The Indian Journal of Pediatrics (February 2020) 87(2):141–149
https://doi.org/10.1007/s12098-019-03066-4

REVIEW ARTICLE

Bone Marrow Failure in Children: Approach to Diagnosis and Treatment

Hannah Fassel[1] · Sujit Sheth[1]

Received: 1 August 2019 / Accepted: 20 August 2019 / Published online: 18 October 2019

Abstract
Bone marrow failure has many different etiologies, including genetic defects which manifest with specific syndromes, as well as acquired conditions as a result of insults to the bone marrow leading to aplasia. The clinical picture is varied and clues for the underlying cause may or may not be evident at the time of presentation, frequently leading to a complex workup with a battery of tests often done to rule out genetic defects. The treatment approach for bone marrow failure is very dependent on the underlying cause, which makes it all the more critical to have an accurate diagnosis. First line management essentially consists of either hematopoietic stem cell transplant or immunosuppressive therapy. In this review authors will provide a broad look at the causes of bone marrow failure, the stepwise diagnostic algorithm and the approach to decision making for treatment. Fine details of each cause, and of each treatment modality are beyond the scope of this review which aims to provide an overview.

Keywords Inherited bone marrow failure syndromes · Secondary aplastic anemia · Immunosuppression · Hematopoietic stem cell transplantation

Introduction

Despite significant advances in management, bone marrow failure in children remains challenging to diagnose and often somewhat frustrating to treat. Specialized diagnostic investigations are now more widely available, including complex molecular and genetic testing, enabling more rapid specific workup based on the clinical presentation. However, in the absence of an inherited syndrome, acquired causes are more difficult to find, and many children are still diagnosed with "idiopathic" aplastic anemia (AA). While the severity is somewhat variable, bone marrow failure remains challenging to manage. The treatment approach for inherited bone marrow failure syndromes (IBMFS) is more straightforward, with hematopoietic stem cell transplantation (HSCT) being widely accepted as the modality of choice. In acquired severe aplastic anemia (SAA), transplant remains the optimal first choice if a matched sibling donor is available. However, if this is not the situation, there is no wide consensus as to the course of treatment. Several options have been proposed for first and second line treatment, and this has changed over the course of the last several years. In this article authors will review the current diagnostic and treatment algorithms, suggesting a more stepwise approach to minimize testing, and provide a rational management approach to maximize treatment benefit with the least risk for morbidity and mortality, keeping in mind that all of the resources needed may not always be available. This review will focus on the diagnostic and therapeutic approach to the management of bone marrow failure. Detailed descriptions of each inherited condition are beyond the scope of this review.

Evaluation of Bone Marrow Failure

The etiology of bone marrow failure is broad and can result from a diverse array of conditions, some inherited and others acquired (Tables 1 and 2). Appropriate evaluation of the etiology is critical to its management since the choice of first line therapy is dependent on it. Broadly, bone marrow failure may result from an inherited syndrome (henceforth called Inherited Bone Marrow Failure Syndrome or IBMFS), in which case stem cell transplantation is the first line treatment of choice, or from an acquired cause (henceforth called

✉ Sujit Sheth
shethsu@med.cornell.edu

[1] Division of Pediatric Hematology and Oncology, Weill Cornell Medical College, New York, NY 10065, USA

Table 1 Inherited (primary) causes of bone marrow failure, organized by most common presenting cytopenia

		Physical Features	Laboratory Features
Thrombocytopenia	Congenital Amegakaryocytic Thrombocytopenia	Congenital malformations may be present, but nonspecific	Thrombocytopenia with progression to pancytopenia
	Fanconi Anemia	Short stature, café au lait macules, hypopigmentation, hypoplastic thumb or radius, microcephaly, ophthalmic anomalies, genitourinary tract anomalies	Macrocytosis; increased fetal hemoglobin; thrombocytopenia, leukopenia, neutropenia
	Telomere Biology Disorder	Dysplastic nails, lacy reticular pigmentation of skin, oral leukoplakia (Classic Dyskeratosis Congenita Triad); prematurely gray hair, alopecia, developmental delay, short stature, microcephaly, hypogonadism, esophageal stenosis, urethral stenosis, liver disease, blepharitis, periodontal disease	Macrocytosis, increased fetal hemoglobin, cytopenia of ≥1 lineage
Anemia	Diamond Blackfan Anemia	Growth retardation; craniofacial, upper-limb, heart, and genitourinary malformations	Macrocytic anemia without other cytopenias, reticulocytopenia, elevated erythrocyte adenosine deaminase activity, elevated fetal hemoglobin
Neutropenia	Shwachman Diamond Syndrome	Short stature, skeletal abnormalities such as chondrodysplasia or congenital thoracic dystrophy, cardiac defects, ear malformations, hearing loss, skin rashes, hepatomegaly	Neutropenia, thrombocytopenia, anemia, macrocytosis
	Severe Congenital Neutropenia	Eczema, developmental delay, epilepsy, hearing loss, dental caries, gingivitis	Neutropenia

Table 2 Acquired (secondary) causes of bone marrow failure

- Idiopathic Aplastic Anemia
- Infection
  - Parvovirus
  - Hepatitis A, B, C
  - CMV
  - EBV
  - HIV
  - HHV-6
  - Influenza
  - Fungal
  - Tuberculosis
- Radiation
- Drug or toxin
  - Phenylbutazone
  - Chloramphenicol
  - Gold
  - Sulfonamides
  - Antiepileptics (ex: felbamate)
  - Nifedipine
  - Benzene
- Bone Marrow Infiltration
  - Leukemia
  - Myelodysplastic syndrome
  - Metastatic malignancy
  - Myeloproliferative disease
  - Myelofibrosis
- Autoimmune
  - SLE
  - RA
  - Sarcoidosis
- Nutrition
  - B12, folate deficiencies
  - Severe malnutrition

CMV Cytomegalovirus; *EBV* Ebstein-Barr virus; *HHV-6* Human herpesvirus 6; *HIV* Human immunodeficiency virus; *RA* Rheumatoid arthritis; *SLE* Systemic lupus erythematosus

Aplastic Anemia or AA), in which case the choice of first line therapy is broader, and includes immunosuppression vs. stem cell transplantation in appropriate situations. The clinical presentation of bone marrow failure is a combination of signs and symptoms related to the pancytopenia as well as any other features which might indicate an underlying cause or inherited syndrome. A stepwise evaluation algorithm (Figs. 1, 2 and 3) should include clinical features, many of which are pathognomonic in inherited syndromes (Table 1), and corroborated with laboratory testing. Examination of the bone marrow is the key initial step, to determine cellularity as well as to look for dysmorphism which might provide specific diagnostic clues. Flow cytometry, cytogenetics and Fluorescent in situ

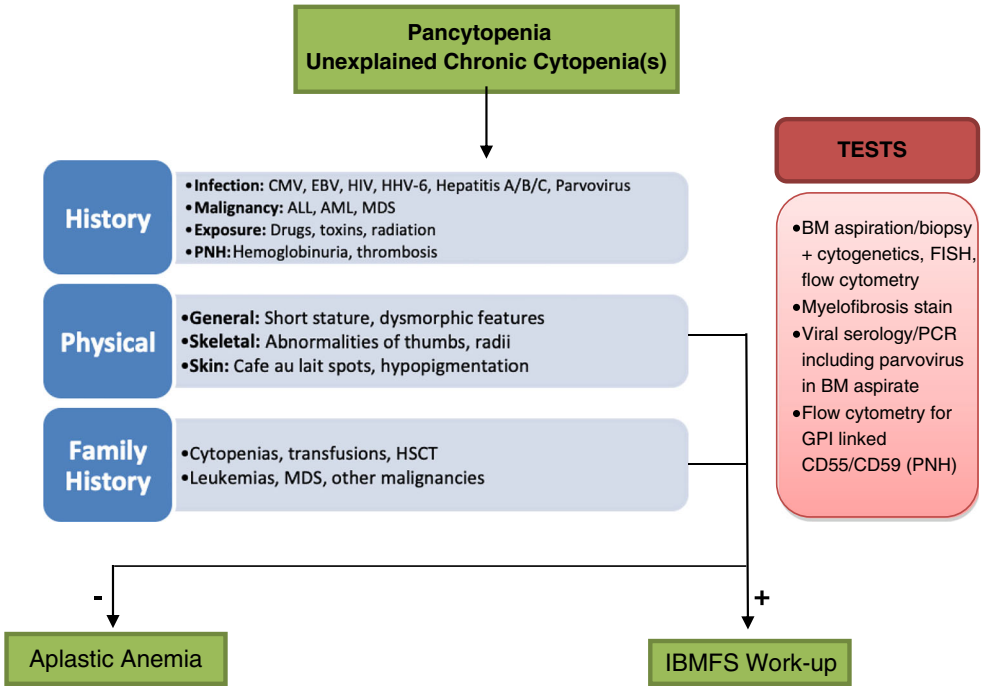

Fig. 1 Diagnostic approach to pancytopenia or unexplained chronic cytopenia(s). The investigations above will assist in determining whether to pursue an aplastic anemia diagnosis (Fig. 2) or further IBMFS work-up (Fig. 3). *ALL* Acute lymphoblastic leukemia; *AML* Acute myeloid leukemia; *BM* Bone marrow; *CMV* Cytomegalovirus; *EBV* Ebstein-Barr virus; *FISH* Fluorescent in situ hybridization; *GPI* Glycosylphosphatidylinositol; *HHV-6* Human herpesvirus 6; *HSCT* Hematopoietic stem cell transplantation; *IBMFS* Inherited bone marrow failure syndrome; *MDS* Myelodysplastic syndrome; *PCR* Polymerase chain reaction; *PNH* Paroxysmal Nocturnal Hemoglobinuria

hybridization (FISH) should be considered routine to look for subpopulations/clones which might point to a specific diagnosis, e.g., Paroxysmal nocturnal hemoglobinuria (PNH) or Myelodysplastic syndrome (MDS). If available, viral polymerase chain reaction (PCR) of the bone marrow may be done in instances where an infectious etiology is

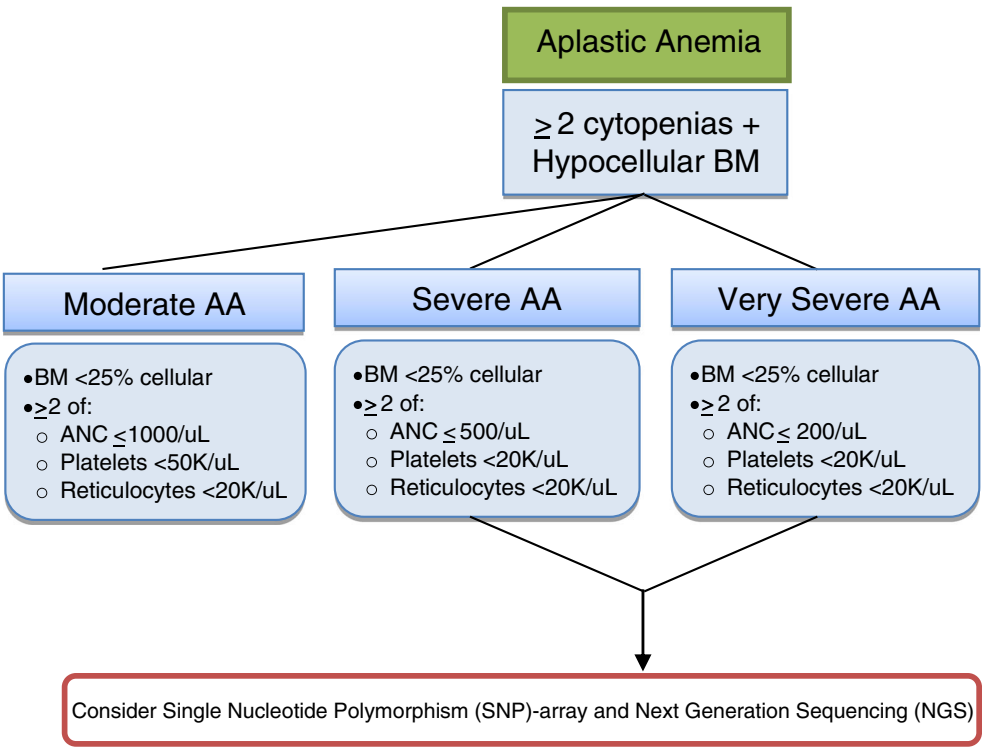

Fig. 2 Diagnostic approach to pancytopenia or unexplained chronic cytopenia(s), Aplastic Anemia. Diagnostic criteria for acquired aplastic anemia. *AA* Aplastic anemia; *ANC* Absolute neutrophil count; *BM* Bone marrow; *SNP* Single nucleotide polymorphism

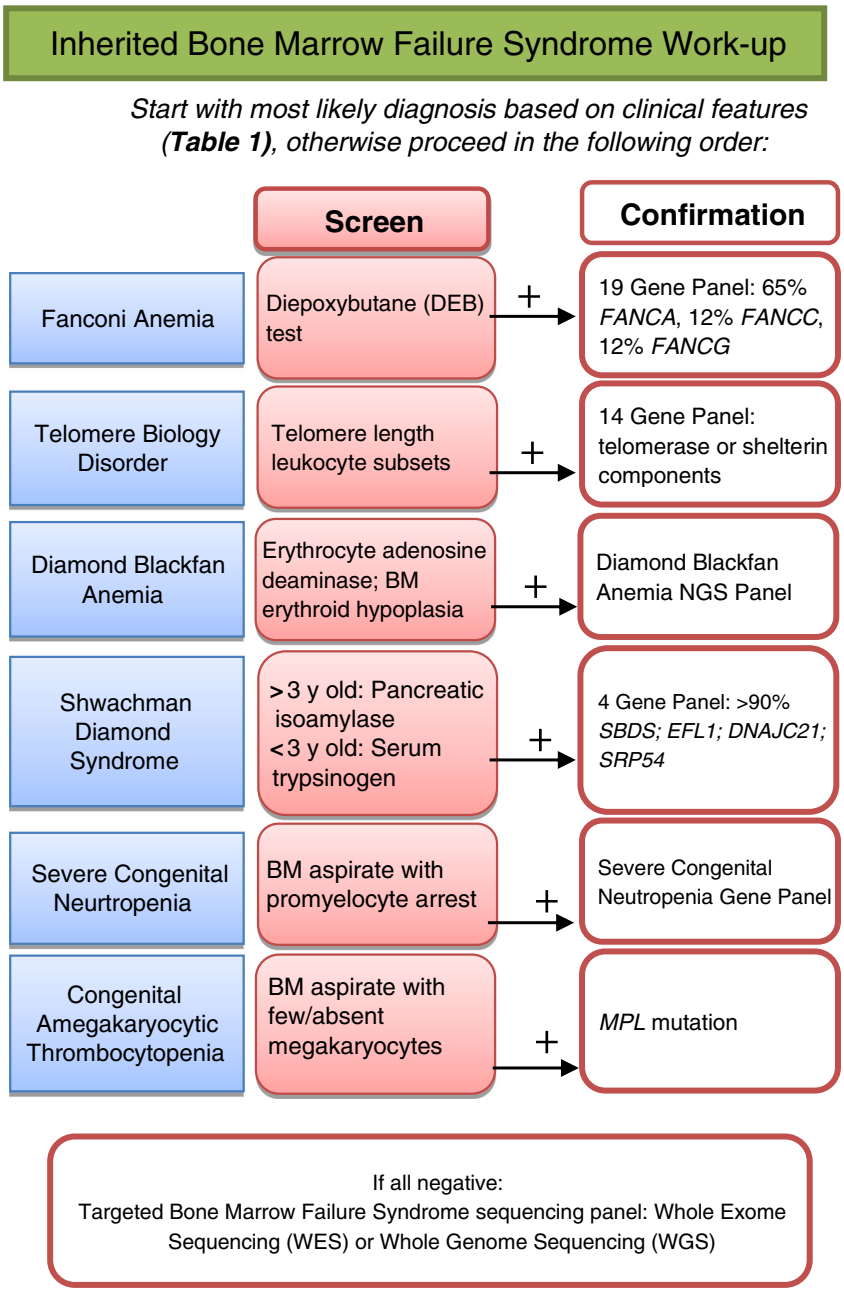

Fig. 3 Diagnostic approach to pancytopenia or unexplained chronic cytopenia(s), - Inherited Bone Marrow Failure Syndrome Work-Up. *BM* Bone marrow

suggested by the clinical presentation or serologic testing. When an inherited syndrome does not seem to be the clear diagnosis at presentation, depending on the likely duration of progression of the marrow failure, there may or may not be some time available to proceed along this algorithm in a step-wise fashion. In situations where the pancytopenia is likely long standing, treatment may be more urgently indicated, and several steps may need to be combined for efficiency. Much of the testing for the inherited syndromes relies heavily on DNA testing, now accomplished using multiplex gene testing in panels specifically designed for the purpose. As our understanding of the biology of bone marrow failure advances, whole exome, genome or next generation sequencing may yield actionable information, pointing to a likely inherited/genetic cause, or a targetable polymorphism/mutation. If available, these tests may be performed if no clear diagnosis is apparent. Aplastic anemia is classified as moderate, severe, or very severe based on accepted criteria (Fig.2), often with progression over time.

Treatment

Without definitive treatment, a child with established IBMFS or SAA will invariably succumb to either a severe infection which would occur as a result of the prolonged and severe

neutropenia, or from a catastrophic hemorrhage, which would result from the prolonged and severe thrombocytopenia. Supportive therapy with transfusions and prophylactic antimicrobials is only a temporizing measure, and the reader is directed to specific disease guidelines for IBMFS and a published supportive care guideline for AA [1]. The goal of therapy must be to induce "remission" of the marrow failure and allow for its reconstitution, with resulting normalization of peripheral blood counts. As discussed previously, the choice of first line therapy depends on whether the bone marrow failure is as a result of an underlying inherited syndrome (IBMFS) or an acquired cause (AA). In the former situation, the response to non-transplant therapies is sub-optimal, and even if there is a response, it is usually short-lived, and HSCT is the only treatment which will result in a lasting response. However, for acquired causes of aplasia, immunosuppression as the first course of treatment has a fair and improving track record. More recently, other treatments, such as eltrombopag, have shown response even in SAA, and have entered the treatment paradigm. HSCT as upfront treatment is only considered if a matched related donor is available, and has gained more acceptance as the initial management because of improving outcomes. Figure 4 provides a guide to the different treatment options with specific regimens in Table 3.

Immunosuppression

First line immunosuppressive therapy (IST) for SAA is a combination regimen of horse antithymocyte globulin (hATG) and cyclosporine (CsA), resulting in an initial response rate of 70–80% in children [8–12]. Specific treatment regimens can be found in Table 3. Horse ATG is preferred to rabbit antithymocyte globulin (rATG) for upfront IST due to superior hematologic response rates (68% vs. 37%) and 3 y overall survival (OS) (96% vs. 76%) [2]. Careful monitoring and supportive care are required while awaiting hematologic recovery, which can take 2–3 mo or longer in some patients [3]. Long-term OS with h-ATG/CsA is 85% in the best case, though response rates vary considerably and may be as low as 37% [9, 13]. The variability in response is not well understood, and possible reasons for a suboptimal result could be delay in initiating treatment, or instances in which the underlying diagnosis is an undiagnosed inherited syndrome. In patients with refractory disease, a second course of IST with rATG and CsA or alemtuzumab yields a 30–40% response [4, 14, 15]. Remission induced by IST may be durable, sometimes requiring long-term CsA to maintain it, which should be continued for a minimum of 6 mo and then tapered very slowly with careful monitoring [12]. However, a substantial proportion (12–35%) will relapse and become pancytopenic again [16–18]. About half of these children will respond to a second course of ATG (usually rabbit), and some of these remissions will be durable as well. However, those who do not respond initially, or who relapse, are considered refractory, and alternate treatment regimens are indicated in such situations. Responders who recover their marrow function need long-term follow up not only because late relapses may sometimes occur, but also for surveillance for the evolution of clonal disease (myelodysplasia or a secondary malignancy) which may occur in approximately 15% [19].

Eltrombopag

The thrombopoietin (TPO) receptor agonist, eltrombopag, can be used in patients with SAA and lack of response to IST. Monotherapy with eltrombopag in refractory SAA results in a 40% response rate with recovery of trilineage hematopoiesis seen [5, 6]. Use of eltrombopag in combination with hATG/CsA as upfront therapy has also been tried in a subsequent trial and yielded the best results yet with an overall hematologic response rate of 95% and complete response rate of 58% at 6 mo in one treatment cohort [7]. Longer follow up is required to determine relapse rates and salvageability, safety regarding clonal evolution, and overall survival. At this time, there is no evidence to suggest increased rate of development of clonal disease with the use of TPO receptor agonists over traditional IST, however the risk of this is lower yet with HSCT compared to medical therapy. There is an ongoing Phase 2 trial evaluating the role of eltrombopag monotherapy for previously treated or untreated moderate aplastic anemia (NCT01328587). The dose of eltrombopag is recommended to be reduced to 50% in individuals of East Asian ancestry with ITP, but specific data are not available for Southeast Asia / Indian subcontinent or in aplastic anemia. While evidence-based, specific dosing recommendations cannot be made, it may be prudent to start at a lower dose and titrate up if there are no untoward changes in liver function testing.

Androgens

While androgens have largely fallen out of favor for medical treatment of AA with an early randomized controlled trial failing to show benefit in the addition of oral androgens to ATG, there may still be a role in certain patients [12, 20]. A randomized trial reported by Bacipalugo et al. did show superior response rates with the addition of androgens to ATG in women, and their group later showed a 59% response rate with oral androgen therapy in patients who failed an initial course of IST [21, 22]. Leleu et al. reported a 77% response rate with the addition of androgens to intensified doses of ATG with a 78% 5 y OS [23]. Therefore, in select scenarios with limited options, such as patients with refractory aplasia following IST who may not tolerate HSCT, for patients who do not have a suitable donor, or in limited resource settings, androgens may

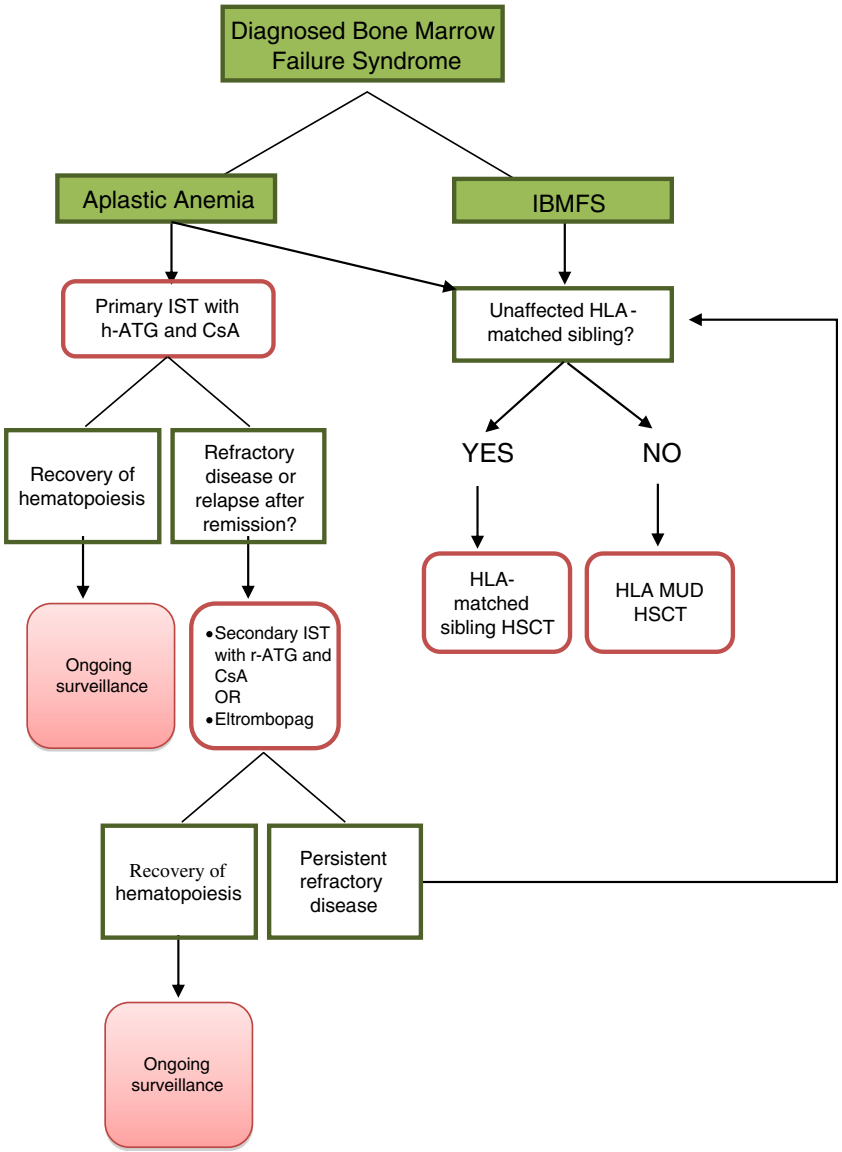

Fig. 4 Management approach to bone marrow failure. A general approach to management of AA or an IBMFS. *AA* Aplastic anemia; *ATG* Antithymocyte globulin; *CsA* Cyclosporine; *HLA* Human leukocyte antigen; *HSCT* Hematopoietic stem cell transplant; *IBMFS* Inherited bone marrow failure syndrome; *IST* Immunosuppressive therapy; *MUD* Matched unrelated donor

prove useful. The side effects, particularly virilization in female patients remains a significant consideration. Androgen therapy (danazole, oxandrolone, and oxymetholone) has also been shown to produce improvement in peripheral blood counts in well over 50% in patients with Fanconi Anemia (FA) and bone marrow failure [24, 25]. The response is primarily seen in hemoglobin and platelet counts, and in some patients is even durable. Again, this treatment modality may be favorable in specific scenarios where patients donot have a suitable donor, access to HSCT, or have too many comorbidities to proceed with HSCT. Careful monitoring is required, however, as bone marrow failure may progress to MDS/acute myeloid leukemia (AML) [26].

Hematopoietic Stem Cell Transplantation

HSCT is the only curative therapy for inherited forms of bone marrow failure and may be the treatment of choice in AA depending on donor options. In IBMFS, a matched and unaffected (based on genetic testing) sibling is the ideal donor, but another matched and unaffected family donor may also be suitable. In cases of consanguinity, parents should have HLA testing performed to assess their suitability as a donor. When a matched family donor is not available, an unrelated donor (UD) would have to be considered, and results from such transplants may be suboptimal as a result of more frequent complications such as rejection and graft vs. host disease (GVHD). For SAA, IST is the most commonly used first

Table 3 Immunosuppressive therapy for acquired aplastic anemia

Regimen	Details	Notes
hATG/CsA [2, 3]	hATG: 40 mg/kg/d for 4 d CsA: • Age ≥ 12: Initiate at 10 mg/kg/d PO divided BID • Age < 12: Initiate at 15 mg/kg/d PO divided BID • Titrate to target trough of 200–400 ng/ml	• Premedication for ATG recommended with prednisone, acetaminophen, and diphenhydramine. • ATG administered IV over 4 h
rATG/CsA [2]	rATG: 3.5 mg/kg/d for 5 d CsA: • Age ≥ 12: Initiate at 10 mg/kg/d PO divided BID • Age < 12: Initiate at 15 mg/kg/d PO divided BID • Titrate to target trough of 200–400 ng/ml	• Premedication for ATG recommended with prednisone, acetaminophen, and diphenhydramine
Alemtuzumab for Relapsed SAA [4]	Alemtuzumab: • Children <50 kg: 0.2 mg/kg/d for 10 d (maximum 10 mg/d) • Adults and children >50 kg: 10 mg/dose/d for 10 d	• 1 mg test dose of Alemtuzumab given on day 1 • Alemtuzumab administered IV over 2 h
Eltrombopag for Refractory SAA [5, 6]	Eltrombopag: 50 mg PO daily to increase by 25 mg Q2 wk to maximum 150 mg, duration 12 wk	• Data available for age range 17–77
Eltrombopag + hATG/CsA [7]	Eltrombopag: • Age ≥ 12: 150 mg PO daily • Age 6–11: 75 mg PO daily • Age 2–5: 2.5 mg/kg PO daily	• Patients of East Asian ethnicity may start at 50% of Eltrombopag dose, and could escalate if no side effects. Duration dependent on response.

The regimens described in the text are listed here with specific dosing details. *ATG* Antithymocyte globulin; *BID* Twice a day; *CsA* Cyclosporine; *IV* Intravenous; *PO* Per oral; *SAA* Severe aplastic anemia

line therapy, but HSCT is preferred if there is a matched sibling donor, as OS is comparable between patients treated with IST vs. HSCT (around 90%), but there is a significantly higher rate of failure free survival of 87% in patients treated with HSCT compared to 56% in patients treated with IST [27]. These excellent outcomes with HSCT vary with age, with younger age being strongly associated with improved outcomes, with a 5 y survival of 82% in patients less than 20 y of age decreasing to 72% or 53% after age 21 or 40, respectively [28]. In cases of SAA without an HLA matched sibling, medical treatment with IST is still considered by most to be first line, though HSCT with a matched UD has increasingly been considered for up front first line HSCT with improving outcomes and lower risk for GVHD. Alternate donor transplant should only be pursued in the setting of failure of IST or in experimental research trials [12]. A search of the marrow registry for an UD should be initiated without delay, however, to prepare for the possibility of refractory SAA, in which case HSCT may be the best treatment option. Mismatched or UD HSCT is usually the only option for children with SAA who are refractory to all other treatments.

Before HSCT is pursued, risks and benefits should be weighed with each patient and family, as there is risk of substantial morbidity and mortality. Appropriate counseling regarding fertility preservation options should be provided. Specific conditioning regimens are beyond the scope of this discussion and the reader is directed to disease specific guidelines. In general, myeloablative conditioning is used for AA and reduced-intensity conditioning is recommended for IBMFS, while total body radiation should be avoided in either scenario to reduce long-term toxicity including secondary malignancy, with the exception of UD HSCT for SAA. Bone marrow is the recommended stem cell source for both acquired and inherited bone marrow failure due to a proven survival advantage and reduced risk of development of GVHD. In matched sibling HSCT for SAA, the rate of development of chronic GVHD is 11–12% using bone marrow vs. 22–27% with peripheral blood stem cells (PBSC) [29, 30]. Additionally, Bacigalupo et al. reported improved survival advantage (90% vs. 76%) using bone marrow as the source of stem cells with no difference in rates of engraftment (approximately 90% regardless of stem cell source) [30, 31]. In cases where an UD must be used for HSCT for SAA, a similar pattern is seen, albeit with much higher rates of chronic GVHD – 31% with bone marrow vs. 48% with PBSC [32]. A recent European Group for Blood and Marrow Transplantation (EBMT) analysis showed that in both matched sibling and UD transplants, the use of peripheral blood as the source of stem cells was the strongest negative predictor of survival [31]. In terms of stem cell source for HSCT in IBMFS, a clear association with rate of GVHD has not been seen in FA, however use of PBSC was associated with significantly higher risk of secondary cancer, therefore bone marrow is also the preferred stem cell source for FA and is also recommended for the remaining IBMFS [33, 34]. GVHD prophylaxis is essential, as development of GVHD in non-malignant transplant is the main contributor to long-term morbidity, mortality, and overall quality of life, and may induce even

more significant toxicity in patients with IBMFS. Standard post transplant GVHD prophylaxis for SAA includes CsA and short course methotrexate, which was shown to be superior to CsA alone, and when combined with early timing of transplant and an ATG-containing preparative regimen in matched sibling HSCT, Storb reported a 95% engraftment rate and 90% 2 y OS [35, 36]. In general, rates of graft rejection have improved dramatically in SAA with improved supportive care and conditioning regimens and reduced amount of time before proceeding to HSCT and therefore, less exposure to blood products from multiple donors prior to transplant. For IBMFS, reports in the literature are limited to small and primarily retrospective reviews of specific inherited conditions and thus generalizations are difficult to make. Perhaps the most data comes from FA, where recipients of matched related donor HSCT have 89–100% engraftment, 20–29% chronic GVHD, and survival rates above 90% at median follow up times of 2–3.7 y. In patients with IBMFS, matched UD or matched related cord blood are also acceptable options, while alternative options such as haploidentical transplantation should only be performed in experienced centers and/or within the confines of a clinical trial [37].

Long-Term Follow-Up

For patients with AA treated with IST, the disease is never completely cured, as there is significant risk of refractory disease, late relapse of disease, or late progression to clonal disease, including myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Relapse of disease, notable by decreasing peripheral blood counts and loss of transfusion independence, may sometimes be rescued with reinstitution of immunosuppression (CsA) or may require more intensive IST or HSCT. Patients require long-term monitoring and supportive care, specifically with regular bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation, perhaps every 6 mo for the first 1–2 y and then annually, as recommended by Bacigalupo, Scheinberg and Young, and the British guideline for adult AA [3, 12, 38]. While the risk of clonal evolution to MDS or AML is approximately 15% as previously mentioned, a recent report indicates that clonal hematopoiesis may occur at a much more frequent rate of 47% with clinical significance that is not yet well understood [19, 39]. Patients with IBMFS or AA treated with HSCT must be monitored long-term for the usual complications of transplant, the most concerning of which being chronic GVHD, loss of engraftment, and/or relapse of disease. These patients should be managed at specialized transplant centers with experience in managing these complications.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Höchsmann B, Moicean A, Risitano A, Ljungman P, Schrezenmeier H. Supportive care in severe and very severe aplastic anemia. Bone Marrow Transplant. 2013;48:168–73.
2. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med. 2011;365:430–8.
3. Scheinberg P, Young NS. How I treat acquired aplastic anemia. Blood. 2012;120:1185–96.
4. Scheinberg P, Nunez O, Weinstein B, Wu CO, Young NS. Activity of alemtuzumab monotherapy in treatment-naive, relapsed, and refractory severe acquired aplastic anemia. Blood. 2012;119:345–54.
5. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood. 2014;123:1818–25.
6. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2012;367:11–9.
7. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med. 2017;376:1540–50.
8. Tichelli A, Socié G, Henry-Amar M, et al. Effectiveness of immunosuppressive therapy in older patients with aplastic anemia. European Group for Blood and Marrow Transplantation Severe Aplastic Anaemia Working Party. Ann Intern Med. 1999;130:193–201.
9. Scheinberg P, Wu CO, Nunez O, Young NS. Long-term outcome of pediatric patients with severe aplastic anemia treated with antithymocyte globulin and cyclosporine. J Pediatr. 2008;153:814–9.
10. Scheinberg P, Wu CO, Nunez O, Young NS. Predicting response to immunosuppressive therapy and survival in severe aplastic anaemia. Br J Haematol. 2009;144:206–16.
11. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. Blood. 2006;108:2509–19.
12. Bacigalupo A. How I treat acquired aplastic anemia. Blood. 2017;129:1428–36.
13. George B, Mathews V, Viswabandya A, Lakshmi KM, Srivastava A, Chandy M. Allogeneic hematopoietic stem cell transplantation is superior to immunosuppressive therapy in Indian children with aplastic anemia–a single-center analysis of 100 patients. Pediatr Hematol Oncol. 2010;27:122–31.
14. Scheinberg P, Nunez O, Young NS. Retreatment with rabbit antithymocyte globulin and ciclosporin for patients with relapsed or refractory severe aplastic anaemia. Br J Haematol. 2006;133:622–7.
15. Di Bona E, Rodeghiero F, Bruno B, et al. Rabbit antithymocyte globulin (r-ATG) plus cyclosporine and granulocyte colony stimulating factor is an effective treatment for aplastic anaemia patients unresponsive to a first course of intensive immunosuppressive therapy. Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Br J Haematol. 1999;107:330–4.
16. Rosenfeld S, Follmann D, Nunez O, Young NS. Antithymocyte globulin and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome. JAMA. 2003;289:1130–5.

17. Bacigalupo A, Bruno B, Saracco P, et al. Antilymphocyte globulin, cyclosporine, prednisolone, and granulocyte colony-stimulating factor for severe aplastic anemia: an update of the GITMO/EBMT study on 100 patients. European Group for Blood and Marrow Transplantation (EBMT) working party on severe aplastic Anemia and the Gruppo Italiano Trapianti di Midolio Osseo (GITMO). Blood. 2000;95:1931–4.
18. Tichelli A, Marsh JC. Treatment of aplastic anaemia in elderly patients aged >60 years. Bone Marrow Transplant. 2013;48:180–2.
19. Socié G, Rosenfeld S, Frickhofen N, Gluckman E, Tichelli A. Late clonal diseases of treated aplastic anemia. Semin Hematol. 2000;37:91–101.
20. Champlin RE, Ho WG, Feig SA, Winston DJ, Lenarsky C, Gale RP. Do androgens enhance the response to antithymocyte globulin in patients with aplastic anemia? A prospective randomized trial. Blood. 1985;66:184–8.
21. Bacigalupo A, Chaple M, Hows J, et al. Treatment of aplastic anaemia (AA) with antilymphocyte globulin (ALG) and methylprednisolone (MPred) with or without androgens: a randomized trial from the EBMT SAA working party. Br J Haematol. 1993;83:145–51.
22. Giammarco S, van Lint MT, Lamparelli T, et al. Androgens may boost hematologic response to anti-thymocyte globulin in acquired aplastic anemia. Blood. 2016;128:3900.
23. Leleu X, Terriou L, Duhamel A, et al. Long-term outcome in acquired aplastic anemia treated with an intensified dose schedule of horse antilymphocyte globulin in combination with androgens. Ann Hematol. 2006;85:711–6.
24. Scheckenbach K, Morgan M, Filger-Brillinger J, et al. Treatment of the bone marrow failure in Fanconi anemia patients with danazol. Blood Cells Mol Dis. 2012;48:128–31.
25. Paustian L, Chao MM, Hanenberg H, et al. Androgen therapy in Fanconi anemia: a retrospective analysis of 30 years in Germany. Pediatr Hematol Oncol. 2016;33:5–12.
26. Dufour C. How I manage patients with Fanconi anaemia. Br J Haematol. 2017;178:32–47.
27. Yoshida N, Kobayashi R, Yabe H, et al. First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor versus immunosuppressive therapy. Haematologica. 2014;99:1784–91.
28. Gupta V, Eapen M, Brazauskas R, et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. Haematologica. 2010;95:2119–25.
29. Schrezenmeier H, Passweg JR, Marsh JC, et al. Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia. Blood. 2007;110:1397–400.
30. Bacigalupo A, Socié G, Schrezenmeier H, et al. Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. Haematologica. 2012;97:1142–8.
31. Bacigalupo A, Socié G, Hamladji RM, et al. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. Haematologica. 2015;100:696–702.
32. Eapen M, Le Rademacher J, Antin JH, et al. Effect of stem cell source on outcomes after unrelated donor transplantation in severe aplastic anemia. Blood. 2011;118:2618–21.
33. Peffault de Latour R, Peters C, Gibson B, et al. Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. Bone Marrow Transplant. 2015;50:1168–72.
34. Peffault de Latour R, Porcher R, Dalle JH, et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. Blood. 2013;122:4279–86.
35. Locatelli F, Bruno B, Zecca M, et al. Cyclosporin a and short-term methotrexate versus cyclosporin a as graft versus host disease prophylaxis in patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EBMT randomized trial. Blood. 2000;96:1690–7.
36. Storb R, Etzioni R, Anasetti C, et al. Cyclophosphamide combined with antithymocyte globulin in preparation for allogeneic marrow transplants in patients with aplastic anemia. Blood. 1994;84:941–9.
37. Peffault de Latour R. Transplantation for bone marrow failure: current issues. Hematology Am Soc Hematol Educ Program. 2016;2016:90–8.
38. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172:187–207.
39. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic mutations and clonal hematopoiesis in aplastic anemia. N Engl J Med. 2015;373:35–47.