Comparative Effectiveness Review
Number 48

Effective Health Care Program

Hematopoietic Stem-Cell Transplantation in the Pediatric Population

Executive Summary

Background

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic progenitor cells, including repopulating stem cells, are infused to restore bone marrow function in patients.[1,2,3] HSCT is categorized by the source of the stem cells, with its role in pediatric diseases dependent in part on the indication for which it is being used.[4] Autologous transplants involve harvesting the patient's own blood stem cells and then returning them, typically after the patient has received doses of chemotherapy that are myeloablative.[1,2] Allogeneic HSCT uses stem cells from a donor who is either matched or unmatched on human leukocyte antigen (HLA) and either related or unrelated; in malignant diseases, it exploits a graft-versus-tumor effect.[5,6]

In the pediatric population, HSCT is used to treat a wide variety of diseases, both malignant and nonmalignant.[7] For many of these diseases, HSCT is a well-established treatment. For example, the literature on the use of HSCT in hematologic malignancies is robust, including randomized controlled trials that date back 20 years, and its practice is supported by evidence-based guidelines. For many less common diseases—for example, the primary immunodeficiencies and hemoglobinopathies—although the evidence consists of case series and case reports, it is sufficient to demonstrate improved outcomes, supporting use of HSCT.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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Effective Health Care

The success of treating many of the pediatric diseases with HSCT has resulted in an increased number of long-term survivors. As improvements in survival have been achieved, there is greater concern about long-term effects and how adverse effects (e.g., graft-vs.-host disease, opportunistic infections, future infertility, developmental delay, and secondary malignancies) might be mitigated.[7,8,9,10] The Key Questions for this review compared benefits and harms of HSCT and conventional therapy for pediatric diseases.

Objectives

Key Questions addressed in this report are split into three groups of two questions each. They pertain to malignant solid tumors, inherited metabolic diseases, and autoimmune diseases.

Key Question 1. For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?

Key Question 2. For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

Key Question 3. For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?

Key Question 4. For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, ERT, and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

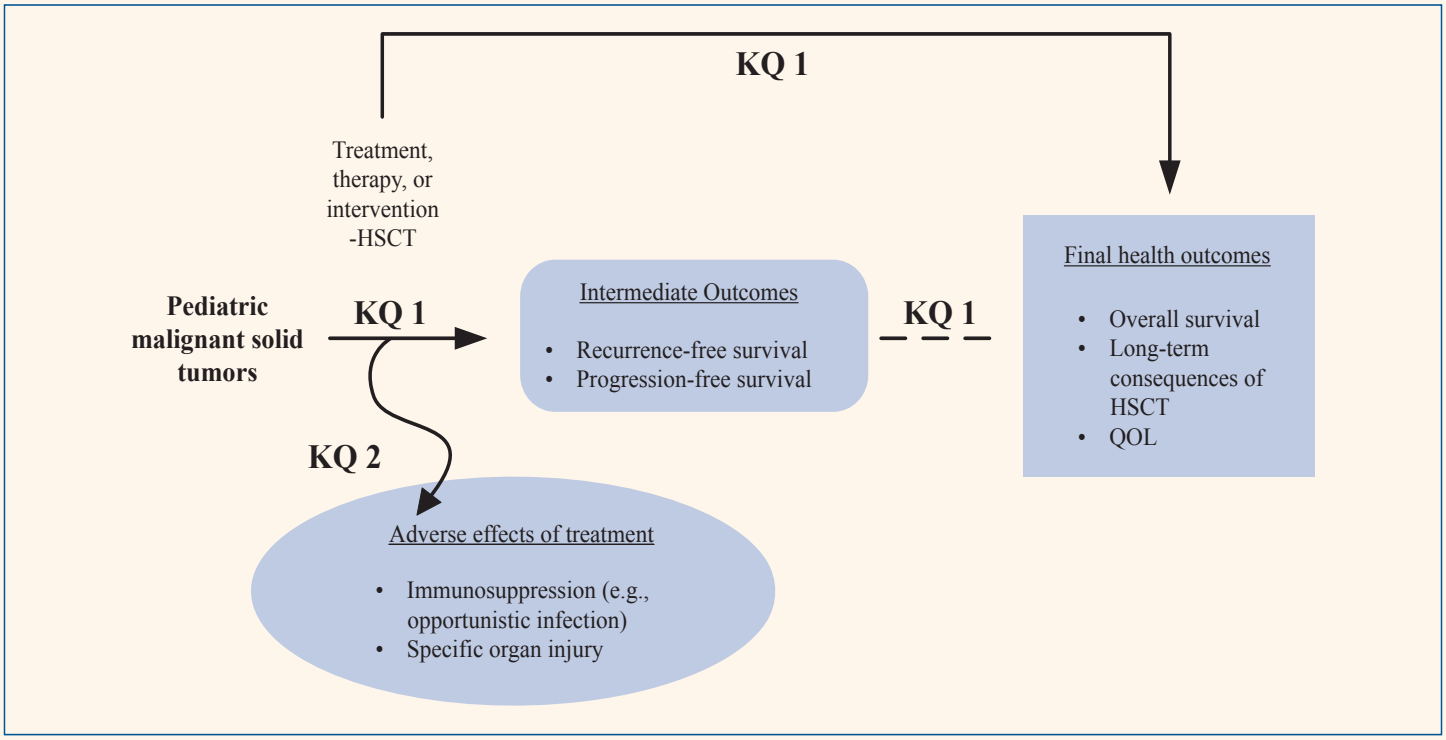
Key Question 5. For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?

Key Question 6. For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

Analytic Framework

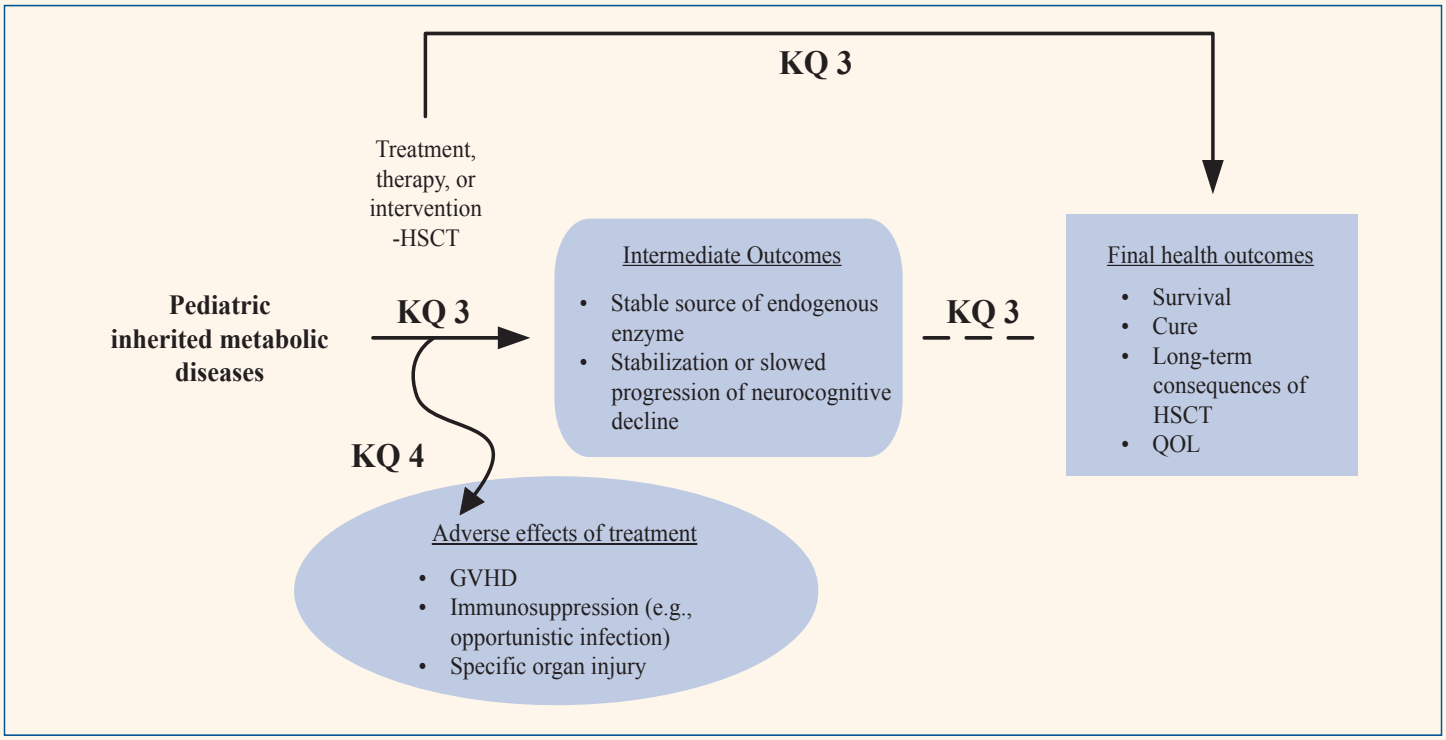
Analytic frameworks are detailed in Figures A, B, and C.

Figure A. Analytic framework for HSCT for pediatric malignant solid tumors



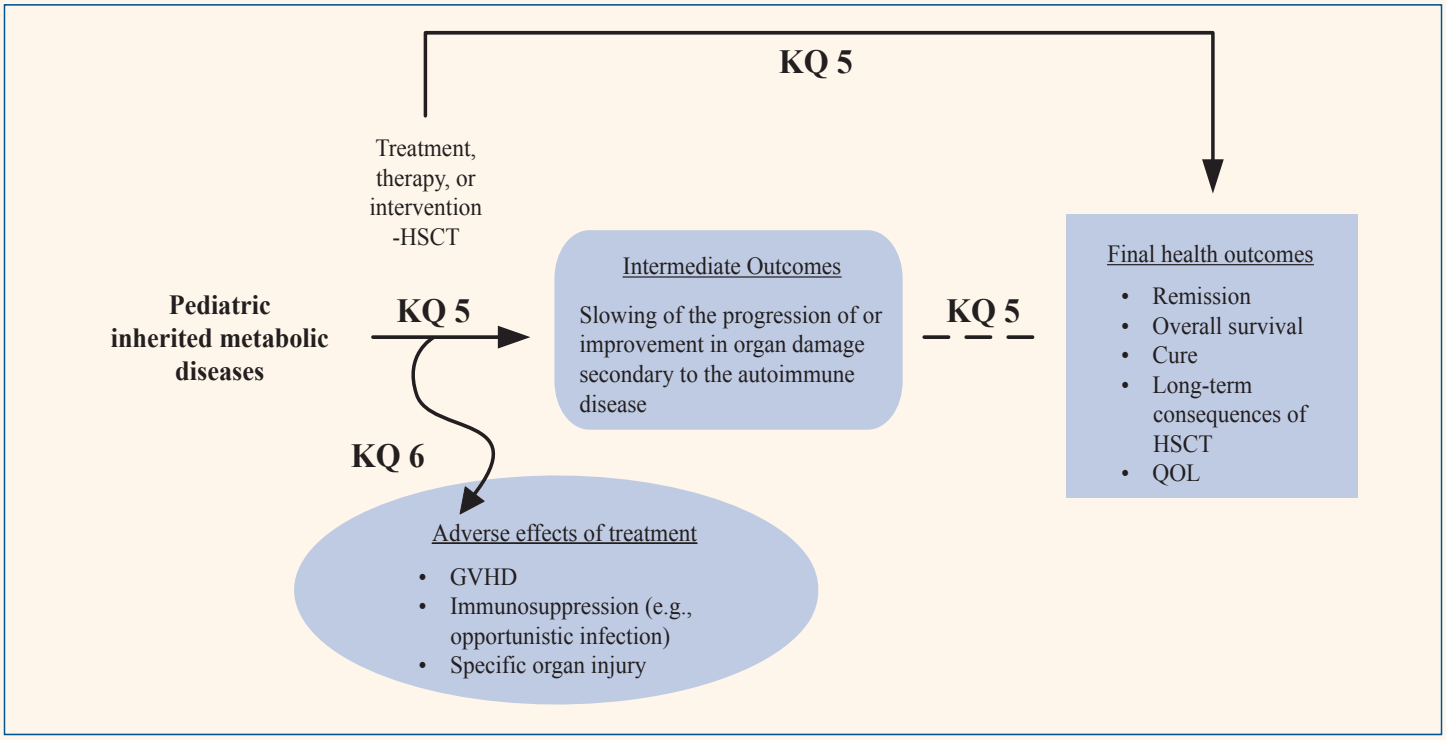
HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Figure B. Analytic framework for HSCT for pediatric inherited metabolic diseases



GVHD = graft-versus-host disease; HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Figure C. Analytic framework for HSCT for pediatric autoimmune diseases



GVHD = graft-versus-host disease; HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Methods

Topic Refinement

This report comprises a set of narrative reviews and systematic reviews that were defined during the topic refinement phase of the project. Topic refinement also outlined the frameworks and PICOTS (patients, interventions, comparator, outcome, timing, setting) that were posted for public comments and incorporated into the final version. Following completion of the topic refinement phase, a Technical Expert Panel (TEP) was formed. The TEP included original Key Informant (KI) panel members and clinical experts not previously involved. The TEP provided consultation on the development of the protocol and evidence tables for the review. In particular, the TEP provided advice on appropriate clinical outcome data to compile for both benefits and harms. Ad hoc clinical questions were also addressed to the TEP.

Narrative Reviews

The narrative review approach to the conditions presented in Table A was based on the recognition that there exists a substantial body of evidence from 20 years or more of transplantation research and experience that has been codified into published guidelines and reviews. Thus, systematic review of the evidence for these diseases would not be expected to offer new insights or information. In contrast, the Evidence-based Practice Center (EPC) recognized that there were a number of diseases for which evidence of benefits and harms was less clear or for which clinical practice was less established, so that systematic review of the literature would be more likely to provide new insight to inform the field (Table B).

The final categorization of indications for the narrative reviews was determined in an iterative process. Information sources for the narrative reviews were not identified by a systematic search of the literature. Rather, the EPC relied on recently published reviews of pediatric transplantation studies and publicly available sources, such as the National Guidelines Clearinghouse and the National Cancer Institute Physicians Data Query (PDQ) Web site, to develop an initial list of diseases for discussion with the KI panel. The EPC subsequently reexamined the lists and compared them with existing evidence in the context of the KI discussions. A final list of indications for narrative reviews compiled by the EPC was posted for public comment. Neuroblastoma, germ cell tumors, and central nervous system embryonal tumors are covered in both narrative and systematic reviews. They are distinguished in each by the specific indication and the type of transplant procedure, as shown in Tables A and B.

Systematic Reviews

Table B shows the indications that were systematically reviewed. Neuroblastoma, germ cell tumors, and central nervous system embryonal tumors are covered in both narrative and systematic reviews. They are distinguished in each by the specific indication and the type of transplant procedure, as shown in Tables A and B.

Table A. Pediatric HSCT indications to be addressed with narrative review

Type	Disease	Indication(s)	Transplant Type
MH	Acute lymphoblastic leukemia (ALL)	In first (high-risk patients), second, or subsequent complete remission (CR)	Allo
MH	Acute myelogenous leukemia (AML)	In first, second, or subsequent CR; early relapse; induction failure	Allo
MH	Juvenile myelomonocytic leukemia (JMML)	As upfront therapy	Allo
MH	Myelodysplastic syndrome (MDS)	As upfront therapy for primary or secondary MDS	Allo
MH	Chronic myelogenous leukemia (CML)	Chronic phase or refractory to tyrosine kinase inhibitor (TKI)	Allo
MH	Non-Hodgkin's lymphoma (NHL)/Hodgkin's lymphoma (HL)	Induction failure; first, second, third CR/partial remission	Auto/allo
MNH	Neuroblastoma (NB)	Consolidate high-risk (initial)	Auto
		Relapsed/refractory	Auto (allo in selected incidences)

Table A. Pediatric HSCT indications to be addressed with narrative review (continued)

Type	Disease	Indication(s)	Transplant Type
MNH	Germ cell tumor (GCT)	Relapsed	Auto (allo if fail auto and in selected incidences)
MNH	Central nervous system embryonal tumors	Relapsed or residual	Auto
NM	Hemoglobinopathies	Variable	Allo
NM	Bone marrow failure syndromes (BMF)	Variable	Allo
NM	Primary immunodeficiencies, including: *Lymphocyte immunodeficiencies* Adenosine deaminase deficiency Artemis deficiency Calcium channel deficiency CD 40 ligand deficiency Cernunnos-XLF immune deficiency CHARGE syndrome with immune deficiency Common gamma chain deficiency Deficiencies in CD45, CD3, CD8 DiGeorge syndrome DNA ligase IV Interleukin-7 receptor alpha deficiency Janus-associated kinase 3 (JAK3) deficiency Major histocompatibility class II deficiency Omenn syndrome Purine nucleoside phosphorylase deficiency Recombinase-activating gene (RAG) 1/2 deficiency Reticular dysgenesis Winged helix deficiency Wiskott-Aldrich syndrome X-linked lymphoproliferative disease Zeta-chain-associated protein-70 (ZAP-70) deficiency *Phagocytic deficiencies* Chediak-Higashi syndrome Chronic granulomatous disease Griscelli syndrome type 2 Interferon-gamma receptor deficiencies Leukocyte adhesion deficiency Severe congenital neutropenias Shwachman-Diamond syndrome *Other immunodeficiencies* Autoimmune lymphoproliferative syndrome Cartilage hair hypoplasia CD25 deficiency Familial hemophagocytic lymphohistiocytosis Hyper IgE syndromes ICF syndrome IPEX syndrome NEMO deficiency NF-κB inhibitor, alpha (IκB-alpha) deficiency Nijmegen breakage syndrome	Variable	Allo

Table A. Pediatric HSCT indications to be addressed with narrative review (continued)

Type	Disease	Indication(s)	Transplant Type
NM	Inherited metabolic diseases, including: *Mucopolysaccharidosis (MPS)* MPS I (Hurler), MPS VI (Maroteaux-Lamy), MPS VII (Sly syndrome) *Sphingolipidosis* Gaucher I, Niemann-Pick disease B, globoid leukodystrophy, metachromatic leukodystrophy *Glycoproteinosis* Fucosidosis, alpha-mannosidosis *Peroxisomal storage disorders* Adrenoleukodystrophy	Variable	Allo
NM	Osteoporosis	Severe	Allo

allo = allogeneic; auto = autologous; HSCT = hematopoietic stem-cell transplantation; MNH = malignant, nonhematopoietic; NM = nonmalignant

Table B. Pediatric HSCT indications to be addressed with systematic review

Type	Disease	Indication(s)	Transplant Type	Comparator
MNH	Ewing sarcoma family of tumors (ESFT)	Consolidate high risk (initial)	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Wilms	Consolidate high risk	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Rhabdomyosarcoma (RMS)	High-risk disease	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Retinoblastoma	Extraocular spread	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Neuroblastoma (NB)	Consolidate high risk (initial) Relapsed/refractory	Tandem auto auto	Single auto
MNH	Germ cell tumor (GCT)	Relapsed	Tandem auto auto	Single auto
MNH	Central nervous system embryonal tumors	Initial therapy	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Central nervous system glial tumors	Consolidate high risk	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy

Table B. Pediatric HSCT indications to be addressed with systematic review (continued)

Type	Disease	Indication(s)	Transplant Type	Comparator
NM	Inherited metabolic diseases: *Mucopolysaccharidosis (MPS)* MPS II (Hunter's), MPS III (Sanfilippo), MPS IV (Morquio) *Sphingolipidosis* Fabry's, Farber's , Gaucher's II-III, GM1 gangliosidosis, Niemann-Pick disease A, Tay-Sachs disease, Sandhoff's disease *Glycoproteinosis* Aspartylglucosaminuria, beta-mannosidosis, mucolipidosis III and IV *Other lipidoses* Niemann-Pick disease C, Wolman disease, ceroid lipofuscinosis *Glycogen storage* GSD type II *Multiple enzyme deficiency* Galactosialidosis, mucolipidosis type II *Lysosomal transport defects* Cystinosis, sialic acid storage disease, Salla disease *Peroxisomal storage disorders* Adrenomyeloneuropathy	Variable	Allo	Enzyme-replacement therapy, substrate reduction with iminosugars and chaperones
NM	Autoimmune, including juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), scleroderma, immune cytopenias, Crohn's	Upfront therapy for severe/ refractory or salvage	Auto/allo	Immunosuppressants, targeted biologic therapies and/or low-dose chemotherapy
NM	Autoimmune type 1 diabetes mellitus (DM)	Variable	Auto	Immunosuppressants, targeted biologic therapies and/or low-dose chemotherapy, conventional management (i.e., insulin injections)

allo = allogeneic; auto = autologous; HSCT = hematopoietic stem-cell transplantation; MNH = malignant, nonhematopoietic; NM = nonmalignant

Systematic Review Data Sources and Study Selection

Electronic databases searched were MEDLINE®, Embase®, and the Cochrane Controlled Trials Register. Databases were initially searched without restriction on date, using the search strategy shown in Appendix A of the full report. However, during the topic refinement phase of this project, the KIs strongly recommended limiting study selection to the past 15 years to ensure that we identified evidence that is comparable in terms of therapeutic regimens and management protocols. Thus, we reviewed the literature from January 1995 up to August 17, 2011, the latter date just prior to delivery of the final report.

Abstract screening and study selection were performed by a single reviewer who was assigned to a specific section. Included studies reported on pediatric patients (age ≤ 21 years) who had a relevant disease and were treated with HSCT or a comparator of interest using a contemporary regimen; to be included, the study also had to report on an outcome of interest. For inherited metabolic diseases, studies reporting outcomes on the disease natural history were included as comparators if they reported on an outcome of interest.

Systematic Review Data Extraction and Quality Assessment

Major elements for data abstraction were patient characteristics (i.e., age, sex, disease stage), treatment characteristics (i.e., chemotherapy vs. chemoradiotherapy, immunosuppressive therapy, and supportive care), and outcomes and details of any data analysis.

Evidence consisted largely of case series and case reports; therefore, we did not attempt to assess the quality of individual studies. According to an Institute of Medicine report,[11] it is well recognized that a common challenge in the study of rare diseases is the preponderance of small uncontrolled studies. Therefore, because studies tended to be homogeneous in design, quality assessment would be unlikely to discriminate between higher and lesser quality studies.

Data were abstracted by a single reviewer and fact checked by another reviewer. If there were disagreements they were resolved through discussion among the review team.

Systematic Review Data Synthesis and Analysis

Data synthesis was qualitative. We attempted to identify subgroups based on prognostic factors such as tumor stage or location in solid tumors, or disease severity or rate of progression in the inborn metabolic disorders, to see if these subgroups showed patterns of treatment success or failure. Quantitative pooling was not attempted. Where possible we calculated confidence intervals for results and reported ranges of results for studies that addressed the same population and treatment.

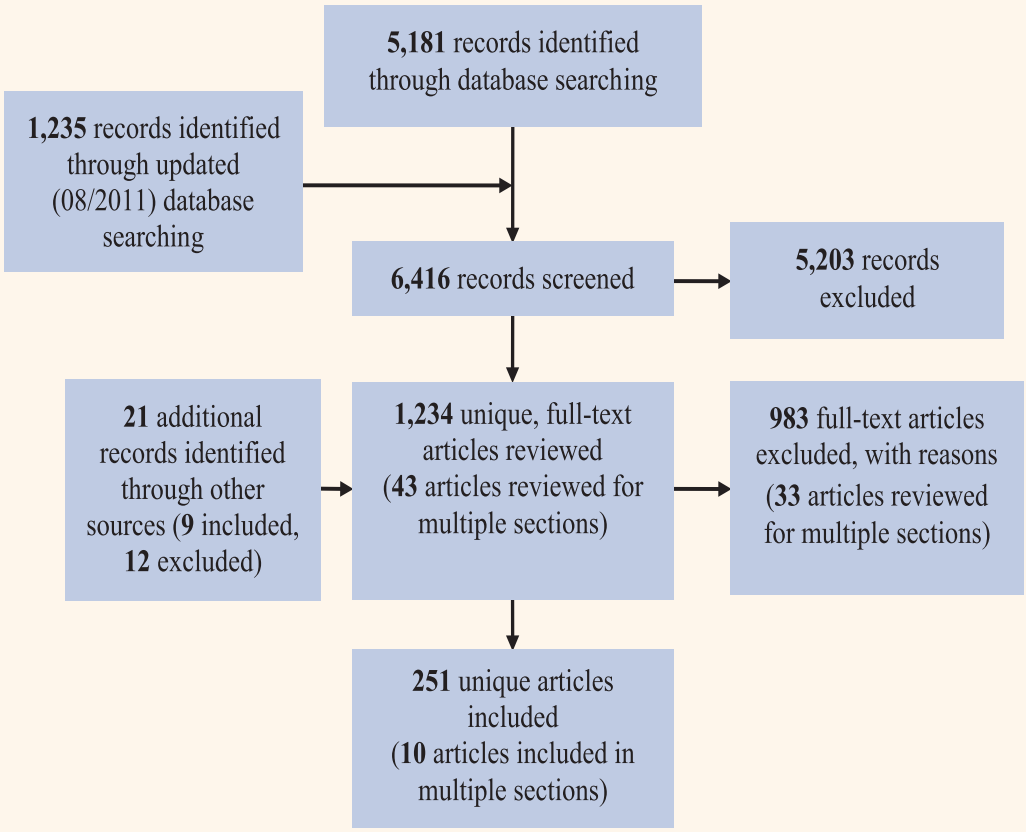
The strength of the body of evidence for each indication was assessed according to the process specified in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews,[12] developed by the EPC Program of the Agency for Healthcare Research and Quality (AHRQ). This is an iterative, qualitative, consensus-driven process among EPC team members familiar with the summarized literature, using the four required domains specified in the Methods Guide: risk of bias, consistency, directness, and precision. There were no head-to-head comparative studies for most diseases; in those situations, directness was based on the outcome (e.g., overall survival or other clinically important health outcomes) rather than on the comparison. For small series or a compilation of case reports in which the prognosis without HSCT is uniformly fatal (e.g., Wolman's disease), the known natural history was considered an indirect comparator. An optional domain, strength of association (SOA, magnitude of effect) was thus ascribed to the body of evidence when there was an apparent benefit or harm, increasing the overall strength beyond what normally might be considered appropriate for such evidence. SOA was deemed not applicable for diseases where there was no clear evidence of benefit or harm with HSCT versus comparators, or if results (e.g., overall survival rates) of individual studies within a body of literature were inconsistent or conflicted. No quantitative scoring method was applied.

Systematic Review Results

Figure D shows a PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses) diagram of the studies included in the systematic review. A list of excluded references with reasons for exclusion is available in Appendix B of the full report.

The strength of the body of evidence for each indication was assessed. For the diseases systematically reviewed here, the strength of evidence for specific indications (see below) was high in 2 instances, moderate or low in 19, and insufficient for the majority (n = 39) of indications and outcomes addressed. The SOA domain provided justification for increasing the overall GRADE (Grading of Recommendations Assessment, Development and

Figure D. PRISMA diagram of articles included in the systematic review



Disease	Total INCL	Total EXCL	(Hand Searched INCL)	(Hand Searched EXCL)	Totals (Total INCL & Total EXCL)
Autoimmune Disease	30	293	0	0	323
Embryonal Tumors	12	54	2	4	66
ESFT	36	88	0	0	124
GCT	4	7	2	7	11
Glial Tumors	38	90	2	1	128
IMD	56	114	0	0	170
Neuroblastoma	9	159	0	0	168
Retinoblastoma	20	21	0	0	41
Rhabdomyosarcoma	26	35	3	0	61
Wilm's Tumor	20	17	0	0	37
Other	0	105	0	0	105
Totals	251	983	9	12	1,234

allo = allogeneic; auto = autologous; HSCT = hematopoietic stem-cell transplantation; MNH = malignant, nESFT = Ewing sarcoma family of tumors; GCT = germ cell tumor; IMD = inherited metabolic diseases; PRISMA = Preferred Reporting Items of Systematic reviews and Meta-Analyses

Evaluation) evidence strength ratings for several diseases, despite the absence of a robust body of literature. SOA was not deemed applicable for settings where evidence was inconsistent.

Malignant Solid Tumors (Key Questions 1 and 2)

Evidence suggesting benefit of HSCT compared with conventional therapy:

- Low-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional therapy for *high-risk recurrent or progressive anaplastic astrocytoma.*

Evidence suggesting harm of HSCT compared with conventional therapy:

- Low-strength evidence on overall survival suggests harm due to higher treatment-related mortality with single HSCT compared with conventional chemotherapy for *nonanaplastic mixed or unspecified ependymoma.*

Evidence suggesting no benefit of HSCT compared with conventional therapy:

- Moderate-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *metastatic rhabdomyosarcoma.*
- Low-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *extraocular retinoblastoma with CNS (central nervous system) involvement, high-risk Ewing's sarcoma family of tumors, and high-risk relapsed Wilm's tumor.*

Insufficient evidence:

- The body of evidence on overall survival with tandem HSCT compared with single HSCT is insufficient to draw conclusions for *high-risk Ewing's sarcoma family of tumors, neuroblastoma, CNS embryonal tumors, and pediatric germ cell tumors.*
- The body of evidence on overall survival with single HSCT compared with conventional therapy is insufficient to draw conclusions for *CNS embryonal tumors, high-risk rhabdomyosarcoma of mixed stages, congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis, allogeneic transplantation for metastatic rhabdomyosarcoma, extraocular retinoblastoma with no CNS involvement, trilateral retinoblastoma, and six types of glial tumors (newly diagnosed anaplastic astrocytoma, newly diagnosed glioblastoma multiforme, anaplastic ependymoma, choroid plexus carcinoma, recurrent/progressive glioblastoma multiforme, and nonanaplastic, mixed, or unspecified ependymoma).*

Nonmalignant Diseases: Inherited Metabolic Diseases (Key Questions 3 and 4)

The inherited metabolic diseases were split into three categories for this review. Rapidly progressive disease was defined as progression to death within 10 years; the outcome of interest is overall survival. Slowly progressive disease was defined as progression to death of 10 years or greater; the outcomes of interest are neurocognitive and neurodevelopmental outcomes. For diseases that have both rapidly and slowly progressive forms of disease, outcomes of interest are overall survival for rapidly progressive forms and neurocognitive and neurodevelopmental outcomes for slowly progressive forms.

Rapidly Progressive Diseases

Evidence suggesting benefit of HSCT compared with conventional therapy:

- High-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional management for *Wolman's disease.*

Evidence suggesting no benefit of HSCT compared with conventional therapy:

- Low-strength evidence on overall survival suggests no benefit with single HSCT compared with symptom management or disease natural history for *Niemann-Pick Type A.*

Insufficient evidence:

- The body of evidence on overall survival with single HSCT compared with symptom management is insufficient to draw conclusions for *mucolipidosis II* (I-cell disease)*, Gaucher disease type II, cystinosis, and infantile free sialic acid disease.*

Slowly Progressive Diseases

Evidence suggesting benefit of HSCT compared with conventional therapy:

- Low-strength evidence on neurodevelopmental outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated and severe forms of MPS* (mucopolysaccharidosis) *II* (Hunter's disease).

- Low-strength evidence on neurocognitive outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated form of MPS II* (Hunter's disease).

Evidence suggesting no benefit of HSCT compared with conventional therapy:

- Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for *Gaucher disease type III.*
- Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for the *severe form of MPS II* (Hunter's disease).
- Low-strength evidence on neurocognitive or neurodevelopmental outcomes suggests no benefit with single HSCT compared with symptom management, substrate reduction therapy, or disease natural history for *MPS III* (Sanfilippo).

Insufficient evidence:

- The body of evidence on neurocognitive or neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *Niemann-Pick type C, MPS IV* (Morquio syndrome), *aspartylglucosaminuria, Fabry's disease, β-mannosidosis, mucolipidosis III, mucolipidosis IV, glycogen storage disease type II* (Pompe disease), *Salla disease, and adrenomyeloneuropathy.*

Diseases With Both Rapidly and Slowly Progressive Forms

Evidence suggesting benefit of HSCT compared with conventional therapy:

- High-strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared with symptom management or disease natural history for *Farber's disease type 2/3.*

Evidence suggesting no benefit of HSCT compared with conventional therapy:

- Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with symptom management or disease natural history for *infantile ceroid lipofuscinosis.*

Insufficient evidence:

- The body of evidence on overall survival and/or neurocognitive and neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *galactosialidosis* (type unspecified), *Sandhoff disease* (type unspecified), *Farber's disease type I, infantile GM1 gangliosidosis, juvenile GM1 gangliosidosis, infantile Tay-Sachs, juvenile Tay-Sachs, and juvenile ceroid lipofuscinosis.*

Autoimmune Diseases: (Key Questions 5 and 6)

The main consideration in this systematic review was the comparative balance of long-term benefits and harms of HSCT. With the exception of newly diagnosed type I juvenile diabetes, children in the studies reviewed had severe, typically disabling disease, refractory to a wide variety of standard therapies. Thus, the disease natural history in those cases assumed the role of comparator.

Insufficient evidence:

- The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (e.g., treatment-related mortality, secondary malignancies) of single autologous or allogeneic HSCT versus conventional therapy or disease natural history in patients with *newly diagnosed type 1 juvenile diabetes mellitus or those with severe, refractory, poor-prognosis autoimmune diseases, including systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, Evans syndrome, autoimmune hemolytic anemia, and autoimmune cytopenia.*
- Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (e.g., treatment-related mortality, secondary malignancies), moderate-strength evidence suggests that extended periods of drug-free clinical remission can be achieved in some cases with single autologous HSCT for patients with newly diagnosed type I juvenile diabetes and patients with severe refractory *juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis, and Crohn's disease.*

Discussion

This systematic review of HSCT in the pediatric population addresses indications for which there is uncertainty or evolving evidence, often consisting of uncontrolled single-arm studies and case reports, although for some solid tumors there were substantial numbers of patients reported. Randomized controlled trials were rare for any of the indications included in this systematic review. HSCT is usually reserved for patients or subgroups of patients who have diseases that have very poor prognosis and often are refractory to the best available treatment.

The strength of the body of evidence for each indication was assessed according to the principles described in Grading the Strength of a Body of Evidence When Comparing Medical Interventions13 in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews produced by AHRQ. The four required domains—risk of bias, consistency, directness, and precision—were considered for all indications. An optional domain, strength of association (magnitude of effect), was used in this process where a large magnitude of effect was particularly evident. This is exemplified by Wolman's disease, a very rare inherited metabolic disorder, where without treatment there is uniformly certain mortality in infancy, so that even very small case examples of survival or cure suggest a large effect of the intervention under consideration. Risk of bias is presumed to be high in a body of evidence comprising small numbers of case reports and series, thus reducing the strength of evidence. However, an obvious strength of association (magnitude of effect)—even if only based on case reports and case series—increases our confidence that the intervention can be effective, thereby permitting assignment of strength greater than "insufficient." This does not imply that the intervention will succeed in all cases, but that the effects observed can be attributed to the intervention despite the absence of controlled data.

For inherited metabolic diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms associated with HSCT. Some of these diseases have a homogeneous and dismal natural history. For example, the implications of transplantation for a rapidly progressing lysosomal storage disorder such as Wolman's syndrome are clear; this is a choice between certain death and potential survival, albeit with a risk of adverse effects associated with transplant.

In contrast, type I autoimmune juvenile diabetes can be managed long term satisfactorily, at relatively low risk, in a large proportion of children with intensive insulin therapy (IIT) and lifestyle modifications. The risk-benefit ratio for HSCT compared with IIT must take into account contextual factors, including potential long-term benefit (cure) and harms, particularly those secondary to cytotoxic chemotherapy. The decision to apply a high-risk procedure such as HSCT to this population is not clear cut. For most conditions addressed in this systematic review, evidence is insufficient to draw conclusions as to the relative risk-benefit ratio of HSCT versus other management approaches.

For solid tumors, HSCT studies focused on a single disease and collected detailed information on prognostic factors that may allow for more refined stratification of high-risk categories of patients. A validated prognostic classification would reduce uncertainty in the interpretation of study results.

Overall, the results of this review are applicable primarily to the specific conditions that were evaluated among pediatric patients. We did not address the question of whether evidence from study of HSCT in adults is applicable to pediatric patients.

Explanation of Terms

- *Hematopoietic stem-cell transplantation (HSCT)* refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients. It is categorized by the source of the stem cells.
- *Autologous transplants* involve returning the patient's own stem cells, typically after the patient has received doses of chemotherapy that are myeloablative or, for autoimmune disorders, lymphoablative.
- *Allogeneic HSCT* uses stem cells from an HLA-matched donor, either related or unrelated. In malignant diseases, it exploits a graft-versus-tumor effect. Myeloablative or reduced-intensity (nonmyeloablative) conditioning regimens may be used.
- *Pediatric* in this document refers to patients aged birth through 21 years. While the upper age limit varies, this definition is consistent with the definition found in several sources.[14,15,16]

References

1. Devetten M, Armitage JO. Hematopoietic cell transplantation: progress and obstacles. Ann Oncol. 2007 Sep;18(9):1450-6.
2. Shimoni A, Nagler A. Non-myeloablative stem-cell transplantation in the treatment of malignant and non-malignant disorders. Isr Med Assoc J. 2002 Apr;4(4):272-9.
3. Urbano-Ispizua A, Schmitz N, de Witte T, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. Bone Marrow Transplant. 2002 Apr;29(8):639-46.
4. Pelus LM. Peripheral blood stem cell mobilization: new regimens, new cells, where do we stand. Curr Opin Hematol. 2008 Jul;15(4):285-92.
5. Barrett AJ, Savani BN. Stem cell transplantation with reduced-intensity conditioning regimens: a review of ten years experience with new transplant concepts and new therapeutic agents. Leukemia. 2006 Oct;20(10):1661-72.
6. Sandmaier BM, Mackinnon S, Childs RW. Reduced intensity conditioning for allogeneic hematopoietic cell transplantation: current perspectives. Biol Blood Marrow Transplant. 2007 Jan;13(1 Suppl 1):87-97.
7. Barfield RC, Kasow KA, Hale GA. Advances in pediatric hematopoietic stem cell transplantation. Cancer Biol Ther. 2008 Oct;7(10):1533-9.
8. Eiser C. Practitioner review: long-term consequences of childhood cancer. J Child Psychol Psychiatry. 1998 Jul;39(5):621-33.
9. Locatelli F, Giorgiani G, Di-Cesare-Merlone A, et al. The changing role of stem cell transplantation in childhood. Bone Marrow Transplant. 2008 Jun;41(Suppl 2):S3-7.
10. Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. JAMA. 2010 Jul 14;304(2):172-9.
11. Field MJ, Boat TF, eds. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington: The National Academies Press; 2010. http://books.nap.edu/openbook.php?record_id=12953.
12. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318pageaction=displayproduct.
13. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [posted July 2009]. Rockville, MD. http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318.
14. Behrman RE, Kliegman RM, Nelson WE. Nelson Textbook of Pediatrics. 15th ed., Philadelphia: Saunders; 1996.
15. Rudolph CD. Rudolph's Pediatrics. 21st ed. New York: McGraw-Hill; 2003.
16. Avery MD, First LR. Pediatric Medicine. 2nd ed. Baltimore: Williams & Wilkins; 1994.

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