative regimen. *British journal of haematology*. 2006; 133(6):649–654. [PubMed: 16704442]
48. Bacigalupo A, Locatelli F, Lanino E, et al. Fludarabine, cyclophosphamide and anti-thymocyte globulin for alternative donor transplants in acquired severe aplastic anemia: a report from the EBMT-SAA Working Party. *Bone Marrow Transplant*. 2005; 36(11):947–950. [PubMed: 16205733]

49. Maury S, Bacigalupo A, Anderlini P, et al. Improved outcome of patients older than 30 years receiving HLA-identical sibling hematopoietic stem cell transplantation for severe acquired aplastic anemia using fludarabine-based conditioning: a comparison with conventional conditioning regimen. *Haematologica*. 2009; 94(9):1312–1315. [PubMed: 19734425]
50. Marsh JC, Gupta V, Lim Z, et al. Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia. *Blood*. 2011; 118(8):2351–2357. [PubMed: 21518925]
51. Marsh JC, Pearce RM, Koh MB, et al. Retrospective study of alemtuzumab vs ATG-based conditioning without irradiation for unrelated and matched sibling donor transplants in acquired severe aplastic anemia: a study from the British Society for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 49. England. 2014:42–48. This large study of 155 patients confirmed successful avoidance of TBI in the conditioning regimens for MUD HSCT in SAA, with less chronic GVHD when using alemtuzumab.
52. Frickhofen N, Heimpel H, Kaltwasser JP, Schrezenmeier H. Antithymocyte globulin with or without cyclosporin A: 11-year follow-up of a randomized trial comparing treatments of aplastic anemia. *Blood*. 2003; 101(4):1236–1242. [PubMed: 12393680]
53. Deeg HJ, Amylon ID, Harris RE, et al. Marrow transplants from unrelated donors for patients with aplastic anemia: minimum effective dose of total body irradiation. *Biol Blood Marrow Transplant*. 2001; 7(4):208–215. [PubMed: 11349807]
54. Kojima S, Matsuyama T, Kato S, et al. Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: the Japan Marrow Donor Program. *Blood*. 2002; 100(3):799–803. [PubMed: 12130489]
55. Gadalla SM, Wang T, Haagenson M, et al. Association between donor leukocyte telomere length and survival after unrelated allogeneic hematopoietic cell transplantation for severe aplastic anemia. *Jama*. 2015; 313(6):594–602. [PubMed: 25668263] This study helped to open new inquiries as to donor related factors that influence survival, in this case longer telomere length being associated with increased survival.
56. Bacigalupo A, Socie G, Lanino E, et al. Fludarabine, cyclophosphamide, antithymocyte globulin, with or without low dose total body irradiation, for alternative donor transplants, in acquired severe aplastic anemia: a retrospective study from the EBMT-SAA Working Party. *Haematologica*. 95. Italy. 2010:976–982.
57. Ngwube A, Hayashi RJ, Murray L, et al. Alemtuzumab based reduced intensity transplantation for pediatric severe aplastic anemia. *Pediatr Blood Cancer*. 2015; 62(7):1270–1276. [PubMed: 25755151] This study showed good results of a novel alemtuzumab, fludarabine, and melphalan based reduced intensity HSCT for children with SAA.
58. Hamad N, Del Bel R, Messner HA, et al. Outcomes of hematopoietic cell transplantation in adult patients with acquired aplastic anemia using intermediate-dose alemtuzumab-based conditioning. *Biol Blood Marrow Transplant*. 2014; 20(11):1722–1728. [PubMed: 25017761] This study showed excellent results of alemtuzumab based conditioning for HSCT in SAA, with no severe chronic GVHD, but high rates of viral complications.
59. Marsh JC, Ball SE, Cavenagh J, et al. Guidelines for the diagnosis and management of aplastic anaemia. *British journal of haematology*. 2009; 147(1):43–70. [PubMed: 19673883]
60. Anderlini P, Wu J, Gersten I, et al. Cyclophosphamide conditioning in patients with severe aplastic anaemia given unrelated marrow transplantation: a phase 1–2 dose de-escalation study. *Lancet*

Haematol. 2015; 2:e367–e375. DOI:[http://dx.doi.org/10.1016/S2352-3026\(15\)00147-7](http://dx.doi.org/10.1016/S2352-3026(15)00147-7). [PubMed: 26685770] This report on the results of BMT CTN 0301 demonstrated for the first time a new potential standard-of-care reduced intensity regimen for 9/10 and 10/10 MUD HSCT in SAA with excellent overall survival and low rates of rejection and GVHD.

61. Chan KW, McDonald L, Lim D, et al. Unrelated cord blood transplantation in children with idiopathic severe aplastic anemia. *Bone Marrow Transplant*. 2008; 42(9):589–595. [PubMed: 18695669]
62. Ciceri F, Lupo-Stanghellini MT, Korthof ET. Haploidentical transplantation in patients with acquired aplastic anemia. *Bone Marrow Transplant*. 2013; 48(2):183–185. [PubMed: 23292235]
63. Jaiswal SR, Chatterjee S, Mukherjee S, et al. Pre-transplant sirolimus might improve the outcome of haploidentical peripheral blood stem cell transplantation with post-transplant cyclophosphamide for patients with severe aplastic anemia. *Bone Marrow Transplant*. 50. England. 2015:873–875. One of a series of small studies showing significant advances in haploidentical HSCT for SAA that has made it a reasonable treatment option for refractory patients or patients that do not have other donors.
64. Zhang Y, Liu XD, He XP, et al. [Retrospective analysis of therapeutic efficacy of haploidentical allogeneic hematopoietic stem cell transplantation for severe aplastic anemia]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology*. 2014; 22(5):1354–1358. One of a series of small studies showing significant advances in haploidentical HSCT for SAA that has made it a reasonable treatment option for refractory patients or patients that do not have other donors.
65. Gupta N, Choudhary D, Sharma SK, et al. Haploidentical hematopoietic SCT for acquired severe aplastic anemia using post-transplant high-dose CY. *Bone Marrow Transplant*. 50. England. 2015:155–156. One of a series of small studies showing significant advances in haploidentical HSCT for SAA that has made it a reasonable treatment option for refractory patients or patients that do not have other donors.
66. Im HJ, Koh KN, Seo JJ. Haploidentical hematopoietic stem cell transplantation in children and adolescents with acquired severe aplastic anemia. *Korean journal of pediatrics*. 2015; 58(6):199–205. [PubMed: 26213547] One of a series of small studies showing significant advances in haploidentical HSCT for SAA that has made it a reasonable treatment option for refractory patients or patients that do not have other donors.
67. Esteves I, Bonfim C, Pasquini R, et al. Haploidentical BMT and post-transplant Cy for severe aplastic anemia: a multicenter retrospective study. *Bone Marrow Transplant*. 2015; 50(5):685–689. [PubMed: 25730184] One of a series of small studies showing significant advances in haploidentical HSCT for SAA that has made it a reasonable treatment option for refractory patients or patients that do not have other donors.
68. Socie G, Henry-Amar M, Bacigalupo A, et al. Malignant tumors occurring after treatment of aplastic anemia. *European Bone Marrow Transplantation-Severe Aplastic Anaemia Working Party. N Engl J Med*. 1993; 329(16):1152–1157. [PubMed: 8377778]
69. Deeg HJ, Socie G, Schoch G, et al. Malignancies after marrow transplantation for aplastic anemia and fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. *Blood*. 1996; 87(1):386–392. [PubMed: 8547667]

70. Deeg HJ, Leisenring W, Storb R, et al. Long-term outcome after marrow transplantation for severe aplastic anemia. *Blood*. 1998; 91(10):3637–3645. [PubMed: 9572999]
71. Sanders JE, Woolfrey AE, Carpenter PA, et al. Late effects among pediatric patients followed for nearly 4 decades after transplantation for severe aplastic anemia. *Blood*. 2011; 118(5):1421–1428. [PubMed: 21653322]
72. Konopacki J, Porcher R, Robin M, et al. Long-term follow up after allogeneic stem cell transplantation in patients with severe aplastic anemia after cyclophosphamide plus antithymocyte globulin conditioning. *Haematologica*. 2012; 97(5):710–716. [PubMed: 22180425]
73. Buchbinder D, Nugent DJ, Brazauskas R, et al. Late effects in hematopoietic cell transplant recipients with acquired severe aplastic anemia: a report from the late effects working committee of the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2012; 18(12):1776–1784. [PubMed: 22863842]
74. Pongtanakul B, Das PK, Charpentier K, Dror Y. Outcome of children with aplastic anemia treated with immunosuppressive therapy. *Pediatr Blood Cancer*. 2008; 50(1):52–57. [PubMed: 17941069]

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Key Points

1. Children presenting with a picture of SAA have a 10–20% chance of having an IBMFS, and careful assessment for signs or symptoms along with genetic screening for these disorders is of major importance.
2. Long-term survival after matched sibling donor (MSD) and matched unrelated donor (MUD) HSCT exceed 90% in children; MSD HSCT is already considered standard of care for up-front therapy and MUD HSCT is being evaluated by some groups as primary therapy.
3. Late effects after HSCT for SAA are minimal with current strategies and compare favorably to up-front immunosuppressive therapy (IST) late effects, except for patients with chronic graft versus host disease (GVHD).
4. Ongoing studies will continue to challenge treatment algorithms and may lead to an even more expanded role for HSCT in SAA.

Figure 1. General Diagnostic Evaluation in SAA

FISH – fluorescent in situ hybridization, MDS – myelodysplasia, GD – Gaucher disease, SM – systemic mastocytosis, IBMFS – inherited bone marrow failure syndrome, DEB – diepoxybutane, PNH – paroxysmal nocturnal hemoglobinuria (*if high level clone and symptomatic with hemolysis or thrombosis), SAA – severe aplastic anemia, CAMT – congenital amegakaryocytic thrombocytopenia, DBA – Diamond Blackfan anemia, WGS – whole genome sequencing, FA – Fanconi anemia, DC – Dyskeratosis Congenita, SDS – Schwachman Diamond syndrome

Figure 2. Algorithm used by UK centers including front line treatment of pediatric patients affected by SAA

Previously Published. Reproduced with permission from John Wiley & Sons Ltd as shown in Samarasinghe and Webb, BJH 2012. UK – United Kingdom, SAA – severe aplastic anemia, vSAA – very severe aplastic anemia, HSCT – hematopoietic stem cell transplantation, MSD – matched sibling donor, MUD – matched unrelated donor, MMUD – mismatched unrelated donor, IST – immunosuppressive therapy, 10/10 MUD refers to a Human Leukocyte Antigen-A, -B, -DRB1, and -DQ matched donor by high resolution

Table 1**History and Exam Features of Inherited Bone Marrow Failure Syndromes**

History or Exam Feature	Associated Syndrome
Abnormal or missing thumbs and/or radius	Fanconi Anemia
Metaphyseal chondrodysplasia and/or narrow chest	Schwachman Diamond
Café au lait spots	Fanconi Anemia
Reticular skin pigmentation	Dyskeratosis Congenita
Hypo/hypertelorism or small eyes	Fanconi Anemia
Dystrophic fingernails or toenails	Dyskeratosis Congenita
Oral leukoplakia	Dyskeratosis Congenita
Microcephaly	Schwachman Diamond, Fanconi Anemia
Developmental delay	Fanconi Anemia
Hypospadias or cryptorchidism	Fanconi Anemia, Dyskeratosis Congenita
Cardiac anomalies	Fanconi Anemia, Dyskeratosis Congenita
Horseshoe kidney	Fanconi Anemia
Personal or family history of pulmonary fibrosis	Dyskeratosis Congenita
Personal or family history of liver fibrosis or cirrhosis	Dyskeratosis Congenita
Small or fatty pancreas with exocrine pancreatic insufficiency	Schwachman Diamond
Osteopenia in a young patient	Schwachman Diamond, Dyskeratosis Congenita
Severe dental abnormalities	Schwachman Diamond
Unusual cancers, such as squamous cell carcinoma of the head, neck, vulva, or cervix	Fanconi Anemia, Dyskeratosis Congenita
Unusual response to treatment, such as severe toxicity or prolonged pancytopenia	Fanconi Anemia, Dyskeratosis Congenita

Table 2

Recent HSCT Late Effects Studies in SAA

Study (number) year	Donor	RT Exposure	Chronic GVHD	Late Effects
Sanders et al [70] (n=137) 2011	MSD – 86% MUD – 12% SYN – 2%	TBI – 18%	26%	BMD abnormal 26% malignancy 13% abnormal thyroid 22% abnormal growth 0% abnormal gonad 17% all raw numbers, not CI
Konopacki et al [71] (n=61) 2011	MSD – 100%	None	32%	osteonecrosis 21% abnormal endo 19% abnormal cardio 2% malignancy 2% all CI at 6 years
Buchbinder et al [72] (n=1718) 2012	MSD – 64% MUD – 10% Other – 12%	TBI <400 cGy – 9 % TBI >400 cGy – 15% TLI/TAI – 5%	22–37%	none 81% neuro 1.8–2.8% cardiac 0.1% cirrhosis 0.3% abnormal gonad 3–10% renal failure 1.4–2.4% osteonecrosis 1.8–6.3% cataracts 1.1–5.1% abnormal growth 0.5–7.2% hypothyroid 1.2–5.5% malignancy 0.1–1.6% all CI at 5 years

HSCT – hematopoietic stem cell transplantation, SAA – severe aplastic anemia, RT – radiation therapy, GVHD – graft versus host disease, MSD – matched sibling donor, MUD – matched unrelated donor, SYN – syngeneic donor, TBI – total body irradiation, TLI – total lymphoid irradiation, TAI – thoraco-abdominal irradiation, BMD – bone mineral density, CI – cumulative incidence