THE SIGNIFICANCE OF MODERN TREATMENT MODALITIES: IMMUNOSUPPRESSIVE THERAPY AND BONE MARROW TRANSPLANTATION IN APLASTIC ANEMIA

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ABSTRACT

Aplastic anemia (AA) is a rare but life-threatening hematological disorder characterized by bone marrow failure, resulting in pancytopenia and significant morbidity and mortality. The management of AA has undergone remarkable transformation over recent decades, with two principal therapeutic modalities—immunosuppressive therapy (IST) and allogeneic hematopoietic stem cell transplantation (HSCT)—forming the cornerstone of modern treatment algorithms. This comprehensive review examines the current state and clinical significance of these approaches in the management of AA. The pathophysiological basis of acquired AA involves a cytotoxic T-cell-mediated autoimmune attack against hematopoietic stem cells, providing the rationale for IST. Standard IST combining antithymocyte globulin (ATG) with cyclosporine achieves overall response rates of 60-70%, while the addition of thrombopoietin receptor agonists such as eltrombopag has revolutionized outcomes, improving both response rates and response quality. Concurrently, advances in transplantation technology—including improved HLA typing, reduced-intensity conditioning regimens, post-transplant cyclophosphamide for GVHD prophylaxis, and expansion of donor options to include matched unrelated and haploidentical donors—have made HSCT safer and more accessible. The choice between IST and HSCT depends on multiple factors including patient age, comorbidities, donor availability, and disease severity. Emerging evidence supports upfront alternative donor transplantation in selected populations, challenging traditional treatment paradigms. This review synthesizes current evidence from recent clinical trials, meta-analyses, and international guidelines, providing a comprehensive overview of modern AA management and future therapeutic directions.

Keywords: *Aplastic anemia, immunosuppressive therapy, hematopoietic stem cell transplantation, antithymocyte globulin, eltrombopag, haploidentical transplantation, bone marrow failure, cyclosporine*

INTRODUCTION

Aplastic anemia (AA) represents a rare but potentially fatal hematological disorder characterized by peripheral blood pancytopenia and hypocellular bone marrow in the absence of abnormal infiltration or fibrosis [Piekarska et al., 2024, p. 2]. The condition, first described at the turn of the 19th and 20th centuries, affects individuals across all age groups with a reported incidence of 2-3 per million population annually in Western countries, though higher rates have been documented in Asia [Piekarska et al., 2024, p. 2]. The clinical consequences of bone marrow failure are profound: patients experience complications related to anemia (fatigue, dyspnea), neutropenia (recurrent, often severe infections), and thrombocytopenia (bleeding manifestations ranging from petechiae to life-threatening intracranial hemorrhage).

The modern understanding of acquired AA pathophysiology centers on immune-mediated destruction of hematopoietic stem cells. Compelling evidence implicates activated cytotoxic T lymphocytes in targeting and eliminating the stem cell compartment, leading to progressive bone marrow failure [Piekarska et al., 2024, p. 3]. This autoimmune process, sustained by type I interferons and polarized T-helper responses, provides the scientific rationale for immunosuppressive approaches that have become mainstays of treatment.

Historically, AA carried a dismal prognosis, with most patients succumbing to complications within months of diagnosis. The therapeutic landscape began transforming in the 1970s with the introduction of bone marrow transplantation and subsequently immunosuppressive therapy. Today, these two modalities represent complementary approaches whose optimal application requires nuanced understanding of patient characteristics, disease features, and available resources.

The Camitta criteria classify AA severity based on bone marrow cellularity and peripheral blood counts. Severe AA (SAA) is defined by bone marrow cellularity below 25% and at least two of three peripheral blood criteria: absolute neutrophil count (ANC) below 0.5×10^9/L, platelet count below 20×10^9/L, and reticulocyte count below 20×10^9/L (manual) or 60×10^9/L (automated) [Piekarska et al., 2024, p. 2]. Very severe AA (vSAA) further requires ANC below 0.2×10^9/L. These distinctions carry therapeutic and prognostic implications.

This review examines the contemporary roles of immunosuppressive therapy and hematopoietic stem cell transplantation in AA management, evaluating their indications, outcomes, limitations, and evolving applications in light of recent clinical advances.

LITERATURE REVIEW

Historical Evolution of Treatment Paradigms - The treatment of aplastic anemia has evolved substantially over five decades. Early efforts focused on supportive care with blood product transfusions and antibiotics, yielding median survival of only 3-6 months. The first successful allogeneic bone marrow transplantation for AA was

reported in 1972, establishing a curative option for patients with matched sibling donors [Maringka & Lestarini, 2024, p. 2]. Concurrently, observations of spontaneous hematologic recovery in patients receiving immunosuppressive preparations for transplantation led to the development of IST as an alternative treatment modality.

The 1980s and 1990s witnessed refinement of both approaches. Standard IST with horse ATG (hATG) and cyclosporine achieved overall response rates of 60-70%, while transplantation outcomes improved with better HLA typing, supportive care, and graft-versus-host disease (GVHD) prophylaxis. The past decade has brought transformative advances: the incorporation of thrombopoietin receptor agonists (TPO-RAs) into IST regimens and expansion of transplantation options to include alternative donors.

Pathophysiological Basis for Current Therapies - Acquired AA is now understood as an organ-specific autoimmune disease targeting hematopoietic stem cells. The immune destruction is mediated by activated cytotoxic T lymphocytes that secrete myelosuppressive cytokines including interferon-γ and tumor necrosis factor-α [Piekarska et al., 2024, p. 3]. These cytokines induce Fas-mediated apoptosis of CD34+ cells and impair residual hematopoiesis.The immune pathogenesis explains both the efficacy of IST and the rationale for allogeneic HSCT. IST aims to abrogate the autoimmune attack, allowing recovery of residual stem cells. HSCT replaces both the target (diseased hematopoietic compartment) and the effector (recipient immune system) through donor-derived hematopoiesis and immune reconstitution.

Recent genomic studies have illuminated clonal dynamics in AA. Approximately one-third of patients harbor somatic mutations in genes associated with myeloid malignancies, including ASXL1, DNMT3A, and TP53 [Piekarska et al., 2024, p. 4]. Some mutations, particularly in PIGA and BCOR/BCORL1, confer favorable prognosis and lower risk of clonal evolution, while others predict inferior IST response and increased risk of transformation to myelodysplastic syndrome or acute myeloid leukemia. These findings have implications for treatment selection and monitoring.

Diagnostic Considerations and Differential Diagnosis - Accurate diagnosis precedes treatment decisions. The evaluation of suspected AA must exclude inherited bone marrow failure syndromes, particularly in children and young adults. Fanconi anemia, dyskeratosis congenita, and other telomeropathies may present with apparently acquired AA but carry different therapeutic implications and prognostic considerations [Piekarska et al., 2024, p. 4]. Comprehensive genetic testing has identified unrecognized inherited syndromes in 6.6% of patients clinically diagnosed with acquired AA, with implications for transplant outcomes and family counseling.

Paroxysmal nocturnal hemoglobinuria (PNH) testing is mandatory, as PNH clones are detectable in 40-50% of AA patients and influence prognosis [Piekarska et al., 2024, p. 4]. Cytogenetic analysis helps exclude hypocellular myelodysplastic

syndrome, though normal karyotype is typical in AA. Viral studies, including hepatitis viruses, parvovirus B19, CMV, and EBV, may identify treatable triggers.

DISCUSSION

Immunosuppressive Therapy: Current Standards and Innovations - Standard IST combines antithymocyte globulin with cyclosporine. Horse ATG (hATG) has demonstrated superiority over rabbit ATG and, after a period of limited availability, has been restocked in Europe since 2022, making it the preferred formulation [Piekarska et al., 2024, p. 2]. The combination yields overall response rates of 60-70% at 6 months, with complete responses in 10-20% of patients. The landmark addition of eltrombopag—an oral thrombopoietin receptor agonist—to IST has revolutionized outcomes for patients ineligible for transplantation. The National Institutes of Health phase 2 study demonstrated that adding eltrombopag to standard IST increased overall response rates to 80-90% and complete response rates to 40-50% [Yang et al., 2024, p. 2]. Importantly, responses were faster, more robust, and durable, with reduced transfusion requirements and improved quality of life.

Subsequent studies have confirmed these findings. The RACE trial (Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia) reported significantly higher response rates with the triple combination of hATG, cyclosporine, and eltrombopag compared to IST alone [Peffault de Latour et al., 2022, cited in Piekarska et al., 2024, p. 5]. Long-term follow-up suggests that improved response quality translates into reduced relapse risk and possibly lower rates of clonal evolution, though continued monitoring remains essential.

Avatrombopag, a second-generation TPO-RA with potential advantages including absence of hepatotoxicity and food-dependent absorption, has shown promise in early studies. Li and colleagues reported that adding avatrombopag to IST improved complete response rates at 3 months (19.0% vs. 4.8%, P=0.024) and overall response rates at 6 months (71.4% vs. 51.2%, P=0.048) compared to IST alone [Li et al., 2024, p. 2]. Event-free survival was also improved, and no hepatic injury was observed even in patients with pre-existing liver impairment.

Age-related differences in IST response have been documented. Historical data showed inferior outcomes in adults compared to children receiving IST alone. However, Yang and colleagues recently demonstrated that adding eltrombopag eliminates this disparity: adults receiving IST plus eltrombopag achieved 12-month overall response rates of 89% compared to 73% in children, with no differences in complete response rates or time to response [Yang et al., 2024, p. 3]. This finding has important implications for adult patients previously considered suboptimal IST candidates.

Hematopoietic Stem Cell Transplantation: Expanding Access and Improving Outcomes - Allogeneic HSCT remains the only curative treatment for AA,

restoring normal hematopoiesis through donor stem cell engraftment. Matched sibling donor (MSD) transplantation is the preferred first-line option for eligible patients, particularly those under 40-50 years of age, with long-term survival exceeding 80-90% in contemporary series [Liu et al., 2024, p. 2].

The major recent evolution in transplantation for AA has been expansion of donor options. For patients lacking MSDs, matched unrelated donor (MUD) transplantation has become increasingly feasible and effective. Improved HLA typing at allelic level, better GVHD prophylaxis, and optimized conditioning regimens have yielded outcomes approaching those of MSD transplantation. A Spanish multicenter study of upfront MUD transplantation in pediatric SAA demonstrated excellent outcomes with careful donor selection and short time to transplant [Uria-Oficialdegui et al., 2024, p. 2].

Haploidentical transplantation—using partially matched family donors—represents the most significant advance in expanding transplant access. With the introduction of post-transplant cyclophosphamide for GVHD prophylaxis, haploidentical HSCT has become a viable option for nearly all patients lacking matched donors. Piekarska and colleagues note that post-transplant cyclophosphamide has "revolutionized the field, offering promising outcomes also in AA" [Piekarska et al., 2024, p. 6].

Comparative Effectiveness: IST versus HSCT - The choice between IST and HSCT requires balancing multiple factors including age, donor availability, disease severity, comorbidities, and patient preference. Recent prospective studies have provided valuable comparative data. Liu and colleagues conducted a multicenter prospective study comparing first-line haploidentical HSCT (n=147) versus IST plus eltrombopag (n=121) in SAA patients [Liu et al., 2024, p. 2]. Results revealed nuanced outcomes: 86.3% of transplant recipients achieved normal complete blood count at 6 months compared to 24.1% in the IST group ($P<0.001$). Time to transfusion independence and neutrophil recovery were significantly shorter with transplantation. However, 3-year overall survival favored IST plus eltrombopag in patients under 40 years (92.4% vs. 82.8%, $P=0.017$), while failure-free survival favored transplantation (81.6% vs. 69.4%, $P=0.002$). In patients over 40 years, overall survival was similar between groups, but failure-free survival remained superior with transplantation (82.4% vs. 58.7%, $P=0.043$). Subgroup analysis suggested that patients with vSAA benefited more from upfront transplantation regardless of age. Quality of life assessments significantly favored transplantation, with haplo-HSCT recipients reporting better scores across multiple domains ($P<0.0001$) [Liu et al., 2024, p. 3]. This finding challenges assumptions that IST offers better quality of life by avoiding transplant-related morbidity. For hepatitis-associated aplastic anemia (HAAA)—a distinct variant comprising approximately 5% of cases where pancytopenia follows

acute hepatitis by 2-3 months—a systematic review and meta-analysis by Hong and colleagues compared HSCT versus IST [Hong et al., 2025, p. 1]. Analyzing 12 studies with 544 patients, HSCT demonstrated superior outcomes with lower overall mortality ($P<0.01$), higher overall response rates ($P<0.001$), and improved 5-year survival ($P<0.05$). The survival advantage was most pronounced in patients under 20 years, supporting early transplantation in this population.

Special Populations: Pediatric Considerations - Children with SAA present unique considerations. Higher response rates to IST, longer life expectancy, and greater vulnerability to transplant-related complications including GVHD and late effects influence treatment selection. Historically, IST was often preferred for children lacking MSDs due to concerns about alternative donor transplantation. This paradigm is shifting. Uria-Oficialdegui and colleagues reported excellent outcomes with upfront MUD transplantation in pediatric SAA, with careful donor selection enabling survival rates comparable to MSD transplantation [Uria-Oficialdegui et al., 2024, p. 3]. The availability of high-resolution HLA typing, better supportive care, and improved GVHD prophylaxis have contributed to these outcomes. The European Society for Blood and Marrow Transplantation (EBMT) and North American Pediatric Aplastic Anemia Consortium guidelines increasingly recognize upfront alternative donor transplantation as a reasonable option for children lacking MSDs, particularly those with vSAA or poor prognostic features [Piekarska et al., 2024, p. 7].

Emerging Therapeutic Approaches - Several innovations are expanding therapeutic options. Second-generation TPO-RAs including avatrombopag and romiplostim offer alternatives to eltrombopag with potentially improved safety profiles. Avatrombopag's lack of hepatotoxicity makes it particularly attractive for patients with liver dysfunction, including those with HAAA [Li et al., 2024, p. 3].

Optimization of IST protocols continues. The reintroduction of hATG in Europe has standardized care, while investigation of optimal cyclosporine duration and tapering schedules aims to reduce relapse. Combination approaches pairing TPO-RAs with other immunomodulatory agents are under investigation.

In transplantation, reduced-intensity conditioning regimens incorporating fludarabine, cyclophosphamide, and low-dose total body irradiation or alemtuzumab have reduced regimen-related toxicity while maintaining engraftment. Post-transplant cyclophosphamide has enabled successful haploidentical transplantation across all age groups [Piekarska et al., 2024, p. 6].

Challenges and Limitations - Despite progress, significant challenges remain. Approximately 10-20% of patients fail to respond to IST plus TPO-RA and require salvage transplantation. Relapse occurs in 10-30% of responders, and clonal evolution to MDS/AML affects 5-10% of patients over long-term follow-up [Piekarska et al., 2024, p. 5]. Identification of patients at highest risk for these complications through

genomic profiling and telomere length assessment may enable risk-adapted strategies. Transplantation carries risks of graft failure (5-10% with current protocols), acute and chronic GVHD (20-40% depending on donor type and prophylaxis), and opportunistic infections. Late effects including infertility, endocrinopathies, and secondary malignancies require lifelong surveillance. Access to optimal care remains uneven. hATG availability has been inconsistent, TPO-RAs are costly, and transplantation expertise is concentrated in specialized centers. Patients in resource-limited settings face substantial barriers to optimal treatment.

RESULTS

Outcomes with Contemporary Immunosuppressive Therapy - The incorporation of eltrombopag into standard IST has transformed response expectations. The NIH cohort receiving hATG, cyclosporine, and eltrombopag achieved overall response rates of 80-90% at 6 months, with complete responses in 40-50% [Yang et al., 2024, p. 2]. Median time to response was 3 months, significantly faster than historical controls. Transfusion independence was achieved in most responders, and quality of life improved substantially. Long-term follow-up from the NIH study demonstrated durable responses with continued eltrombopag maintenance. At 2 years, overall survival exceeded 95% in responders, though continued monitoring for clonal evolution remains essential [Piekarska et al., 2024, p. 5]. Avatrombopag combined with IST yielded comparable outcomes in a retrospective propensity-matched study. At 6 months, overall response rate was 71.4% versus 51.2% with IST alone (P=0.048), with complete response rates of 31.0% versus 14.3% [Li et al., 2024, p. 2]. Importantly, no hepatotoxicity was observed, suggesting potential advantages for patients with liver dysfunction. Age-related outcomes with IST plus eltrombopag showed elimination of the historical pediatric advantage. Adults achieved 12-month overall response of 89% versus 73% in children (P=0.027), with similar complete response rates (54% vs. 50%) [Yang et al., 2024, p. 3]. Time to response and complete response were comparable between age groups, supporting IST plus TPO-RA as a viable option for adults.

Outcomes with Hematopoietic Stem Cell Transplantation - Matched sibling donor transplantation in contemporary series yields overall survival of 85-95% at 5 years, with graft failure rates below 5% and grade III-IV acute GVHD below 10% [Liu et al., 2024, p. 3]. Chronic GVHD remains a challenge, affecting 20-30% of recipients and impacting long-term quality of life. Matched unrelated donor transplantation outcomes have improved substantially. The Spanish pediatric MUD cohort reported 2-year overall survival of 92% with careful donor selection and short time to transplant [Uria-Oficialdegui et al., 2024, p. 4]. Graft failure occurred in 8%, and moderate-severe chronic GVHD in 12%, comparable to MSD outcomes. Haploidentical transplantation using post-transplant cyclophosphamide has emerged as a viable option for patients lacking matched donors. In the prospective comparison by Liu and colleagues,

haploidentical HSCT achieved 3-year overall survival of 82.8% and failure-free survival of 81.6%, with acceptable GVHD rates [Liu et al., 2024, p. 3]. Complete hematologic recovery was achieved in 86.3% by 6 months, significantly exceeding IST plus eltrombopag. For hepatitis-associated AA, meta-analysis demonstrated superior outcomes with HSCT compared to IST. Pooled relative risk for overall response was 1.67 (95% CI: 1.15-2.44) favoring HSCT, with improved 5-year survival (RR 0.88, 95% CI: 0.78-0.99) [Hong et al., 2025, p. 2]. The advantage was most pronounced in patients under 20 years, supporting early transplantation in this subgroup.

Comparative Outcomes by Treatment Strategy

The prospective comparison of first-line haploidentical HSCT versus IST plus eltrombopag revealed important trade-offs [Liu et al., 2024, p. 4]:
• **Hematologic recovery**: Faster with HSCT (median time to neutrophil >1.0 × 10^9/L: 12 days vs. 3 months)
• **Complete response at 6 months**: 86.3% (HSCT) vs. 24.1% (IST) (P<0.001)
• **3-year overall survival (<40 years)**: 82.8% (HSCT) vs. 92.4% (IST) (P=0.017)
• **3-year failure-free survival (<40 years)**: 81.6% (HSCT) vs. 69.4% (IST) (P=0.002)
• **Quality of life**: Significantly better with HSCT across multiple domains (P<0.0001)

These results highlight that survival alone does not capture the full therapeutic picture. HSCT offers higher likelihood of complete hematologic recovery and better quality of life but carries early mortality risk that impacts overall survival in younger patients. IST offers excellent survival with lower early risk but lower rates of complete recovery and higher likelihood of treatment failure requiring subsequent intervention.

CONCLUSION

The management of aplastic anemia has evolved dramatically over recent decades, with immunosuppressive therapy and hematopoietic stem cell transplantation representing complementary approaches whose optimal application requires nuanced clinical judgment. The addition of thrombopoietin receptor agonists to standard IST has improved response rates and quality, making this regimen increasingly attractive for patients ineligible for or deferring transplantation. Concurrent advances in transplantation—particularly expansion of donor options through matched unrelated and haploidentical donors—have made curative therapy accessible to nearly all patients.

The choice between IST and HSCT is no longer binary but involves consideration of patient age, disease severity, donor availability, comorbidity profile, and patient preference. For young patients with matched sibling donors, MSD-HSCT remains the preferred first-line option. For those lacking MSDs, the decision between IST plus TPO-RA and alternative donor transplantation requires weighing the excellent survival with IST against the higher likelihood of complete hematologic recovery and better quality of life with transplantation. Very severe AA, poor-risk genomic features, and age under 20 years (particularly in hepatitis-associated AA) favor transplantation.

Several priorities for future research emerge from this review. Longer-term follow-up of patients receiving IST plus TPO-RA is needed to fully characterize risks of relapse and clonal evolution. Optimization of TPO-RA selection and dosing may further improve outcomes while minimizing toxicity. Refinement of transplant conditioning regimens and GVHD prophylaxis aims to reduce regimen-related mortality and late effects while maintaining engraftment. Identification of biomarkers predicting response to each modality would enable truly personalized treatment selection.

Access to optimal care remains a global challenge. hATG availability must be secured, TPO-RA costs addressed, and transplant expertise disseminated to ensure that advances benefit all patients regardless of geography or resources. International collaboration through registries and clinical trials will accelerate progress and ensure that emerging evidence translates into improved outcomes.

In conclusion, modern treatment of aplastic anemia exemplifies the power of translational medicine—understanding disease pathogenesis has enabled rational therapeutic targeting, while clinical investigation has refined application of complementary modalities. Patients diagnosed with this once-uniformly fatal condition now face multiple treatment options with excellent prospects for long-term survival and quality of life.

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