This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

FDA INDICATIONS

Stem cell transplantation is a procedure that is not subject to FDA regulation.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does have a National Coverage Determination (NCD) called Stem Cell Transplantation (110.8.1) and covers allogeneic hematopoietic stem cell transplantation (HSCT) for aplastic anemia. 11

CMS indicates that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered. 11

INITIAL COVERAGE CRITERIA

All transplants must be approved by the Medical Director prior to authorization

Members must meet the criteria outlined below for transplantation and the diagnosis must be made by a Hematologist, Oncologist and/or transplant surgeon.
Pre-Transplant Evaluation:

1. General requirements for transplant evaluation include all of the following: 1 2 12 13 40 43:

- **History and physical examination**: [ALL]
  - Complete blood transfusion history including RBC’s and Plasma 43
  - Radiation History 43

- **Psychosocial evaluation and clearance**: This must be completed and documentation submitted for review before any additional transplant work-up or testing is initiated.

- **Dietary consult and clearance for transplant**: 1

- **Disease evaluation may include all the following**: 1:
  - Bone marrow biopsy and/or bone marrow aspiration 43
  - CT scan
  - PET scan
  - Examination of a peripheral smear 43

- **Cardiac Echocardiogram or MUGA scan**: Ejection fraction > 50% 1 13 43

- **EKG**: 1 13 43

- **Chest X-ray**: 1 26

- **Performance Status**: [ONE]
  - *Karnofsky score 70-100%*
  - **Eastern Cooperative Oncology Group (ECOG) grade 0-2**

- **Neurological exam and clearance for transplant**: 13 43

- **Pulmonary function testing**: [ALL]
  - Diffusion capacity (DLCO) >60%
  - Forced expiratory volume (FEV) >60%
  - Forced capacity (FVC) >60%

- **Lab studies**: 1 43:
  - Complete blood cell count, platelets, differential, reticulocyte count 43
  - Electrolytes, calcium homeostasis 43
  - Serum ferritin, iron, total iron-binding capacity (TIBC) 43
  - RBC folate, serum B12 43
  - Serum erythropoietin (prior to RBC transfusion) 43
  - Liver function tests [ALL]:
    - SGOT: 1-2x normal, and
    - SGPT: 1-2x normal;
  - Thyroid stimulating hormone (TSH) 43
  - HIV testing 43
  - Cytomegalovirus (CMV) serology 43
  - Liver, renal and immunological parameters 43
  - HLA typing 43
  - Serum creatinine: <1.5mg% 13 43
  - Creatinine clearance: > 60 ml/min 13 43
  - Bilirubin < 2mg% 13 43
### Karnofsky Performance Score*  

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Able to carry on normal activity, no evidence of disease</td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>Normal activity with effort, some signs and symptoms of disease</td>
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<tr>
<td>70%</td>
<td>Cares for self, unable to carry on normal activity or to work</td>
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<tr>
<td>60%</td>
<td>Requires occasional assistance from others but able to care for most needs</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>Requires considerable assistance from others and frequent medical care</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>Disabled, requires special care and assistance</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>Severely disabled, hospitalization indicated, death not imminent</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>Very sick, hospitalization indicated, active support treatment necessary</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>Moribund</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>Dead</td>
<td></td>
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</tbody>
</table>

### Eastern Cooperative Oncology Group (ECOG) Scale**  

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
<td></td>
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<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
<td></td>
</tr>
</tbody>
</table>

### Criteria for Transplantation:

1. **Hematopoietic Allogeneic stem-cell transplantation (HSCT)** is considered medically necessary and may be authorized in adults and children who have a *fully matched-HLA sibling donor* for the treatment of bone marrow failure syndrome when ALL of the following criteria are met:
   - Must be < 60 years of age; 
   - Must have a diagnosis of aplastic anemia (includes congenital and acquired) defined as:
     - Severe aplastic anemia (SAA) : [ONE]
       - A marrow biopsy showing less than 25 percent of normal cellularity; OR
       - A marrow showing less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present: [TWO]
- absolute reticulocyte count <40,000/microL;
- absolute neutrophil count (ANC) <500/microL;
- platelet count <20,000/microL

OR

○ Very severe aplastic anemia (vSAA)\(^3\)\(^7\) defined as:
  ◊ the ANC is <200/microL

**And must meet age criteria:**

- For age < 50 years\(^3\)\(^7\): [ALL]
  ○ Stem cells are obtained from bone marrow\(^3\)\(^{10}\)\(^{39}\)

- For age >50 years\(^3\): [ALL]
  ○ Failed at least one course of immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporin;
  ○ Stem cells are obtained from bone marrow\(^3\)\(^{10}\)\(^{39}\)

2. **Hematopoietic Allogeneic stem-cell transplantation (HSCT)** is considered medically necessary and may be authorized in adults and children who have a *matched unrelated donor (MUD)* for the treatment of bone marrow failure syndrome when ALL of the following criteria are met: \(^3\)\(^7\)\(^8\)\(^{10}\)\(^{15}\)\(^{25}\)\(^{44}\): [ALL]

- Must be <60 years old;\(^10\)
- Failed at least one course of immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporin;\(^3\)\(^{10}\)
- Stem cells are obtained from bone marrow\(^3\)\(^{10}\)\(^{39}\)
- Must have aplastic anemia (includes congenital and acquired) defined as:\(^3\)
  ○ Severe aplastic anemia\(^3\)\(^7\): [ONE]
    ◊ A marrow biopsy showing less than 25 percent of normal cellularity; OR
    ◊ A marrow showing less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present: [TWO]
      ➢ absolute reticulocyte count <40,000/microL;
      ➢ absolute neutrophil count (ANC) <500/microL;
      ➢ platelet count <20,000/microL.

  OR

○ Very severe aplastic anemia\(^3\)\(^7\) defined as:
  ◊ the ANC is <200/microL; and
CONTINUATION OF THERAPY

A review for any stem cell transplantation procedure is valid for one year from the time the request was approved. Due to potential lengthy organ donor waiting time, an annual review of clinical information should be conducted to evaluate any changes in the member’s clinical status.

COVERAGE EXCLUSIONS

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Autologous stem cell transplant
3. Umbilical cord blood as a hematopoietic stem cell source is considered investigational due to the lack of sufficient evidence in the peer reviewed published literature.
4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant.
5. The following are absolute contraindications to stem cell transplantation:  
   - Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
   - Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
   - Irreversible brain damage or active central nervous system disease
   - Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
   - No behavioral health disorder by history or psychosocial issues: [One]
     - If history of behavioral health disorder, no severe psychosis or personality disorder
     - Mood/anxiety disorder must be excluded or treated
     - Member has understanding of surgical risk and post procedure compliance and follow-up required
       
       Note: Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

   - No adequate social/family support

6. Relative contraindications to stem cell transplantation include all of the following:  
   - Poor cardiac function (ejection fraction < 50%)
   - Poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal)
   - Poor renal function (creatinine clearance < 60ml/min)
   - Poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
   - Active central nervous system involvement
   - Presence of human immunodeficiency virus (HIV)
   - An active infection with any ONE of the following:
     - Hepatitis B virus (HBV)
     - Hepatitis C virus (HCV)
     - Human T-cell lymphotropic virus (HTLV)-1
   - Karnofsky rating <70% ; OR
   - Eastern Cooperative Oncology Group (ECOG) performance status >2
Aplastic Anemia

Aplastic anemia (AA) also called hypoplastic anemia, is a potentially fatal bone marrow failure disorder that is characterized by pancytopenia and a hypocellular bone marrow and can be acquired or congenital. The most common causes of acquired aplastic anemia include idiopathic (no known cause), hepatitis, drugs, chemical toxins, pregnancy, pure red cell anemia, paroxysmal nocturnal hemoglobinuria and parovirus B19. Congenital aplastic anemia usually is caused by genetic mutations in the hTR gene or a rare autosomal recessive inherited disease (Fanconi anemia). Affected patients generally present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and fatigue due to anemia. The diagnosis of AA is established following bone marrow aspiration and biopsy. Aplastic anemia is classified as non-severe (NSAA), severe (SAA) and very severe based on the degree of the peripheral blood cytopenias.\(^8\)\(^9\)

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person’s own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

Allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor can provide curative therapy for individuals with SAA. It is considered a standard of care for individuals younger than 50 years of age, despite treatment-related morbidity and mortality. Older individuals and those without HLA-identical related donors generally receive first-line therapy with immunosuppressive drugs. Alternative donor transplantation may be an option in children who do not have a matched donor.\(^3\)

Pretransplant Evaluation

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiology evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated
medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.  

**GENERAL INFORMATION**

**Summary of Medical Evidence**

*The clinical efficacy for stem cell transplantation as a treatment for aplastic anemia is from a large number of case series and retrospective analyses that have reported improved outcomes with the use of allogeneic HSCT. Randomized controlled trials are lacking in this population.*

Kikuchi et al. (2013) reported on outcomes of childhood aplastic anemia patients who underwent allogeneic hematopoietic SCT from an HLA-matched sibling donor in Japan. 329 childhood severe aplastic anemia (SAA) patients who underwent hematopoietic SCT (HSCT) from an HLA-matched sibling donor in the Japanese Hematopoietic Cell Transplantation Registry were reviewed. OS and EFS at 10 years were as high as 89.7+/−1.7% and 85.5+/−2.0%, respectively. Five cases of late malignancies (LM) were identified (malignant peripheral nerve sheath tumor, thyroid carcinoma, colon carcinoma, MDS and hepatoblastoma). Cumulative incidence of LM was 0.8% at 10 years and 2.5% at 20 years, respectively, which was lower than that in previous reports. This low incidence is in keeping with the low occurrence of skin cancer in Japanese population and of acute GVHD in our study group. Radiation-containing conditioning was not significantly associated with the incidence of LM after HSCT probably because of absolute low patient number who developed LM in our series. In terms of LM development after HSCT, low-dose TBI in HSCT for SAA to avoid graft rejection, which is commonly used in Japan, might be tolerable in the Japanese population because of its low incidence.

Buchbinder and colleagues (2012) conducted a descriptive analysis of 1718 patient’s post-HCT for acquired SAA between 1995 and 2006 that were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). This study describes the malignant and nonmalignant late effects in survivors with SAA after HCT and reported the prevalence and cumulative incidence estimates of late effects for 1-year HCT survivors with SAA. Of the HCT recipients, 1176 (68.5%) and 542 (31.5%) patients underwent a matched sibling donor (MSD) or unrelated donor (URD) HCT, respectively. The median age at the time of HCT was 20 years. The median interval from diagnosis to transplantation was 3 months for MSD HCT and 14 months for URD HCT. The median follow-up was 70 months and 67 months for MSD and URD HCT survivors, respectively. Overall survival at 1 year, 2 years, and 5 years for the entire cohort was 76% (95% confidence interval [CI]: 74-78), 73% (95% CI: 71-75), and 70% (95% CI: 68-72). Among 1-year survivors of MSD HCT, 6% had 1 late effect and 1% had multiple late effects. For 1-year survivors of URD HCT, 13% had 1 late effect and 2% had multiple late effects. Among survivors of MSD HCT, the cumulative incidence estimates of developing late effects were all <3% and did not increase over time. In contrast, for recipients of URD HCT, the cumulative incidence of developing several late effects exceeded 3% by 5 years: gonadal dysfunction 10.5% (95% CI: 7.3-14.3), growth disturbance 7.2% (95% CI: 4.4-10.7), avascular necrosis 6.3% (95% CI: 3.6-9.7),
hypothyroidism 5.5% (95% CI: 2.8-9.0), and cataracts 5.1% (95% CI: 2.9-8.0). The authors concluded that the results indicated that all patients undergoing HCT for SAA remain at risk for late effects, must be counseled about, and should be monitored for late effects for the remainder of their lives. 

Kim et al (2012) retrospectively analyzed the impact of older age on transplantation outcomes and survival in a total of 225 adult patients with AA who underwent allo-HSCT: 57 patients >40 years old (older patient group [OPG]) and 168 patient’s ≤40 years old (younger patient group [YPG]). Age at allo-HSCT ≤40 years, time from diagnosis to allo-HSCT ≤6 months, and matched related donor (MRD) were favorable prognostic factors in all study patients. Risk analysis of survival in the OPG showed that age >50 years was the only poor prognostic factor. Survival did not differ significantly between the YPG and patients <50 years old in the OPG. In conclusion, patients between the ages of 41 and 50 years with severe AA and MRDs should undergo allo-HSCT as early as possible to optimize survival.

In 2011 Peinmann and associates performed a meta-analysis to compare outcomes of first-line matched related donor hematopoietic stem cell transplantation to immunosuppressive therapy in patients with acquired severe aplastic anemia. 26 non-randomized controlled trials (7,955 patients enrolled from 1970 to 2001) were identified. No RCTs were identified. Risk of bias was high except in 4 studies. Young age and recent year of treatment were identified as factors for improved survival in the HSCT group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the IST group. In 19 studies (4,855 patients), summary statistics were sufficient to be included in meta-analysis. Considerable heterogeneity did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies. The review concluded that young age and recent year of treatment were identified as factors for improved survival in the transplant group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the immunosuppressive group. Considerable heterogeneity of non-randomized controlled studies did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies.

A randomized controlled trial reported by Scheinberg et al in 2011 compared horse versus rabbit antithymocyte globulin in acquired aplastic anemia. The study was designed to enroll 60 patients each for the rabbit-ATG and horse-ATG groups and was powered to detect a difference of 25 percentage points in the response rate. The primary outcome was hematologic response at 6 months, as determined by blood counts. The results showed a large, unexpected difference in the rate of hematologic response at 6 months in favor of horse ATG (68%; 95% confidence interval [CI], 56 to 80) as compared with rabbit ATG (37%; 95% CI, 24 to 49; P<0.001). Overall survival at 3 years also differed, with a survival rate of 96% (95% CI, 90 to 100) in the horse-ATG group as compared with 76% (95% CI, 61 to 95) in the rabbit-ATG group (P=0.04) when data were censored at the time of stem-cell transplantation, and 94% (95% CI, 88 to 100) as compared with 70% (95% CI, 56 to 86; P=0.008) in the respective groups when stem-cell-transplantation events were not censored. The authors concluded that
rabbit ATG was inferior to horse ATG as a first treatment for severe aplastic anemia, as indicated by hematologic response and survival.  

Eapen and associates (2011) sought to compare the outcomes of peripheral blood stem and progenitor cells (PBPC) and unrelated donor bone marrow (BM) transplantation for severe aplastic anemia (SAA). Outcome after unrelated donor bone marrow (BM) transplantation for severe aplastic anemia (SAA) has improved, with survival rates now approximately 75%. 296 patients who received either BM (n = 225) or PBPC (n = 71) from unrelated donors matched at human leukocyte antigen-A, -B, -C, -DRB1 were studied. Hematopoietic recovery was similar after PBPC and BM transplantation. Grade 2 to 4 acute graft-versus-host disease risks were higher after transplantation of PBPC compared with BM (hazard ratio = 1.68, P = .02; 48% vs 31%). Chronic graft-versus-host disease risks were not significantly different after adjusting for age at transplantation (hazard ratio = 1.39, P = .14). Mortality risks, independent of age, were higher after PBPC compared with BM transplantation (hazard ratio = 1.62, P = .04; 76% vs 61%). The authors concluded that these data indicate that BM is the preferred graft source for unrelated donor transplantation in SAA.  

Yoshida and colleagues (2011) reported the results of a retrospective study that evaluated whether clinical and laboratory findings before treatment in aplastic anemia could predict response in a pediatric cohort from the multicenter AA-97 study in Japan. Between 1997 and 2006, 312 newly diagnosed children were enrolled and treated with a combination of antithymocyte globulin and cyclosporine. In multivariate analyses, lower white blood cell count was the most significant predictive marker of better response; patients with white blood cell count less than 2.0×109/L showed a higher response rate than those with white blood cell count of 2.0×109/L or more (P=0.0003), followed by shorter interval between diagnosis and therapy (P=0.01), and male sex (P=0.03). In conclusion, pre-treatment clinical and laboratory findings influence response to therapy. The finding that response rate worsens with increasing interval between diagnosis and treatment highlights the importance of prompt immunosuppressive therapy for patients with aplastic anemia.  

Gupta and associates (2010) sought to identify age or ages at transplantation at which survival differed by studying the effect of patients' age, adjusting for other significant factors affecting outcomes, in 1307 patients with severe aplastic anemia after HLA-matched sibling transplantation using logistic and Cox regression analysis. Age categories (<20 years, 20-40 years, >40 years) were determined using Martingale residual plots for overall survival and categories based on differences in survival. Patients aged over 40 years old were more likely to have had immunosuppressive therapy, a poor performance score and a longer interval between diagnosis and transplantation. Neutrophil recovery was similar in all age groups but patients aged over 40 years had a lower likelihood of platelet recovery compared to patients aged less than 20 years (OR 0.45, P=0.01) but not compared to those aged 20-40 years (OR 0.60, P=0.10). Compared to the risk of mortality in patients aged less than 20 years, mortality risks were higher in patients over 40 years old (RR 2.70, P<0.0001) and in those aged 20-40 years (RR 1.69, P<0.0001). The mortality risk was also higher in patients aged over 40 years than in those 20-40 years old (RR 1.60, P=0.008). The authors concluded that mortality risks increased with age. Risks
were also higher in patients with a poor performance score and when the interval between diagnosis and transplantation was longer than 3 months, implying earlier referral would be appropriate when this treatment option is being considered. 38

Sangiolo et al. (2010) retrospectively reviewed the outcomes after allogeneic HCT from HLA-identical sibling donors for all older patients with SAA. At the Fred Hutchinson Cancer Research Center, 23 consecutive patients ranged in age from 40 to 68 years. The conditioning regimen was cyclophosphamide (200 mg/kg) and horse antithymocyte globulin. Methotrexate and cyclosporine were given for postgrafting immunosuppression. The cumulative incidences of grades II, III, and IV acute graft-versus-host-disease were 30%, 4%, and 0%, respectively; that for chronic GVHD was 26%. With a median follow-up of 9.1 years, overall survival was 65%. Documented infections within 1 month before HCT were significantly associated with risk of early treatment-related mortality (P<.001). The median time to discontinuation of post-transplant immunosuppression was 6.2 (range: 5.9–92.0) months. Three patients developed superficial basal cell carcinoma between 5.5 and 15 years after HCT. The review concluded that the data favored a practice of extending HLA-identical sibling HCT for treatment of SAA in patients older than 40 years of age who are without significant medical comorbidities. 27

In 2009, Peinemann and colleagues performed a systematic review to investigate the outcome of aplastic anemia patients treated with unrelated donor transplants. Systematic literature searches were performed in MEDLINE, EMBASE, and The Cochrane Library. All databases were searched from inception to June 2009. Only full-text publications and studies including at least 10 patients were considered. The primary outcome was 5-year overall survival from the day of transplantation and the secondary outcomes were graft failure and graft-versus-host disease. A meta-analysis of survival estimates was conducted and heterogeneity was investigated. A total of 18 studies, one controlled trial and 17 case series were identified. The overall survival at five years and the corresponding confidence interval was stated in 8 studies and ranged from 28% to 94%. A meta-analysis revealed considerable heterogeneity between the studies that could not be explained and was also present in subgroups of the studies. The proportion of acute graft failure was 45% in one study using only umbilical cord blood, and it was reported to be 0–26% in 15 studies using mainly bone marrow as stem cell source after different follow-up periods. Acute GVHD grade II–IV was reported for 8–86% and extensive chronic GVHD for 0–38% of the evaluated patients in 16 studies. Recipient age, human leukocyte antigen match, performance status, year of transplantation, and conditioning with serotherapy were identified as significant factors for improved survival. The review outcome concluded that unrelated donor hematopoietic stem cell transplantation in patients with acquired severe aplastic anemia after failure to immunosuppressive therapy is a treatment option. A stable physical condition of the patients before receiving the transplant (for example, performance and age) may be associated with a better survival. Detailed HLA-matching facilitated by DNA-based typing, among other factors, may have contributed to recent improvements on survival after unrelated donor HSCT as a second-line treatment. 24
Perez-Alburne et al. (2008) analyzed data from 195 children with acquired SAA who underwent unrelated donor transplantation between 1989 and 2003 to determine if unrelated donors provide a source of hematopoietic stem cells in children with severe aplastic anemia (SAA) who fail immunosuppressive therapy and lack a human leucocyte antigen (HLA)-matched sibling donor. Neutrophil recovery (86% at day-28) was higher with total body irradiation-containing conditioning regimen and in younger recipients (aged < or =16 years) receiving grafts from older donors (aged >40 years). Recovery was lower after mismatched transplants and transplantations prior to 1997. Mortality rates were higher after mismatched transplants, in recipients with a poor performance score, and when the interval between diagnosis and transplantation was longer than 4 years. When restricted to donor-recipient pairs with allele-level HLA typing (8-loci; n = 118), mortality rates were also higher after mismatched transplants and older recipients receiving grafts from older donors; 5-year probabilities of overall survival after HLA-A, -B, -C, -DRB1 matched and mismatched transplants adjusted for donor and recipient age were 57% and 39%, respectively (P = 0.008). The authors concluded that unrelated donor transplantation is an acceptable alternative for children; early referral for transplantation and identification of an HLA-matched (allele-level) donor offers the best outcome.  

Champlin et al. (2007) performed a randomized controlled study of conditioning regimens to determine whether the addition of ATG to cyclophosphamide would improve survival at 1 year from 65% to 85% and lower the rate of graft rejection from the anticipated 15% to less than 5%. Eligibility criteria included patients with SAA (marrow cellularity < 20%) and 2 of the following criteria: absolute neutrophil count (ANC) no greater than 0.5 × 109/L; platelet counts no greater than 20 × 109/L; and reticulocyte count no greater than 50 × 109/L, be no older than 60 years age, and have an HLA-matched sibling donor. 134 patients were randomly assigned to receive cyclophosphamide alone or in combination with ATG. All patients received T-cell–replete bone marrow from an HLA-matched sibling. With a median follow-up of 6 years, the 5-year probabilities of survival were 74% for the cyclophosphamide alone group and 80% for the cyclophosphamide plus ATG group (P = .44). Graft failure and graft-versus-host disease (GVHD) rates were similar in both groups. With the survival rates achieved, this study is not adequately powered to detect significant differences between the 2 treatment groups. In conclusion, the results of allogeneic BMT for SAA have improved over time related to advances in supportive care. The addition of ATG to the preparative regimen did not significantly improve the outcome.  

Kennedy-Nasser et al. (2006) retrospectively analyzed 36 pediatric patients who received 38 bone marrow or peripheral blood stem cell transplants; 15 from matched sibling donor (MSD) and 23 from alternate donor (AD); for SAA from April 1997 to October 2005. Nineteen AD recipients received reduced intensity conditioning with cyclophosphamide, low-dose total body irradiation, and antithymocyte globulin (ATG) or Campath. The 4-year overall survival for MSD recipients was 93% versus 89% for AD recipients treated with reduced intensity conditioning regimens at a median follow-up of 52 months (range, 6-99 months). No patient receiving Campath, compared with 3 of 9 patients receiving ATG, developed extensive, chronic GVHD. The authors concluded that for children with SAA, AD transplantation is as effective as MSD transplantation. Further, compared with ATG, preparatory regimens containing Campath may be associated with a lower incidence of extensive, chronic GHVD.
Ades and colleagues (2004) reported on 133 subjects treated with matched related allogeneic bone marrow transplants for the treatment of aplastic anemia. The conditioning regimen included thoracoabdominal irradiation (TAI) and cyclophosphamide for 100 subjects, and cyclophosphamide and antithymocyte globulin (ATG) for 33 subjects. The long-term study had a median follow-up of 13.6 years. Survival estimates for 5-, 10-, and 15-years were 69% + 4.0%, 64.5% + 4.5% and 58.7% + 5.2% respectively. Four individuals did not achieve engraftment and were not included in the long-term outcome data analysis. A total of 52 (79%) subjects developed extensive graft versus host disease (GVHD). Forty six deaths after transplantation occurred primarily resulting from GVHD, infection and one individual died of cancer. 18

Kojima and associates (2000) reported the results of a retrospective study that included a total 100 children under the age of 17 years with acquired aplastic anaemia (AA). The participants were initially treated with immunosuppressive therapy (IST) (n = 63) or bone marrow transplantation (BMT) (n = 37) from an HLA-matched family donor. The projected 10-year survival rates were 55 +/- 8% and 97 +/- 3% respectively (P = 0.004). Because the IST group included 11 non-responders who were salvaged by BMT from an HLA-matched unrelated donor, we compared failure-free survival (FFS) between the groups. The probability of FFS at 10 years was 97 +/- 3% for the BMT group, compared with 40 +/- 8% for the IST group (P = 0.0001). Seven patients evolved to myelodysplastic syndrome (MDS) with monosomy 7 and the estimated cumulative incidence of MDS 10 years after diagnosis was 20 +/- 7% in the IST group. We compared the outcome of children treated with IST during the two consecutive periods of 1983-91 (group A, n = 40) and 1991-8 (group B, n = 23) to assess the impact of combined therapy with antithymocyte globulin and cyclosporin. The probability of FFS at 7 years follow-up was the same in the two groups (50 +/- 8% vs. 40 +/- 15%, P = 0.40). The authors concluded that BMT is recommended as first-line therapy in paediatric severe AA patients with an HLA-matched family donor. Alternative donor BMT is recommended as salvage therapy in patients who relapse or do not respond to initial IST. 19

Allogeneic hematopoietic stem cell transplantation may also be an option under specific circumstances for Diamond-Blackfan anemia (DBA), Fanconi's anemia (FA) and paroxysmal nocturnal hemoglobinuria. In a report from the DBA registry, 20 of 354 registered individuals underwent hematopoietic stem cell transplantation, and the 5-year survival rates were 87.5% when recipients received HLA-identical sibling grafts (Gluckman, 2008). Dufour and colleagues (2008) reported in a summary of allogeneic hematopoietic stem cell transplantation from matched related donors over 6 years in FA, totaling 103 individuals, that overall survival ranged from 83–88%, with transplant-related mortality ranging from 8%–18.5% and average chronic GVHD of 12%. Santarone and colleagues (2010) performed a retrospective study of 26 individuals with paroxysmal nocturnal hemoglobinuria and concluded that hematopoietic stem cell transplantation may lead to a long-term cure rate as high as 60% in a heterogeneous cohort of seriously ill individuals with paroxysmal nocturnal hemoglobinuria. 20 21
Goldberg and colleagues (1998) sought to determine the value of pretransplant studies in predicting day 100 nonrelapse toxic mortality following high-dose therapy. A retrospective review of 383 consecutive hematopoietic stem-cell transplants was performed with attention to toxic mortality and pretransplant factors. Univariate log-rank analysis was used to yield the most significant cut-off values for individual factors. Multivariate analysis using Cox proportional hazards regression determined factors independently predictive of early toxic death. Nonrelapse toxic mortality before day 100 occurred in 23 of 383 (6.0%) transplant recipients. Factors associated with an increased risk of toxic death by univariate analysis included forced expiratory volume in 1 second (FEV1) less than 78% of predicted (P = .0002), allogeneic versus autologous transplant (P = .0003), diffusion capacity of carbon monoxide less than 52% of predicted (P = .002), serum creatinine concentration greater than 1.1 mg/dL (P = .003), Eastern Cooperative Oncology Group performance status greater than 0 (P = .006), preparative regimen containing total-body irradiation versus chemotherapy alone (P = .006), marrow versus blood stem cell (P = .01), serum ALT greater than 50 IU/L (P = .02), diagnosis of hematologic disorder versus solid tumor (P = .06), serum bilirubin level greater than 1.1 mg/dL (P = .08), left ventricular ejection fraction (P = .09), and growth factor use (P = .09). In the multivariate model, transplant type (relative risk, 4.2), FEV1 (relative risk, 4.5), performance status (relative risk, 3.7), serum creatinine (relative risk, 3.8), and serum bilirubin (relative risk, 3.7) were found to be independent predictors of early toxic mortality. The pretransplant evaluation is a useful tool to identify patients at risk for early toxic mortality following high-dose therapy.

Hayes, Cochrane, UpToDate, MD Consult etc.

Hayes does not have a medical technology report on the topic of stem cell transplantation for the diagnosis aplastic anemia.

UpToDate:

In a report called Hematopoietic cell transplantation in aplastic anemia the following recommendations are summarized: Hematopoietic cell transplantation (HCT) is an effective and potentially curative treatment option for patients with severe (SAA) or very severe aplastic anemia (vSAA). HCT compares favorably to immunosuppression, the other major treatment option for aplastic anemia, under a number of different clinical situations, depending upon patient age, prior treatment, presence of medical comorbidities, and the availability of a matched related or matched unrelated transplant donor. Initial treatment of AA in any patient includes withdrawal of potentially offending agents, supportive care (eg, transfusion, antibiotics), and some form of definitive therapy (eg, hematopoietic cell transplantation, immunosuppressive regimens). Blood and platelet transfusions should be used selectively in patients who are candidates for HCT to avoid sensitization and should never be used from the potential HCT donor prior to transplantation.

Age related recommendations include:

- Allogeneic HCT over treatment with an immunosuppressive regimen is recommended in patients with SAA or vSAA who are <20 years of age with an HLA-matched sibling.
• Allogeneic HCT over treatment with an immunosuppressive regimen is recommended in patients with SAA or vSAA who are 20 to 50 years of age in otherwise excellent health with a fully HLA-matched sibling donor.

• The use of immunosuppressive therapy over HCT is recommended for most patients with SAA or vSAA over the age of 50 because of the very high risk of graft versus host disease and other transplant-related complications in this group of patients.

• For patients over the age of 50 who are free of significant medical comorbidities and have an HLA-identical sibling donor, HCT rather than immunosuppressive therapy is recommended.

• For patients who have not adequately responded to one to two courses of immunosuppressive therapy, or who relapse following such therapy, matched unrelated donor HCT over further repeated course(s) of immunosuppressive therapy is recommended.

In a report called *Hematopoietic cell transplantation for idiopathic severe aplastic anemia and Fanconi anemia in children* the following recommendations are summarized: Allogeneic hematopoietic cell transplantation (HCT) from an HLA-identical sibling donor is the treatment of choice for a child with severe aplastic anemia (SAA), offering a cure by restoration of normal hematopoiesis. Long-term survival (currently ≥90 percent) has been achieved by the following:

- A reduction in the incidence, severity, and mortality from acute graft-versus-host disease
- A reduction in the incidence of marrow graft rejection
- Early transplantation before the onset of severe infections
- Avoidance of blood product transfusions from the proposed HCT donor

If an HLA-matched donor is not immediately available, children with SAA should receive immediate treatment with an immunosuppressive regimen. A search for an HLA-matched unrelated donor can be initiated at that time, with the expectation that the outcome following an HLA-identical unrelated donor transplant in children with SAA is comparable to that from an HLA-identical sibling donor.

*First Consult*

In a report called Aplastic Anemia the first choice of treatment is bone marrow transplantation (BMT) or immunosuppressive treatment using antithymocyte globulin, and/or cyclosporine (this is an off-label indication) for patients who are not eligible for BMT (because of age or lack of a suitable donor). A supplementary treatment consists of platelet/red blood cell transfusion. In addition to the above treatments, meticulous attention must be paid to the prevention of infections in these patients. Hand-washing, as well as precautions in the face of neutropenia (isolation, gown and gloves) should be instituted in the care of these patients. Prompt treatment of infections is essential.

*Professional Organizations*
The British Committee for Standards in Haematology published guidelines for the diagnosis and management of aplastic anaemia in 2009. These guidelines recommend that allogeneic BMT from an HLA-identical sibling donor is the initial treatment of choice for newly diagnosed patients if they have severe or very severe aplastic anaemia, are <40 years old, and have an HLA-compatible sibling donor. Bone marrow is the recommended source of stem cells for transplantation in aplastic anaemia. Immunosuppressive therapy is recommended for patients with non-severe aplastic anaemia who are transfusion dependent, patients with severe or very severe disease who are >40 years old, and younger patients with severe or very severe disease who do not have an HLA-identical sibling donor. Matched unrelated donor (MUD) BMT may be considered when a patient has a fully matched donor, is <50 years old (or 50–60 years old with good performance status), has failed at least one course of ATG and ciclosporin, and has severe aplastic anaemia. There is currently insufficient data on outcome for patients >60 years of age.

National Marrow Donor Program (NMDP): The NMDP lists severe aplastic anemia and other bone marrow failure (including Fanconi anemia, Diamond-Blackfan anemia and others) as indications for HSCT.

The Cancer Care Ontario Program in Evidence-based Care Advisory Panel on Bone Marrow and Stem Cell Transplantation published guidelines (2009) for Stem cell transplantation in adults: recommendations in Aplastic Anemia (AA). These guidelines recommend the following:

- Allogeneic stem cell transplantation is the recommended treatment option for eligible patients under age 30-40 years of age with severe or very severe AA
- Allogeneic stem cell transplantation is an option for selected patients with severe or very severe AA over the age of 30-40 years of age
- Autologous stem cell transplantation is not recommended for patients with AA

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45. Advanced Medical Review: Policy reviewed by MD board certified in Internal Medicine, Oncology and Hematology