



TRANSPLANT REVIEW GUIDELINES

Hematopoietic Stem Cell Transplantation

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Table of Contents

Hematopoietic Stem Cell Transplant

Introduction.....	3
General Information	3
Indications	5
Relative Contraindications.....	15
Special Considerations	17
Hematopoietic Stem Cell Transplant — Timing for Stem Cell Transplant Consultation...	18

Chimeric Antigen Receptor T-cell Therapy.....27

Appendix..... 28

AIDS-defining Conditions	28
Clinical, Cytogenetic and Mutational Risk Stratification for AML	30
The Dynamic International Prognostic Scoring System (DIPSS) for Primary Myelofibrosis (PMF)	31
Complete Remission and Partial Remission Highlights from Revised Response Criteria for Malignant Lymphoma (Cheson et al.)	32
Hematopoietic Stem Cell Transplant Reference Sheet	33
Updated Criteria for Diagnosis of Multiple Myeloma (Rajkumar, 2014).....	36

Hematopoietic Stem Cell Transplant

Introduction

Hematopoietic stem cell transplants, including peripheral blood, bone marrow, and cord blood transplants are used most often to treat cancers affecting the blood or immune system. There are two main types of stem cell transplant: autologous and allogeneic. Autologous stem cells come from the person who will be receiving the transplant and are mainly used to treat leukemias, lymphomas, and multiple myeloma as well as other cancers such as testicular cancer and neuroblastoma. Autologous stem cell transplants are also used to treat certain childhood cancers. Allogeneic stem cells come from another individual. They can be from a matched related or unrelated donor or a donor without a complete match. Allogeneic stem cells are most commonly used to treat leukemias, lymphomas or non-malignant inherited disorders. An allogeneic transplant provides the advantage of a graft vs. cancer effect but occurs with the potential risk of graft vs. host disease. The need to balance these two outcomes makes this a more complicated procedure.

The purpose of this guideline is to identify the indications and contraindications for hematopoietic stem cell transplant as well as provide helpful reference tools to better understand a request for transplant.

General Information

- “Back-up” autologous harvesting for patients in complete remission (CR) with no evidence of marrow involvement by malignancy is appropriate. For example, bone marrow or peripheral blood progenitor cell harvesting is appropriate for patients with multiple myeloma in CR and who might be transplanted in the future. Consult benefit document.
- Donor lymphocyte infusion (DLI) following allogeneic stem cell transplant is appropriate for incomplete chimerism and disease relapse in the setting of incomplete chimerism. This is not a second stem cell transplant. (Bacigalupo, 2006)
- Repeat stem cell transplant is appropriate for primary and secondary failure to engraft and disease relapse.
- Primary failure is the failure to reach three consecutive days with a neutrophil count (absolute neutrophil count/ANC) $> 500 \mu\text{l}$ ($0.5 \times 10^9/\text{liter}$) after SCT, while secondary failure is associated with a successful SCT graft where neutrophils increase to $> 500 \mu\text{l}$ ($0.5 \times 10^9/\text{liter}$) for at least three consecutive days and subsequently decrease to a lower level until additional treatment is given to obtain engraftment. (There can be a loss of an allogeneic graft with normal blood cell counts due to autologous reconstitution. This can be confirmed with chimerism studies).
- Stem cell boost is a Hematopoietic Stem Cell Infusion (HSCI) provided to a transplant recipient to assist with hematopoietic recovery or declining donor chimerism. It is not preceded by a preparative regimen and is not considered a new transplant event. Stem cell boost is a non-standardized term and has been used interchangeably with terms such as reinfusion, support and rescue. For the purposes of this guideline, we endorse use of the term “boost” based on the recommendation of the task force set up by the American Society for Blood and Marrow Transplantation in collaboration with National Marrow Donor Program (LeMaistre, 2013) and the existence of a CPT code for the term boost (CPT 38243).

- Autologous stem cell transplant with or without a second autologous transplant (tandem transplant) is considered a standard of care for the treatment of multiple myeloma although controversy does exist particularly in the era of newer and more effective chemotherapy agents such as bortezomib, lenalidomide and thalidomide. (Blade, 2010; Harousseau, 2009; Bashey, 2008; Kumar, 2009) As the primary and salvage treatment for multiple myeloma has become increasingly successful in recent years, it is likely that, going forward, multiple factors will need to be considered prior to making decisions regarding the use of transplantation procedures; e.g., risk stratification, age, comorbidities, etc. and that the role of transplantation may decrease for certain subgroups.
- During a tandem transplant, a patient receives two sequential courses of high-dose chemotherapy with stem cell transplant. 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 hematopoietic progenitor cells (HPCs) collected during the initial mobilization. Both transplantations are planned in advance and typically are performed a few weeks to a few months apart. (LeMaistre, 2013)
- Tandem stem cell transplants require review by the Medical Director except for the following conditions: multiple myeloma, testicular and other germ cell tumors, neuroblastoma, pediatric brain tumors, and other conditions as part of an IRB-approved clinical trial.
- Third stem cell transplants require Medical Director review.
 - If part of a sequence of high-dose chemotherapy followed by rescue stem cell infusion as is the case with some neuroblastoma, medulloblastoma and testicular germ cell tumor protocols, the entire course may be approved initially.
- Stem cell source:
 - Single unit umbilical cord blood stem cell transplants are standard of care for children in many programs. Children > 45 kg who receive a single cord blood unit may experience prolonged time to engraftment and other post-transplant complications; therefore, a calculation of 2.5×10^7 nucleated cells per kilogram may improve response. (de Lima, 2006)
 - Umbilical cord blood and haploidentical donor cells are appropriate stem cell sources (Brunstein et al., 2007; Klingebiel et al., 2010) and can be used at the discretion of the treating team.
- The stem cell transplant expert panels have confirmed that the treatment of any pediatric patient under a Children's Oncology Group (COG) protocol should be considered Standard of Care.
- Patients who have undergone stem cell transplant have altered immune systems post-transplant. In the case of allogeneic stem cell transplant, the immune system may never fully recover. These patients have unique care needs in the post-transplant period and will require lifelong follow-up and management. (Optum Expert Panel, 2015)
- The definition of multiple myeloma has been updated. (Rajkumar et al.) As such the diagnoses of frank myeloma, smoldering myeloma and MGUS have changed and can affect indications for treatment. (See Appendix.)

- In an effort to improve outcomes of blood and marrow transplantation, the use of maintenance therapy has become standard over the past few years. Maintenance therapy is considered an important component of the transplant event and therefore is covered if supported by adequate clinical evidence. Requests for maintenance therapy should be referred to the Medical Director.
- Traditionally the treatment of veno-occlusive disease (VOD) has been supportive and the outcomes poor. In March 2016, FDA gave approval to the new drug defibrotide for the treatment of active VOD. At the present time there is not an approved indication for its use in a prophylactic manner which is commonly done overseas in Europe.
 - Defibrotide is covered for the treatment of adult and pediatric patients with active hepatic VOD with renal or pulmonary dysfunction following hematopoietic stem cell transplant.
 - Defibrotide is not covered for the prevention of VOD
- Minimal Residual Disease (MRD) is an emerging measure of lingering disease which may have a role in both prognosis and treatment of hematologic malignancies. MRD detection has evolved over the past several decades and is measured through the use of flow cytometry, real-time quantitative polymerase chain reaction (RQ-PCR) or, more recently, next-generation sequencing based assays (Malmberg et al., 2015). The clinical utility of assessing MRD status has yet to be clearly defined.

Indications

If an indication is listed as “Not standard of care”, the requested service may be covered if there is a state mandate, the member has a cancer clinical trial benefit, can be covered under the CRS program, if there is a life threatening illness clause in the benefit plan, etc. and all provisions of the applicable benefit(s) have been met.

CHECK FOR STATE MANDATES AND THE MEMBER’S BENEFIT PLAN TO DETERMINE ELIGIBILITY.

- ✓ = COVERED INDICATION
- N = NOT A COVERED INDICATION
- □ = If nothing is indicated, this generally means that this is not considered an indication for stem cell transplant of the type requested and we do not expect to see requests for authorization for this particular type of stem cell transplant for this indication. Any requests for stem cell transplant for one of these indications will be referred to the Medical Director for review.

Disease/Indication	Auto	Allo	Comment
Leukemia			
Acute Lymphoblastic Leukemia (ALL) (Hahn et al., 2005; Oliansky et al. 2012; Schultz et al., 2007)	✓	✓	<p>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</p> <p>The following cytogenetic features are associated with pediatric high-risk disease and may influence the decision to transplant in CR1:</p> <ul style="list-style-type: none"> • Hypodiploid ALL (< 44 chromosomes) • iAMP21
Acute Myeloid Leukemia (AML) (Oliansky et al., 2007 & 2008)	✓	✓	<p>Intermediate and high-risk AML including but not limited to:</p> <ul style="list-style-type: none"> • First complete response (CR1) with poor-risk cytogenetics or molecular markers • AML after relapse • CR2 and beyond <p>See Appendix for the definition of risk markers and clinical risk factors.</p> <p>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</p>
Chronic Lymphocytic Leukemia (CLL)	N	✓	<p>There is a lack of data supporting auto for CLL; however, the availability of new agents such as idelalisib and ibrutinib, which are highly effective against this condition will likely change how stem cell transplantation is used in this disease. A history of prior treatment should be obtained with every transplant request.</p>

Disease/Indication	Auto	Allo	Comment
Chronic Myeloid Leukemia (CML)	N	✓	There are minimal to no data supporting auto in CML. Allo being used much less frequently in the era of tyrosine kinase inhibitors and primarily for the relatively rare very young patients and those exhibiting less than optimal responses to targeted therapy.
Prolymphocytic Leukemia (Krishnan et al., Kalaycio et al.)	✓	✓	
Myelodysplastic & Pre-Leukemic Syndromes (Oliansky et al., 2009)			
Myelodysplastic Syndrome (MDS)	N	✓	
Myelofibrosis and related conditions (e.g. PRV)	N	✓	Allo approved with Intermediate-2 or High Risk score using the Dynamic International Prognostic Scoring System (DIPSS). See Appendix for DIPSS scoring system.
Juvenile Myelo-Monocytic Leukemia (JMML/JCML)	N	✓	
Brain Tumors			
Anaplastic Astrocytoma	N		Not standard of care
Brain stem glioma	N		Not standard of care
Ependymoma	N		Not standard of care
Germinoma	N		Not standard of care
Glioblastoma Multiforme (GBM)	N		May be considered in infants
Medulloblastoma	✓		
Oligodendroglioma	✓		
Pineoblastoma	✓		

Disease/Indication	Auto	Allo	Comment
Embryonal Tumors with Multi-layered Rosettes (ETMR). Formerly known as Primitive Neuroectodermal Tumor (PNET)	✓		
Germ Cell Tumors			
Testicular Germ Cell Tumor	✓		Tandem auto can be approved
Extragonadal Germ Cell Tumor	✓		Tandem auto can be approved
Seminoma	✓		Tandem auto can be approved
Choriocarcinoma	✓		Tandem auto can be approved
Embryonal Carcinoma	✓		Tandem auto can be approved
Mixed Germ Cell Tumors	✓		Tandem auto can be approved
Teratoma	✓		Tandem auto can be approved
Yolk-Sac Tumor (Endodermal Sinus Tumor)	✓		Tandem auto can be approved
Germ Cell Tumor of the Ovary	✓		Tandem auto can be approved
Multiple Myeloma/ Plasma Cell Disorders			
Multiple Myeloma			Refer allograft request to Medical Director
a) Single auto	✓		
b) Tandem (auto followed by auto)	✓		

Disease/Indication	Auto	Allo	Comment
c) Tandem (auto followed by allo)	See SPECIAL CONSIDERATIONS		
d) Allogeneic	See SPECIAL CONSIDERATIONS		
AL-Amyloidosis	✓	N	Allogeneic SCT may be appropriate on clinical trial. Refer to Medical Director
Waldenstrom Macroglobulinemia	✓	✓	
Monoclonal gammopathy of uncertain significance (MGUS)	N	N	No transplant indicated
POEMS (Polyneuropathy Organomegaly Endocrinopathy, Monoclonal Gammopathy Skin defects Syndrome) (D'Souza et al., Ji et al., Li et al.)	✓	N	Autologous SCT may be appropriate. Refer to Medical Director.
Solitary Plasmacytoma	N	N	No transplant indicated
Hodgkin's Lymphoma			
Hodgkin's Lymphoma	✓	✓	For autologous transplants, tumors must be chemo-sensitive which is defined as a complete or partial response based on the Cheson criteria. See Appendix for Cheson criteria.
Non-Hodgkin's Lymphoma (NHL)			For autologous transplants, tumors must be chemosensitive which is defined as a complete or partial response based on the Cheson criteria. See Appendix for Cheson criteria.
Small B-cell lymphocytic lymphoma	N	✓	Auto not standard of care. This is treated in the same manner as CLL. Refer to Medical Director.
Follicle center lymphoma (Oliansky et al., 2010)	✓	✓	

Disease/Indication	Auto	Allo	Comment
Lymphoplasmacytoid lymphoma/immunocytoma	✓	✓	
Marginal zone lymphoma (mucosa-associated lymphoid tissue, splenic, nodal)	✓	✓	
Burkitt lymphoma	✓	✓	
Diffuse, large cell lymphoma (mediastinal large cell, primary effusion) (Oliansky et al. 2011)	✓	✓	
Mantle cell lymphoma	✓	✓	
Precursor B-cell leukemia/lymphoma	✓	✓	
T-cell Lymphoma	✓	✓	
Other Malignancies			
Atypical Teratoid Rhabdoid Tumors	✓	N	Tandem auto may be indicated. May be appropriate as part of a clinical trial. (Nikolaides et al.)
Blastic Plasmacytoid Dendritic Cell Neoplasm	N	✓	Dietrich et al.
Epithelial Ovarian Cancer	N	N	Not standard of care
Ewing Tumor (Ewing Sarcoma)	✓	N	Allogeneic not standard of care
Neuroblastoma	✓	N	Tandem auto can be approved
Osteogenic sarcoma	N	N	Not standard of care
Renal Cell Carcinoma	N	N	Not standard of care
Retinoblastoma	✓	N	Allogeneic not standard of care
Rhabdomyosarcoma/soft tissue sarcoma	N	N	May be appropriate as part of a clinical trial. (Stiff et al.) Refer to Medical Director

Disease/Indication	Auto	Allo	Comment
Supratentorial ependymoma	✓		Venkatramani et al.
Wilms Tumor	✓	N	May be appropriate in relapsed disease as part of a clinical trial. (Brown et al., Campbell et al.) Refer to Medical Director
Hematological Disorders			
Aplastic Anemia		✓	
Blackfan-Diamond Syndrome		✓	
Chronic Granulomatous Disease		✓	
Congenital Agranulocytosis (Kostmann Syndrome)		✓	
Congenital Amegakaryocytic Thrombocytopenia		✓	
Dyskeratosis Congenita		✓	
Fanconi Anemia		✓	
Paroxysmal Nocturnal Hemoglobinuria (PNH)		✓	
Shwachman-Diamond Syndrome		✓	
Sickle Cell Disease		✓	
Thalassemia Major		✓	
Immunodeficiency Syndromes			
CD40 Ligand Deficiency		✓	
Chediak-Higashi Syndrome		✓	

Disease/Indication	Auto	Allo	Comment
Hemophagocytic Lymphohistiocytosis (HLH) (same as Familial Erythrophagocytic Lymphohistiocytosis - FEL)		✓	
Leukocyte Adhesion Deficiency		✓	
Omenn Syndrome		✓	
Severe Combined Immunodeficiency Disease (SCID)		✓	In addition to classical SCID, there are a variety of severe mixed (B- and T- cell) immune deficiency syndromes, with or without defined genetic abnormalities, which can be treated with allogeneic stem cell transplant.
Wiskott-Aldrich Syndrome		✓	
X-linked Lymphoproliferative Syndrome		✓	
Gaucher disease type I (Pastores et al., Charrow et al., Peters & Steward, Jmoudiak & Futerman)		✓	Patients with the non-neuropathic type may benefit from a stem cell transplant following failed enzyme replacement therapy or if significant bone pain exists in spite of enzyme replacement therapy.
Niemann-Pick type B (Schuchman)		✓	In a non-cerebral form, transplantation may effectively diminish the impact of the accumulation of metabolic byproducts in lung and liver. These patients die from lung and liver disease and are candidates for stem cell transplantation.

Disease/Indication	Auto	Allo	Comment
Fucosidosis (Miano et al., Vellodi et al.)		✓	There is little experience with transplantation for fucosidosis, a very rare entity among rare entities, but reports indicate that stem cell transplantation performed early effectively ameliorates disease progression.
Lysosomal storage diseases (Heese)		✓	
Autoimmune Diseases			
Crohn's Disease	N	N	Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member's benefit plan supports participation in a clinical trial.
Multiple Sclerosis	N	N	Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member's benefit plan supports participation in a clinical trial.
Rheumatoid Arthritis	N	N	Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member's benefit plan supports participation in a clinical trial.
Systemic lupus erythematosus (SLE)	N	N	Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member's benefit plan supports participation in a clinical trial.

Disease/Indication	Auto	Allo	Comment
Systemic Sclerosis (Scleroderma)	N	N	Not standard of care. Studies are ongoing. May be considered life threatening if significant end-organ involvement, particularly kidneys and lungs. Refer to Medical Director.
Inherited Metabolic Disorders			
Adrenoleukodystrophy		✓	
Epidermolysis Bullosa		✓	
Globoid Cell Leukodystrophy (Krabbe Disease)		✓	
Hurler Syndrome (MPS I)		✓	
Hunter Syndrome (MPS II)		✓	
Mannosidosis		✓	
Maroteaux-Lamy Syndrome (MPS VI)		✓	
Metachromatic Leukodystrophy		✓	
(MNGIE) Mitochondrial Neurogastrointestinal Encephalopathy (Halter et al., Filosto et al.)		✓	
Osteopetrosis		✓	
Rett Syndrome		✓	

Disease/Indication	Auto	Allo	Comment
Cardiac Conditions			
Heart Disease	N	N	Not standard of care. It would only be considered for approval under a clinical trial if the member's benefit plan supports participation in a clinical trial.
Additional Condition/Disease Indications			
Refer to section titled: Hematopoietic Stem Cell Transplant Reference Sheet in the Appendix		✓	The reference sheet includes a list of rare and unusual conditions where allogeneic transplant may be indicated. If there is a condition found within this reference that is not included above, refer to Medical Director.

Relative Contraindications

NOTE: The following list contains potential contraindications for hematopoietic stem cell transplant. While the conditions listed below would not be absolute contraindications for treatment they need to be addressed prior to transplant.

- Infections
 - Acquired Immunodeficiency Syndrome (AIDS) or certain serious and life-threatening diseases that occur in HIV-positive people. These diseases are called "AIDS-defining" conditions. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS. See Appendix for a complete list of these conditions.
 - Systemic or uncontrolled infection including sepsis.
- Significant uncorrectable life-limiting medical conditions.
- Severe end stage organ damage including but not limited to: Severe diabetes mellitus with end organ damage, irreversible severe pulmonary disease, with FEV₁ < 1 L or FVC < 50%, irreversible severe hepatic disease, irreversible severe renal disease.
- Irreversible, severe brain damage.
- Social and Psychiatric Issues — It is expected that a patient has demonstrated adherence to all treatment plans and scheduled appointments and there is documentation of a support system and/or caregiver available to provide necessary care. A case should be referred for psychosocial evaluation and/or psychiatry consultation for guidance in any of the following circumstances:

- Emotional instability, significant depression or other psychiatric illness that cannot be controlled that would impact ability to comply with a complex evaluation process, surgical procedure and post-transplant plan of care and/or ability to give informed consent (and does not have a representative/guardian/conservator).
- Limited cognitive ability (memory loss, dementia, etc.) that would impact ability to comply with a complex evaluation process, surgical procedure and post-transplant plan of care and/or ability to give informed consent (and does not have a representative/guardian/conservator).
- Lack of psychosocial support as indicated by either no identified caregiver or an uncommitted caregiver. This would include the lack of transportation to and from transplant related appointments, patient and/or caregiver is unable to adhere to the requirements of transplant related treatment plan. A care contract may be needed.
- Lack of sufficient financial means to purchase post-transplant medications.
- History of non-adherence that has not been successfully remediated.
- Inability to give informed consent. If the patient has an authorized representative/guardian/conservator or parent in the case of a minor, that individual must understand and support the ongoing health care needs of the patient.
- Post-transplant lymphoproliferative disease (PTLD) unless no active disease demonstrated by negative positron emission tomography (PET) scan and resolved adenopathy on computed tomography (CT) and/or magnetic resonance imaging (Blaes, 2009; Khedmat, 2009).
- Limited irreversible rehabilitative potential (Bunnapradist, 2007).

References

Blaes AH et al. Positron emission tomography scanning in the setting of post-transplant lymphoproliferative disorders. *Clin Transplant*. 2009 Nov-Dec;23(6):794-9.

Bunnapradist S, Danovitch G. Evaluation of Adult Kidney Transplant Candidates. *Am J Kidney Dis*. 2007 Nov; 50(5):890-898.

Khedmat H. Early onset post transplantation lymphoproliferative disorders: analysis of international data from 5 studies. *Ann Transplant*. 2009;14(3):74-7.

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

- Multiple Myeloma

Allogeneic stem cell transplant for multiple myeloma is controversial either as a single allogeneic transplant as initial therapy with curative intent or as the second stage of a planned tandem transplant preceded by an autologous transplant. The following recommendations are consistent with the evolving practice and recognize the expertise of treating physicians within network programs. The recommendations may change as additional experience is gained with the newer disease modifying agents for the treatment of myeloma and as more experience is gained with reduced intensity allogeneic stem cell transplant for this disease.

Note: Refer all requests for allogeneic stem cell transplant in multiple myeloma to Medical Director for review.

- Allogeneic stem cell transplant may be appropriate therapy under the following circumstances
 - Initial therapy in newly diagnosed patients with high-risk disease and in otherwise good health
 - High risk myeloma has been defined by the International Myeloma Working Group (IMWG) based on cytogenetics [Presence of at least one of the following: del(17p), t(4;14) or t(14;16) determined by FISH] and the Mayo Clinic classification adds hypoploidy and t(14;20) to the IMWG definition. Regardless of the source of definition, the requestor should present evidence of sufficient factors that cause the case to be considered high risk.
 - Early relapse (less than 24 months) after primary therapy that included an autologous stem cell transplant or with high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they respond favorably to salvage therapy. (Giralt, 2015)
 - Reduced intensity matched related donor (MRD) and matched unrelated donor (MUD) allogeneic SCT as the second transplant of a planned tandem transplant. (Bruno, 2009; Rotta, 2009)
- HIV infection
 - Patients should have a formal infectious disease consult indicating adequate treatment and proper assessment of risks related to this transplant
- Refer to requesting program Patient Selection Criteria for age specific criteria.
 - If outside the program's patient selection criteria, refer to Medical Director
- Serum creatinine < 2.5 mg/dl (\leq 1.5 mg/dl in children) or GFR > 50 ml/min.
 - Serum creatinine may be higher in patients with multiple myeloma or other plasma cell dyscrasias. Patients with multiple myeloma with reduced renal function are not prohibited from undergoing autologous BMT when the decreased renal function is related to the multiple myeloma (myeloma kidney). This includes patients on hemodialysis with no other contraindications.

- Pediatric patients should have a Lansky score > 50. Adult patients should have a Karnofsky score > 70. If these criteria not met, refer to Medical Director.
- Active untreated or untreatable malignancy in patients undergoing stem cell transplantation for non-malignant indications
 - Refer to Medical Director

Hematopoietic Stem Cell Transplant — Timing for Stem Cell Transplant Consultation

RECOMMENDED TIMING FOR STEM CELL TRANSPLANTATION CONSULTATION (National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation)

<https://bethematchclinical.org/transplant-indications-and-outcomes/additional-outcomes/timing-impact-on-outcomes/>

These guidelines for transplant consultation were developed jointly, and updated for 2015, by the National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT). They are based on current clinical practice and the medical literature, including comprehensive evidence based reviews. One critical factor in the outcome of hematopoietic cell transplantation is the appropriate planning and timing of the transplant. The intent of these guidelines is to identify patients at risk of disease progression and, therefore, which patients should be evaluated for transplantation.

While transplant may be immediately indicated for some patients with these factors, it may not be for all patients. The consultation helps ensure there are plans in place for the patient to move quickly to transplant, if needed, before disease progresses or complications develop. If allogeneic transplant is a possibility, it helps provide adequate time for an unrelated donor or cord blood search.

ADULT LEUKEMIAS AND MYELOYDYSPLASIA

Acute Myelogenous Leukemia (AML)

- High resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all AML patients including:
 - CR1—except favorable risk AML (defined as: t (16;16); inv 16; t (8;21); t (15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD)
 - Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
 - Treatment-related leukemia
 - Primary induction failure or relapse
 - Presence of minimal residual disease after initial or subsequent therapy
 - CR2 and beyond, if not previously evaluated

Acute Lymphoblastic Leukemia (ALL)

- High resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all ALL patients including:
 - CR1
 - Primary induction failure or relapse
 - Presence of minimal residual disease after initial or subsequent therapy
 - CR2 and beyond, if not previously evaluated

Myelodysplastic Syndromes (MDS)

- Any intermediate or high IPSS score
- Any MDS with poor prognostic features, including:
 - Treatment-related MDS
 - Refractory cytopenias
 - Adverse cytogenetics
 - Transfusion dependence

Chronic Myelogenous Leukemia (CML)

- Inadequate hematologic or cytogenetic response to tyrosine kinase inhibitor (TKI) therapies
- Disease progression
- Intolerance to TKI therapies
- Accelerated phase
- Blast crisis (myeloid or lymphoid)

Chronic Lymphocytic Leukemia (CLL)

- High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VH mutational status)
- Short initial remission
- Poor initial response
- Fludarabine-resistant
- Richter's transformation

PEDIATRIC ACUTE LEUKEMIAS

Acute Myelogenous Leukemia (AML)

- High resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all AML patients including:
 - CR1—except favorable risk AML (defined as: t (16;16); inv 16; t (8;21); t (15;17); normal cytogenetics with PM1 or biallelic CEBPA mutation and without FLT3-ITD)
 - Primary induction failure or relapse
 - Monosomy 5 or 7
 - Age <2 years at diagnosis
 - Treatment-related leukemia
 - Presence of minimal residual disease after initial or subsequent therapy
 - CR2 and beyond, if not previously evaluated

Acute Lymphoblastic Leukemia (ALL)

- Infant at diagnosis
- High Risk CR1 including:
 - Philadelphia chromosome positive
 - WBC >100,000 at diagnosis
 - 11q23 rearrangement
- Mature B-cell phenotype (Burkitt's lymphoma)
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

LYMPHOMAS

Non-Hodgkin Lymphoma

- Follicular
- Poor response to initial treatment
- Initial remission duration <12 months
- First relapse
- Transformation to diffuse large B-cell lymphoma

Diffuse Large B-Cell or High-Grade Lymphoma

- At first or subsequent relapse
- CR1 for patients with high or high-intermediate IPI risk
- No CR with initial treatment
- Second or subsequent remission

Mantle Cell

- After initiation of therapy

Other High Risk Lymphomas

- After initiation of therapy

Hodgkin Lymphoma

- Primary induction failure or relapse
- Second or subsequent remission

Multiple Myeloma

- All patients after initiation of therapy
- At first progression

OTHER MALIGNANT DISEASES

Germ cell tumors

- Short initial remission
- Poor initial response

Myeloproliferative Disorders (including BCR-ABL–negative myeloproliferative neoplasms, myelofibrosis and later stages of polycythemia vera and essential thrombocytosis)

- Intermediate or high-risk disease including:
 - High-risk cytogenetics
 - Poor initial response or at progression

Neuroblastoma

- Short initial remission
- Poor initial response or at progression

NON-MALIGNANT DISORDERS

Immune Deficiency Diseases (including Severe Combined Immunodeficiency syndromes, Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, Kostmann syndrome)

- At diagnosis

Inherited Metabolic Disorders (including Hurler's syndrome, adrenoleukodystrophy, and others)

- At diagnosis

HEMAGLOBINOPATHIES

Transfusion-Dependent Thalassemias

- At diagnosis

Sickle Cell Disease

- With aggressive course (end-organ complications, frequent pain crises)

Hemophagocytic Lymphohistiocytosis (HLH)

- At diagnosis

Severe Aplastic Anemia and other marrow failure syndromes (including Fanconi anemia, Diamond-Blackfan anemia, and others)

- At diagnosis

References

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Chimeric Antigen Receptor T-cell Therapy

Chimeric Antigen Receptor T-cell (CAR-T) therapy is a form of adoptive cell transfer that has shown great promise in the treatment of certain hematologic malignancies most notably pediatric acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma. Clinical studies have shown significant response rates with durable remissions in patients who have been heavily pre-treated (Maude, 2014). CAR-T cell therapy also has a potential role in the treatment of other malignancies for which clinical trials are in less developed stages.

CAR- T therapy using tisagenlecleucel-T (*Kymriah™*, Novartis) has received Food and Drug Administration (FDA) approval for use in pediatric and young adult patients, age 25 years and under with relapsed or refractory ALL.

CAR- T therapy using axicabtagene ciloleucel (*Yescarta™*, Kite Pharma) and tisagenlecleucel-T (*Kymriah*) has received FDA approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, after two or more lines of systemic therapy.

Effective 01/01/2018 prior authorization will be required through Optum Transplant Resource Services for FDA-labeled indications. FACT-accreditation as well as manufacturer certification to administer the agents will be required of programs seeking to provide this treatment for our members. A list of certified transplant programs is available at each manufacturer's website.

Appendix

AIDS-defining Conditions

Certain serious and life-threatening diseases that occur in HIV-positive people are called "AIDS-defining" conditions. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS.

The Centers for Disease Control and Prevention (CDC) has developed a list of these conditions (see below). No single patient is likely to have all of these problems. Some of the conditions are rare.

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus[†]
- Cervical cancer, invasive[§]
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)[†]
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma[†]
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*[†]
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary[†]
- *Mycobacterium tuberculosis* of any site, pulmonary,^{†§} disseminated,[†] or extrapulmonary[†]
- *Mycobacterium*, other species or unidentified species, disseminated[†] or extrapulmonary[†]
- *Pneumocystis jiroveci* pneumonia[†]
- Pneumonia, recurrent^{†§}

Appendix

- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month[†]
- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

[†] Condition that might be diagnosed presumptively.

[§] Only among adults and adolescents aged \geq 13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17]).

Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged 18 Months and for HIV Infection and AIDS Among children Aged 18 Months to <13 Years—United States 2008. Morbidity and Mortality Weekly Report, December 5, 2008/57 (RR-10).

Clinical, Cytogenetic and Mutational Risk Stratification for AML

Favorable risk:

- Cytogenetics
 - t(8;21)
 - inv(16) or t(16;16)
- Mutations
 - Kit

Intermediate risk (one or more of the following)

- Cytogenetics
 - Normal
 - +8
- Mutations
 - Flt3 ITD-positive
 - Mutant TET2, MLL-PTD, DNMT3A, ASXL1, PHF6

Unfavorable (high) risk (one or more of the following):

- Cytogenetics
 - -5/-7
 - 11q23, 20q
 - 3 or more
- Clinical features:
 - CR2 and beyond
 - Age > 70
 - Refractory to induction chemotherapy
 - Persistence of minimal residual disease following induction

Patel JP, Levine RL. How do novel molecular genetic markers influence treatment decisions in acute myeloid leukemia? *Hematology Am Soc Hematol Educ Program*. 2012; 2012:28-34.

The Dynamic International Prognostic Scoring System (DIPSS) for Primary Myelofibrosis (PMF)

The DIPSS for PMF uses five risk factors to predict survival. Values for score calculation are as follows:

Risk Factors	Point Value
Age > 65	1
Hemoglobin level < 10 g/dl	2
White blood cell count (WBC) > 25 x 10 ⁹ /L	1
Peripheral blood blasts ≥ 1%	1
Presence of constitutional symptoms	1

Risk categories: Low (score 0), intermediate-1 (score 1 or 2), intermediate-2 (score 3-4), high (score 5-6).

Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115:1703-1708.

Complete Remission and Partial Remission Highlights from Revised Response Criteria for Malignant Lymphoma (Cheson et al.)

Complete Remission (CR): Disappearance of all evidence of disease.

Nodal masses

- FDG-avid or PET positive prior to therapy: mass of any size permitted if PET negative
- Variably FDG-avid or PET negative: regression to normal size on CT

Spleen, Liver

- Not palpable, nodules disappeared

Bone marrow

- Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

Partial Remission (PR): Regression of measurable disease and no new sites.

Nodal masses

- Greater than 50% decrease in sum of the products of diameters (SPD) of up to 6 largest dominant masses; no increase in size of other nodes
 - FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site
 - Variably FDG-avid or PET negative; regression on CT
- NOTE: In the absence of adequate size measurements one can use a greater than 50% decrease in the Standardized Uptake Value (SUV) to document PR.

Spleen, Liver

- Greater than 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen.

Bone marrow

- Irrelevant if positive prior to therapy; cell type should be specified.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579–86. Available at: <http://jco.ascopubs.org/content/25/5/579.full.pdf+html>.

Hematopoietic Stem Cell Transplant Reference Sheet

The following is a list of rare and unusual conditions where allogeneic transplant may be indicated. The list was reviewed and accepted by the 2018 Optum Hematopoietic Stem Cell Transplant Expert Panel. If there is a condition found on this list that is not included in the "Indications" section above, refer to Medical Director.

1. Lymphocyte Immunodeficiencies (many of these fall under 'severe combined immunodeficiency' classification)

- Adenosine deaminase deficiency
- Artemis deficiency
- Calcium channel deficiency
- Cernunnos-XLF immunodeficiency
- CHARGE syndrome with immune deficiency
- Common gamma chain deficiency
- Deficiencies in CD 45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV
- DOCK8 immunodeficiency syndrome
- GATA2 deficiency
- Interleukin-7 receptor alpha deficiency
- Janus-associated kinase 3 (JAK3) deficiency
- Major histocompatibility class II deficiency
- Purine nucleoside phosphorylase deficiency
- Recombinase-activating gene (RAG) 1/2 deficiency
- Reticular dysgenesis
- Winged helix deficiency
- Zeta-chain-associated protein-70 (ZAP-70) deficiency

2. Phagocytic Deficiencies

- Chediak-Higashi syndrome
- Griscelli syndrome, type 2
- Interferon-gamma receptor deficiencies
- Leukocyte adhesion deficiency
- Shwachman-Diamond syndrome*

*may be considered as marrow failure syndrome rather than immunodeficiency

3. Other Immunodeficiencies

Autoimmune lymphoproliferative syndrome
Cartilage hair hypoplasia
CD25 deficiency
Familial hemophagocytic lymphohistiocytosis
Hyper IgD and IgE syndromes
ICF syndrome IPEX syndrome NEMO deficiency
NF- κ B inhibitor, alpha (I κ B-alpha)

Antoine C, Muller S, Cant A, et al. Long term survival and transplantation of hematopoietic stem cells for immunodeficiencies: report of the European experience 1968-99. *Lancet*. 2003 Feb;361(9357):553-60. PMID: 12598139254.

Burroughs L, Woolfrey A, Shimamura A. Shwachman-Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am*. 2009 Apr;23(2):233-48. PMID: 19327581.

Coppa GV, Gabrielli O, Zampini L, et al. Bone marrow transplantation in Hunter syndrome (mucopolysaccharidosis type II): two-year follow-up of the first Italian patient and review of the literature. *Pediatr Med Chir*. 1995 May-Jun;17(3):227-35. PMID:7567644.

Ehlert K, Roth J, Frosch M, et al. Farber's disease without central nervous system involvement: bone-marrow transplantation provides a promising new approach. *Ann Rheum Dis*. 2006;65(12):1665-6.

Filipovich A. Hematopoietic cell transplantation for correction of primary immunodeficiencies. *Bone Marrow Transplant*. 2008 Aug;42 Suppl 1:S49-S52. PMID: 18724301.

Guffon N, Bertrand Y, Forest I, et al. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. *J Pediatr*. 2009 May;154(5):733-7.

Heese BA. Current strategies in the management of lysosomal storage diseases. *Semin Pediatr Neurol*. 2008 Sep;15(3):119-26. PMID: 18708002.

Myers KC, Davies SM. Hematopoietic stem cell transplantation for bone marrow failure syndromes in children. *Biol Blood Marrow Transplant*. 2009 Mar;15(3):279-92. PMID:19203719.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2006 Apr;117(4 Suppl):S525-53. PMID: 16580469.

Tolar J, Blazar BR, Wagner JE. Concise review: Transplantation of human hematopoietic cells for extracellular matrix protein deficiency in epidermolysis bullosa. *Stem Cells*. 2011 Jun;29(6):900-6. doi: 10.1002/stem.647. Review. PubMed PMID: 21557391.

Appendix

Vellodi A, Young E, Cooper A, et al. Long term follow-up following bone marrow transplantation for Hunter disease. *J Inherit Metab Dis.* 1999 Jun;22(5):638-48.

Vormoor J, Ehlert K, Groll AH, et al. Successful hematopoietic stem cell transplantation in Farber disease. *J Pediatr.* 2004 Jan;144(1):132-4.

Updated Criteria for Diagnosis of Multiple Myeloma (Rajkumar, 2014)

MULTIPLE MYELOMA

DIAGNOSTIC CRITERIA: ALL 3 REQUIRED

- Monoclonal plasma cells in the bone marrow > 10% and/or presence of a biopsy-proven plasmacytoma
- Monoclonal protein present in the serum and/or urine *
- Myeloma-related organ dysfunction (1 or more) **

Traditional CRAB Criteria:

[C] Calcium elevation in the blood S. Calcium >10.5 mg/l or upper limit of normal

[R] Renal insufficiency S. Creatinine > 2 mg/dl

[A] Anemia Hemoglobin < 10 g/dl or 2 g < normal

[B] Lytic bone lesions or osteoporosis *

NOTE: THESE CRITERIA IDENTIFY STAGE IB and STAGES II and III A/B MYELOMA BY DURIE/SALMON STAGE. Stage IA becomes smoldering or indolent myeloma.

* If no monoclonal protein is detected (non-secretory disease), then > 30 % monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

** The revised International Myeloma Working Group (IMWG) criteria will allow, in addition to the classic CRAB features, the following three markers as “myeloma defining events” (MDEs):

- Sixty percent or greater clonal plasma cells on bone marrow examination
- Serum involved/uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved free light chain is at least 100 mg/l (a patient’s “involved” free light chain – either kappa or lambda – is the one that is above the normal reference range; the uninvolved light chain is the one that typically is in, or below, the normal range)
- More than one focal lesion on MRI that is at least 5 mm or greater in size

The presence of at least one of these markers will be considered sufficient for a diagnosis of multiple myeloma, regardless of the presence or absence of symptoms or CRAB features. Each of these markers has been shown in two or more independent studies to be associated with an approximately 80 % or higher risk of developing myeloma-related organ damage within two years.

In addition, the IMWG criteria allow the use of CT and PET-CT for detecting osteolytic bone lesions in order to make the diagnosis of myeloma. In patients with equivocal findings on MRI, CT, and/or PET-CT, the IMWG recommends follow-up imaging. The use of modern imaging methods at diagnosis and follow-up will enable the diagnosis of myeloma to be made before serious bone damage, such as pathologic fractures, can develop.

MGUS: MONOCLONAL GAMMOPATHY of UNDETERMINED SIGNIFICANCE

DIAGNOSTIC CRITERIA: ALL 3 REQUIRED

- Serum monoclonal protein and/or urine monoclonal protein level low*
- Monoclonal bone marrow plasma cells < 10 %
- Normal serum calcium, hemoglobin level and serum creatinine

* Low is defined as:

- Serum IgG < 3.5 g/dl
- Serum IgA < 2.0 g/dl

No bone lesions on full skeletal x-ray survey and/or other imaging if performed

No clinical or laboratory features of amyloidosis or light chain deposition disease

Urine monoclonal kappa or lambda < 1.0 g/24 hours

The definition of MGUS has not changed. However, a new entity termed light chain MGUS has been defined.

SMOLDERING OR INDOLENT MYELOMA

DIAGNOSTIC CRITERIA: ALL 3 REQUIRED

- Monoclonal protein present in the serum and/or urine
- Monoclonal plasma cells present in the bone marrow and/or a tissue biopsy
- Not meeting criteria for MGUS, multiple myeloma, or solitary plasmacytoma of bone

NOTE: THESE CRITERIA IDENTIFY STAGE IA MYELOMA BY DURIE/SALMON STAGE.

The diagnosis of smoldering myeloma will now have an upper limit of 60 % for the percentage of clonal plasma cells in the marrow. Patients considered to have smoldering myeloma should not have any myeloma defining events or amyloidosis.

A new kind of smoldering multiple myeloma, termed light chain smoldering multiple myeloma, has been recently described in a study conducted at the Mayo Clinic, and the specific monoclonal protein level required for this diagnosis has also been added.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15: e538-48.

The following are approved changes incorporated into the revision numbers indicated below.	
Revision	Date, Description of Change, and Name
1.0	07/19/2012: New. Lynn Wetherbee. Approved by Medical Technology Assessment Committee
1.0	08/14/2012: Approved by National Medical Care Management Committee
2.0	10/10/13: Revised and updated. Lynn Wetherbee Approved by Medical Technology Assessment Committee
2.0	10/16/2013: Approved by Complex Medical Conditions Policy Committee
2.0	11/12/13: Approved by the National Medical Care Management Committee
3.0	08/07/2014: Approved by Medical Technology Assessment Committee
3.0	09/09/2014: Approved by National Medical Care Management Committee
4.0	8/25/2015: Revised and updated: Lorraine Staver
4.0	09/03/2015: Approved by Medical Technology Assessment Committee
4.0	10/13/2015: Approved by National Medical Care Management Committee
5.0	08/15/2016: Revised and updated. Transplant Review Guidelines separated into two documents: Hematopoietic Stem Cell Transplantation and Solid Organ Transplantation.
5.0	09/01/2016: Approved by Medical Technology Assessment Committee
5.0	09/13/2016: Approved by National Medical Care Management Committee

Appendix

6.0	6/22/2017: Approved by Optum Policy and Guideline Committee
6.0	07/06/2017: Approved by Medical Technology Assessment Committee
6.0	07/11/2017: Approved by National Medical Care Management Committee
7.0	09/07/2017: New content relevant to CAR-T Therapy approved by Medical Technology Assessment Committee.
7.0	09/12/2017: New content relevant to CAR-T Therapy approved by National Medical Care Management Committee.
7.0	11/1/2017: Updated to reflect FDA-approval of new CAR-T Therapy agent axicabtagene ciloleucel (<i>Yescarta™</i> , Kite Pharma).
8.0	11/13/2017: Corrected CAR-T prior authorization statement on page 7.
9.0	08/02/2018: Approved by Medical Technology Assessment Committee
9.0	09/11/2018: Approved by National Medical Care Management Committee



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