# Hematopoietic Stem Cell Transplantation in Children and Adolescents

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## Educational Gap

Hematopoietic stem cell transplantation (HSCT) indications and practices have changed significantly over the last 20 years. Evolving hematopoietic stem cell sources, less toxic conditioning regimens, and improving graft-versus-host disease prophylaxis and therapy have broadened the application of HSCT from malignant conditions to increasing numbers of nonmalignant diseases.

## Objectives

After completing this article, the reader should be able to:

1. Understand general principles of allogeneic and autologous hematopoietic stem cell transplantation (HSCT), including the variety of hematopoietic stem cell sources.
2. Discuss the variability in intensity of current conditioning approaches, which influences the risks and applicability of HSCT.
3. Recognize that HSCT involves acute and chronic complications and the importance of general clinicians and subspecialists in their management.
4. Review the pathophysiology of graft-versus-host disease, its presentation, and its prevention and management.
5. Identify the increasing number of nonmalignant indications for HSCT in children such that children who might benefit from this procedure are considered for timely referral as appropriate.

### CASE STUDY

A 1-year-old child is referred to your office for a developmental assessment due to delayed speech and gross motor skills. You notice coarse facial features and on physical examination document corneal clouding, hepatosplenomegaly, and numerous skeletal deformities. You suspect a metabolic disorder and request an urgent referral to a metabolic specialist. The specialist clinically diagnoses Hurler syndrome (mucopolysaccharidosis IH) and confirms $\alpha$-L-iduronidase deficiency with urinary glycosaminoglycan testing and subsequently by enzyme

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deficiency in fibroblasts. While genetic testing results are pending, you discuss the case with the metabolic specialist and agree that an urgent referral to a pediatric hematopoietic stem cell transplantation (HSCT) specialist is warranted before genetic testing results are available. The best neurologic outcomes are seen when HSCT is performed as soon as possible, preferably before age 2 years. Having general knowledge about HSCT planning and complications, you help the family prepare for their meeting with the pediatric HSCT specialist, allowing for a more productive consultation, and offer to share ongoing care of the child both before HSCT and during subsequent follow-up.

## NOMENCLATURE

HSCT is the procedure of infusing blood stem cells from a donor into a recipient. When the donor and recipient are different people, the procedure is termed an allogeneic HSCT; if the donor and recipient is the same person, it is an autologous HSCT. Syngeneic HSCT describes a donation between identical twins.

Hematopoietic stem cells (HSCs) may be collected from bone marrow, peripheral blood, or the umbilical cord/placental unit of a newborn (UCB).

Human leukocyte antigens (HLAs) are tested at major histocompatibility loci: Class I (A, B, and C) and Class II (DR; DQ in some centers). At least 6 loci routinely are analyzed for a UCB product and 8 to 10 loci for a live donor product (ie, bone marrow or peripheral blood). The degree of matching is expressed as the numerator of matched loci over the denominator of loci tested. HLA matching may be tested at low (antigenic), medium, or high (allelic) levels of resolution.

Graft-versus-host disease (GVHD) is a serious and potentially life-threatening complication of HSCT in which the donor T cells cause an inflammatory response in the recipient tissues. This complication is described in detail later, but the risk of its development has been historically reduced by the best possible HLA matching at major loci as well as the use of a related donor due to closer matching at untested minor histocompatibility antigens. Newer approaches to haploidentical HSCT (see definition later) and novel GVHD prevention strategies, however, are reducing GVHD rates, even in the setting of greater HLA disparity.

Allogeneic HSC donors are further characterized in terms of the relationship between the donor and recipient (Table 1). Fully matched related donations can come from a minor or adult sibling or rarely a parent (often with a history of consanguinity). Haploidentical HSCT involves donation from a first-degree relative (usually a mother) who shares 1 haplotype, typically matched at 5 to 8 of 10 HLA loci. Unrelated HSC products may come from UCB donations or a living adult donor (not minors).

**TABLE 1. Nomenclature for Hematopoietic Stem Cell Donors**

| | |
|---|---|
| Matched Sibling Donor | MSD |
| Mismatched Sibling Donor | MMSD |
| Matched Familial Donor (eg, parent) | MFD |
| Mismatched Familial Donor | MMFD |
| Matched Unrelated Donor | MUD |
| Mismatched Unrelated Donor | MMUD |

*Matched indicates all tested human leukocyte antigen (HLA) loci are the same between donor and recipient.*
*Mismatched means at least 1 HLA locus differs between donor and recipient (at either allelic or antigenic level of testing).*

Conditioning refers to the preparative chemotherapy, immunotherapy, and/or radiotherapy given to a recipient before stem cell infusion to facilitate engraftment of allogeneic donor HSCs and to prevent rejection. In this setting, the HSCs are a primary component of the curative therapy; in autologous HSCT, the conditioning is the actual therapy and the HSCs are administered to rescue the hematopoietic system. Myeloablative conditioning refers to intensive chemotherapy and/or radiation doses sufficient to cause bone marrow aplasia in the absence of HSC infusion. Reduced-intensity conditioning (RIC) describes nonmyeloablative or less intensive conditioning regimens.

HSCs for UCB and autologous donation must be cryopreserved, whereas most allogeneic live donor products are donated during the conditioning of the recipient. Allogeneic products may also be manipulated to reduce plasma, red blood cells, or T cells, depending on the donor-recipient blood group matching/mismatching, the stem cell source, the routine practices of the HSCT center, and the indication for HSCT.

## TRENDS IN PRACTICE

Internationally, more than 2,000 allogeneic HSCTs were reported to have been performed in recipients younger than age 20 years in 2012. (1) The use of UCB has increased over the last 20 years, as have donations from unrelated live donors. These trends are affected by improvements in supportive care (including GVHD prevention and treatment) as well as donor availability, with expanded live donor and UCB registries.

RIC was developed for older recipients who were ineligible for myeloablative conditioning due to comorbidities. Its use has expanded to many nonmalignant indications for children in whom a phenotype can be reversed with even relatively low numbers of engrafted donor HSCs (mixed donor chimerism) and there is a mix of hematopoietic cells of donor and recipient origin. Several conditions, such as severe combined immune deficiency, hemophagocytic lymphohistiocytosis, and hemoglobinopathies, are known to be cured with stable mixed-donor chimerisms as low as 20% to 30%. (2) The appeal of RIC lies in reduced rates of GVHD and transplant-related mortality (TRM) in addition to fewer acute and late toxicities due to lower doses of conditioning agents.

The increased use of RIC and haploidentical HSCT has also influenced the growing proportion of HSCT recipients with nonmalignant diseases. This trend toward HSCT for nonmalignant conditions is due to improved outcomes with upfront non-HSCT childhood leukemia therapies as well as advancements in the safety of HSCT. As the risks of morbidity and mortality decrease, the potential application of HSCT as a curative option for various nonmalignant diseases broadens.

Expertise in haploidentical HSCT is increasing worldwide, particularly in Europe and the United States. Its appeal lies in the almost universal availability of a donor, particularly for potential recipients whose HLA haplotypes are underrepresented on existing volunteer registries. Risks of GVHD and infection (due to T-cell depletion) as well as required laboratory infrastructure complicate its application, but improved supportive care options have increased the practice of haploidentical HSCT. Newer techniques such as the use of cyclophosphamide after HSC infusion have resulted in markedly improved rates of engraftment and reduced rates of GVHD and infectious complications. (3)

## PRINCIPLES OF HSCT

Allogeneic HSCT involves the replacement of the deficient recipient hematopoietic system with that of the donor. The best possible HLA-matched donor is used, with a preference for matched sibling, followed by matched related donors. HLA testing and matching is currently limited to 8 to 10 major histocompatibility loci for living donors, yet minor histocompatibility (H) antigens also influence the risk of GVHD. Minor H antigens are potentially immunogenic peptides genetically coded outside of the major histocompatibility complex (MHC). (4) The coding loci for H antigens are scattered throughout the genome in contrast to the MHC being coded on chromosome 6. As a result, a related fully HLA-matched donor is almost always preferred to an unrelated donor with the same number of matched loci. Unrelated donors may be identified through international live donor registries or accredited public UCB banks. Identifying an unrelated donor and proceeding with HSCT usually takes 1 or more months, depending on the rarity of the recipient HLA-typing, donor availability to proceed with donation, and medical clearance of both donor and recipient. This process is generally shorter for UCB products because the donation has already been made and the product has been cryopreserved.

Allogeneic stem cells can be donated as 1 of 3 stem cell sources:

- Bone marrow
- Peripheral blood stem cells
- Umbilical cord blood

Table 2 describes the method of donation as well as advantages and disadvantages of each source of allogeneic HSCs. Peripheral blood stem cells are less commonly used in pediatric HSCT recipients due to higher risks of chronic GVHD; they are typically only used for malignant indications or as part of a RIC protocol. Many considerations are balanced in choosing a stem cell source: the recipient's underlying condition, the degree of HLA matching, the urgency of the HSCT, the risk to the donor (particularly for minor sibling donors who cannot consent for themselves), donor preference for method of donation, donor health status (which may preclude a method of donation), ABO status of donor and recipient, and size discrepancy between donor and recipient. The stem cell dose (ie, number of donor HSCs) required for the HSCT recipient is calculated based on *recipient* weight, which may not be achievable based on the size of a prospective living donor. Donations from living donors are almost always collected within 2 days of infusion to ensure that the HSCT is not subsequently cancelled due to a change in the recipient's eligibility status and to avoid cell loss with cryopreservation. UCB products contain a fixed number of cryopreserved stem cells. A given UCB unit may have sufficient stem cells for a smaller recipient but may be inadequate for a larger patient.

Additional considerations include the age of the donor, the donor sex, and any pregnancies (if applicable). Younger donors generally have more cellular bone marrows and produce greater HSC yields. In addition, their donations are associated with lower GVHD rates in recipients. Donations from females, particularly with increasing parity, are associated with higher rates of GVHD. Male recipients with female donors are at highest risk. (10)

Autologous stem cell collections are almost always from peripheral blood, with bone marrow harvests usually reserved for failed peripheral blood collections. Such

TABLE 2. **Review of Hematopoietic Stem Cell Sources**

| HSC STEM CELL SOURCE | METHOD OF COLLECTION | ADVANTAGES | DISADVANTAGES |
|---|---|---|---|
| Bone Marrow | Donor undergoes anesthesia, is placed prone, and marrow harvested bilaterally from iliac crests | High engraftment rates | Pain after harvest for donor |
| | Collection proceeds until donor maximum volume collected (10-20 mL/kg) or target HSC dose achieved (whichever comes **first**) | Lower rates of chronic GVHD compared to peripheral blood (6) | Donor size limits volume of marrow that can be harvested (transfusion of donor is discouraged) |
| | Research underway regarding benefits of G-CSF administration before donation to improve yield (5) | | High volumes of product can cause volume overload for recipient |
| | | | ABO incompatibility warrants processing of sample to reduce red blood cells and/or plasma (HSC loss occurs with each processing step) |
| Peripheral Blood | Donor receives G-CSF for 3-5 days prior to donation | High engraftment rates | G-CSF exposure to donor can cause bone pain |
| | Apheresis catheter placement for donor (often a femoral venous line under anesthesia for pediatric donors) | Higher stem cell yields<br>*Possibly* lower relapse rates for malignant diseases (6)(7) | Ongoing concern over long-term risks of G-CSF exposure to donor bone marrow (although data show no clear evidence of harm)<br>Higher rates of chronic GVHD (6) |
| | 1-2 days of donation on apheresis machine (typically 4-8 hr/day) | May allow for lower-intensity conditioning | Smaller donors unable to undergo apheresis without blood product exposure due to extracorporeal blood volume (transfusion of donor is discouraged) |
| | Collection proceeds until target HSC dose achieved (diminishing yield with ongoing time on circuit) | | Donor may not mobilize stem cells peripherally (more common in adult donors) |
| Umbilical Cord Blood | Collected after clamping of umbilical cord blood | Product can be procured quickly for HSCT | Higher rates of nonengraftment (graft failure) (9) |
| | Method of collection should not compromise mother or neonatal donor in any way | HLA mismatching more permissive (ie, 4-6/6 match can be used) due to lower rates of GVHD | Cell dose per recipient weight is limited to existing cryopreserved product (fixed) and may be lowered, depending on viability before freezing and after thawing |
| | Sample is processed and cryopreserved | May be superior for metabolic disorders (8) | |
| | | May obviate the need for minor sibling donation if sibling UCB available | Higher rates of viral infections (delayed immune recovery) (9) |
| | | No donor risk | Cannot access additional HSCs if nonengraftment or early relapse for donor lymphocyte infusion |
| | | | Medical history of donor generally unknown |

*G-CSF=granulocyte colony-stimulating-factor, GVHD=graft-versus-host disease, HLA=human leukocyte antigen, HSC=hematopoietic stem cell, HSCT=hematopoietic stem cell transplantation, UCB=umbilical cord blood*

collections are typically timed at the point of initial hematopoietic recovery following myelosuppressive chemotherapy, in combination with granulocyte colony-stimulating factor (G-CSF). "Steady-state" collections can also be performed with G-CSF administration alone. The HSCs are then cryopreserved to be used later to rescue the patient following high doses of chemotherapy or radiation, allowing for more rapid hematopoietic recovery.

HSCs are infused into the recipient after conditioning chemotherapy and/or radiation (see next section). Such cells

are infused into the venous system using a central vascular access device but may also be infused into a peripheral intravenous catheter. No filters can be placed on the tubing, which could block the HSCs from entering the circulation. Premedication is required for cryopreserved products to avoid reaction to the preservative required for the cells to tolerate freezing, and such premedication is also used for ABO incompatibilities with bone marrow products. The HSCs enter the marrow via adhesion molecule recognition and start to grow and mature immediately. However, 2 to 3 weeks generally is required for measurable neutrophil counts (or engraftment) and for red blood cell and platelet transfusion independence. The fastest rates of HSC engraftment are seen with autologous rescues and with peripheral blood stem cell products; UCB products are often the slowest to engraft. (9)

## CONDITIONING FOR HSCT

Conditioning, or the preparative regimen, refers to the combination of chemotherapy, immunotherapy, and/or radiation therapy given to an HSCT recipient before the HSC infusion. Such conditioning is usually administered over 1 to 2 weeks before HSC infusion. Immune suppression, notably reduction or ablation of innate immune and T cells, is necessary to prevent rejection of the HSCs in the setting of allogeneic HSCT. Conditioning may also serve as disease-directed therapy in allogeneic HSCT for malignant disease. Serotherapy is a form of immunotherapy typically involving antithymocyte globulin or alemtuzumab (monoclonal antibody to CD52) that is intended to address host immune cell depletion, although it is primarily administered for in vivo GVHD prophylaxis. Total body irradiation (TBI) is highly myelosuppressive but is associated with many undesirable acute and late toxicities.

Myeloablative conditioning is standard for malignant disease HSCT indications and has been used historically for nonmalignant conditions as well. The goal of myeloablation is to replace all cell lines of the hematopoietic system (eg, lymphoid, myeloid) completely with donor HSCs. Although most experts consider eradication of all recipient blood cells to be essential for a person with leukemia, as few as 20% donor cells in the deficient cell line can reverse the abnormal phenotype in a nonmalignant condition. (2) The ability to cure a nonmalignant disease in the setting of mixed-chimerism following RIC has greatly increased the safety and application of HSCT to a broader number of nonmalignant diseases. Graft failure after RIC often results in autologous recovery of the recipient's original HSCs.

Autologous HSCT conditioning regimens are almost exclusively composed of high-dose combinations of chemotherapy with or without radiation therapy targeted at the underlying disease (usually malignant). The goal is to rescue the patient after otherwise intolerable doses of these agents given to intensify therapy.

## RISKS OF HSCT

HSCT is associated with numerous acute and long-term toxicities. The conditioning, its intensity (myeloablative versus RIC), preexisting comorbidities, prior chemotherapy exposure, and the stem cell source all influence the risks of complications and TRM. Children and adolescents generally tolerate myeloablative conditioning better than adults, but TRM rates are still typically 5% to 10%. RIC was initially designed to offer HSCT to patients with comorbidities, so TRM rates are inherently lower, as are rates of many toxicities. HSCT adverse effects on growth, development, and fertility are especially pertinent in children and adolescents (Table 3). (11)(12) A detailed discussion of these late effects is beyond the scope of this article, but comprehensive follow-up by general pediatricians and a team with expertise in HSCT late effects care and surveillance is recommended. Surveillance guidelines have been published by the Children's Oncology Group and other research bodies. (11)(12)(13)

### Infections/Immune Reconstitution

HSCT usually involves myelosuppression as well as functional impairment of adaptive immunity. (14) As mentioned previously, neutrophil engraftment typically occurs 2 to 3 weeks after HSC infusion, which is an important milestone for innate immune protection against bacteria and fungi. Natural killer cell recovery usually is complete by 1 month post-HSCT, offering additional protection against infection. T-cell function is impaired by intent during periods of prophylaxis or therapy for GVHD, and GVHD in itself is a dysregulated immune state, with poor function and protection against infection. For those HSCT recipients who can stop GVHD prophylaxis by 6 months post-HSCT, lymphocyte class switching (producing immunoglobulin [Ig]G after IgM production) can be seen between 6 and 8 months after HSC infusion.

Children must be monitored for opportunistic infections after HSCT. Bacteremia and sepsis are frequent, particularly during the neutropenic phase before engraftment. Fungal infections are also a concern during neutropenic phases or corticosteroid therapy. Respiratory viruses such as respiratory syncytial virus and adenovirus can be devastating in an immunocompromised host. Primary infection or reactivation with cytomegalovirus and Epstein-Barr virus (EBV) warrant preemptive surveillance and intervention based

TABLE 3. **Late Effects of Pediatric Hematopoietic Stem Cell Transplantation (11)( 12)**

| | |
|---|---|
| Endocrine | Growth disturbance (including growth hormone deficiency)<br>Hypothyroidism<br>Thyroid nodules<br>Hypogonadism<br>Delayed or precocious puberty<br>Infertility<br>Obesity (including sarcopenic obesity)<br>Osteopenia/osteoporosis<br>Avascular necrosis<br>Metabolic syndrome |
| Ophthalmologic | Cataracts<br>Xerophthalmia |
| Auditory | Hearing loss |
| Neurologic | Neurocognitive impairment<br>Cerebrovascular disease |
| Pulmonary | Pulmonary fibrosis<br>Bronchiolitis obliterans with or without organizing pneumonia (usually chronic GVHD) |
| Cardiovascular | Congestive heart failure<br>Conduction abnormalities<br>Valvular disease |
| Renal | Chronic kidney disease<br>Hypertension<br>Proteinuria |
| Gastrointestinal | Hepatic siderosis<br>Focal nodular hyperplasia of liver<br>Esophageal strictures<br>GVHD of upper or lower tracts<br>Hepatic GVHD |
| Secondary malignancy | Acute myelogenous leukemia (almost exclusive to autologous HSCT)<br>Posttransplant lymphoproliferative disease (non-Hodgkin lymphoma)<br>Solid tumors (skin, brain, thyroid, musculoskeletal, oral cavity, breast, gynecologic) |
| Dental | Disordered tooth eruption<br>Increased risk of caries<br>Xerostomia |
| Psychosocial | Depressed mood<br>Anxiety<br>Posttraumatic stress disorder<br>Relationship difficulties<br>Vocational difficulties<br>Chronic fatigue |

*GVHD=graft-versus-host disease, HSCT=hematopoietic stem cell transplantation*

on international guidelines and institutional practices. EBV can be associated with posttransplant lymphoproliferative disorder. Acyclovir prophylaxis for herpes simplex virus-1 (HSV-1) in seropositive recipients is generally administered for up to 1 year post-HSCT and may also confer some protection against varicella-zoster virus. (15)(16) BK virus is a polyoma virus that is generally harmless in an immunocompetent host. However, it can cause hemorrhagic cystitis and renal dysfunction in HSCT recipients if viremia is present. *Pneumocystis jiroveci* prophylaxis is also indicated until immune suppression has been withdrawn.

The Centers for Disease Control and Prevention, in collaboration with several international HSCT organizations, have established guidelines for infectious prophylaxis, and international guidelines also exist for the management of fever and neutropenia in pediatric HSCT recipients. (16)(17) Finally, children require reimmunization after HSCT, but clinicians must exercise caution regarding the timing of live vaccine administration. Recommendations for the timing of immunizations for children who have undergone HSCT can be referenced and are updated regularly. (16)(18)

## Mucositis

Almost all children who undergo myeloablative HSCT experience mucositis. This painful inflammation of the gastrointestinal mucosa is due to direct toxicity from conditioning agents and is compounded by a local inflammatory state in the setting of neutropenia. It can occur anywhere between the oral mucosa and rectum, and intensive intervention with narcotic and adjuvant therapies is often required, with resolution typically occurring after neutrophil engraftment. As the intensity of the conditioning is reduced, the severity of mucositis decreases. Nutrition support is commonly required while mucositis is present. The risk of bacterial translocation across the lining of the mucosa and secondary HSV-1 and fungal infections are a concern.

## Nutritional Support

Many children require nutritional supplementation post-HSCT due to decreased intake, which may be related to nausea, anorexia, malabsorption, or mucositis. Even when many other complications abate, many children and adolescents need support to ensure adequate hydration and caloric intake. In addition, metabolic needs are often increased due to a catabolic state, with extensive tissue healing required postconditioning. HSCT centers often have strong preferences regarding the safest and most beneficial method of nutritional supplementation. Intractable nausea and gut integrity, with potential compromise due to mucositis or GVHD, should be considered when deliberating about enteral feeding. In the absence of contraindications, enteral feeding has potential benefits to the liver in promoting biliary flow, which is important because the liver

is at risk of toxicity from conditioning, sinusoidal obstructive syndrome (SOS), GVHD, and polypharmacy.

### Transfusions

Transfusion support is expected pre-engraftment, particularly for more intensive conditioning regimens. Optimization of iron load pre- and post-HSCT may reduce complications (such as SOS), and phlebotomy post-HSCT is employed for patients with high iron burdens post-HSCT once stable engraftment has occurred. New research is exploring the role of iron burden on inflammation after HSCT. (11)

### Sinusoidal Obstructive Syndrome

SOS is a serious hepatoxicity seen in 1% to 10% of HSCT recipients, with risk increased for those with preexisting liver disease, allogeneic HSCT recipients, children with high-risk neuroblastoma, and those who receive busulfan, cyclophosphamide, or TBI. (19) It involves occlusion of sinusoidal venules due to microthrombi, with resulting liver swelling and enlargement, pain, fluid retention, and hepatorenal syndrome. Cholestasis is present, with variable degrees of hepatic enzyme elevation. Although prevention is ideal, treatment can vary from diuresis in moderate cases to promising agents such as defibrotide in severe cases with end-organ failure. (20) Defibrotide has yet to receive approval from the US Food and Drug Administration.

### Pulmonary Complications

The differential diagnosis of pulmonary complications after HSCT is broad, with common causes being infection and volume overload. Other considerations include pneumonitis from radiation or alkylating agents, idiopathic pneumonia syndrome, and chronic GVHD. Respiratory failure requiring intubation and ventilation is associated with significant rates of mortality in immunocompromised recipients of HSCT. (21)

### Graft-Versus-Host Disease

GVHD is an immune-based complication seen almost exclusively in allogeneic HSCT. It involves tissue damage and antigen exposure, antigen presentation, and alloimmune reactivity of donor T cells against recipient tissues. (22) Acute GVHD affects the skin, gastrointestinal tract (typically colon, stomach, or duodenum), and liver. Notably, these organs are prone to chemotherapy and radiation damage and are rich in antigen-presenting cells. Staging systems describe the severity of each affected organ, with an overall grading assigned. (23) Grading determines the need to treat with corticosteroids and potentially additional agents. Although some degree of GVHD can be associated with better overall survival for those with malignancy (due to a graft-versus-leukemia effect), there is no benefit in nonmalignant disease, and GVHD remains a barrier to the application of HSCT for many nonmalignant conditions, particularly if no matched family donor exists. (24)

Chronic GVHD is often seen months after HSCT (average onset at 6 months) and can be a devastating complication. (25) Clinically this entity resembles systemic lupus erythematosus (SLE) or systemic sclerosis and can result in debilitating skin, muscle, joint, liver, gut, and lung disease. Dry eyes, dry mouth, and fatigue can also affect quality of life. Prolonged immune suppression is required for more severe cases, which can result in opportunistic infection. (25) End-organ dysfunction, particularly of lung and liver, is a major concern. Chronic GVHD can replace the condition for which HSCT was performed, and although less common in children than in adults, must always be considered during the decision-making process for HSCT.

Tolerance between the donor T cells and the HSCT recipient eventually results in the ability to reduce and usually discontinue immune-suppressive medications. Tapering of immune suppression occurs at scheduled time points after HSC infusion in the absence of GVHD, with longer periods of prophylaxis and higher target levels for nonmalignant HSCT disease indications. (26)( 27) For those who develop GVHD, once the GVHD is inactive for a sufficient period of time, immune suppression is weaned

**TABLE 4. Malignant Disease Indications for Allogeneic Pediatric HSCT**

| |
|---|
| Acute lymphoblastic leukemia |
| • Very high-risk features |
| • Relapsed disease |
| Acute myelogenous leukemia |
| • High-risk features |
| • Relapsed disease |
| Myelodysplastic syndrome (preleukemic state) |
| Non-Hodgkin lymphoma |
| • Relapsed/primary refractory disease |
| • Disease subtype may indicate allogeneic versus autologous HSCT |
| Hodgkin lymphoma |
| • Relapsed disease after autologous HSCT or primary refractory disease (usually second relapse) (28) |

*HSCT=hematopoietic stem cell transplantation*

## TABLE 5. Nonmalignant Disease Indications for Allogeneic Pediatric HSCT

| |
|---|
| Primary Immune Deficiencies |
| • Phenotype must be severe enough to justify HSCT |
| • Specific genetic mutation identification ideal (can support indication for HSCT as well as influence conditioning) |
| Hemoglobinopathies |
| • Thalassemia major |
| ◦ Matched sibling or unrelated live donor |
| ◦ Unrelated UCB and haploidentical HSCT experimental |
| • Sickle cell disease (Hg SS, Sß$^0$, or SC) |
| ◦ Matched sibling donor |
| ◦ Unrelated donor and haploidentical HSCT experimental |
| ◦ Indications vary among centers, often some evidence of prior sickle cell complications required |
| Inherited Bone Marrow Failure Syndromes |
| • Severe aplastic anemia |
| • Fanconi anemia |
| • Shwachman-Bodian-Diamond syndrome |
| • Diamond-Blackfan anemia |
| • Dyskeratosis congenita |
| • Amegakaryocytic thrombocytopenia |
| |
| Metabolic/Genetic Disorders (29) |
| • Infantile osteopetrosis |
| • Mucopolysaccharidoses |
| ◦ Hurler syndrome (MPS IH), standard of care |
| ◦ Optional indications (after frontline enzyme replacement therapy, if available) |
| ■ Hurler/Scheie (MPS IH/S) |
| ■ Scheie (MPS IS) |
| ■ Maroteaux-Lamy (MPS VI) |
| ■ Sly (MPS VII) |
| • Leukodystrophies |
| ◦ Cerebral X-linked adrenoleukodystrophy |
| ■ *Before* advanced disease |
| ◦ Metachromatic leukodystrophy, late onset |
| ◦ Krabbe disease, generally early onset |
| • Miscellaneous disorders, optional indications |
| ◦ Fucosidosis |
| ◦ α-mannosidosis |

*Continued*

TABLE 5. (Continued)

| |
|---|
| ◦ Aspartylglucosaminuria |
| ◦ Farber |
| ◦ Gaucher types 1 (non-neuronopathic) and 3 (Norrbottnian) |
| ◦ Niemann-Pick type C-2 |
| ◦ Wolman syndrome |

*HSCT=hematopoietic stem cell transplantation, MPS=mucopolysaccharidosis, UCB=umbilical cord blood*

and subsequently stopped. For this reason, HSCT recipients are not expected to receive lifelong immune suppression, in contrast to patients who receive solid organ transplantation.

## INDICATIONS FOR HSCT

Historically, most allogeneic HSCT procedures in children were for malignant diseases such as leukemias and lymphomas. With improving cure rates using chemotherapy for such cancers, the proportion of nonmalignant disease indications for pediatric HSCT continues to increase.

### Malignant Disease

Common malignant disease indications for allogeneic HSCT in children are acute leukemias and some non-Hodgkin and Hodgkin lymphomas. High-risk clinical/biological features or relapse are usually present (Table 4). Myelodysplastic syndrome, a preleukemic state with risk of conversion to acute myeloid leukemia, is almost always treated with HSCT in children. Chronic myelogenous leukemia is often managed with tyrosine kinase inhibitors alone, so fewer affected children and adolescents are recommended to undergo HSCT.

Autologous HSCT is performed routinely for children with high-risk neuroblastoma and for relapsed lymphomas. Many brain tumor treatment plans are incorporating high-dose chemotherapy and autologous HSCT, particularly for children younger than age 3 years, in an effort to spare or delay radiation therapy to the developing brain. Current research is exploring the use of autologous HSCT in children and adolescents with solid tumors, such as Ewing sarcoma, who have high-risk features.

### Nonmalignant Disease

Allogeneic HSCT is increasingly performed for nonmalignant disease indications as rates of TRM and GVHD are reduced. These diseases confer lifelong risks of morbidity or mortality and often require complex supportive care (Table 5). Chronic transfusions for hemoglobinopathies are associated with significant risks of iron overload and resultant complications. For some of these conditions, the risks of HSCT are affected substantially by the type of donor available, and the resulting recommendation for HSCT may be affected. Primary immune deficiencies such as severe combined immune deficiency, X-linked chronic granulomatous disease, and Wiskott-Aldrich syndrome are examples of nonmalignant diseases for which HSCT is commonly performed. A large body of evidence supports the safety and efficacy of HSCT for severe aplastic anemia, with increasing data to guide clinicians in decision-making for inherited bone marrow failure syndromes. Thalassemia major has an established track record for related and unrelated HSCT, with a clear phenotype of lifelong transfusion dependence and risk of iron overload.

Sickle cell disease (SCD) is increasingly recognized as a disease with limited life expectancy and variable quality of life despite best supportive care. As a result, interest is growing in the application of HSCT to those with sickling syndromes. Although a history of complications of SCD had been mandated in the past to justify HSCT, the safer HSCT techniques have prompted increasing interest from patients, hematologists, and HSCT practitioners to intervene before organ dysfunction occurs, notably neurologic and lung injury.

Some metabolic diseases such as mucopolysaccharidoses are routine indications for HSCT, although the potential benefits are less clear for other metabolic diseases. (29) Table 5 summarizes some of the more standard indications, with an acknowledgement that HSCT is performed in some centers for life-threatening metabolic diseases with fewer data regarding potential benefit. (29) HSCT can help prevent neurologic progression in a metabolic disease due to replacement of the deficient enzyme by monocytes produced from the HSCs following engraftment. Because HSCT generally only halts and does not reverse neurologic progression and knowing that HSC-derived enzyme replacement can take months to reach the central nervous

system (CNS) due to slow migration of donor-derived monocytes into the CNS, *early* HSCT is critical for indicated conditions. Generally other non-CNS manifestations of the metabolic disorders are not reversed with HSCT. Discussions about the appropriateness of HSCT should happen relatively soon after making a diagnosis, and those who manage such conditions routinely should be aware of evolving indications for this group of diseases.

The practice of autologous HSCT for nonmalignant conditions is relatively limited. Some encouraging results for those with severe SLE suggest that some patients may derive *temporary* benefit in terms of corticosteroid-sparing or reduced disease activity. (30) Repopulation of the bone marrow and peripheral blood with fewer autoreactive clones, in addition to the use of disease-modifying agents such as cyclophosphamide as part of the conditioning, may explain this period of improvement. Gene therapy trials for hemoglobinopathies are incorporating autologous HSC collection and ex vivo manipulation, with reinfusion following conditioning designed to give the manipulated cells a survival advantage. (31) The use of autologous HSCT for traumatic brain injuries and cerebral palsy is an area of intense research, but these indications are experimental at present.

## Summary

- Hematopoietic stem cell transplantation (HSCT) refers to the infusion of either allogeneic or autologous hematopoietic stem cells.
- Newer techniques to reduce the risk of complications are expanding the applicability of HSCT.
- Nonmalignant disease indications for HSCT are increasing.
- Observational and cohort studies (level C evidence) indicate that acute and long-term toxicities remain an important consideration for patients, families, and clinicians in making a recommendation for HSCT and warrant lifelong surveillance. (11)(12)(13)(21)
- Based on overwhelming evidence from observational studies (level B evidence), graft-versus-host disease can be a significant cause of morbidity and mortality in allogeneic HSCT. (22)(24)
- General pediatricians and subspecialists should be aware of evolving and newly established nonmalignant indications for HSCT to make appropriate referrals (level D evidence). (28)(29)(30)

***CME quiz and references for this article are at http://pedsinreview.aappublications.org/content/37/4/135.***

## Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Cancer-Therapies.aspx
- Spanish: https://www.healthychildren.org/Spanish/health-issues/conditions/cancer/Paginas/Cancer-Therapies.aspx

# PIR Quiz

*There are two ways to access the journal CME quizzes:*
*1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.*
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1. A 13-year-old girl with acute myeloblastic leukemia has relapsed 6 months after completing her initial course of chemotherapy. You explain to the parents that the only potential cure will be hematopoietic stem cell transplantation (HSCT). Which of the following options is the best donor for this girl?
    A. Allogenic transplant using a first cousin who matches at 8/10 loci.
    B. Allogenic transplant using a sibling who matches at 8/10 loci.
    C. Allogenic transplant using an unrelated donor who matches at 8/10 loci.
    D. Allogenic transplant using her mother who matches at 8/10 loci.
    E. Autologous transplant.
2. Which of the following would be the best therapy for the child described in the previous question?
    A. Chemotherapy alone to attempt prolonged remission.
    B. Myeloablative conditioning prior to transplant.
    C. Reduced-intensity conditioning prior to transplant.
    D. Serotherapy prior to transplant.
    E. Total body irradiation prior to transplant.
3. A 5-year-old boy underwent HSCT 12 days ago because of neuroblastoma. He is now complaining of increasing abdominal pain. You note that he has icterus and mild generalized edema. Laboratory studies reveal a total bilirubin of 4.5 mg/dL (76.9 $\mu$mol/L) and conjugated bilirubin of 2 mg/dL (34.2 $\mu$mol/L) but only mild elevations in transaminase values. The most likely cause of his symptoms is:
    A. Cytomegalovirus.
    B. Hepatitis A.
    C. Hepatitis B.
    D. Sepsis.
    E. Sinusoidal obstructive syndrome.
4. A 7-year-old girl with homozygous sickle cell anemia underwent HSCT from an unrelated, human leukocyte antigen-identical donor 7 months ago. She has been complaining of fatigue for 2 weeks and now has developed a feeling of her mouth being dry. On physical examination she has a widespread nonspecific erythematous rash over her trunk and arms. There is no cyanosis or jaundice. She has shotty anterior cervical nodes but no other significant adenopathy. The most likely cause of her symptoms is:
    A. Acute graft-versus-host disease.
    B. Chronic graft-versus-host disease.
    C. Cytomegalovirus.
    D. Epstein-Barr virus.
    E. Human herpesvirus 6.
5. A 4-year-old girl presents with bruising and pallor. She is found to have pancytopenia. A bone marrow aspirate and biopsy are diagnostic of myelodysplastic syndrome. Which of the following is the most appropriate treatment for this child's myelodysplastic syndrome?
    A. Begin chemotherapy and evaluate the response long term.
    B. Begin prophylactic antibiotics to prevent sepsis.
    C. Maintain the patient on transfusions until she becomes unresponsive to them.
    D. Observe the child until the pancytopenia becomes severe.
    E. Proceed to HSCT once an appropriate donor is identified.

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