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Diagnosis and Treatment of Pediatric Acquired Aplastic Anemia (AAA): an Initial Survey of the North American Pediatric Aplastic Anemia Consortium (NAPAAC)

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The authors disclose no conflict of interest relevant to this manuscript.

Abstract

Background—Randomized clinical trials in pediatric aplastic anemia (AA) are rare and data to guide standards of care are scarce.

Procedure—Eighteen pediatric institutions formed the North American Pediatric Aplastic Anemia Consortium to foster collaborative studies in AA. The initial goal of NAPAAC was to survey the diagnostic studies and therapies utilized in AA.

Results—Our survey indicates considerable variability among institutions in the diagnosis and treatment of AA. There were areas of general consensus, including the need for a bone marrow evaluation, cytogenetic and specific fluorescent in-situ hybridization assays to establish diagnosis and exclude genetic etiologies with many institutions requiring results prior to initiation of immunosuppressive therapy (IST); uniform referral for hematopoietic stem cell transplantation as first line therapy if an HLA-identical sibling is identified; the use of first-line IST containing horse anti-thymocyte globulin and cyclosporine A (CSA) if an HLA-identical sibling donor is not identified; supportive care measures; and slow taper of CSA after response. Areas of controversy included the need for telomere length results prior to IST, the time after IST initiation defining a treatment failure; use of hematopoietic growth factors; the preferred rescue therapy after failure of IST; the use of specific hemoglobin and platelet levels as triggers for transfusion support; the use of prophylactic antibiotics; and follow-up monitoring after completion of treatment.

Conclusions—These initial survey results reflect heterogeneity in diagnosis and care amongst pediatric centers and emphasize the need to develop evidence-based diagnosis and treatment approaches in this rare disease.

Keywords

Acquired aplastic anemia; NAPAAC; diagnosis; treatment

Introduction

Aplastic anemia is a rare disorder most with a bi-modal age presentation, arising both early and late in life (1). Although aplastic anemia is relatively rare in childhood, its medical impact remains high with life-threatening consequences entailing complex medical therapies and potential long-term complications. Published evidence to guide clinical management of aplastic anemia in children remains scarce. The rapidly growing armamentarium of tests for genetic factors contributing to aplastic anemia raises new questions with regard to diagnostic workup and treatment decisions.

Methods

Because of the paucity of data to guide medical management of aplastic anemia in children, eighteen pediatric hematology centers with an interest in aplastic anemia have initiated the North American Pediatric Aplastic Anemia Consortium (NAPAAC). The NAPAAC collaborative working group conducted a survey of its members to determine current practices for the diagnostic workup, treatment, and medical management of pediatric aplastic anemia in North America.

Results

Diagnosis definition, severity classification and initial diagnostic evaluations

We surveyed 18 children's hospitals in the United States and Canada regarding laboratory-based diagnostic and treatment practices for pediatric aplastic anemia. All institutions completed the survey in its entirety. Sixty percent of the respondents used criteria for severe aplastic anemia (SAA) modified after those described by Camitta and colleagues (2) with an absolute neutrophil count (ANC) <500/μL, platelets < 20,000/μL and absolute reticulocytes <20,000/μL and bone marrow (BM) cellularity <25% for age. Forty percent of respondents noted that two out of three blood count criteria along with marrow hypocellularity were sufficient. The absolute reticulocyte count (ARC) required for diagnosis varied among some institutions between <40,000 to <60,000/μL. An ANC <200/μL uniformly defined very severe aplastic anemia (vSAA) from SAA. Three respondents used the ARC to distinguish SAA (ARC <60,000/μL) from vSAA (ARC <40,000/μL). Taken together, these institutions see approximately 75–80 new patients ages 1–18/year with acquired aplastic anemia.

Moderate AA (mAA) was defined in 60% of the centers as Hb <10 g/dL, ANC <1,500/μL, platelets <50,000/μL, ARC <40,000/μL, and BM cellularity 25–50%. Some institutions used a platelet count <60,000/μL and/or BM cellularity <50% for the diagnosis of mAA. Several institutions utilized broader criteria comprising any abnormal decreased blood count with a hypocellular BM and not fulfilling the criteria for SAA or vSAA.

All 18 centers uniformly included BM cytogenetics in the diagnostic work-up at presentation (Table I). Sixty percent of institutions included fluorescent in situ hybridization (FISH) studies for monosomy 7, 5q-, and 8 chromosome gain, while 22% included chromosomes 22q-, 20, and 9 FISH probes. Over 90% of those who do cytogenetics or FISH would await these results prior to IST or hematopoietic stem cell transplantation (HSCT). Two-thirds of respondents analyzed BM for T, B, and $CD34^+$ cells by flow cytometry. Eighty-nine percent evaluated paroxysmal nocturnal hemoglobinuria (PNH) by flow cytometry. Almost all (94%) respondents performed HLA typing of patient and siblings, while 78% of institutions routinely included parental typing at the time of diagnosis.

Diagnostic tests to exclude viral causes of AA included EBV, CMV, and hepatitis A, B and C in 80% of centers. The status of HIV, HSV, VZV, or HHV6 was also evaluated in 33–44% of centers, while parvovirus B19 was assayed in <17% of institutions. Eleven percent of respondents did not do viral testing at initial evaluation. Of the centers that do viral testing, up to 70% would await results prior to therapy. Approximately half of respondents measured vitamin B12 and folate levels, while a similar proportion (44%) assessed immune function by measuring lymphocyte numbers, T and B cell subsets and immunoglobulin levels.

Evaluations for constitutional etiologies—Most respondents excluded inherited bone marrow failure syndromes which would lead to alternative therapies (Table I). Eighty-nine percent of institutions performed testing for Fanconi anemia (FA). Fifty-eight percent of those institutions which perform these tests delay IST or HSCT until results are available. Sixty-seven percent performed telomere length analysis for dyskeratosis congenita (DC). If

telomere length testing was suspicious for DC, follow-up genetic testing was typically sent. Additionally, a diagnosis or suspicion of DC or FA led to testing of family members. Some centers utilized DC testing upon re-evaluation of patients whose disease is refractory to IST and for research purposes (see below). As an initial molecular diagnostic workup, 71% ordered sequencing of the *Shwachman-Bodian-Diamond* syndrome gene (*SBDS)*, while 40% of respondents evaluated genes causing DC (*DKC1*, *TERT*, *TERC*, *TINF2*, *NOP10/NHP2*) and the and amegakaryocytic thrombocytopenia-associated gene (*c- MPL*, the thrombopoietin receptor). Biochemical, radiographic, and ultrasound investigations for internal physical anomalies for SBDS, FA and Diamond-Blackfan Anemia (DBA), were infrequently (0–22%) performed as a routine diagnostic workup for aplastic anemia.

Initial Treatment of SAA

There was consensus to proceed with a matched sibling donor (MSD) HSCT if a donor was identified at the time of initial diagnosis of SAA or vSAA. Thirty eight percent of respondents, however, would consider IST as primary treatment despite the availability of a MSD under certain circumstances. These circumstances include family concerns regarding fertility (39%), family preference for IST (28%), an anticipated delay of greater than 6–8 weeks until HSCT (33%), and significant psycho-social barriers to BMT (28%). If the blood counts dropped during CSA tapering, 78% would repeat bone marrow testing, and 39% would perform additional work-up including evaluation for inherited marrow failure (e.g. telomere length and *SBDS* testing, if not previously performed) and flow cytometry for PNH. In this situation, 83% would increase the CSA dose in an effort to re-induce remission. Seventy-five percent of respondents did not feel comfortable using autologous cord blood as a source for HSCT.

Immunosuppression Therapy—All but one of the institutions used an IST regimen consisting of anti-thymocyte globulin (ATG) and cyclosporine A (CSA). The remaining institution utilized high-dose cyclophosphamide alone for immunosuppression. The majority of institutions (67%) consider initiating IST within 21 days of diagnosis to be very important for successful outcome. All institutions would utilize horse ATG rather than rabbit ATG for initial IST. Most commonly the patients receive a test dose of ATG followed by 40 mg/kg/dose daily for 4 days, but 25% of institutions treat patients for 5 days. The ATG is given over 4–10 hours with most centers using an 6–8 hour infusion duration. Half of the centers escalate the dose of ATG slowly on the first day of treatment. Premedication with diphenhydramine and acetaminophen is common. Methylprednisolone is added by the majority of centers to minimize the risk for serum sickness as well as to reduce infusion reactions. Most protocols include intravenous methylprednisolone 2 mg/kg/day with ATG, given every 6 or 12 hours, which is changed to oral prednisone to complete a 4–14 day course followed by a tapering schedule. The institutions vary with respect to the location where IST is carried out, utilizing either positive pressure single occupancy rooms (50%), standard single occupancy rooms (44%), an open general hematology ward with two or more patients (28%), or a bone marrow transplant ward (17%).

ATG is uniformly given with CSA. Most commonly used CSA formulations were Neoral® or Gengraf®, both of which are modified formulations. The starting dose of CSA ranged

from 2.5–7.5 mg/kg/dose given every 12 hours to maintain CSA trough levels of 150–250 μg/L, measured by monoclonal antibody (33%) assay or HPLC (28%) in local laboratories. Some institutions utilized a range of 100–200 μg/L while others utilized 200–400 μg/L.

Supportive Care

Practices for blood product support are summarized in Table I. Leukoreduced/"CMV-safe products" were universally utilized while 59% of institutions specifically requested CMV-negative donors if the patient's initial CMV serology is negative. Irradiated blood products are specifically requested by 80% of those surveyed (44% of institutions irradiate all blood products).

There is also variability in packed red blood cell transfusion practices as outlined in Table II. Based on concerns with alloimmunization and iron overload, there was a uniform approach to utilize as few transfusions as possible to keep the patient relatively asymptomatic. Nearly all institutions (87%), however, agree that there is a lower limit of acceptable hemoglobin for which most patients should be transfused regardless of symptoms, although this level varied significantly from 5.0–8.0 G/dL. Some programs utilize patient-specific parameters including clinical symptoms, degree of reticulocytopenia, proximity of a weekend, distance from the hospital, expected follow up and planned activities to develop a tailored approach to transfusion therapy.

A significant number (71%) of institutions prophylactically maintain platelet counts at least above 10,000/μl throughout treatment and the majority of these (92%) attempt to maintain the platelet count at least above 20,000 /μl during administration of ATG (Table II). Granulocyte transfusions are used very rarely in the treatment of pediatric patients with aplastic anemia. In these instances they are employed only in the setting of refractory or life-threatening infection in patients with severe neutropenia and no anticipated immediate neutrophil recovery.

Thirty-seven percent of responding institutions report using granulocyte colony stimulating factor (G-CSF) in patients from the beginning of therapy (Table III). Sixty-nine percent of respondents said they would use G-CSF in the setting of an active infection and no ANC recovery. GM-CSF is occasionally used in combination with G-CSF if there is an active infection and the patient's ANC has not responded to G-CSF.

Prophylactic antimicrobial practices are summarized in Table IV. Most institutions provide *Pneumocystis jiroveci* prophylaxis throughout the treatment course. Seventy-two percent of institutions use antifungal medications. However, 22% of the institutions surveyed do not use any prophylactic antibacterial or antifungal agents regardless of blood counts. Those institutions that provide antibiotic prophylaxis generally discontinue the medications once the ANC has met a specific threshold, ranging from 500–1000/μl. The most commonly used broad-spectrum antibiotics reported are ciprofloxacin and levofloxacin; the most commonly reported anti-fungal agents are fluconazole and voriconazole. Acyclovir prophylaxis is used by some institutions.

Participants were asked to comment on neutropenic precautions and vaccination policy. Free text comments ranged from not providing any specific precautions, using “common sense” regarding people who are obviously ill, avoiding construction and demolition sites, to specific instructions regarding cooking foods, hand washing, bathing daily, wearing of masks and other instructions. Patients are uniformly instructed to seek medical attention for any temperature elevation. Instructions regarding returning to school were also quite varied from “any time they are not in the hospital” to more detailed recommendations. Similarly, recommendations regarding immunizations were varied from “no set policy and no restrictions”, no live virus vaccines, to administration after specific time periods and/or keyed to the absolute lymphocyte count.

Follow-Up and Evaluation of Treatment Responses

The majority of survey respondents used a variety of measures as treatment response markers justifying a continuation of IST. A complete response (CR) to IST was defined as return to normal blood counts. A partial response (PR) was present when the patient was transfusion independent in the setting of continued abnormal counts. These definitions were consistent across all institutions. Only 22% of respondents felt that positive changes in more than one cell line were required to indicate a treatment response. However, less than half of institutions (44%) used a specific ANC and/or platelet threshold to define a minimal response. Moreover, the specific threshold value used in these institutions varied widely, for ANC from 200 to 1000/μL and for platelets from 20 to 100 × 10^3/ μL. All respondents considered failure to respond to IST by lack of attainment of transfusion independence and ANC <500/μL in 6 months post treatment initiation as treatment failure although some institutions considered 3 months post-treatment initiation as an early indication of IST failure.

Upon achievement of a complete response, there was considerable variation in evaluations performed prior to weaning CSA (Table V). Thirty-nine percent of surveyed institutions recommended a repeat BM aspirate and biopsy with cytogenetic evaluation while 28% specifically recommended no repeat testing. Seventeen percent of institutions performed PNH and CBC screening only. However, for patients who achieved only a stable partial response, a higher proportion of survey respondents (61%) would perform BM aspirate and biopsy prior to weaning therapy, whereas only 6% would do no further testing. One-third (33%) of respondents would continue CSA for a period ranging from 2–12 months beyond the time a stable partial response is achieved in order to determine whether further count improvement would occur before considering weaning therapy. There was consensus among all respondents that CSA should not be discontinued as soon as a complete response is established; however, there was considerable variability among respondents with regard to the duration of full dose CSA therapy from the time of therapy initiation (range 3 –15 months), and specifically in the duration of consolidation treatment with full dose CSA after achieving complete remission (range 2–12 months).

Once treatment is discontinued, most respondents included routine clinic visits (61%) and blood counts (72%) as part of ongoing monitoring. However, the period of frequent monitoring after therapy discontinuation ranged from 3–12 months for patients with CR and

from 3–24 months for patients with stable PR, with blood counts every 0.5–2 months. Thirty-one percent of institutions would perform follow-up bone marrow exam once off therapy with CR or stable PR annually. Some institutions would perform at least one bone marrow exam with cytogenetics following therapy cessation, particularly for patients with stable PR.

With regard to long-term monitoring after recovery, about 80% of respondents reported a consistent approach at their institution, but the specifics of the monitoring protocols varied widely. The frequency of routine physical exams and blood counts during later follow-up varied from every 2 months to every 12 months. Sixty-six percent would consider discharging patients with CR from their hematology clinics at 5–10 years post-therapy cessation, whereas only 11% would discharge a patient with stable partial response. Notably, nearly 10% of respondents stated they would never discharge a patient with aplastic anemia from follow-up. All respondents agreed that a bone marrow aspirate with cytogenetics should be performed with a change in blood counts indicative of recurrence or worsening of marrow failure or of malignant transformation.

Treatment of Resistant and Relapsed Disease

Lack of response to initial IST—With regard to treatment options when there was no response to IST with the patient still meeting criteria for SAA, 72% of respondents would refer the patient for HSCT and/or start a search for a matched unrelated donor (MUD). If no acceptable MUD was available for a patient who failed IST, most centers would consider a second course of ATG/CSA. Alternative second line therapies, other than a second course of ATG/CSA, included eltrombopag (33%), cyclophosphamide (28%), and alemtuzumab (28%). Some centers would consider haploidentical HSCT in the absence of an acceptable MUD. For the second course of ATG, 13% of respondents would use horse ATG, 27% would use horse ATG unless there had been a severe reaction to the initial treatment, 20% would use rabbit ATG, and 40% would use the opposite form of ATG to the one given initially.

Relapse on treatment—For patients whose counts were declining after an initial response to IST while still on CSA, 78% of respondents would repeat the bone marrow aspirate, biopsy, and cytogenetics. Eighty-three percent would increase the dose of CSA to reach therapeutic levels if a taper had been started. Twenty-two percent would continue the current CSA dose (assuming that there were adequate blood levels of CSA) unless and until criteria for SAA developed again. No respondents indicated that they would immediately repeat treatment with ATG before criteria for SAA were reached. None of the surveyed institutions would utilize MUD HSCT for first line therapy.

Relapse off treatment—Fifty-six percent of respondents would re-start treatment as soon as there was a clear trend of recurrent marrow failure in patients off treatment. Seventeen percent would continue to observe until the patient met the criteria for SAA again. Sixty-one percent advocated “rescue” treatment for first relapse after IST with ATG/CSA. Among those who would treat with IST as first-line therapy for relapse, 73% would start searching for a donor at the same time as initiation of the second IST, but two respondents would start

a search for a donor only if there were no response to the second IST within 3 or 6 months. If no acceptable donor were found, for a second (or higher) relapse, 61% would consider repeating IST. A variety of other second-line therapies would be considered with similar frequency, including cyclophosphamide, eltrombopag and alemtuzumab. Less frequently used approaches in this setting included danazol and haploidentical HSCT.

Discussion

Severe aplastic anemia in children and adolescents is a rare disease with an estimated incidence of 1–3 cases per million (3, 4). The rarity of pediatric aplastic anemia poses difficulties for establishing guidelines for front-line treatment, salvage therapies, and supportive care. To address this challenge, a group of pediatric hematologists formed the North American Pediatric Aplastic Anemia Consortium. As a first step toward the development of diagnostic and therapeutic protocols, we surveyed 18 prominent pediatric hematology services. We found considerable variability in diagnostic work-up, supportive care, and the approach to patients with disease that is refractory to treatment or with relapsed disease.

Congruent with published algorithms for the initial treatment of acquired SAA in the pediatric age group (5–7), all surveyed institutions recommend HSCT if a MSD is identified. In light of improved outcomes of MUD for acquired SAA, some have proposed upfront therapy with a 10/10 HLA-A, -B, -C, -DRB1, -DQ high resolution MUD HSCT (8). However, the NAPAAC centers uniformly recommended IST, rather than MUD, if an HLA-matched sibling donor was not identified due to the morbidity and mortality still associated with MUD in this setting.

All surveyed institutions preferentially use horse- rather than rabbit-derived ATG in their ATG-CSA regimens, a choice supported by results of a randomized trial demonstrating significantly lower response rates and survival with rabbit ATG (9). Although this trial did include children, it was not powered to evaluate pediatric patients as an independent variable. A retrospective study in children has recently been published (10). Therefore, whether horse ATG is superior to rabbit ATG in the pediatric population remains to be determined (11). The timing and duration of the CSA taper varied widely among respondents. Whether these differences translate into differences in relapse rates is unknown. Overall the majority of supportive care practices were consistent with published reviews (7, 12). However, some practice differences and deviations from published literature highlighted persistent, important management questions.

The use of upfront IST as first line therapy in the absence of MSD and transfusion practices were the areas of most consistency amongst surveyed institutions. More than a third of institutions surveyed reported using G-CSF from the onset of disease despite a multi-center, randomized study that demonstrated no difference in overall or event-free survival (13). Since this study did demonstrate reduced numbers of febrile events and in-patient hospital days, the variable practices may reflect differences in importance placed on costs versus risks of side effects of G-CSF. Antimicrobial prophylaxis was an interesting areas of divergence in practice. Twenty-two percent of the respondents use no prophylaxis. Three

fourths use prophylaxis against *Pneumocystis jiroveci* as recommended by a recent review (7) although the literature is not definitive on *Pneumocystis sp.* as a frequent complication in aplastic anemia outside the setting of HSCT (14). Similarly, use of antibacterial and antifungal agents was common in spite of their controversial efficacy in prolonged neutropenia (7, 15).

For patients with disease refractory to initial IST, only a minority recommended repeat IST treatment unless no MUD was available. If a patient initially responded but was becoming more cytopenic during CSA taper, the large majority of respondents return to full dose CSA treatment. For patients who "relapsed" off treatment, the majority of respondents would promptly initiate "rescue" treatment with ATG/CSA, but would simultaneously pursue the availability of a MUD transplant.

Summary

Acquired aplastic anemia is a rare disorder and randomized clinical trials in pediatric aplastic anemia are infrequent (16, 17, 18) although some adult trials include small numbers of children. While reported in Japanese, Korean and European populations (19–22), large, multi-institutional studies focused on North American patients have not been described. Standards of care in North America are currently institution-specific. While the results presented from this survey of multiple pediatric institutions demonstrate some areas of consensus in diagnostic work-up and treatment, a great deal of variability exists. These data suggest opportunities to standardize care and develop multi-institutional prospective trials to compare treatment approaches and outcomes of pediatric AA in North America with those of other regions and collaborative groups, with the goal of advancing the field with new therapeutic interventions.

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Table I

Diagnostic Workup

Test	% Centers
Bone Marrow Asp/Bx	100%
Cytogenetics	100%
HLA typing of siblings	94%
Chromosome breakage analysis-MMC[1]/DEB[2]	89%
PNH[3] Screen by Flow	89%
EBV[4], CMV[5]	83%
Hepatitis screen	78%
SBDS[6] gene sequencing	71%
Telomere length	67%
FISH (chr 5, 7, 8)	61%
BM Flow for T, B, CD34	67%
Immunological work-up	55%
Vit B12, Folate	50%
DC[7] Genetic Testing	43%
HSV[8], VSV[9], HHV6[10]	33%
Ferritin	28%
Pancreas U/S	22%
Kidney U/S	16%
Skeletal survey/Hand film	0%

[1] MMC is defined as Mitomycin C.

[2] DEB is defined as Diepoxybutane.

[3] PNH is defined as Paroxysmal Nocturnal Hemoglobinuria.

[4] EBV is defined as Epstein-Barr Virus.

[5] CMV is defined as Cytomegalovirus.

[6] SBDS is defined as Shwachman–Bodian–Diamond Syndrome.

[7] DC is defined as Dyskeratosis Congenita.

[8] HSV is defined as Herpes Simplex Virus.

[9] VSV is defined as Vesicular Stomatitis Virus.

[10] HHV6 is defined as Human Herpesvirus 6.

Table II

Blood product utilization

Blood product preparation	
Leukoreduced blood products	100%
Routine extended cross matching	20%
Radiated blood products specifically requested	81%
All blood products radiated at institution	44%
Use CMV negative product if initial serology is negative	59%
Red cell administration	
Maintain RBC above a certain level (6 – 8 g/dL)	50%
Transfuse RBC only when patient is symptomatic	31%
Use minimal transfusion to keep patients asymptomatic	88%
Have lower acceptable hemoglobin level (5 – 8 g/dL)	88%
Think that excessive transfusion delays recovery	20%
Platelet administration	
Maintain platelets above a certain level during ATG[1]	82%
10,000/μl	8%
20,000/μl	64%
30,000/μl	14%
50,000/μl	14%
Prophylactically transfuse platelets in steady state	71%
10,000/μl	91%
15,000/μl	8%
Granulocyte Transfusions	
Utilization	
Sometimes	13%
Rarely	63%
Never	25%

[1] ATG is defined as Anti-Thymocyte Globulin.

Table III

Myeloid growth factor usage

G-CSF[1]	
Routine use throughout treatment	37.5%
Use for infection with neutropenia	68.8%
GM-CSF[2]	
Use for infection if no response to G-CSF	23%
Use for duration of active infection	38%

[1] G-CSF is defined as Granulocyte Colony-Stimulating Factor.

[2] GM-CSF is defined as Granulocyte Macrophage Colony-Stimulating Factor.

Table IV

Antimicrobial prophylaxis

Antimicrobial agent	% Centers	Throughout	First month
No prophylactic antibiotics	22%		
Bactrim	28%	100%	0%
Aerosol pentamidine	39%	86%	
Fluconazole	33.3%	66.7%	33.3%
Voriconazole	39%	86%	
Other	44%		

Table V

Lab tests prior to tapering cyclosporine

Complete response:	
Bone marrow aspirate/biopsy/cytogenetics	39%
PNH[1]	17%
No further testing	28%
Other	16%
Partial response:	
Bone marrow aspirate/biopsy/cytogenetics	61%
No further testing	6%
Other	33%

[1] PNH is defined as Paroxysmal Nocturnal Hemoglobinuria.