Special issues related to the diagnosis and management of acquired aplastic anemia in countries with restricted resources, a report on behalf of the Eastern Mediterranean blood and marrow transplantation (EMBMT) group and severe aplastic anemia working party of the European Society for blood and marrow transplantation (SAAWP of EBMT)

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ARTICLE

Special issues related to the diagnosis and management of acquired aplastic anemia in countries with restricted resources, a report on behalf of the Eastern Mediterranean blood and marrow transplantation (EMBMT) group and severe aplastic anemia working party of the European Society for blood and marrow transplantation (SAAWP of EBMT)

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Abstract

Aplastic anemia is a relatively rare but potentially fatal disorder, with a reported higher incidence in developing countries in comparison to the West. There are significant variations in epidemiological as well as etiological factors of bone marrow failure syndromes in the developing countries in comparison to the developed world. Furthermore, the management of bone marrow failure syndromes in resource constraint settings has significant challenges including delayed diagnosis and referral, limited accessibility to healthcare facilities, treatment modalities as well as limitations related to patients who require allogeneic stem cell transplantation. Here we will provide a review of the available evidence related to specific issues of aplastic anemia in the developing countries and we summarize suggested recommendations from the Eastern Mediterranean blood and bone marrow transplantation (EMBMT) group and the severe aplastic anemia working party of the European Society of blood and marrow transplantation (SAAWP of EBMT) related to the diagnosis and therapeutic options in countries with restricted resources.

Introduction

Aplastic anemia (AA) is characterized by pancytopenia with a hypocellular marrow in the absence of abnormal infiltrates or reticulin fibrosis [1]. It is a rare disease in North America and the West in general, with a higher incidence in Asia [2] and Africa [3]. In the absence of aggressive supportive care, immunosuppressive therapy (IST) and allogeneic hematopoietic cell transplant (allo-HCT) most severe aplastic anemia (SAA) patients die from infections and other cytopenia-related complications [4]. Management of AA in resource-constrained settings is challenging for various

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reasons, including but not limited to affordability, availability, accessibility, sociocultural values, sustainability, and impaired referral systems. Health sectors in developing countries are also marked by urban–rural disparities in healthcare facilities and an imbalance in the workforce, with insufficient doctors, nurses, and paramedics in the rural peripheral areas. Consequently, the management strategies must be tailored according to the available diagnostic and therapeutic resources for a rapidly fatal disease if left untreated [5]. This perspective is a joint work of an expert team from the Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) Group and Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (SAAWP of EBMT) focusing on special considerations of AA-management in the resource-constrained settings.

Epidemiology and pathogenesis

Most data regarding the epidemiology of AA is derived from western literature [6–10] with only few published studies from the developing world [2, 11–16]. As noted above, marked geographic variation exist with higher prevalence in Asia [2, 11] and Africa [3] as compared to Europe and the United States (US) [2, 17]. Demographics, clinical features and care considerations of AA patients presenting in countries with restricted resources is summarized in Table 1.

The incidence of AA is 2–3 cases/million inhabitants per year in US, Europe [18], and France [19], whereas, it is 2–3 folds higher in Asia [20] with variable rates between different Asian countries (7.4/million in China, 3.7–5.0/million in Thailand [21], 4.8/million in Malaysia [22] 6.8/million in India [23], 3.9/million in Bangkok, 5.16/million in Korean children [24], and 6–7/million in Pakistan) [11]. A report from Tanzania also confirmed the higher incidence (5.9/million) as compared to European and US data [3].

Table 1 Demographics, clinical features, and care considerations.

Demographics
• Overall younger median age
• Higher proportion of male patients presenting with aplastic anemia
Etiology
• Higher proportion of inherited BMF syndrome as a result of marital consanguinity and larger family size
• Family history of blood disorders or inherited syndromes
• Higher prevalence of HBV and HCV infection is some Asian countries
• Drug induced bone marrow failure due to usage of herbal and alternative remedies
• Limited access to genomic testing to ascertain possibility of inherited bone marrow failure syndromes
Access to care
• Long delay before presentation to specialized care center with the consequences of multiple transfusions and infectious complications
• Inadequate provision of healthcare facilities in rural areas and distances from specialized centers

Age distribution in developing counties

The incidence in developed countries is bimodal, with a first peak at 15–24 years of age and a second peak at age greater than or equal to 65 years [19]. Conversely, in developing countries, there is a single peak with a median age of presentation being 22 years in Nigeria [25] and 25 years in India with almost half of the cases occurring during the first three decades of life [15]. One of the largest published epidemiological studies came from Pakistan on 1324 cases of AA reported median age of 20 years with 87% of the patients younger than 40 years [11]. The second peak is less obvious, probably due to the lower life expectancy in the developing countries [25]. The younger median age of the population and high prevalence of marital consanguinity should alert the practitioner about the possible higher incidence of cryptic type of inherited bone marrow failure syndromes (IBMF) including Fanconi anemia (FA) and dyskeratosis congenita (DC) among others.

Sex ratio

The male-to-female ratio is ~1:1 in the developed countries [26], but more males seem to be reported in the developing countries with a male-to-female ratio of 3.4:1 in Malaysia [22], 1.2:1 in Korea [24], 2.3:1 in India [15], and 2.8:1 in Pakistan [27], even though one can expect that being an immunologically mediated disorder, AA would be more common in females. This difference could be as a result of social bias as in a rural setting in particular, where males may have more and faster access to healthcare and hence, this may contribute to predominance of male sex patients in developing countries [11].

Etiology

Earlier reports suggested sporadic occurrence with lack of an apparent cause [28]. Later reports suggested some occupational relation (e.g.,: Swedish bicycle makers and exposure to benzene) [29, 30]. There is no satisfactory explanation to the reported difference in geographical incidence of AA although this is likely attributable to

combination of environmental and genetic factors [31]. The inherited form of bone marrow failure (BMF) represents up to 10% of adults and 25% of children presenting with AA [32]. Most cases however, are idiopathic and acquired. While the cause of marrow failure cannot be identified in the majority of patients with idiopathic AA, as mentioned above, a high consanguinity and early age of onset may point toward some genetic predisposition in the pathogenesis of BMF in developing countries. This warrants a careful clinical and laboratory evaluation for accurate diagnosis to rule out underlying inherited disorders in patients with BMF, though needed laboratory facilities for genetic diagnosis are not available at most resource constraint countries as discussed below.

Genetic predisposition

Various studies suggest a genetic predisposition as the cause of high incidence of AA among Asian populations. A study by McCahon et al. evaluated the incidence of AA in people of Asian descent, residing in British Columbia, Canada. A selected pediatric cohort (0–14 years) was included in the study to minimize effect of environmental factors. A higher incidence of AA was found in children of East/ Southeast Asian descent (6.9/million/year) and South Asian descent (7.3/million/year) as compared to those of white/mixed ethnic descent (1.7/million/year). The study concluded that increased incidence of AA is mainly related to genetic predisposition among Asian children [33] and for the environmental factors to be of less relevance [33]. It has been reported that 1/3 of the Asian population lacks aldehyde dehydrogenase, an important enzyme involved in the metabolism of alcohol. This deficiency leads to the accumulation of acetaldehyde which causes irreversible DNA damage to the hematopoietic stem cells and eventually AA [34].

Kojima [2] reported a significantly increased frequency of certain human leukocyte antigens (HLA) amongst Asian AA patients that were not observed in AA patients of white or mixed race. Rehman et al. studied HLA allele frequency in patients with AA and compared it with healthy controls. The study concluded that HLA DRB1*15 may be a susceptible allele and DRB1*03 may be a protective allele in Pakistani AA patients [35]. Another study from Pakistan found that single nucleotide polymorphism of FAS/FASL system results in aberrant apoptosis as compared to controls, which supports the immune pathogenesis of AA [13]. Another study from Pakistan by Akram et al. showed higher levels of granulocyte colony stimulating factor (G-CSF) and thrombopoietin among AA patients as compared to healthy controls and TERC, TERT mutations in 4.6% of study population [12].

A significantly higher incidence of deletion of genes involved in detoxifying enzymes glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) was reported in Korean AA patients when compared to healthy Korean population. This deficiency could lead to a reduction in the ability to metabolize environmental toxins and hence, potentially increase the risk of developing AA [36]. A similar study from Pakistan by Rehman et al. found GSTM0 polymorphism in 49.6% of AA patients as compared to 30% among control ($p = 0.006$) [14].

Environmental factors

AA can occur as idiosyncratic complication of certain drugs (chloramphenicol, allopurinol, etc.) [37]. Irradiation and viruses, can lead to AA [38]. Benzene is the oldest and most widely accepted etiological agent [29, 30]. Other exposures including pesticides [39] (carbamates, DDT, organophosphate, etc.) [40], arsenic and unsafe drinking water [38] were also associated with higher AA incidence. In rural Thailand, organophosphates, carbamates and paraquat exposure was found to carry significant risk of AA [21]. The study from Pakistan, however, did not show significant association with exposure to chemicals, pesticide and drugs [11]. Additionally, low socioeconomic status, illiteracy and rural residence were linked to higher AA incidence by different groups [23, 41]. Another proposed etiology for AA in developing countries is infectious etiology, serving as trigger of autoimmunity [9]. Post-hepatitis AA is a very well recognized cause: However, studies from Thailand and Korea have documented similar incidence of post-hepatitis AA as compared to western data [21, 42]. In addition, water source and use of animal fertilizers have been reported as likely etiological factors, but data from different studies is conflicting [9, 11, 43].

Diagnosis of AA in resource-constrained setting

Low incidence, overlap with other entities presenting with hypocellular marrow and lack of clear clinical delineation between inherited and acquired BMF makes diagnosis of AA challenging [44]. Disorders such as hypoplastic MDS, hypoplastic AML, PNH, large granular lymphocytic leukemia (LGL), lymphoma infiltrating marrow, mycobacterial infection, and anorexia nervosa can be difficult to differentiate from AA [1]. A careful family history and thorough physical examination is essential to rule out IBMF. History of anemia, myelodysplasia, acute leukemia or dysmorphic features among siblings and first-degree relatives should raise the suspicion of underlying constitutional BMF [45].

In addition, history of drug intake, exposure to toxins, recent infection, pregnancy and autoimmune disorders are relevant in assessing underlying cause of AA. The onset of AA is often insidious with symptoms related to decreased marrow production of hematopoietic cells. Majority of the patients present with fatigue, pallor and shortness of breath; symptoms related to anemia. Other presentations due to neutropenia or thrombocytopenia include neutropenic fever, respiratory tract and skin infections, easy bruising, petechiae, gum bleeding and at times, life-threatening hemorrhage [15, 46, 47]. A number of patients may present with severe thrombocytopenia and progress over weeks to months to pancytopenia [48]. Workup of AA requires confirmation of diagnosis, assessment of underlying cause, excluding probable differential diagnosis, assessing complications and workup for specific treatment. Due to resource constraints selection of patients for genetic testing may be based upon detailed clinical and family history plus physical examination. Figure 1 provides a diagnostic algorithm of AA in resource-constrained settings. Obviously secondary causes such as folate and cobalamin deficiency and other secondary causes needs to be excluded beforehand.

Issues related to the overall management

Healthcare delivery in most of the developing countries is poorly developed due to combination of factors like availability, accessibility, sociocultural values, economic affordability, sustainability, and impaired referral systems [49]. Significant urban–rural disparities in healthcare services exist, with lower numbers of medical and paramedical personnel in the peripheral areas. All this leads to delays in diagnosis and referrals, which in the case of AA leads to two important consequences, the acquisition of multiple infections and excessive transfusions leading to significant alloimmunization [48]. Moreover, irradiation of blood products is almost nonexistent, and directed family donation of blood products is widely practiced. There is also a trend for seeking treatment from faith healers, alternative and traditional medicine practitioners and indiscriminate use of steroids. By the time the patients present to the proper healthcare facility, platelet refractoriness, severe infections, malnutrition, and poor performance status have already developed [50].

Allo-HCT remains the only curative treatment option for the majority of SAA patients [51]. Despite improvements in transplant outcomes in last decade [52–54], the role of HCT is less clear in patients with non-severe disease and older adults [1]. In western countries, improvements in supportive care, improvements in IST responses by addition of eltrombopag to horse antithymocyte globulin (hATG) and cyclosporine (CsA) has led to the use of IST as first line treatment in older adults with SAA and younger patients lacking a MRD or MUD with favorable outcomes [1]. In developing countries, the delay in diagnosis (with subsequent infections and excessive transfusions), lack of adequate supportive care and transfusion services, financial constraints, limited access to (hATG) and eltrombopag, limited numbers of transplantation centers and prolonged waiting time prior to HCT, absence of MUD registries and experience with alternate donor transplant contribute to poor treatment outcomes [55]. Obviously countries with transplant centers available should make it a priority to get young patients with matched siblings to transplant rapidly, i.e., needs education logistics.

Issues related to supportive care

Supportive care in AA aims to alleviate symptoms of pancytopenia as a bridge to specific therapy [48]. Infectious complications (mainly bacterial and fungal) and life-threatening bleeding are responsible for majority of deaths in AA patients. In resource-limited settings, aim should be to reduce the risk of infectious and bleeding-related deaths by adequate prophylaxis and timely intervention. As it applies to all AA cases, patients should take adequate hygienic precautions, which can be an issue in developing countries, be advised to avoid exposure to construction sites, potted plants, garbage and compost to reduce risk of mold infections especially aspergillosis. Patients should be counseled regarding hand washing, avoiding use of dry fruits, unwashed fruits and uncooked vegetables and other appropriate dietary restrictions [56]. Regular oral care with saline rinses, chlorhexidine mouthwash, and nystatin oral suspension is advisable. In addition, meticulous general body care with daily baths and good toilet hygiene is recommended. Antibacterial and antifungal prophylaxis should be considered for patients with VSAA and selected high risk patients after IST or HCT. A mold active azole (posaconazole, voriconazole, if not available itraconazole) should be used for prophylaxis [1]. Some generic mold active azoles are available in many developing countries. Antiviral prophylaxis is recommended on case-to-case basis and for post-HCT patients.

Transfusion is recommended for patients with hemoglobin <70 g/l and platelets $<10 \times 10^9$/L. A higher hemoglobin threshold is needed for elderly and those with comorbidities [1]. Repeated platelet transfusions lead to sensitization and platelet refractoriness. Since HLA matched platelets are frequently not available and there is limited availability of single donor platelets in resource-constrained settings, our recommendation for platelets transfusions are to transfuse if count is $<5 \times 10^9$/l in

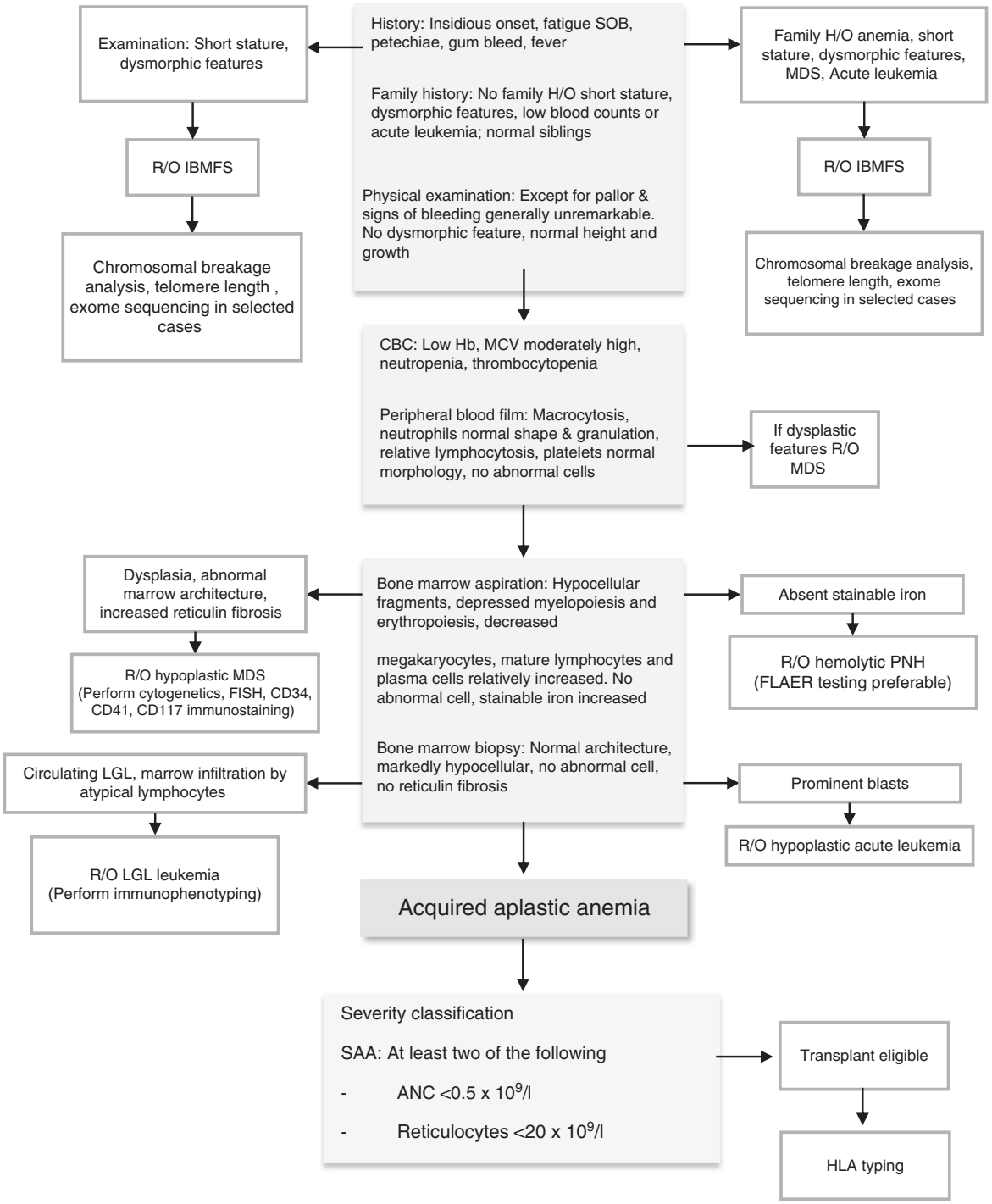

Fig. 1 Diagnostic algorithm for aplastic anemia patients; Essential components include a detailed history, physical examination, bone marrow examination, PNH testing and chromosomal breakage analysis to exclude IBMFS, PNH, and MDS. H/O history of, R/O rule out, SOB shortness of breath, IBMFS inherited bone marrow failure syndromes, PNH paroxysmal nocturnal hemoglobinuria, MDS myelodysplastic syndromes.

asymptomatic young patients and $<10 \times 10^9$/l with any signs of bleeding. The threshold for platelet transfusion for febrile neutropenia should be at a higher cutoff ($<20 \times 10^9$/l). As noted earlier, repeated red cell and platelet transfusions increase the risk of both HLA and non-HLA alloimmunization, leading to platelet refractoriness and increased risk of graft rejection for potential candidates for HCT [1]. Leukodepleted and irradiated blood products, if available, should preferably be used for all patients.

There are few reports on use of adjuvant granulocyte transfusion in patients with severe infections due to neutropenia from USA [57] and India [58]. However, risk of

worsening of preexisting lung injury and other potential adverse effects of granulocyte transfusion should be considered; hence the routine use of granulocyte transfusion may not be recommended. There is no evidence to support the use of erythropoietin or G-CSF in AA patients and their routine use is not recommended [59].

Immunosuppressive therapy

While high response rates have been reported with IST using horse ATG plus cyclosporine ± eltrombopag particularly in young patients [60], in most of developing countries, access to hATG is limited and responses to rATG are disappointing [61]. Substantial proportion of the patients do not survive immediate cytopenia resulting from ATG administration and others do not survive long enough to witness the response following ATG based combination treatments. As the use and availability of ATG are limited in the developing world, the experience to deal with its complications is limited.

Indications of IST

Frontline IST is indicated for NSAA patients who are transfusion dependent, having bleeding or recurrent infections. For SAA/VSAA, frontline IST can be used in transplant ineligible patients (lacking a suitable donor and older adults) [1]. The optimal outcomes are reported with the combination of CsA, hATG, and eltrombopag [60, 62]. However, the prohibitive cost of hATG and eltrombopag limit their use in resource-constrained settings.

Cyclosporine monotherapy

Cyclosporine is typically used in combination with ATG as IST, but due to nonavailability of ATG particularly horse ATG, financial constraints and lack of adequate blood components and other support facilities; it has been used as a single agent for treatment of acquired AA [63]. Most of the available evidence of CsA monotherapy outcomes come from small single center reports. A study by Maschan et al. in pediatric patients showed overall response rate (ORR) (CR + PR) of 45% with CsA monotherapy [64]. In another study of CsA monotherapy use in 57 patients from India, the ORR was 19.6% at 6 months; the median age was 37 years (range 6–81 years) [65]. A study from Yemen resulted in 14.3% CR and 35.7% PR at 6 months and 78.6% OS at 1 year [63]. Unpublished data from the Armed Forces Bone marrow transplant center; Rawalpindi, Pakistan on a large cohort of 355 AA patients, showed an ORR of 30.9% (CR 12.9%, PR 18%) with the use of CsA monotherapy (P. Ahmed personal communication). Higher responses were seen in patients with less severe disease (54% in NSAA, 28% in SAA, and 9% in VSAA patients). These data suggest that CsA monotherapy can be used for selected patients with NSAA if there is no access to hATG/eltrombopag.

Combination IST

Combination CsA + hATG has resulted in superior response rates (40–68%) in AA patients treated with frontline IST [60, 66]. Use of hATG has been associated with higher responses as compared to rATG in most studies [66–68], moreover, rATG is more immunosuppressive and associated with high infectious deaths according to EBMT and Spanish data, an issue of great importance in countries with limited access to supportive care and effective antimicrobials, particularly effective antifungal agents [1, 69].

Addition of eltrombopag to standard IST (CsA + hATG) yielded marked improvement of responses without increasing toxicity [60]. In resource-constrained setting, the cost of adding eltrombopag to CsA and hATG is prohibitive. In many developing countries, the cost of IST using triple combination remarkably exceeds the total cost of HCT procedure in local centers. A prospective trial (NCT04328727) is planned to recruit patients from East Asia using CsA + eltrombopag. Studies employing different IST in AA from resource constraint countries are summarized in Table 2. Addition of other immunosuppressive agents (mycophenolate mofetil, and sirolimus) did not improve the response rates [66, 70].

Use of eltrombopag as a single agent

Use of single agent eltrombopag is associated with favorable responses in AA patients. A French nationwide survey showed 46% response rate at 6 months [71]. Ecsedi et al. performed a retrospective survey on the use of eltrombopag among EBMT member countries and reported 62% ORR [72]. Similarly, a study from Japan reported 55% response rate [73]. Eltrombopag monotherapy may be useful in selected cases (those with renal dysfunction, active infection) requiring IST. Again, the prohibitive cost of eltrombopag limits its availability, however, it has the great advantage of simplicity and relative safety to administer compared to ATG in less experienced centers.

Hematopoietic stem cell transplantation

A meta-analysis of 15 studies comparing HCT with IST for patients with AA has shown superiority of first line MRD-HCT over IST [74]. Allo-HCT should be the first line treatment in patients ≤50 years of age with

Table 2 Studies performed in developing countries comparing responses of different immunosuppressive treatments in AA.

Study	Year of publication/country	Study design	Type of IST	Number (*n*)	Age years median (range)	Overall response	Overall survival
Atta et al. [107]	2010/Brazil	Retrospective	hTAG vs. rATG	42 and 29	21 (4–63)	60% vs. 35%	78% vs. 55%
Shin and Lee [108]	2013/South Korea	Retrospective	hTAG vs. rATG	46 and 53	37 (15–66)	39% vs. 45%	48% vs. 51%
Agarwal et al. [109]	2015/India	Prospective	hATG + CsA	30	30 (9–58)	50%	–
Al-Ghazaly et al. [63]	2005/Yemen	Prospective	CsA	14	22 (10–48)	50%	78.6% at 1 yr
Zheng et al. [110]	2006/China	Prospective	hATG alone	142	34 (2–71)	57.6%	70%
			hATG + CsA			78.7%	91%
			hATG + CsA + growth factors			73%	83%
			rATG + CsA			53%	78%
AFBMTC (unpublished data)	Pakistan	Retrospective	CsA alone	355	23 (2–85)	30.9%	65%
			CsA + hATG	25		48%	71%
			CsA + rATG	69		30.4%	53%

CsA Cyclosporine, *hATG* horse antithymocyte globulin, *rATG* rabbit antithymocyte globulin, *AFBMTC* Armed Forces Bone Marrow Transplant Center.

SAA/VSAA if MRD is available. Studies have shown better disease-free survival in younger patients undergoing MRD transplant when compared with IST as frontline therapy [74]. For patients receiving upfront MRD-HCT, long-term survival is more than 90% for young children [75] and more than 80% for adolescents [76]. For patients between 40–50 years without MRD and those >50 years of age with MRD, the frontline treatment should be individualized based on transplant risk factors, physical status, comorbidities, disease severity, genetic markers and probability of responding to IST [77]. Although treatment with triple therapy (ATG, CSA, and eltrombopag) has good outcome, the HCT option may be more affordable and readily available in many developing countries. Older patients with VSAA may be considered for upfront HCT if they are fit and have MRD. Recent data from King's College Hospital London showed similar outcomes in patients > or < than 50 years old receiving MRD and MUD transplant [78]. With encouraging results using haploidentical transplants [79–81], this option should be considered if MUD is not available in centers having experience with haploidentical transplants. At present, haploidentical transplant remains the only practical alternate donor option for HCT in countries with restricted resources. Various risk factors are associated with poor HCT outcomes including increasing age, longer disease duration, higher transfusion burden, active infection, comorbidities, and disease severity at presentation. As mentioned earlier, many of these risk factors are highly prevalent in developing countries. In addition, center's experience with mismatched and alternate donor transplant and availability of essential drugs and blood components should guide the treatment decision. Figure 2 shows proposed treatment algorithm for acquired SAA.

Donor choice and availability

MRD availability may reach more than 50% in many developing countries due to the large family size; hence MRD constitutes the main donor source in developing countries. While MUD and UCB are available in most of the developed world, it is not an attractive option for resource-constrained countries. The reasons are: less likelihood of finding a suitable donor in the international unrelated donor registries due to under representation of some ethnic groups in donor registries; high cost and difficult logistics of transporting stem cell product; delay in finding suitable HLA match, lack of expertise for MUD transplantation in most centers, and nonavailability of local donor registries. On the other hand, haploidentical donors are readily available and virtually every patient has a donor, with the resultant increased interest in haploidentical transplant for patients with AA [82]. In developed countries, outcomes of MUD are comparable to MRD transplants for children and most guidelines [83] now recommend upfront MUD for children lacking MRD with OS exceeding 90% [84]. Recent reports comparing haplo-HCT with MUD transplant in children and adolescent revealed little differences in OS [85, 86]. In a study involving 89 patients with SAA, 41 patients received haplo-HCT while 48 patients had MUD. Three-year OS was 85.4% with no statically significant difference

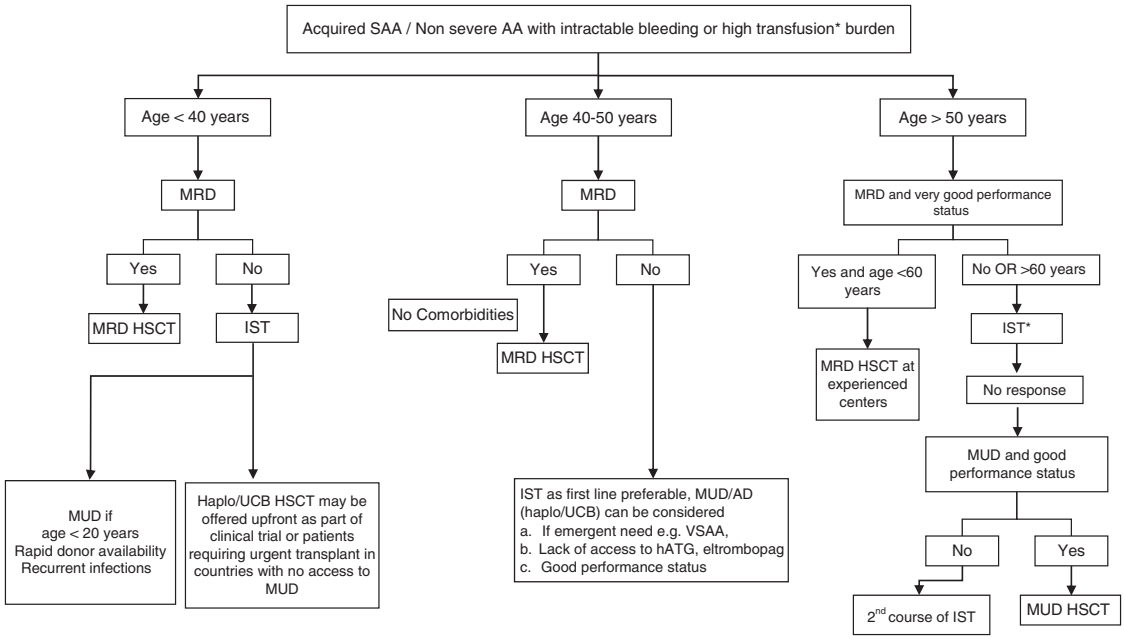

Fig. 2 Proposed treatment algorithm of AA in resource-constrained countries. MRD matched related donor, MUD matched unrelated donor, IST immunosuppressive treatment, Haplo Haploidentical, CB cord blood, IST cyclosporine, horse antithyomcyte globulin, and eltrombopag.

between haplo-HCT and MUD-HCT in terms of 3-year OS (80.3% vs. 89.6%, $p = 0.210$) and 3-year FFS (76.4% vs. 89.4%, $p = 0.127$) [87]. Another retrospective study compared the results from patients who were treated with haplo-HCT to patients treated with MRD-HCT. The study reported statistically significant difference favoring MRD-HCT with 3-year OS (82.8% vs. 75%, $p < 0.001$) [88]. Although, haplo-HCT group showed inferior 3-year OS in comparison with the MRD-SCT group, the numbers are still acceptable and show promising efficacy in patients who are not candidate for IST or have failed IST.

Stem cell source and dose

Bone marrow is the preferred stem cell source for patients undergoing MRD transplant for AA [1, 89, 90]. Data from EBMT and CIBMTR showed superior outcomes with BM as compared to peripheral blood stem cells (PBSC) grafts [90, 91]. In special circumstances PBSCs can be preferred as in cases of donor–patient weight disparity or in patients with active infections where early neutrophil engraftment is needed and in patients at high risk of graft failure. A CIBMTR study comparing outcomes of BM vs. PBSC as graft source for MRD in SAA across different economic regions concluded that PBSC graft may be an appropriate graft source in countries with limited resources when treating patients at high risk of graft failure and infectious complications [92]. Some centers prefer G-CSF primed bone marrow over PBSCs when a higher stem cell count is targeted, as primed BM grafts may have less GvHD [93].

Compared to HCT for malignant diseases, the stem cell dose requirement is higher for AA patients in order to avoid graft failure. The preferred dose is $>3 \times 10^6$/kg CD34 or $>3 \times 10^8$/kg TNC [1]. The optimal dose for haplo-HCT is not known, but generally higher doses (CD34 $> 5 \times 10^6$/kg) are preferred by most centers [81, 94].

Conditioning regimens and GVHD prophylaxis

The choice of conditioning regimen depends on the type of transplant, patient's age, presence of risk factors for graft rejection, comorbidities, and center experience. The standard conditioning regimen for MSD is cyclophosphamide 200 mg/kg (CY 200) and ATG, as originally described by Storb et al. [95]. Recent EBMT data suggest that survival of patients older than 40 years can be improved with a fludarabine-based regimen, in addition to ATG or alemtuzumab (CAMPATH). Current guidelines from EBMT and the British Society for Standards in Hematology call for a combination of FLU-CY with ATG (FCA) or alemtuzumab (CAMPATH) (FCC) for patients with SAA who are older than 30 years and receiving a matched sibling donor transplant [1, 96, 97]. The CY dose to be combined with FLU is a matter of discussion, ranging from 40 to 120 mg/kg. In resource-limited countries and where availability of ATG is problematic, fludarabine with cyclophosphamide is an

Table 3 Considerations related to aplastic anemia management in resource-constrained countries.

Donor related
• Large family size, with a higher likelihood of finding a related sibling donor
• Possibility of finding a non-sibling related donor in consanguineous pedigrees
• Alternate donor HCT
∘Mostly focused on related haplo HCT
∘Limited number of local unrelated donor registers
∘Limited access to international MUD registry donors
∘Low likelihood of finding a match in international registries
∘Limited cord blood banks and limited access to international cord blood banks
Cost
• The cost of performing related HCT is lower in developing countries than combined IST using hATG, CsA, and eltrombopag
Conditioning and GVHD prophylaxis
• Limited access to ATG
• Limited availability of radiation therapy facilities
• Consider Flu/Cy conditioning where ATG is not available
• Consider the use of peripheral blood as a graft source in heavily transfused patients particularly with preexisting infection
• May consider the use of CSA and MMF as GVHD prophylaxis in the presence of significant infections to avoid delay in count recovery with methotrexate administration
Viral Infections
• High prevalence of CMV seropositivity, in patients and donors and hence higher risk of CMV reactivation post HCT: vigilant CMV monitoring and preemptive treatment strategy is required
• Higher prevalence of Hepatitis B and/or hepatitis C in patients and donors: appropriate viral hepatitis treatment/prophylaxis in HCT recipients is required in consultation with hepatology service
Nontransplant treatment
• Consider treatment with CsA alone in the absence of ATG and/or eltrombopag
• Use of androgens
• Use of tranexamic acid to reduce risk or severity of mucosal bleeding episodes in patients with severe thrombocytopenia
• Gynecological referral and/or hormonal therapy for menstrual bleeding in female patients
Supportive care
• Use generic azoles, antimicrobials, G-CSF, and oral chelating agents
• Limiting routine platelet transfusion to a cutoff of 5×10^9/L in the absence of bleeding
• Limiting routine packed red cell transfusions to cutoff of 70 g/L

CsA Cyclosporine, *MMF* mycophenolate mofetil, *ATG* antithyomcyte globulin, *Flu/Cy* fludarabine and cyclophosphamide, *CMV* cytomegalovirus, *G-CSF* granulocyte colony stimulating factor.

alternative [55, 98]. TBI based conditioning is used in haplo-HCT, HCT from alternate donor and for some patients at a high risk for graft rejection. The TBI option is not available in some HCT centers in developing countries. A phase 2 study NCT03955601 is being carried out on outcome without TBI in patient with SAA receiving haplo-HSCT.

Recommendations for conditioning regimens and GVHD prophylaxis in resource-limited countries are summarized in Table 3. Monitoring levels of CsA and tacrolimus (Tac) is recommended with optimal levels around 200–300 ng/ml for CsA and 10–15 ng/ml for Tac. Consideration should be given for using generic alternative of calcineurin inhibitors for cost reduction purposes as traditionally AA HCT patient will remain on calcineurin inhibitors for longer duration than many other transplantation indications. A very slow tapper of calcineurin inhibitors should be carried out, avoiding discontinuation of calcineurin inhibitors before 9 months after HSCT with full count recovery. This is to be followed by a very slow and extended tapper with careful follow up on counts in every step of dose reduction. This should be strictly followed in all patients, but in heavily pre transfused patient in particular.

Post-HCT monitoring of blood counts and donor chimerism

Unlike malignant diseases, the conditioning used for AA is nonmyeloablative. This requires optimum manipulation of the posttransplant immunosuppression to balance the risk of GvHD and graft rejection. About 10% of patient experience low blood counts with poor graft function. These patients show improvement in blood counts after stepping up immunosuppression. Some of the patients show normalization of blood count following administration of low dose prednisolone e.g., 10–15 mg/day for 2–4 weeks. If donor chimerism continues to fall despite increase in immunosuppression, patient is likely to have late graft rejection and may need rescue stem cell boost with or without conditioning. As noted above, we recommend continuing immunosuppression in full dose for at least 9 months and subsequently very gradual tapper over 3–6 months with blood count check with every tapper step.

Regular surveillance by post-HCT chimerism has become an important investigation to monitor graft function and to assess need for any preemptive therapeutic intervention. Chimerism studies, preferably split chimerism should be done at day +30, at 3, 6, 9, and 12 months post-HCT. Low initial donor chimerism is more likely to represent a poor graft function while decreasing donor chimerism over time is more likely to indicate impending immune mediated graft rejection. Lineage specific chimerism with progressively decreasing donor T-cell and NK-cell predict late graft failures. Risk factors for graft rejection are increasing patient age, heavy pre-transplant sensitization, CMV reactivation, ABO mismatch, and low stem cell dose. In resource-limited centers, FISH studies for sex chromosomes in sex mismatched transplants can be used to monitor graft status post HCT.

Posttransplant infections

Cytomegalovirus infection

Data from EMBMT shows very high cytomegalovirus (CMV) seropositivity among donors and recipients undergoing HCT reaching close to a 100% in many Eastern Mediterranean region countries [99]. High seroprevalence is

also documented from other centers in the region [100]. Reactivation of CMV posttransplant can be a major concern for AA patients as it is among causes of secondary graft failure, can lead to CMV disease and drugs used to treat CMV can lead to myelosuppression and graft failure. Accordingly, vigilant preemptive treatment of CMV viremia by monitoring post-HCT PCR according to standard risk-based strategy should be followed. Letermovir will be an optimal to use in high CMV seropositivity HCT population however the prohibitive coast of this medication is a major issue about its availability.

Hepatitis status and HCT in AA

The prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) is high among patients with AA in developing countries due to multiple exposures to sub optimally screened blood products, with higher seroprevalence in middle and older age patients. Active HCV infection is not an absolute contraindication for HCT unless complicated by decompensated chronic liver disease. For nonurgent transplant cases and patients with less severe cytopenias, a consultation with a hepatologist regarding the appropriateness of treatment with the new oral HCV drugs should be considered before HCT with most of patients achieving PCR reduction within few weeks. For patients requiring urgent transplant, they can proceed to HCT unless they have significant elevation in liver enzymes and they shall be monitored for level of viremia and treated for HCV post HCT [101]. Patients with active HBV infection are likely to develop fulminant hepatitis during transplant, accordingly, it is preferable for these patients to be treated with the appropriate antiviral before transplantation. Newer antiviral therapies are very effective and lead to PCR negativity in short time. Of note, HCV and HBV infections may increase the risk of hepatic VOD/SOS post HCT [101].

Tuberculosis (TB)

Recipients of HCT should be asked about prior history, current symptoms or signs suggestive of TB or contact with patient with active TB. Tuberculin skin testing (TST) and interferon gamma release assay (IGRA) should be done to look for latent TB. For patient with active TB, standard antituberculosis treatment (ATT) should be started and transplant deferred until active infection is settled. Many centers in developing counties would defer HCT until after induction phase of ATT (8 weeks) is completed and patient becomes asymptomatic. Continuation of rifampicin post treatment is challenging due to interaction with CsA. For such patients, we switch to modified ATT comprising of isoniazid, ethambutol, moxifloxacin posttransplant and continue ATT until patient is off immunosuppression. Recipients with positive TST or IGRA in absence of active TB needs prophylactic regimen for latent TB until immunosuppression is completed [101]. Diagnosis of tuberculosis in posttransplant patient is challenging and may need exhaustive workup due to paucibacillary nature of infection in immunocompromised patients. For donors with active TB, transplant should be deferred until symptoms are settled and induction phase of treatment with 4 drugs is completed. There is no evidence to suggest transmission of TB from donors having latent TB [101].

HSCT survival statistics; comparison with developed world

Advances in conditioning regimens, GVHD prophylaxis and supportive care has significantly improved transplant outcomes of AA. OS >90% is reported from developed countries especially in children. Burroughs et al. reported OS of 100% in children receiving MRD grafts for AA in Seattle, US [102], Marsh et al. reported median OS of 95% in adult patients receiving MRD, and 83% among patients receiving MUD using FCC regimen [103]. A recent cohort study from Sweden involving 68 patients with SAA who were treated with HCT either first line or second line reported a 5-year OS of 86%. The study also reported a better 5-year OS for patients who got first line HCT compared to the patients who got HCT later during management (96% versus 81.4% $P = 0.095$). A significant survival benefit was observed in patients age ≤18 years with 5-year OS of 96.3% compared to 80.5% in patients ≥19 years ($P = 0.064$). However, no difference in OS was observed between MRD and MUD recipients (5-year OS: 90.6% versus 83.3% $P = 0.411$) [104].

Several HCT outcome reports have been published from developing countries. One of the largest single center study from developing countries by Chaudhry et al. reported that 97% of patients receiving transplant had 1 or more high risk features. The study included 147 high risk patients transplanted using fludarabine-based conditioning with reported OS of 84% [55]. George et al. reported superior OS with fludarabine-based regimen (82.8%) as compared to Cy 200/antilymphocyte globulin (46.1%) [105]. Another study by Iftikhar et al. comparing fludarabine-based versus conventional cyclophosphamide conditioning documented OS (85.8% vs. 77.2%; $p = 0.15$), DFS (84.1% vs. 68.4%; $p = 0.02$) and GRFS (77.9% vs. 54.4%; $p = 0.01$) with fludarabine-based conditioning [98]. Jalili et al. reported OS of 82% and DFS 75% in Iranian patients receiving MRD transplant [106]. Overall, although the reported HCT outcome are encouraging, it remains lower than data reported from developed countries. Possible explanations include factors mentioned above.

Conclusion

Despite better understanding of disease pathogenesis and availability of advanced treatment options, management of acquired AA still remains a challenge in most of the developing world due to inadequate healthcare facilities. AA is more prevalent in the developing countries and seen more often in younger age groups. Various genetic factors may play a role in disease susceptibility among some populations and it is important to rule out underlying IBMF by appropriate investigations. Upfront allogeneic HCT using MRD or MUD is the best treatment option for majority of the patients. Recent advancements in haploidentical transplants with encouraging results means that most of the younger patients without MRD or MUD should be able to get bone marrow transplant. IST using horse ATG and cyclosporine with or without addition of eltrombopag is associated with up to 70–80% response and can be offered to older patients or patients unfit for transplant due to comorbidities. Due to lack of access to advanced healthcare facilities, essential drugs, and optimum blood component support; certain changes can be made in the established protocols without compromising the outcomes. Long-term survival in the order of 70–80% is achievable in the resource-constrained countries for a disease that was historically associated with very high mortality.

Bone marrow transplant centers in most of the developing world lack advanced facilities like high resolution HLA typing, infectious disease support for diagnosis of fungal and viral infections, prestorage leukodepletion, molecular hematology laboratories for assessment of genetic mutations, donor registries, limited access to international registries, limited cord blood banks, and optimally trained human resource. Not all centers have the access to TBI as part of conditioning regimen, as a result non-TBI based conditioning protocols are more often used. All these factors have to be integrated when decisions are made on how to best treat an AA patient in a resource-limited setting.

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