



Report

Standardization of Terminology for Episodes of Hematopoietic Stem Cell Patient Transplant Care

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ABSTRACT

The nomenclature describing hematopoietic stem cell transplantation has evolved, adding precision and definition in research and regulation. The lack of coordination and standardization in terminology has left some gaps in the definition of episodes of clinical care. These voids have caused particular problems in contracting for payment and billing for services rendered. The purpose of this report is to propose definitions for cell products, cell infusions, and transplantation episodes.

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INTRODUCTION

Rapid progress in the clinical development of cellular therapies has fostered a dramatic expansion in the application of hematopoietic stem cell transplantation (HSCT) to new diseases and patient populations. This expansion is evident in the finding of the Agency for Healthcare Research and Quality that blood and marrow transplantation had the largest associated percentage cost increase of any inpatient hospital procedure in the United States for the period 2004–2007 [1].

The terminology used to describe the cell products and the corresponding procedures is also evolving to address clinical, regulatory, and financial needs. There are clear definitions of individual cell products recognized by the United States Food and Drug Administration and such agencies as the Foundation for the Accreditation of Cellular Therapy, the AABB, and the Center for International Blood and Marrow Transplant Research (CIBMTR) have clarified the application of these terms as they apply to clinical research [2,3]. Reimbursement code systems, including the Medicare severity diagnosis-related groups used by the Centers for Medicare and Medicaid Services and the International Classification of Diseases codes, encompass broad definitions of stem cell transplantation contained within very few codes. Various American Medical Association Current Procedural

Terminology (CPT) codes also describe the physician component in the acquisition (CPT 38205, 38206, 38230, and 38232) and subsequent infusion (CPT 38240–38243) of cellular products. The CPT codes have precise definitions that must be followed for billing of physician services and hospital services on the day of the procedure (data not shown). Finally, the terminology of the methods used to prepare a patient for HSCT has also undergone evolution [4].

Although the nomenclature describing HSCT has undergone modifications that have added precision to defined areas of research and regulation, the lack of coordination and standardization of terms has left clinical gaps in the definition of episodes of care. These voids have become particularly problematic for administrative purposes, such as contracting for payment and billing for services rendered. The purpose of this report is to propose standard definitions for cell products, cell infusions, and transplantation episodes. Implications for contracting for transplantation services are discussed.

PROCESS

In collaboration with the National Marrow Donor Program, the American Society for Blood and Marrow Transplantation established a task force to address the cell infusion definitions associated with defining and contracting for episodes of transplantation care. The task force convened a panel of transplantation physicians, health plan/transplantation network representatives, and additional stakeholders to discuss the need for more defined language and generate common definitions of various cell infusion

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procedures. The panel reviewed existing definitions from several sources, as well as those developed by meeting participants. Applicable reimbursement codes (International Classification of Diseases, CPT, and diagnosis-related groups) were mapped to draft definitions and flagged for potential issues. Aims of procedures, technical definitions, and corresponding reimbursement coding system information were also considered by the panel.

PROCEDURE DEFINITION

The task force's recommendations for standardization of procedure definitions are summarized in [Appendix A](#). There was consensus that procedure terminology lacked standardization and was being used for differing purposes. Recognizing that the CIBMTR created a series of procedural definitions describing only the types of infusions as a means to clarify therapeutic and research efforts, the task force nevertheless recommends that these definitions serve as the foundation for its recommendations for descriptions of episodes of care [3].

The term "hematopoietic stem cell infusion" (HSCI) is recommended to describe the infusion of a product that contains hematopoietic progenitor cells (ie, bone marrow, peripheral blood stem cells, or umbilical cord blood) intended to restore hematopoiesis or immunity. "Hematopoietic stem cell transplantation" (HSCT) is defined as HSCI commonly performed after administration of a preparative regimen. "Allogeneic HSCT" is defined as allogeneic HSCI infused most commonly after a preparative regimen of variable intensity. Allogeneic HSCT may be performed without a preparative regimen in selected clinical situations, such as the treatment of some immunodeficiency disorders. "Syngeneic HSCT" is an uncommon type of HSCT in which the recipient receives an HSCI from an identical twin. Clinical management of recipients of syngeneic HSCT is similar to that of autologous HSCT, although complications typical of allogeneic HSCT may occur infrequently. As with other allogeneic HSCTs, the identical-twin donor must still be evaluated and qualified before harvesting of the stem cell product.

Although traditionally considered a transplantation procedure, some investigators are now questioning whether autologous HSCI after chemotherapy is consistent with the broader definition of transplantation (ie, transfer of an organ or tissue from one part of the body to another or from one person to another). This consideration is important for 2 reasons. First, distinguishing the infusion of a cell product from the episode of care encompassing high-dose chemotherapy and autologous HSCI is necessary for defining and contracting for the resources needed to deliver quality patient care. Second, there is a need to distinguish these procedures from others in which less-intensive chemotherapy is delivered with HSCI support or even without chemotherapy as somatic cell therapy. The task force proposes that autologous HSCT be defined as always preceded by a myeloablative preparative regimen. In turn, a myeloablative preparative regimen is defined as "a combination of agents expected to produce profound pancytopenia and myeloablation within 1–3 weeks of administration; pancytopenia is long-lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hematopoietic stem cell infusion" [4]. Although this definition varies somewhat from that of the CIBMTR, the intent is to distinguish autologous HSCT from autologous HSCI performed after each cycle of multiple cycles of nonmyeloablative chemotherapy, to prevent marrow exhaustion

[2]. It should also encompass settings in which tandem transplantations may be considered standard of care, such as the treatment of multiple myeloma and testicular cancer.

The term "retransplantation" refers to a subsequent HSCT after a primary autologous or allogeneic HSCT. The recipient will typically require reevaluation and qualification, and must meet the institution's eligibility requirements for transplantation. The transplantation procedure also must meet the previously proposed criteria for allogeneic or autologous HSCT. Retransplantation is typically performed more than 3 months after the first HSCT, and HSCI is typically provided at the completion of the preparative regimen on day 0. These definitions should be compatible with the primary transplantation infusion CPT codes 38240 and 38241.

Various terms, including "boost," "reinfusion," "support," and "rescue," have been used to describe an HSCI provided to a transplantation recipient after the initial transplantation to assist with hematopoietic recovery or declining donor chimerism. The task force strongly endorses "boost" as the preferred term for either autologous or allogeneic HSCI for this indication and recommends eliminating other terms. The term "boost" is already linked to CPT 38243. A boost is not preceded by a preparative regimen. A potential source of confusion is that a boost is often required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HSCI, which is typically given days to weeks after reinduction chemotherapy.

The cell product used for HSCI in either a retransplantation or a boost may be a previously cryopreserved cell product that contains stem cells. Alternatively, the donor may need to undergo additional evaluation, stem cell mobilization, and cell harvest.

A donor cell infusion (DCI) is a cell product used as immunotherapy to treat infections (eg, viral), recurrent disease, or graft-versus-host disease. Standard cell products include peripheral blood mononuclear cells and lymphocytes, whereas investigational DCI includes dendritic cells, T regulatory cells, natural killer cells, mesenchymal cells, and others currently in development. The most common DCI, and the only one with an associated CPT code (CPT 39242), is donor lymphocyte infusion. Previously cryopreserved cell products such as those collected for HSCI contain the cell populations of interest and may be used for DCI, but the intent is not to restore hematopoiesis. The recipient does not receive a preparative regimen, but may require concomitant therapy for the underlying problem.

The task force endorsed the description of "supplemental infusion" as defined by CIBMTR. These cell products are given before day 0 of HSCT for any reason other than to produce engraftment. A supplemental infusion is distinct from a DCI, in that a DCI is given after HSCT. Presently there are no standard indications for supplemental infusions, but investigational cell products include natural killer cells, regulatory T lymphocytes, and mesenchymal cells.

The task force also reviewed the terms describing preparative regimens and endorsed the recommendations of the CIBMTR [4]. The preferred terms for preparative regimens are "myeloablative," "nonmyeloablative," and "reduced-intensity conditioning." Terms that have been commonly used such as "mini-transplant" and "lite" transplantation are nonspecific colloquial references that have been applied to both nonmyeloablative and reduced-

intensity conditioning preparative regimens. The task force strongly recommends that these terms be eliminated to avoid confusion.

The applicable reimbursement codes associated with the various infusion types are listed in [Appendix B](#). A decision tree providing a visual overview of the procedures is provided in [Appendix C](#).

IMPLICATIONS FOR CONTRACTING

Along with promoting scientific and regulatory accuracy, the terminology defining the elements of care surrounding HSCT must encompass the necessary resources to deliver, and contract for, care of the patient. Because healthcare financing relies on proper identification and coding of procedures, the lack of clarity in HSCT terminology pertaining to the elements of care has created confusion in the development and management of contracts with payors. For example, some payor contracts depend on CPT codes to trigger payment for an entire episode of HSCT care; however, the CPT codes describe physician work and hospital payment coding pertaining only to cell infusions. This has created a risk that payment for an entire transplantation episode might be delivered for a cell infusion remote from the transplantation itself.

The task force recommends that the term “HSCT” refer to the entire episode of care and all associated processes including pretransplantation evaluation, preparative regimens, HSCI, post-infusion supportive care, and immunosuppression. HSCT is now commonly reimbursed based on global or case rates for the entire episode of care, typically for a period of 30–100 days. Anticipated infusions such as HSCI or DCI, if preplanned, should be described and included in the case rate. Cell infusions that are not part of the initial treatment plan, such as a boost for poor graft function or DCI for incomplete chimerism occurring outside of the contract period, should be negotiated separately. Payment for an entire case rate should be based on the intent of the procedure(s) and resources involved and should not be dictated solely by the inclusion of specific CPT codes in the claim.

Although incomplete, the HSCT-associated CPT codes are useful in defining elements of care for contracting. Collection

codes (CPT 38205, 38206, 38230, and 38232) can be helpful for contract interpretation and collection. Cell processing codes are useful in defining the contracted techniques (CPT 38207–38215). The infusion codes (CPT38240–38243) should be used only to describe services on the date of infusion, not for the entire episode of care.

CONCLUSION

These recommendations for standardization of the terms describing of cell products and types of HSCT are intended to provide a framework that will facilitate clarity in the definition of the programmatic resources required for an episode of care for the patient, as well as contracting discussions with payors. The hope is that they will also serve as a foundation for the vast potential of cellular therapies going forward.

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Appendix A

Recommended Procedure Terms and Definitions

Term	Definition	Intent	Additional Notes	Sample Clinical Scenario
HSCI	Infusion of a product (bone marrow, peripheral blood stem cells, cord blood) that contains hematopoietic progenitor cells (HPCs), often characterized by CD34 expression.	To restore hematopoiesis and immunity.	Usually preceded by a preparative regimen for HSCT or retransplantation, but also may be used for a boost.	
HSCT	An episode of care starting with a preparative regimen and continuing through HSCI and recovery.			
Allogeneic HSCT	HSCI using products collected from a donor and usually following a preparative regimen. Donors may be a biological relative of the recipient or anonymous and unrelated.		Provided after a preparative regimen is administered, regardless of intensity, or in the absence of a preparative regimen in selected clinical situations, such as treatment of immunodeficiency.	A patient with acute myelogenous leukemia in first complete remission prepared with busulfan and cyclophosphamide in standard doses, followed by HSCI with bone marrow from a matched unrelated donor.
Syngeneic HSCT	HSCI using products collected from an identical sibling.		Donor is an identical twin. Patient is generally managed as an autologous HSCT recipient. However, the identical twin donor must still be evaluated and undergo stem cell harvest, so the transplantation should be categorized as allogeneic. Graft-versus-host disease remains a possibility in these cases.	
Autologous HSCT	HSCI using products collected from the recipient before myeloablative chemotherapy.			A patient with non-Hodgkin lymphoma prepared with BEAM followed by autologous HSCI with filgrastim mobilization, infused with cryopreserved peripheral blood HSCs.
Tandem transplantation	Peripheral blood hematopoietic stem cells (HSCs) are collected either during recovery of a cycle of induction chemotherapy or after filgrastim mobilization. The patient receives a second preparative regimen, along with HPCs collected during the initial mobilization. Both transplantations are planned in advance and typically are performed a few weeks to a few months apart.	To prevent marrow exhaustion.		A patient with relapsed testicular cancer placed into second remission with reinduction chemotherapy.
Multiple-cycle intensive chemotherapy	Repeated cycles of intensive chemotherapy followed by HSCI.		Involves single stem cell mobilization and division of the collected stem cell product into multiple cryopreserved aliquots. This is followed by repeated cycles of intensive, but often reduced-intensity, conditioning regimens supported by stem cell infusion meant to expedite hematologic recovery, allowing for prompt administration of a subsequent intensive cycle of chemotherapy.	A patient with a disease process such as neuroblastoma, central or peripheral primitive neuroectodermal tumors, or germ cell cancer.

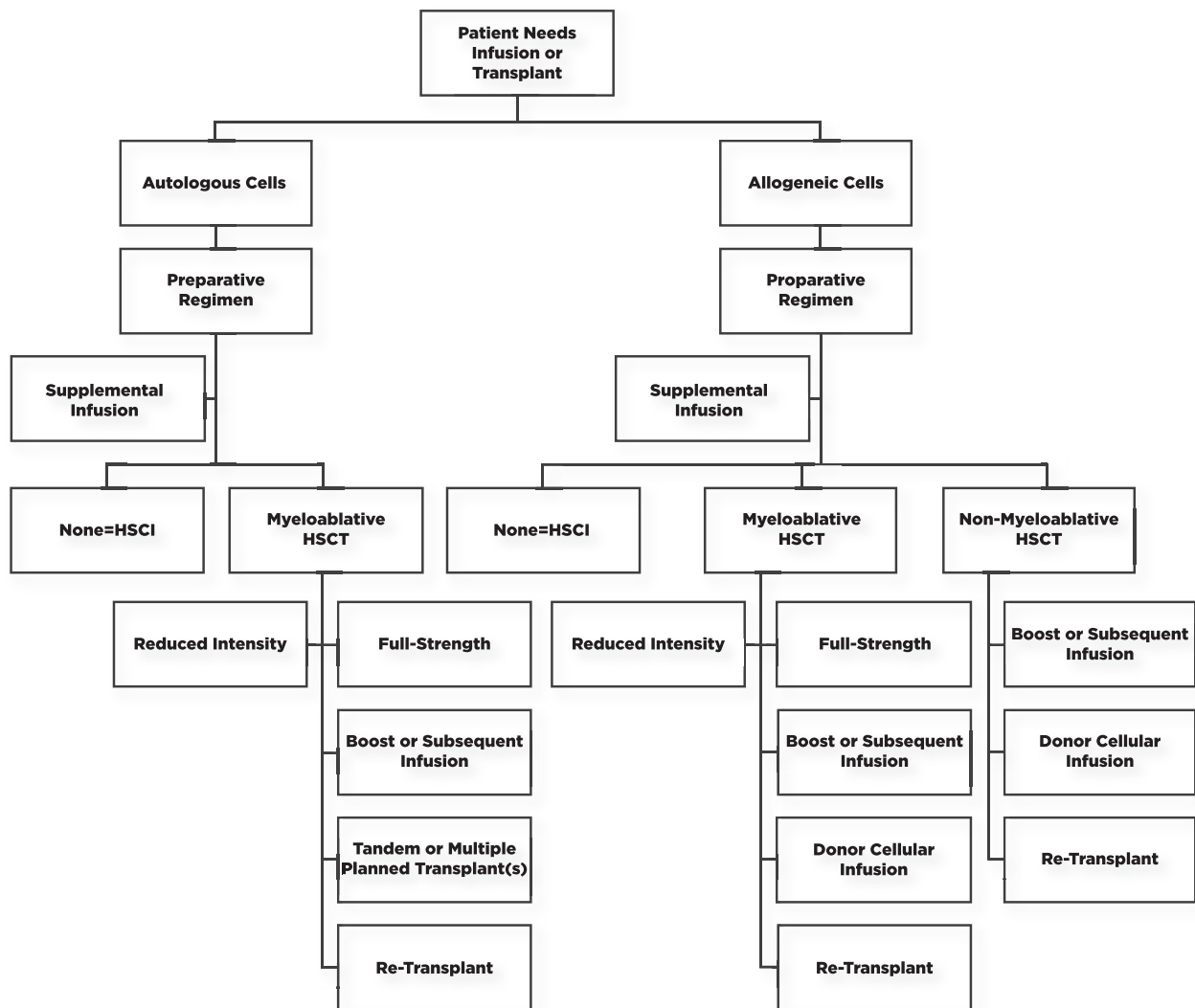
DCI	<p>An infusion of cells from an allogeneic donor typically given after HSCT. Types of cells used for DCI include, but are not limited to, the following:</p> <ul style="list-style-type: none"> • Lymphocytes/T cells (donor lymphocyte infusion): a therapeutic product from any source containing a quantified T cell population • Peripheral blood mononuclear cells (both stimulated and unstimulated): whole blood collected as a source of nucleated cells intended for therapeutic use other than HPCs • Dendritic cells from the original donor: a therapeutic cell product containing dendritic cells for therapeutic use • Mesenchymal cells: a therapeutic product containing mesenchymal stromal cells for therapeutic use 	<p>DCI is a form of immunotherapy commonly used to treat infections (eg, viral) or recurrent disease. DCI also may be used to treat graft-versus-host disease or to promote engraftment or enhancement of chimerism when studies reveal <100% donor cells. The recipient does not undergo a preparative regimen before receiving the additional donor cells, but may receive additional preinfusion treatment.</p>	<p>The product may contain HSCs, but the restoration of hematopoiesis is generally not the primary intent of the infusion. CPT 38242 is assigned for allogeneic lymphocyte infusions.</p>	<p>A patient with acute myelogenous leukemia who underwent allogeneic HSCT and relapsed at 6 months posttransplantation without graft-versus-host disease. If stored cells were not cryopreserved from the donor, then the original donor undergoes apheresis to collect T cells to give back to the recipient. Any extra cells from the initial collection are cryopreserved in a freezer bottle at the transplantation center. Dosing of these cryopreserved cells is based on T cell doses of product infused, not on HSC dose. Sometimes limited chemotherapy precedes these infusions. Cell types, standard: T cells (donor lymphocyte infusion), peripheral blood mononuclear cells; investigational: dendritic cells, mesenteric stem cells.</p>
Supplemental infusion	<p>An infusion of cells given before clinical day 0 (day of HSCT) for any reason other than to produce engraftment. An infusion of supplemental cells is often given in conjunction with a preparative regimen for HSCT.</p>	<p>Used for any reason other than to produce engraftment.</p>	<p>A supplemental infusion differs from a DCI in being given before HSCT, whereas a DCI is given after HSCT. Examples of supplemental infusions include, but are not limited to, natural killer cells, T regulatory cells, and mesenchymal stem cells.</p>	<p>An investigational study involving infusion of CD3⁺-CD19⁺-selected and IL-2-activated, haploidentical donor natural killer cells on day 12 before a standard preparative regimen and matched sibling allogeneic HSCT.</p>
Retransplantation	<p>HSCT after undergoing a previous transplantation.</p>		<p>Requires requalification of patient for transplantation; transplantation must meet the definition for allogeneic or autologous HSCT.</p>	<p>A patient who relapses after initial HSCT and is placed back into remission with additional induction chemotherapy. The patient is then requalified for HSCT. Collection of additional HSCs may be required in the setting of allogeneic HSCT.</p>
Subsequent (boost) infusion	<p>Subsequent transfusion of allogeneic or autologous HSCs.</p>	<p>Used in cases of weak hematopoiesis in an attempt to augment the original graft.</p>	<p>“Boost” is the primary term used for this procedure. A boost is not preceded by a conditioning regimen. CPT 38243 is assigned to HSC boost. May require the recipient and/or donor to undergo additional workup, mobilization, harvest/procurement, and ultimately HSC infusion, procedures also associated with subsequent HSCT. A boost is not preceded by a preparative regimen, but may be provided days to weeks after induction chemotherapy. Retransplantation commonly involves a conditioning regimen directly followed by HSC infusion (ie, on day 0).</p>	<p>An allogeneic HSCT recipient has 100% donor cells but with a weak or poorly functioning hematopoietic graft and low peripheral blood counts. Excess cryopreserved cells collected at the time of transplantation would be infused. A patient with acute myelogenous leukemia who received a busulfan/cytosan-containing preparative regimen before allogeneic HSCT. Approximately 4 months after HSCT, the patient has severe cytomegalovirus and fungal infections, but with 100% donor cells, 10% cellularity on bone marrow biopsy, an absolute neutrophil count <1000, and platelet and RBC transfusion-dependency. Extra cells have been cryopreserved, or more fresh cells are collected from the donor with granulocyte colony-stimulating factor mobilization. These cells are infused with the intent of fully recovering hematopoiesis. Dosing is based on the CD34 cell count of product infused.</p>

Appendix B

Infusion Types and Associated Reimbursement Codes

Term	International Classification of Diseases 9 Procedure Codes	CPT Codes	MS-DRG
Autologous HSCT/HSCI <ul style="list-style-type: none"> • Single autologous HSCT • Tandem autologous HSCT • Multiple-cycle autologous • Retransplantation (autologous) 	41.01: Autologous bone marrow transplantation without purging 41.04: Autologous hematopoietic stem cell transplantation without purging 41.07: Autologous hematopoietic stem cell transplantation with purging 41.09: Autologous bone marrow transplantation with purging	38241: Hematopoietic progenitor cell (HPC); autologous transplantation	016: Autologous bone marrow transplantation with complications and comorbidities/major complications and comorbidities (CC/MCC) 017: Autologous bone marrow transplantation without CC/MCC
Allogeneic HSCT/HSCI <ul style="list-style-type: none"> • Related donor • Unrelated donor • Syngeneic • Retransplantation (allogeneic) 	41.02: Allogeneic bone marrow transplantation with purging 41.03: Allogeneic bone marrow transplantation without purging 41.05: Allogeneic hematopoietic stem cell transplantation without purging 41.06: Cord blood stem cell transplantation 41.08: Allogeneic hematopoietic stem cell transplantation with purging 99.09: Transfusion of other substance	38240: HPC; allogeneic transplantation per donor	014: Allogeneic bone marrow transplantation
Supplemental infusion			No MS-DRG assignment based on this code. The DRG assignment is driven by other codes submitted as part of the inpatient stay.
DCI	99.09: Transfusion of other substance	38242: Allogeneic lymphocyte infusion	No MS-DRG assignment based on this code. The DRG assignment is driven by other codes submitted as part of the inpatient stay.
Subsequent (boost) infusion	99.09: Transfusion of other substance	38243: HPC; HPC boost	No MS-DRG assignment based on this code. The DRG assignment is driven by other codes submitted as part of the inpatient stay.

MS-DRG indicates Medicare severity diagnosis-related group.



Appendix C. Infusion Decision Tree.