

# Hematopoietic Stem-Cell Transplantation for Rare Diseases in the Pediatric Population

## Research Focus for Clinicians

A systematic review was undertaken to evaluate the evidence about the effectiveness, benefits, and adverse effects of using hematopoietic stem-cell transplantation (HSCT) to treat rare diseases in the pediatric population (age  $\leq 21$  years) for which no guidelines or recommendations based on extensive clinical study are available. HSCT was compared with standard therapies or the disease's natural history. The systematic review did not cover the pediatric indications for which substantive evidence supports the use of HSCT. The systematic review included 251 primary studies, mostly case series and case reports, published from January 1995 through August 2011. An online version of this summary provides links directly to the sections of the full report with references for individual findings, inclusion criteria for the studies, and an explanation of the methods for rating the studies and determining the strength of evidence for individual findings. The online version of this summary and the full report are available at [www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm](http://www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm).

## Background

HSCT is used to restore bone marrow function, to provide antitumor benefit, or to establish a cellular process absent in other tissues. The use of HSCT for several pediatric diseases is supported by a large evidence base and/or guidelines. These diseases are discussed in a narrative review that is available in the full report at [www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm](http://www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm).

This summary describes the results of a systematic review of studies where HSCT is used to treat pediatric diseases, some of which are rare, where evidence is still evolving and may only come from uncontrolled studies, case reports, and case series.

Pediatric diseases covered in the systematic review include select malignant solid tumors, autoimmune diseases, and metabolic disorders for which the role of HSCT remains uncertain. Most of these are severe, refractory diseases with such a poor prognosis that allogeneic or autologous HSCT is being investigated despite the known risks for both short- and long-term adverse effects. The timing of HSCT for these patients is also an important consideration. For example, with inherited metabolic diseases, HSCT is considered in order to prevent severe neurologic damage in patients in whom the damage is minimal or has not yet occurred.

## Conclusions

- Evidence supports the use of allogeneic HSCT when compared with conventional management to improve overall survival for patients with Wolman disease and to improve neurodevelopment-related outcomes for patients with Farber disease.
- HSCT may provide some benefit for neurological outcomes for patients with attenuated mucopolysaccharidosis type II.
- Patients with high-risk anaplastic astrocytoma may have improved 5-year overall survival after autologous HSCT.
- Treatment-related mortality may be higher in patients with nonanaplastic mixed or unspecified ependymoma treated with HSCT.
- Some evidence suggests the potential for extended drug-free remission following autologous HSCT for several autoimmune disorders, most of which are severe, refractory, and/or progressive.
- In most cases, there is not enough evidence to permit conclusions about the relative adverse effects when HSCT is compared with conventional management approaches.
- Decisionmaking for using HSCT in the pediatric population should consider many factors including the potential for a complete or partial cure and for short- and long-term adverse events, particularly those secondary to cytotoxic chemotherapy and/or radiation prior to HSCT.

## Clinical Bottom Line

Allogeneic HSCT Treatments*	
<i>Inherited Metabolic Disorders</i>	<i>Outcomes (HSCT Versus Conventional Therapy)</i>
Wolman disease (N = 7)	Improved overall survival ●●● Three out of seven patients who received allogeneic HSCT have been followed for 4 to 11 years with normal or near normal functioning.
Farber disease types 2 and 3 (N = 5)	Reduced number of subcutaneous nodules ●●●
	Reduced number of joints with limited range of motion ●●●
Mucopolysaccharidosis type II (MPS II; Hunter syndrome): Attenuated form (N = 6)	Stabilization of neurocognitive outcomes ●○○
	Improved neurodevelopmental outcomes ●○○
MPS II: Severe form (N = 8)	No benefit for neurocognitive outcomes ●○○
	Improved neurodevelopmental outcomes ●○○
Niemann-Pick disease type A (N = 3)	Overall survival not improved ●○○
Gaucher disease type III (N = 18)	
MPS III (Sanfilippo syndrome; N = 9)	Neurocognitive and neurodevelopmental outcomes not improved ●○○
Infantile neuronal ceroid lipofuscinosis (NCL; N = 3)	
Autologous HSCT Treatments*	
<i>Malignant Solid Tumors</i>	<i>Outcomes (HSCT Versus Conventional Therapy)</i>
High-risk recurrent or progressive anaplastic astrocytoma	Improved 5-year overall survival (40%; n = 10) when compared with patients who received conventional therapy (0%; n = 71) ●○○
Metastatic rhabdomyosarcoma	Overall survival not improved ●●○
Extraocular retinoblastoma with central nervous system involvement	Overall survival not improved ●○○
High-risk Ewing's sarcoma	
High-risk Wilms' tumor, relapsed	
Nonanaplastic mixed or unspecified ependymoma	Associated with higher treatment-related mortality than conventional therapy and leads to shorter overall survival ●○○
<i>Autoimmune Disorders</i>	<i>Outcomes (HSCT Versus Conventional Therapy)</i>
Severe, refractory, juvenile idiopathic arthritis	Extended periods of drug-free clinical remission have been achieved by a single autologous HSCT. ●●○
Systemic lupus erythematosus	
Severe, refractory, systemic sclerosis	
Severe, refractory, malignant multiple sclerosis	
Severe, refractory, disabling Crohn's disease	
Newly diagnosed type-1 juvenile diabetes	Extended interval of insulin independence ●●○

\* Several additional diseases have insufficient evidence to determine if there are benefits from allogeneic or autologous HSCT. A description of these analyses can be found in the full report at [www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm](http://www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm).

### Strength of Evidence Scale

High: ●●● High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: ●●○ Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low: ●○○ Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient: ○○○ Evidence is either unavailable or does not permit a conclusion.

---

## Adverse Effects

- A meta-analysis with evidence grades was not performed for adverse effects from HSCT versus standard therapy for the pediatric diseases covered in the systematic review.
- However, in all applications of HSCT, chemotherapy with or without radiation is used for immunosuppression or to eliminate diseased cells in preparation for the transplant.
- HSCT-related adverse effects can include:
  - Cytotoxicity
  - Pancytopenia
  - Opportunistic infections (bacterial, viral, and fungal; rapid and later onset)
  - Graft-versus-host disease (acute and chronic; only for allogeneic HSCT)
  - Risk of secondary malignancies
  - Veno-occlusive disease
  - Serious hemorrhagic events
  - Other long-term complications (e.g., endocrine, sensory, musculoskeletal, pulmonary, dental, renal, and cardiovascular complications, developmental delays, and future infertility)
  - Treatment-related mortality

---

## Gaps in Knowledge

- Controlled trials with sufficient followup are needed to evaluate the long-term balance of benefits with adverse effects for most of these rare pediatric diseases.
- For pediatric patients with solid tumors, a validated prognostic classification system would help reduce the uncertainty in the interpretation of study results.
- Followup should be sufficient to assess the impact of HSCT on the development of adverse effects such as the long-term impact on neurocognitive development and fertility.
- Standardized measures of neurocognitive and neurodevelopmental outcomes are needed.

---

## What To Discuss With Your Patients' Parents or Caregivers

- The difficulties and dilemmas of treating rare pediatric disorders
- Appropriate therapeutic interventions to treat a specific disorder
- Realistic outcomes to expect from each therapeutic option
- The trade-offs between benefits and harms of possible therapeutic interventions
- Overview of relevant clinical trials enrolling patients
- Referrals to institutions with expertise in a particular disorder
- How treatment decisions will affect the quality of life for patients and their families

---

## Resources for Parents and Caregivers

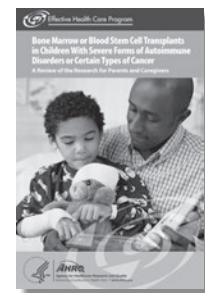
*Bone Marrow or Blood Stem Cell Transplants in Children With Certain Rare Inherited Metabolic Diseases, A Review of the Research for Parents and Caregivers* is another free companion to this clinician research summary.



It can help parents and caregivers talk with their health care professionals about:

- Information about Wolman disease, Farber disease, Niemann-Pick disease, Gaucher disease, infantile NCL, Hunter syndrome, and Sanfilippo syndrome
- What an allogeneic HSCT is and how it is done
- What researchers have found about treating children who have one of these illnesses with an allogeneic HSCT
- Possible risks of an allogeneic HSCT

*Bone Marrow or Blood Stem Cell Transplants in Children With Severe Forms of Autoimmune Disorders or Certain Types of Cancer, A Review of the Research for Parents and Caregivers* is a free companion to this clinician research summary.



It can help parents and caregivers talk with their health care professionals about:

- Information on severe autoimmune diseases and certain types of cancer
- What an autologous HSCT is and how it is done
- What researchers have found about children with one of these illnesses who received an HSCT using their own stem cells
- Possible risks of an autologous HSCT

---

## Ordering Information

Visit [www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm](http://www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm) for electronic copies of this clinician research summary; *Bone Marrow or Blood Stem Cell Transplants in Children With Severe Forms of Autoimmune Disorders or Certain Types of Cancer, A Review of the Research for Parents and Caregivers*; *Bone Marrow or Blood Stem Cell Transplants in Children With Certain Rare Inherited Metabolic Diseases, A Review of the Research for Parents and Caregivers*; and the full systematic review. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

---

## Source

The information in this summary is based on *Hematopoietic Stem-Cell Transplantation in the Pediatric Population, Comparative Effectiveness Review No. 48*, prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10058 for the Agency for Healthcare Research and Quality, February 2012. Available at [www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm](http://www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm). This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

