Published in final edited form as:

Pediatr Clin North Am. 2018 June ; 65(3): 597–606. doi:10.1016/j.pcl.2018.02.006.

Acquired Aplastic Anemia:

What Have We Learned and What Is in the Horizon?

Süreyya Sava an, MD

Division of Hematology/Oncology, Pediatric Blood and Marrow Transplant Program, Children's Hospital of Michigan, Barbara Ann Karmanos Cancer Center, Wayne State University School of Medicine, 3901 Beaubien Boulevard, Detroit, MI 48201, USA

Keywords

Acquired aplastic anemia; Hematopoietic stem cell; Autoimmunity; Immunosuppressive therapy; Hematopoietic stem cell transplantation; Clonality; Myelodysplastic syndrome

Idiopathic acquired aplastic anemia (aAA) is a rare disorder with an estimated incidence of 300 to 600 cases in the United States annually; it is less frequent in children. It is characterized by peripheral pancytopenia and significantly decreased cellularity in the bone marrow (BM). Though isolated cytopenias may seem to be the only manifestation, all 3 lines are often affected at presentation. For instance, severe thrombocytopenia may be the prominent finding; however, an increased mean corpuscular volume and/or mild decrease in other counts may accompany the thrombocytopenia. Therefore, close monitoring and keeping the possibility of aAA in mind is prudent because therapeutic approaches to thrombocytopenia significantly depend on the underlying cause and delay in aAA diagnosis establishment may be very consequential. Infections and bleeding are the most common causes of morbidity and mortality in the very severe and severe forms of aAA. Severe aAA is characterized by peripheral blood absolute neutrophil count less than $0.5 \times 10^9/L$ and the very severe form by less than $0.2 \times 10^9/L$, in addition to platelets less than $20 \times 10^9/L$ and reticulocytes less than $20 \times 10^9/L$ with decreased hematopoietic and overall cellularity in the BM.¹

Although phenotypic findings in inherited BM failure syndromes (iBMFS) are not uncommon, some patients may not have any. Ruling out an underlying iBMFS is a prerequisite for establishing the diagnosis of aAA. Whereas lymphocyte chromosomal breakage testing is standard and practical in investigating underlying Fanconi anemia (FA), telomere length assessment is used for detecting disorders characterized by shortened telomeres in both myeloid and lymphoid cells in peripheral blood.² Telomere length in residual granulocytes are shortened in aAA. Not infrequently, there is a fine line between aAA and hypoplastic myelodysplastic syndrome (MDS) or refractory cytopenia of childhood (RCC) due to similarities in clinical presentation and laboratory findings.³ In that regard, cytogenetic analysis of BM cells using karyotyping and fluorescence in situ hybridization (FISH) technique may provide some help, though they are not sensitive or specific enough.

Beyond the previously mentioned iBMFS, such as FA and short telomere disorders, BM aplasia may be in the spectrum of some inherited or familial conditions that are associated with immune dysregulation and/or tendency to develop myelodysplasia or myeloproliferation. It has become reasonable to run large gene panels to investigate for these underlying disorders at the time of diagnosis of BM failure.⁴⁻⁶ Whether the utility of this approach can be justified is debatable; however, discovery of such genetic background may significantly affect treatment decisions. Paroxysmal nocturnal hemoglobinuria (PNH) is caused by an acquired hematopoietic stem cell (HSC) defect, leading to intravascular hemolysis, anemia, and thrombotic complications closely associated with aAA. Therefore, investigating for PNH is also a necessary step in patients with newly diagnosed aAA. Clinically evident PNH may be present around the time of aAA diagnosis and would require additional interventions.⁷ Even flow cytometric detection of small clonal PNH populations may indicate the need for closer monitoring for the development of symptomatic PNH down the road and also points to possibility of a greater response to immunosuppressive therapy (IST).⁸

HISTOLOGY AND PATHOGENESIS

The BM tissue in acquired severe aplastic anemia (aSAA) displays severely decreased cellularity with some degree of reactive changes. There is no histologic evidence of acute inflammation at the time of diagnosis. As seen in tissue atrophy, blood supply to BM is diminished. Microvascular density and vascular endothelial growth factor (VEGF) expression were found to be lower in aSAA BM tissue, along with decreased serum levels of VEGF, which were substantially improved following successful IST.⁹ Despite severely decreased hematopoiesis, typically there is no accompanying fibrosis in the BM. Space emptied by the elimination of hematopoiesis appears to have been partially filled by adipocytes. Relative lymphocyte predominance, primarily of T lymphocytes, is characteristic of BM histology. Additionally, relative increase in mast cells, plasma cells, and histiocytes, some displaying hemophagocytosis, is common. Among these changes, visible mast cell presence has been thought to be related to their longer life span following HSC injury; however, the possibility of their compensatory effort to stimulate angiogenesis¹⁰ has not been specifically investigated.

Though the knowledge on the pathogenesis of aAA has increased enormously in recent years, it still continues to be an enigmatic disease in many ways.^{11,12} Research in aAA has been somewhat hampered by the lack of availability of a sufficient number of hematopoietic stem cells for experiments. This has led to focusing on the aAA BM microenvironment. Furthermore, studying the recovering BM tissue following IST in comparison with diagnostic samples has significantly contributed to the understanding of the disease process. With technological advancements, molecular genetic studies on stored samples have helped improve the understanding of the genetic basis and the heterogeneity of aAA, emphasizing the importance of storing samples after obtaining signed consents in such rare disorders.

Early observations of chemical (benzene and pesticides) or radiation exposure and idiosyncratic drug (chloramphenicol) reaction-associated BM aplasia cases thought to be pointing at a direct injury to HSC.¹³⁻¹⁵ Incidental observation of autologous recovery of BM

after allografting conditioned with antilymphocytic serum in aSAA patients led to use of IST in aSAA.¹⁶ Moreover, this observation has also provided additional evidence for potential role of immune response in the disease pathogenesis. Furthermore, autologous recovery following failed allogeneic HSCT conditioned by high-dose cyclophosphamide pointed to the potential role of IST in aAA treatment.¹⁷ Demonstration of oligoclonal expansion of cytotoxic CD81CD28–T cells and production of helper type-1 T lymphocyte cytokines, such as interferon-gamma and tumor necrosis factor-alpha, by the lymphocytes and stromal cells in aAA BM microenvironment supported an immune reaction directed toward HSC. However, what triggers the autoimmune reaction is still not well-understood. Although an alteration in HSC population due to an infection inciting an autoimmune reaction could be speculated in hepatitis-associated aAA cases, there is no detectable history of recent infection at diagnosis in the majority of aAA cases.¹⁸ Not surprisingly, hepatitis-associated aSAA cases also respond to IST. Even in some of the cases of aSAA associated with chemical or drug exposure, IST has been successful, again suggesting a potential role of autoimmune reaction to HSC in those patients.¹⁵

There seems to be a fine line between some cases of idiopathic aAA and MDS. BM dysplastic changes may provide an important clue in distinguishing idiopathic aAA from RCC and some inherited BM disorders associated with identified genetic defects.¹⁹ In a third of the study population, somatic mutations in MDS or acute myeloid leukemia (AML)-associated genes with increasing prevalence by aging were detected; clonal hematopoiesis determined mostly by the presence of acquired mutations was observed almost in half of the cases in aAA.^{20,21} The incidence of those mutations at diagnosis was much lower. Among the mutated genes, *DNMT3A* and *AXSL1* showed an increasing clonal population and were associated with progression to MDS or AML. On the other hand, mutations in *PIGA* and *BCOR/BCORL1* were stable or decreased over time and represented a better outcome. These observations are reminiscent of the recently described entity clonal hematopoiesis of indeterminate potential (CHIP), more frequently described with aging.²² It might be interesting to see if detection of incidence of clonality would increase if methods other than detection of mutations were used.

Copy-number neutral loss of heterozygosity or uniparental disomy of the chromosome 6p (6pUPD) leading to HLA haplotype loss was seen in clonal aAA and escape from autoreactive T-cell attack due to lack of appropriate HLA class I molecule expression was proposed as the mechanism.²³ Furthermore, recurrent HLA class-I mutations suggested HLA class I-driven autoimmune reaction and also providing mechanistic evidence for clonal evolution.²⁴ In summary, observation of somatic mutations at diagnosis in some idiopathic aAA cases and preferential elimination of HSC without the mutations through autoimmune attack, leading to increased presence of HSC with the mutations following IST provides the explanation for clonal evolution.²⁵

Several findings indicate heterogeneity of aAA. The reason for unresponsiveness to IST is not well-understood. Persevering autoimmune reaction due to inadequate immune suppression is possible because some cases, but not all, respond to other forms of IST.²⁶ Furthermore, a thrombopoietin mimetic agent, eltrombopag, has shown some efficacy in refractory patients,²⁷ pointing at the potential role of HSC stimulation, maybe overriding

ongoing autoimmunity to a certain degree, similar to results with eltrombopag observed in another immune-mediated disorder, idiopathic thrombocytopenic purpura.²⁸ Although slow versus fast responses obtained with IST may be a consequence of the adequacy of the immune suppression provided, there may be more to this observation. One question is: are recovering HSC completely normal following IST in all cases? The author recently showed evidence for increased response to tunicamycin-induced endoplasmic reticulum (ER) stress in myeloid cells in aAA. Interestingly, there was no difference (albeit using small numbers) in induced ER stress in vitro between active disease and post-IST response state in culture-grown myeloid cells, raising the possibility of continuing altered HSC recovery despite improvements in BM cellularity and peripheral counts.²⁹ The health of the recovering HSC without detectable genetic abnormalities is another area of research that may expand understanding of aAA pathophysiology.

There are several similarities between hereditary iBMFS, such as FA, and idiopathic aAA BM tissue findings, including increased fat cells, mast cells, and lymphocytes, as well as a lack of significant fibrosis, pointing at common tissue reaction to depletion of the HSC compartment regardless of the cause in these disorders. Cellular stress, such as repeated infection, plays an important role in the development of BM aplasia in FA.³⁰ The evolution of a clinical picture is much more gradual in most iBMFS cases compared with idiopathic aAA. Often, isolated peripheral cytopenia, such as thrombocytopenia, is the first finding, followed by a long lag time to the development of significant pancytopenia.

Recipient origin of nonhematopoietic supportive cells, such as fibroblasts and mesenchymal stem cells (MSC), following successful allogeneic hematopoietic stem cell transplantation (HSCT) does not support a primary role for BM microenvironment defects in the pathogenesis of aAA.^{31,32} Several aberrations have been described in hematopoietic microenvironment MSC, likely contributing to impaired quality and decreased quantity of hematopoietic BM niches, and indicating changes in nonhematopoietic cells.³³ However, this matter remains controversial because some investigators point to the preserved integrity of MSC in aAA.³⁴ Impaired hematopoietic niche in BM in aAA, and restoration of vascular and perivascular niches, are shown following successful allogeneic HSCT independent of donor-derived BM MSC.^{35,36}

TREATMENT

Similar to basic research efforts, obtaining clinical data on aSAA cases has been challenging due to rarity of this condition. The great majority of published reports originate from review and analysis of the results retrospectively. The results often include data from both pediatric and adult cases. Spontaneous remissions have been reported infrequently, usually taking place within the first 2 months of diagnosis.³⁷ Pregnancy-associated aAA is an entity in which spontaneous remissions are seen more frequently.³⁸ Although a wait-and-see strategy is not practical, tests to investigate for underlying inherited BMFS or RCC with or without myelodysplasia and searching for potential related or family donors generally takes some time, during which the patients receive transfusion support. Prophylactic antimicrobials and good oral hygiene may be necessary based on the severity of aAA. Use of granulocyte colony stimulating factor (G-CSF) can increase neutrophil counts marginally in some patients. Such

supportive care measures, and red blood cell and platelet transfusions, continue during IST, increasing the possibility of transfusion-associated allergic reactions and alloimmunization to red blood cells and platelets. Treatment options and approaches in aAA were recently reviewed.³⁹ The 2 top choices for the treatment of idiopathic aSAA are allogeneic matched sibling donor (MSD) or matched related donor (MRD) HSCT. If such a donor is not available, IST including steroids, cyclosporine A (CSA), and antithymocyte globulin (ATG) is the preferred treatment form.

Immunosuppressive Therapy

The response to IST is generally assessed at 6 months of therapy. Due to incomplete response, some patients were kept on CSA for longer periods. In a retrospective analysis of 455 children, overall survival was superior statistically at 92% with equine ATG, including IST, compared with 84% rabbit ATG at 10 years.⁴⁰ Use of equine ATG in IST has been associated with improved response rates in the first 6 months in a systematic review and meta-analysis report.⁴¹ One of the common and major shortcomings of retrospective studies comparing the effectiveness of equine with rabbit ATG has been the lack of equal dosing of the each of the ATG products. In a randomized prospective clinical trial comparing rabbit ATG (Thymoglobulin, Genzyme) and equine ATG (ATGAM, Pfizer), 60 pediatric and adult subjects were enrolled in each arm. Equine ATG was superior with a 6-month response rate of 68% to 37% in the rabbit ATG group. Furthermore, overall survival was also better in the equine ATG arm (96% vs 76%) at 3 years.⁴²

Severe allergic reactions during ATG infusion may necessitate switching to another product. Attention should be given to controlling hypertension at the early stages of IST when CSA and steroids are administered together, owing to the possibility of posterior reversible encephalopathy syndrome (PRES). Some patients may not be able to continue CSA treatment due to recurrent PRES when challenged again following the first episode. Because IST containing tacrolimus has been shown to be as effective as the CSA-containing regimen,⁴³ in case of CSA intolerance, a trial of tacrolimus may be reasonable.

Approximately one-third of the cases do not respond to IST and other cases may recur after initial response. High-dose cyclophosphamide has been used with a certain degree of success associated with high incidence of infectious complications in children.⁴⁴

Alemtuzumab has been used as a single agent in refractory cases with a response rate of 37% and 56% in recurrent cases⁴⁵ and, therefore, it can be considered as an option for those cases.²⁶ Eltrombopag showed promising results in IST-refractory aSAA subjects.²⁷ It has also improved the outcome when added to standard IST regimen in untreated aSAA subjects.⁴⁶ Clonal cytogenetic evolution was seen in 7 subjects (8%) at a median 2-year follow-up; 5 occurred within the first 6 months and 2 later. The investigators reported that the incidence was not different from the historic cohort. Although these are encouraging results, one must be careful about the potential long-term MDS or AML risk of eltrombopag administration, given the recent findings of significant presence of somatic mutations in certain genes.

Hematopoietic Stem Cell Transplantation

Because BM is already aplastic, there is no need for myeloablative conditioning in aSAA HSCT. On the other hand, immune suppression is very critical for engraftment and prevention of graft-versus-host disease (GvHD). Exposure to repeated blood and platelet transfusions increase the risk of alloimmunization and sets the immune system in a more active state. Current commonly used conditioning regimens include various combinations of cyclophosphamide, fludarabine, and ATG or alemtuzumab, and/or low-dose total body irradiation.

A survival advantage was reported for marrow grafting over peripheral HSC in all ages in a report from European Group for Blood and Marrow Transplantation.⁴⁷ The risk of acute and chronic GvHD was lower in the BM graft group. Furthermore, inclusion of ATG in conditioning was associated with less incidence of both forms of GvHD and superior survival in the same study. Equine ATG and rabbit ATG have different biological and clinical properties in HSCT setting; rabbit ATG was associated with higher incidence of stable mixed chimerism.⁴⁸ Unrelated donor (UD) HSCT did not lead to a statistically significant different survival rate compared with MSD HSCT; however, it was associated with increased risk of both acute and chronic GvHD.⁴⁹ In a recent multiinstitutional retrospective analysis of 833 aSAA MSD or UD HSCT recipients, use of rabbit ATG in conditioning was found to be associated with lesser incidence of acute GvHD compared with equine ATG. Chronic GvHD was also higher in the equine ATG group without overall survival difference in MSD cases.⁵⁰ Greater lymphodepletion and enhancement of regulatory T cells following rabbit ATG were proposed as the mechanisms of the observed effects. UD HSCT has also been associated with successful outcomes in children.^{51,52} Progression into MDS and AML was seen an average of 2.9 (1.2–13) years after aSAA diagnosis in 17 children and young adults; event-free survival in those cases following allogeneic HSCT for MDS or AML was 41%.⁵³

Late graft rejection is a known experience in aSAA HSCT and a study revealed its close association with decreasing donor chimerism.⁵⁴ In MRD HSCT cases, a second attempt using the same donor was commonly done with or without donor leukocyte infusions. Alternative donor sources are also used for aSAA HSCT after failing IST or MRD HSCT in recent years, including umbilical cord blood cells and haploidentical family members.⁵⁵ In mismatched donors, investigating for anti-HLA antibodies is a common practice. Given the risk of graft failure in HSCT for aSAA, and increased risk in cord blood cell transplants in general, umbilical cord blood cell transplantation has a higher nonengraftment risk.⁵⁶ Haploidentical HSCT with postinfusion cyclophosphamide has shown promising results.⁵⁷ Although return to recipient hematopoiesis is the most common pattern in late graft failure, donor-derived recurrent aAA cases due to immune reaction have been described.⁵⁸ Treatment with ATG may resolve the late graft failure in such cases.

SUMMARY

Recent discoveries of clonal hematopoiesis due to identification of somatic mutations and other genetic changes at presentation, more frequently in the long-term following IST in some cases, and HLA class-I gene mutations playing a central role in the development of

autoimmune reaction in some other cases, have shed light on the aAA pathogenesis, as well as pointing at aAA heterogeneity. MRD HSCT provides great outcomes in aSAA. However, in patients without a matched family donor, equine ATG in combination with CSA as IST has been associated with superior outcomes compared with rabbit ATG. Addition of eltrombopag to classic IST regimen has improved the response rate, opening a new dimension to medicinal treatment of aSAA because HSC stimulation with erythropoietin and G-CSF therapies had not been successful in the past. Alternative donor HSCT has been increasingly used in patients who failed IST or MRD HSCT, with improved results indicating the potential for it to be considered as a first-line approach in the future. There is still need for progress and long-term follow-up of recovered patients and out-of-box thinking would help open new avenues to better understanding and treatment of aAA.

REFERENCES

1. Guinan EC. Diagnosis and management of aplastic anemia. *Hematology Am Soc Hematol Educ Program* 2011;2011:76–81. [PubMed: 22160015]
2. Townsley DM, Dumitriu B, Young NS. Bone marrow failure and the telomeropathies. *Blood* 2014;124:2775–83. [PubMed: 25237198]
3. Niemeyer CM, Baumann I. Classification of childhood aplastic anemia and myelodysplastic syndrome. *Hematology Am Soc Hematol Educ Program* 2011;2011: 84–9. [PubMed: 22160017]
4. Babushok DV, Bessler M. Genetic predisposition syndromes: when should they be considered in the work-up of MDS? *Best Pract Res Clin Haematol* 2015;28: 55–68. [PubMed: 25659730]
5. Erlacher M, Strahm B. Missing cells: pathophysiology, diagnosis, and management of (pan)cytopenia in childhood. *Front Pediatr* 2015;3:64. [PubMed: 26217651]
6. Bannon SA, DiNardo CD. Hereditary predispositions to myelodysplastic syndrome. *Int J Mol Sci* 2016;17 [pii:E838].
7. Narita A, Muramatsu H, Okuno Y, et al. Development of clinical paroxysmal nocturnal haemoglobinuria in children with aplastic anaemia. *Br J Haematol* 2017;178:954–8. [PubMed: 28643364]
8. Narita A, Muramatsu H, Sekiya Y, et al., Japan Childhood Aplastic Anemia Study Group. Paroxysmal nocturnal hemoglobinuria and telomere length predicts response to immunosuppressive therapy in pediatric aplastic anemia. *Haematologica* 2015;100:1546–52. [PubMed: 26315930]
9. Füreder W, Krauth MT, Sperr WR, et al. Evaluation of angiogenesis and vascular endothelial growth factor expression in the bone marrow of patients with aplastic anemia. *Am J Pathol* 2006;168:123–30. [PubMed: 16400015]
10. Krystel-Whittemore M, Dileepan KN, Wood JG. Mast cell: a multi-functional master cell. *Front Immunol* 2016;6:620. [PubMed: 26779180]
11. Young NS. Pathophysiologic mechanisms in acquired aplastic anemia. *Hematology Am Soc Hematol Educ Program* 2006;72–7. [PubMed: 17124043]
12. Young NS. Current concepts in the pathophysiology and treatment of aplastic anemia. *Hematology Am Soc Hematol Educ Program* 2013;2013:76–81. [PubMed: 24319166]
13. Aksoy M, Erdem S, Akgün T, et al. Osmotic fragility studies in three patients with aplastic anemia due to chronic benzene poisoning. *Blut* 1966;13:85–90. [PubMed: 5932539]
14. Fleming LE, Timmeny W. Aplastic anemia and pesticides. An etiologic association? *J Occup Med* 1993;35:1106–16. [PubMed: 8295035]
15. Malkin D, Koren G, Saunders EF. Drug-induced aplastic anemia: pathogenesis and clinical aspects. *Am J Pediatr Hematol Oncol* 1990;12:402–10. [PubMed: 2285121]
16. Mathé G, Amiel JL, Schwarzenberg L, et al. Bone marrow graft in man after conditioning by antilymphocytic serum. *Br Med J* 1970;2:131–6. [PubMed: 4909449]

17. Territo MC. Autologous bone marrow repopulation following high dose cyclophosphamide and allogeneic marrow transplantation in aplastic anaemia. *Br J Haematol* 1977;36:305–12. [PubMed: 329854]
18. Brown KE, Tisdale J, Barrett AJ, et al. Hepatitis-associated aplastic anemia. *N Engl J Med* 1997;336:1059–64. [PubMed: 9091802]
19. Ganapathi KA, Townsley DM, Hsu AP, et al. GATA2 deficiency-associated bone marrow disorder differs from idiopathic aplastic anemia. *Blood* 2015;125:56–70. [PubMed: 25359990]
20. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic mutations and clonal hematopoiesis in aplastic anemia. *N Engl J Med* 2015;373:35–47. [PubMed: 26132940]
21. Ogawa S. Clonal hematopoiesis in acquired aplastic anemia. *Blood* 2016;128: 337–47. [PubMed: 27121470]
22. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* 2015;126:9–16. [PubMed: 25931582]
23. Katagiri T, Sato-Otsubo A, Kashiwase K, et al., Japan Marrow Donor Program. Frequent loss of HLA alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. *Blood* 2011;118:6601–9. [PubMed: 21963603]
24. Babushok DV, Duke JL, Xie HM, et al. Somatic HLA mutations expose the role of class I-mediated autoimmunity in aplastic anemia and its clonal complications. *Blood Adv* 2017;1:1900–10. [PubMed: 28971166]
25. Stanley N, Olson TS, Babushok DV. Recent advances in understanding clonal haematopoiesis in aplastic anaemia. *Br J Haematol* 2017;177:509–25. [PubMed: 28107566]
26. Risitano AM, Schrezenmeier H. Alternative immunosuppression in patients failing immunosuppression with ATG who are not transplant candidates: campath (Alemtuzumab). *Bone Marrow Transplant* 2013;48:186–90. [PubMed: 23222381]
27. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *N Engl J Med* 2012;367:11–9. [PubMed: 22762314]
28. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007;357:2237–47. [PubMed: 18046028]
29. Sidhu A, Callaghan MU, Gadgeel MS, et al. Evidence for increased response to induced endoplasmic reticulum stress in myeloid cells in acquired aplastic anemia. *J Pediatr Hematol Oncol* 2017;39:e163–6. [PubMed: 28333839]
30. Longerich S, Li J, Xiong Y, et al. Stress and DNA repair biology of the Fanconi anemia pathway. *Blood* 2014;124(18):2812–9. [PubMed: 25237197]
31. Golde DW, Hocking WG, Quan SG, et al. Origin of human bone marrow fibroblasts. *Br J Haematol* 1980;44:183–7. [PubMed: 6990960]
32. Bartsch K, Al-Ali H, Reinhardt A, et al. Mesenchymal stem cells remain host-derived independent of the source of the stem-cell graft and conditioning regimen used. *Transplantation* 2009;87:217–21. [PubMed: 19155975]
33. Balderman SR, Calvi LM. Biology of BM failure syndromes: role of microenvironment and niches. *Hematology Am Soc Hematol Educ Program* 2014;2014:71–6. [PubMed: 25696837]
34. Bueno C, Roldan M, Anguita E, et al. Bone marrow mesenchymal stem cells from patients with aplastic anemia maintain functional and immune properties and do not contribute to the pathogenesis of the disease. *Haematologica* 2014;99: 1168–75. [PubMed: 24727813]
35. Wu L, Mo W, Zhang Y, et al. Impairment of hematopoietic stem cell niches in patients with aplastic anemia. *Int J Hematol* 2015;102:645–53. [PubMed: 26440975]
36. Wu L, Mo W, Zhang Y, et al. Vascular and perivascular niches, but not the osteoblastic niche, are numerically restored following allogeneic hematopoietic stem cell transplantation in patients with aplastic anemia. *Int J Hematol* 2017;106: 71–81. [PubMed: 28303517]
37. Lee JH, Lee JH, Shin YR, et al. Spontaneous remission of aplastic anemia: a retrospective analysis. *Haematologica* 2001;86:928–33. [PubMed: 11532620]
38. Kwon JY, Lee Y, Shin JC, et al. Supportive management of pregnancy-associated aplastic anemia. *Int J Gynaecol Obstet* 2006;95:115–20. [PubMed: 16934813]

39. Bacigalupo A. How I treat acquired aplastic anemia. *Blood* 2017;129:1428–36. [PubMed: 28096088]
40. Jeong DC, Chung NG, Cho B, et al. Long-term outcome after immunosuppressive therapy with horse or rabbit antithymocyte globulin and cyclosporine for severe aplastic anemia in children. *Haematologica* 2014;99:664–71. [PubMed: 24213150]
41. Yang N, Chen J, Zhang H, et al. Horse versus rabbit antithymocyte globulin in immunosuppressive therapy of treatment-naïve aplastic anemia: a systematic review and meta-analysis. *Ann Hematol* 2017;96(12):2031–43. [PubMed: 28965225]
42. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. *N Engl J Med* 2011;365:430–8. [PubMed: 21812672]
43. Alsultan A, Goldenberg NA, Kaiser N, et al. Tacrolimus as an alternative to cyclosporine in the maintenance phase of immunosuppressive therapy for severe aplastic anemia in children. *Pediatr Blood Cancer* 2009;52:626–30. [PubMed: 19148946]
44. Gamper CJ, Takemoto CM, Chen AR, et al. High-dose cyclophosphamide is effective therapy for pediatric severe aplastic anemia. *J Pediatr Hematol Oncol* 2016;38:627–35. [PubMed: 27467367]
45. Scheinberg P, Nunez O, Weinstein B, et al. Activity of alemtuzumab monotherapy in treatment-naïve, relapsed, and refractory severe acquired aplastic anemia. *Blood* 2012;119:345–54. [PubMed: 22067384]
46. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. *N Engl J Med* 2017;376:1540–50. [PubMed: 28423296]
47. Bacigalupo A, Socié G, Schrezenmeier H, et al., Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT). 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;97:1142–8. [PubMed: 22315497]
48. Atta EH, de Sousa AM, Schirmer MR, et al. Different outcomes between cyclophosphamide plus horse or rabbit antithymocyte globulin for HLA-identical sibling bone marrow transplant in severe aplastic anemia. *Biol Blood Marrow Transplant* 2012;18:1876–82. [PubMed: 22796534]
49. Bacigalupo A, Socié G, Hamladji RM, et al., Aplastic Anemia Working Party of the European Group for Blood Marrow Transplantation. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. *Haematologica* 2015;100:696–702. [PubMed: 25616576]
50. Kekre N, Zhang Y, Zhang MJ, et al. Effect of antithymocyte globulin source on outcomes of bone marrow transplantation for severe aplastic anemia. *Haematologica* 2017;102:1291–8. [PubMed: 28341733]
51. 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. *Br J Haematol* 2012;15:339–46.
52. Yagasaki H, Takahashi Y, Hama A, et al. Comparison of matched-sibling donor BMT and unrelated donor BMT in children and adolescent with acquired severe aplastic anemia. *Bone Marrow Transplant* 2010;45:1508–13. [PubMed: 20118992]
53. Yoshimi A, Strahm B, Baumann I, et al. Hematopoietic stem cell transplantation in children and young adults with secondary myelodysplastic syndrome and acute myelogenous leukemia after aplastic anemia. *Biol Blood Marrow Transplant* 2014; 20:425–9. [PubMed: 24316460]
54. Lawler M, McCann SR, Marsh JC, et al., Severe Aplastic Anaemia Working Party of the European Blood and Marrow Transplant Group. Serial chimerism analyses indicate that mixed haemopoietic chimerism influences the probability of graft rejection and disease recurrence following allogeneic stem cell transplantation (SCT) for severe aplastic anaemia (SAA): indication for routine assessment of chimerism post SCT for SAA. *Br J Haematol* 2009;144:933–45. [PubMed: 19183198]
55. Onishi Y, Mori T, Kako S, et al., Adult Aplastic Anemia Working Group of the Japan Society for Hematopoietic Cell Transplantation. Outcome of second transplantation using umbilical cord blood for graft failure after allogeneic hematopoietic stem cell transplantation for aplastic anemia. *Biol Blood Marrow Transplant* 2017;23(12):2137–42. [PubMed: 28844947]

56. Chan KW, McDonald L, Lim D, et al. Unrelated cord blood transplantation in children with idiopathic severe aplastic anemia. *Bone Marrow Transplant* 2008;42: 589–95. [PubMed: 18695669]
57. DeZern AE, Zahurak M, Symons H, et al. Alternative donor transplantation with high-dose post-transplantation cyclophosphamide for refractory severe aplastic anemia. *Biol Blood Marrow Transplant* 2017;23:498–504. [PubMed: 28013015]
58. Maruyama K, Aotsuka N, Kumano Y, et al. Immune-mediated hematopoietic failure after allogeneic hematopoietic stem cell transplantation: a common cause of late graft failure in patients with complete donor chimerism. *Biol Blood Marrow Transplant* 2018;24(1):43–9. [PubMed: 28860001]

KEY POINTS

- Refractory cytopenias of childhood, inherited bone marrow failure syndromes, and familial disorders associated with myelodysplasia or immune dysregulation should be investigated during the diagnosis of acquired aplastic anemia.
- Although pancytopenia is the norm at diagnosis, it must be kept in mind that isolated cytopenias may be the predominant presenting symptom, along with milder decreases in other lineages in some cases.
- The role of autoimmune reaction targeting hematopoietic stem cells is well-understood in the pathogenesis of acquired aplastic anemia; however, alterations in stem cells leading to this response or, in other words, drivers of autoimmunity are not clearly identified.
- Although matched related donor hematopoietic stem cell transplantation is the treatment of choice with great outcomes, immunosuppressive therapy provides response in two-thirds of the patients who do not have matched family donors. Alternative donor transplants have been associated with much improved results in recent years.
- Acquired aplastic anemia can be associated with hematopoietic stem cell clonal disorders: paroxysmal hemoglobinuria can accompany at diagnosis or develop later. Clonal abnormalities leading to myelodysplasia and acute myeloid leukemia may follow immunosuppressive therapy.