

Hematopoietic Progenitor Cell Transplantation: Background & History

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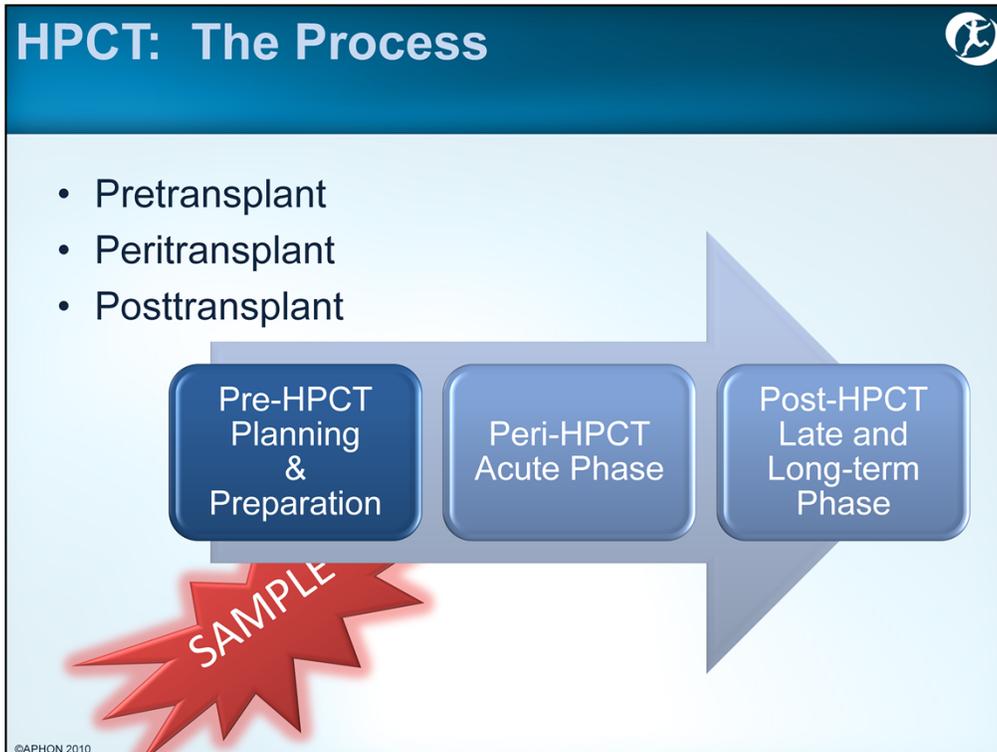
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Hematopoietic progenitor cell transplantation (HPCT) is a rapidly evolving, relatively new field.

Successful human application of HPCT has emerged over the last 40 to 45 years. What once may have been considered a “desperate clinical maneuver” now provides a cure for thousands of patients.

HPCT is a complex process that will have life-long implications for the recipient. To develop an understanding of HPCT concepts, one must be knowledgeable about the immune system and its components. A discussion of HPCT must begin with a definition of the terms and an overview of how far and how fast we have traveled to get to this point.



Autologous, allogeneic, or syngeneic HPCT consists of three phases:

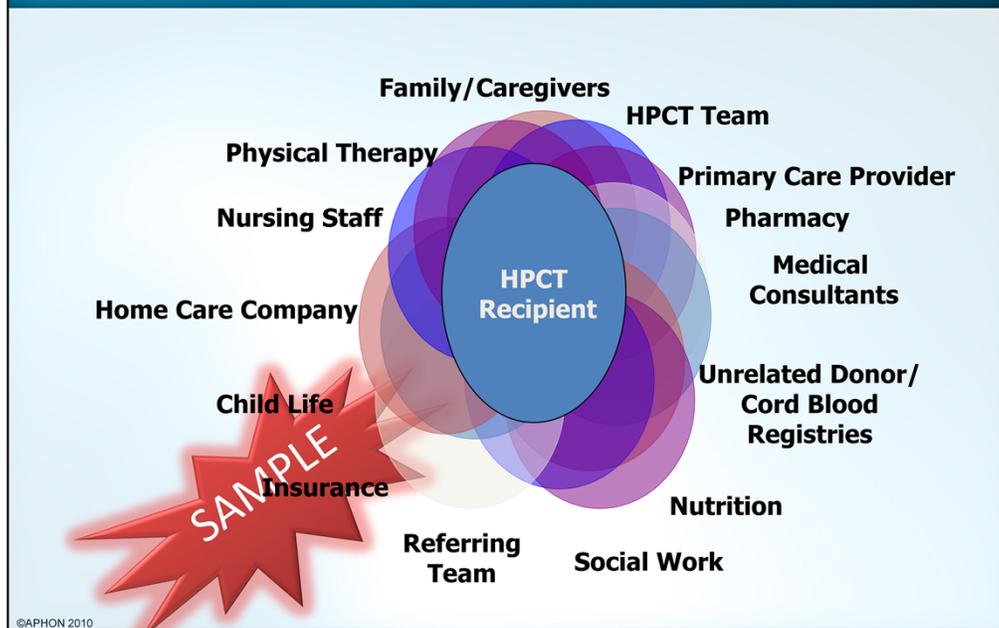
The pretransplant phase is initiated with the identification of the potential HPCT candidate (and donor source in allogeneic HPCT) and concludes when transplant-related therapy is initiated.

The peritransplant phase consists of the chemotherapy and/or radiation given prior to transplant for conditioning or preparation of the recipient and concludes around day +100 posttransplant.

The posttransplant phase begins when there is resolution of the acute toxicities of transplant. Once the recipient has entered this phase, he or she is looking toward late and long-term effects of HPCT and survivorship issues.

(For the purposes of discussion, the acute phase is classified as the peritransplant phase and the posttransplant phase is identified as the long-term period focusing on more chronic issues of HPCT. There is usually not a clear cut demarcation between these two phases.)

HPCT: The Players



The complex nature of HPCT necessitates a collaborative effort on behalf of the HPCT recipient. A transplant requires the effort of a multi-disciplinary team. A tremendous amount of interdisciplinary communication and collaboration required between the team optimizes the care delivered throughout the transplant process.

Hematopoietic Progenitor Cell Transplantation: Human Leukocyte Antigen

Barbara Adler Brecher, MS CHTC

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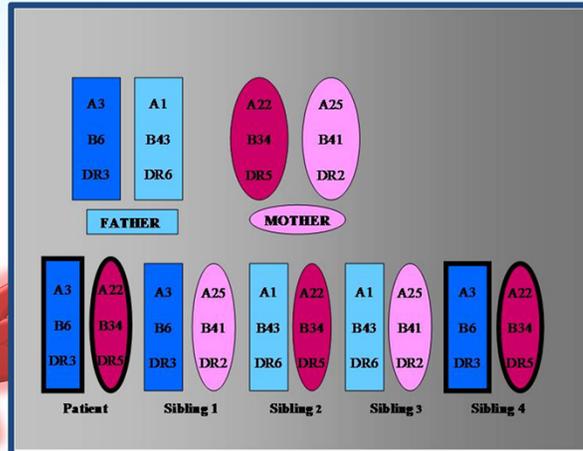


This module will give an overview of the human leukocyte antigen (HLA) system and the effect of HLA on allogeneic hematopoietic progenitor cell transplantation (HPCT).

Understanding HLA: Genotypically Identical Match



- Sibling 4 is an HLA identical match to the patient
- 6/6 HLA match

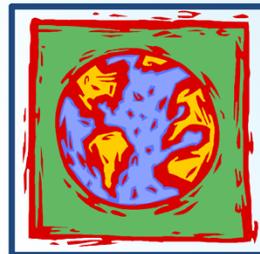


Sibling 4 is a genotypically identical HLA match to the patient. Like the patient, sibling 4 inherited the same haplotypes from each parent. Patient and sibling donor are matched at ABDR and a 6/6 match. Once we have a match at ABDR, we can safely assume that they will match at C and DQ also.

Unrelated Donor



- No sibling donor
 - National Marrow Donor Program (NMDP)
<http://www.marrow.org/>
 - Be the Match <http://www.bethematch.org>
 - Bone Marrow Donors World Wide <http://www.bmdw.org/>
 - International registries
 - NMDP and NMDP-affiliated cord blood banks
 - International cord blood banks
- Computerized databases
- Access donors globally



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For patients who do not have a sibling donor, the next best chance is finding an unrelated donor. Donor registries, such as the NMDP, other international registries, and cord blood banks, are sources of unrelated donor matches. These donor registries have a database of donor HLA typing information. The NMDP and other registries can be queried for potential donors with almost immediate results. The time to HPCT varies depending on the unrelated HPC source.

Hematopoietic Progenitor Cell Transplantation: Education

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Before a patient and family can consent to hematopoietic progenitor cell transplantation (HPCT), they must understand, to the best of their ability, the procedure and its risks and benefits. There is a tremendous amount of information to convey in the pre-HPCT phase. However, education continues throughout the HPCT process and into the future.

Assent: Description of Procedure



- Assent versus consent
- Helps child to achieve a developmentally appropriate awareness of nature of condition
- Tells child what to expect with tests and treatments
- Makes clinical assessment of child's understanding
- Solicits an expression of the willingness to accept proposed care

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Children and adolescents may not have full capacity to make decision in their own best interests. Therefore, children and adolescents are considered a vulnerable population, and they are unable to legally provide informed consent. Because they cannot provide informed consent they are asked to assent to treatment. This is the child or adolescent's agreement to the treatment or agreement to participate in a study. The parents give permission or legal consent for the child to undergo the therapy.

Institutional internal review boards (IRBs) are responsible to determine when assent is required and at what age. The IRB should consider the age, maturity, and psychological state of children involved, as well as the complexity of the study when determining assent. They also determine when assent is not required such as a treatment that is known to benefit the child without significant risks.

A child should be involved in the consent process if applicable as a participant in his or her care. Obtaining assent takes into account the child's understanding and the factors influencing how the child is responding to the proposed HPCT. Should the child refuse, an assessment needs to be made regarding the harm that may come to the child by this decision and proceed accordingly. This will often require the assistance of the institutional ethics committee.

Hematopoietic Progenitor Cell Transplantation: Cellular Collection

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In the last decade, the use of peripheral blood stem cells (PBSC) has become the preferred source of hematopoietic reconstitution post high dose chemotherapy and radiotherapy in the adult transplant candidate.

Stem cells, also known as hematopoietic progenitor cells (HPCs), are immature cells that grow and divide into mature red blood cells, white blood cells, or platelets. HPCs can be collected from the peripheral blood (a PBSC collection), the bone marrow via a bone marrow harvest, or from umbilical cord blood collection.

Although the main means of collection in the pediatric patient is bone marrow harvest, the uniqueness of apheresis in the pediatric population, particularly those < 25kg, can be challenging. The potential limiting factors are venous access, toxicity management, and extracorporeal fluid balance. Other factors which also preclude HPC collection may include the inexperience of the apheresis staff and the normal developmental activities of the child.

This module will discuss the process of HPC collection, bone marrow harvest, and peripheral stem cell apheresis in the pediatric patient.

ABO Incompatible Product Manipulations



Donor	Recipient	Processing
A	O	RBC deplete
A	B	RBC & plasma deplete
A	AB Plasma deplete	AB Plasma deplete
B	O	RBC deplete
B	A	Plasma and RBC deplete
B	AB	Plasma deplete
O	A, B, or AB	Plasma deplete
AB	A, B, or O	RBC deplete
Rh Positive	Rh Neg	RBC deplete
Rh negative	Rh Pos	No manipulation if no ABO incompatibility

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This table reviews the ABO incompatible product manipulations necessary prior to administering the HPC product to the recipient.

Hematopoietic Progenitor Cell Transplantation: Conditioning Regimens

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The *conditioning regimen*, also known as *preparative regimen*, is the treatment administered just prior to the hematopoietic progenitor cell (HPC) infusion. Its purpose is to prepare the body to accept the infused cells. The properties, goals, and agents of the conditioning regimen will be discussed in this module. There are two categories of conditioning regimens: myeloablative and nonmyeloablative, both will be discussed in this module.

HPCT Conditioning Regimens: Myeloablative versus Nonmyeloablative



Variables	Myeloablative	Nonmyeloablative
Chemotherapy	High dose	Lower dose
Cell dose	Standard	High
GHVD prophylaxis	Standard	Reduced
Supportive care	In patient	In- or outpatient
Engraftment	Standard	Delayed
Toxicity	High	Minimal

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This table compares and contrasts the differences between myeloablative and nonmyeloablative conditioning regimens. (Kletzel 2003)

The majority of pediatric BMT procedures are myeloablative in nature. However, research is exploring nonmyeloablative regimens in both malignant and nonmalignant diseases

Chemotherapeutic Agents



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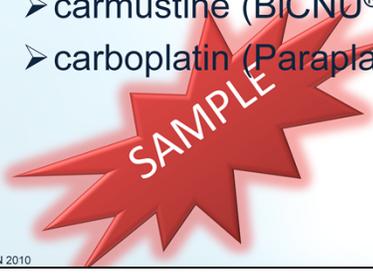
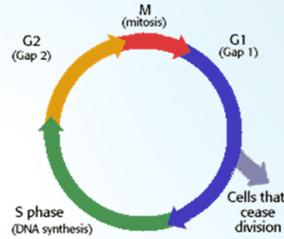
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Preparative Regimens: Alkylators



- Cell cycle-nonspecific agents that work by binding to DNA and preventing DNA replication
 - cyclophosphamide (Cytoxan[®], Neosar[®])
 - busulfan (Myleran[®], Busulfex[®])
 - thiotepa (Thioplex[®])
 - melphalan (Alkeran[®])
 - carmustine (BiCNU[®])
 - carboplatin (Paraplatin[®])



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Chemotherapy remains the backbone of transplant preparative regimens. Some of the most common agents used in the process include alkylating agents. Alkylating agents work by binding to DNA and preventing DNA replication, which in turn prevents cellular replication. These agents work regardless where a cell is in its replication cycle; they are cell cycle nonspecific. Alkylating agents are more effective when given at higher doses; however, significant organ toxicity is experienced at higher doses, including myelosuppression. A HPCT allows higher doses to be administered to patients because destroyed bone marrow cells will be replaced with new graft cells during the transplant procedure. Other organ toxicities (such as liver, kidney, heart, lung, and brain) remain a concern and require prophylactic measure to prevent their occurrence. Judicious monitoring to identify toxicities and prompt interventions will help to alleviate symptoms.

Hematopoietic Progenitor Cell Transplantation: Infusion of Hematopoietic Progenitor Cells

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The infusion of the hematopoietic progenitor cells (HPCs) is similar to a blood component transfusion. This module will address the HPC infusion process including the commonly utilized pre-medications, types of infusions (fresh or frozen), potential side effects, ABO incompatibility, nursing assessment, and education of the patient and family. Foundation for the Accreditation of Cellular Therapy (FACT) has a Circular of Information that is provided for education purposes and is an outline for administration of cellular products.

ABO Incompatible Product Manipulations



DONOR	RECIPIENT	PROCESSING
A	O	RBC deplete
A	B	RBC & plasma deplete
A	AB Plasma deplete	AB Plasma deplete
B	O	RBC deplete
B	A	Plasma and RBC deplete
B	AB	Plasma deplete
O	A, B, or AB	Plasma deplete
AB	A, B, or O	RBC deplete
Rh Positive	Rh Neg	RBC deplete
Rh negative	Rh Pos	No manipulation if no ABO incompatibility

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This table reviews the ABO incompatible product manipulations necessary prior to administering the HPC product to the recipient.

Hematopoietic Progenitor Cell Transplantation: Assessment

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This module will give an overview of the components of assessment that the nurse needs to be knowledgeable of when caring for the pediatric hematopoietic progenitor cell transplant (HPCT) recipient.

Please refer to the acute toxicities modules for further systems approaches to nursing assessment and management. For differential diagnosis, there are also several textbooks in the various reference lists to refer to for further information.

Slides 10 to 27 (HPCT review of systems) may be omitted by instructor if a shorter version of this class is preferred.

Physical Examination: Oral Cavity



- Color
- Swelling
- Ulcers
- Bleeding
- Mucus
- Plaques
- Lip changes
- Gingival integrity
- Hoarseness
- Teeth and teething
- Pain



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The picture shows a nurse assessing an HPCT patient's oral cavity. Listed here are the key factors to assess when looking at the oral cavity. They are:

Color

Swelling

Ulcers

Bleeding

Mucus

Plaques

Lip changes

Gingival integrity

Hoarseness

Teeth and teething

Pain

Hematopoietic Progenitor Cell Transplantation: Nonmalignant Diseases and Disorders

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Allogeneic hematopoietic progenitor cell transplantation (HPCT) can prolong life, improve its quality, and provide the only known cure for a variety of nonmalignant diseases and disorders.

Several of the slides in this module, primarily principles of nonmalignant HPCT (slides 3 to 20), Hurler syndrome, and severe combined immune deficiency (SCID) sections, are provided courtesy of Ann Haight, MD, and are taken or modified from her lecture at the BMT Tandem Meetings in Tampa, Florida, February 2009.

Pediatric Nonmalignant Diseases Amenable to BMT



- **Marrow failure syndromes**
 - Severe aplastic anemia (SAA)
 - Diamond Blackfan anemia (DBA)
 - Fanconi anemia (FA)
 - Dyskeratosis congenita (DC)
- **Hemoglobinopathies**
 - Sickle-cell disease (SCD)
 - Thalassemia
- **Macrophage and granulocyte disorders**
 - Severe congenital neutropenia (Kostmann)
 - Reticular dysgenesis
 - Cartilage, hair hypoplasia
 - Shwachman-Diamond syndrome (SDS)
 - Chronic granulomatous disease (CGD)
 - Leukocyte adhesion deficiency (LAD)
 - Chediak-Higashi syndrome
- **Bone disorders**
 - Osteogenesis imperfecta (OI)
 - Osteopetrosis
- **Histiocytic disorders**
 - Hemophagocytic lymphohistiocytosis (HLH)
 - Langerhans cell histiocytosis (LCH)
- **Immune system disorders**
 - WAS
 - SCID
 - Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX)
 - Autoimmune disorders
 - Juvenile rheumatoid arthritis (JRA)
 - Autoimmune lymphoproliferative syndrome
- **Metabolic storage disorders**
 - Mucopolysaccharidosis (MPS)
 - Leukodystrophies
 - Glycogen disorders

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Within the major categories of nonmalignant diseases, there are several different disorders and syndromes as seen here (presenter may read each category from slide and diseases within each category now). Each category will be discussed throughout this module.

Slide courtesy of Ann Haight, MD

Nonmalignant Disease HPCT: Unique Principles



- **No** malignant disease to be ablated
- **No** graft versus malignancy desired
- **Aggressively avoid** GVHD
- Partial donor chimerism **can** be sufficient
- Need a **tolerant environment** for the new hematopoietic stem cells

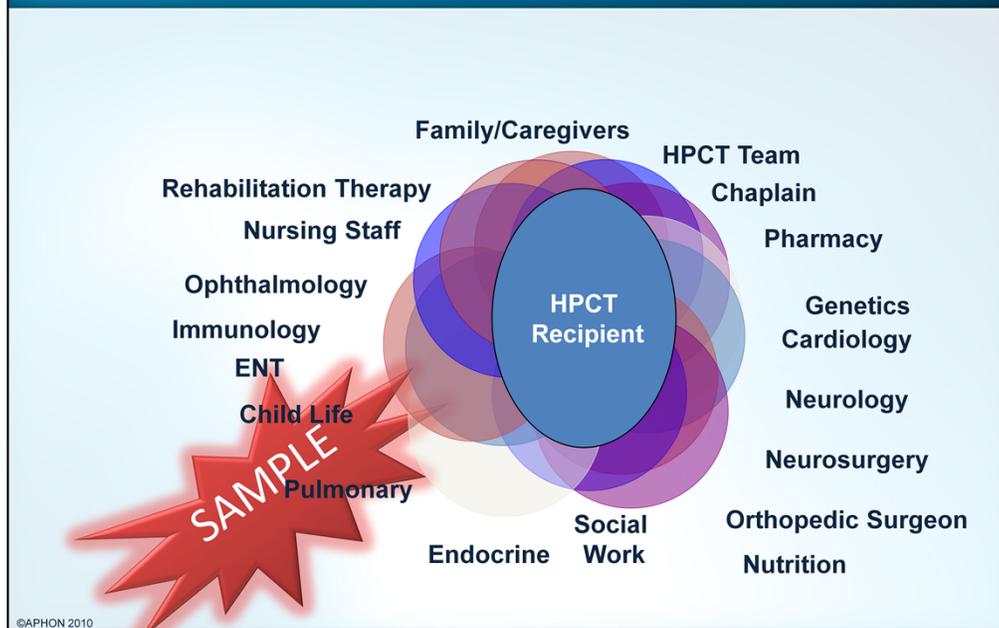


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Goals differ from HPCT for malignancy in that there is no malignant disease to be ablated. There is no advantage to graft versus malignancy. In fact, the goal is to aggressively avoid GVHD. Partial donor chimerism can be sufficient to treat the underlying disorder, and only a tolerant environment for the new hematopoietic stem cells need be established.

Slide courtesy of Ann Haight, MD

Nonmalignant Pediatric Multidisciplinary HPCT Team



The nonmalignant patient undergoing HPCT may have additional needs that require other disciplines to become involved. A patient with a storage disorder may require a cardiologist, endocrinologist, ophthalmologist, orthopedic surgeon, and genetic counselor, as well as the standard HPCT Team. Increased multidisciplinary approach is necessary; the consultants will vary by patient and disease. These HPCT recipients are unique because they do not readily conform to the routine long-term follow-up program profile because they are not cancer patients.

Hematopoietic Progenitor Cell Transplantation: Pharmacology

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The infrastructure of pharmacology is the cornerstone of the hematopoietic progenitor cell transplant (HPCT) process. A broad knowledge of HPCT pharmacology is vital to the clinician. These medications are used throughout the trajectory of HPCT. High-dose chemotherapy is addressed in the conditioning regimen.

This module is divided into sections:

Medication dosing

Fluid calculation

Monitoring (therapeutic drug and systems)

Drug-drug interactions

Drug-induced cytopenias

Supportive care

Therapeutic Drug Monitoring: Antibiotics



Drug	Time of Peak ¹	Peak Range ²	Time of Trough ¹	Trough Range ²
Amikacin	0.5 hour after dose	25-35 mcg/ml	Within 0.5 hour before dose	5-10 mcg/ml
Gentamicin	0.5 hour after dose	5-10 mcg/ml	Within 0.5 hour before dose	< 2 mcg/ml
Tobramycin	0.5 hour after dose	5-10 mcg/ml	Within 0.5 hour before dose	< 2 mcg/ml
Vancomycin	1 hour after dose	20-40 mcg/ml	Within 0.5 hour before dose	10-20 mcg/ml

¹Time of drug level may vary among institutions. Refer to your institution's policies and procedures as well as patient's research protocol.
²Ranges provided are suggested reference ranges only. Actual patient-specific values may fall outside of the range on the basis of clinical condition and tolerability. Consult with the medical team for specific goals when assessing therapy.

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Therapeutic drug monitoring (TDM) is an important aspect in the clinical care of the pediatric HPCT patient. This slide and the next outline peak, trough, and trough ranges. This information assists clinicians with determining the most appropriate medication regimen for a patient while balancing therapeutic efficacy (maintaining levels above a minimum threshold) and toxicity (maintaining levels below a maximum threshold). Assisting with ensuring accuracy of measured values means that it is important that requested levels are drawn at the most appropriate times relative to infusions of scheduled doses. All blood sampling times should be precisely noted in the patient's medical record and/or nursing medication administration record so pharmacokinetic calculations can be performed accurately. In the table above, reference ranges and suggested timing of blood sampling are provided, although specific recommendations for each may vary among institutions and depend on the patient's clinical status.

Levels should be reported to the healthcare team in a timely fashion, especially if they fall out of the therapeutic range. Changes to medications regimens should be made as soon as possible when levels are sub- or suprathereapeutic or when a patient is experiencing an adverse event. On the basis of critical values set by individual institutions, subsequent doses may need to be held until a dose adjustment is made and/or levels fall to within the prescribed therapeutic range.

These medications are just a sampling of many medications used in HPCT; please consult

your institutional guidelines and professionals.

These are the notes for next slide also.

Drug-Induced Pancytopenias



- Agranulocytosis—mechanisms
 - Decreased granulocyte production
 - Immune mechanism



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Many medications used during HPCT can affect bone marrow function and cause various degrees of drug-induced pancytopenias. In addition to chemotherapeutic and biological agents, there are other medications that can produce agranulocytosis (low white blood cell count). Although the exact mechanism of drug-induced agranulocytosis has not been completely elucidated, there are some postulated causes—a decrease in granulocyte production in the bone marrow and an immune-mediated reduction in circulating granulocytes.

Hematopoietic Progenitor Cell Transplantation: Overview of Acute Toxicities

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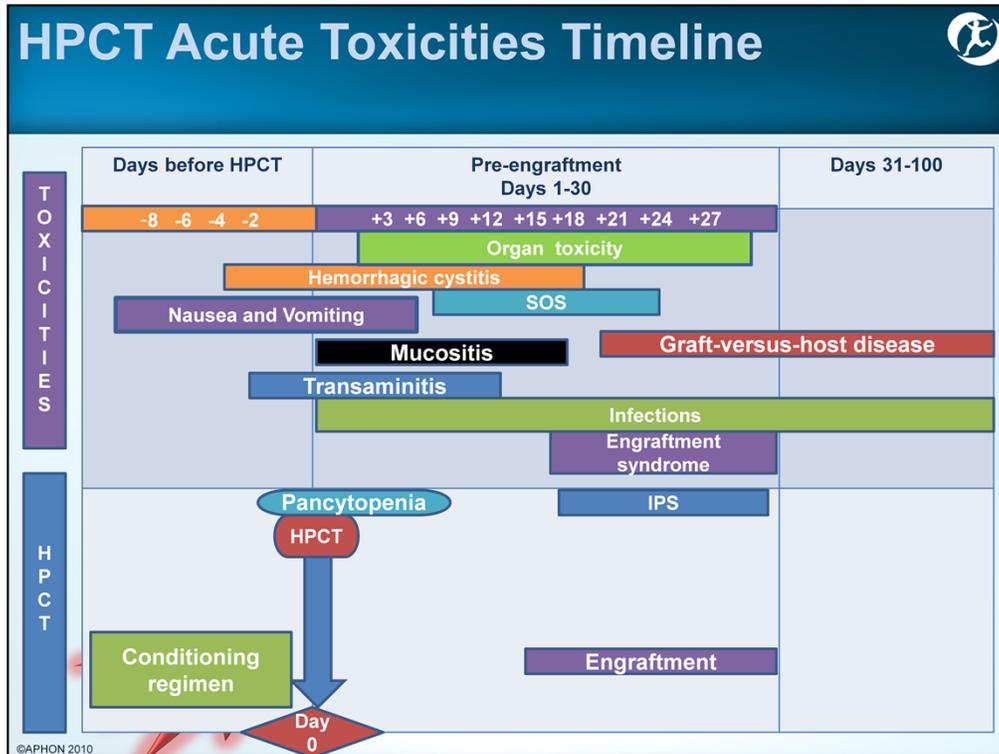


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Hematopoietic progenitor cell transplant (HPCT) is a procedure that carries a wide range of toxicities. Acute complications that are not recognized and treated promptly can lead to significant morbidity and mortality.



There are many toxicities seen during HPCT, and all patients will see some degree of toxicity. There is a well defined group that will experience serious and life-threatening toxicities. This slide represents the acute toxicity timeline showing the possible toxicities and the HPCT timeline. Unfortunately, as depicted in this diagram, no single organ system is affected at a single point in time. Toxicity is happening in multiple systems (gastrointestinal, hepatic, pulmonary, cardiac, neurologic, fluid and electrolyte derangement, and skin) at the same time and overlapping each other.

Nurses who provided professional care to HPCT recipients are challenged with management of acute toxicities and reassuring the patient and family during this intense time. This section of the HPCT core curriculum contains eight modules that review the most common acute toxicities (by system) seen within the first 100 days of HPCT.

The details of infections in relation to the different types of infections is discussed in the infection module.

Acute Toxicities



- Complications occurring < in 100 days post HPCT infusion
- Multifactorial etiology
 - pre-HPCT status
 - Lansky or Karnofsky score
 - infection history
 - Pre-HPCT damage
 - nutritional status
 - disease status
 - remission
 - transplant factors
 - type of HPCT
 - conditioning regimen
 - ▶ traumatic brain injury containing
 - HPC source

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Acute toxicities are those that occur within the first 100 days post stem cell infusion. The etiology of the acute toxicities seen with HPCT are multifactorial based on the recipients' pre-HPCT status, disease status, and transplant factors.

During the pre-HPCT evaluation, which is a time of discovery, all organ systems are assessed. This provides a comprehensive status of function, identifies problems that can be corrected prior to HPCT, or allow the HPCT team to make adjustments in planned therapy. Identifying the recipient's prior infection history, Lansky or Karnofsky performance score, damage from prior therapy in the patient with a malignancy, and determination of nutritional status all can impact the occurrence of acute toxicities. In children with malignancies and certain nonmalignant diseases (e.g., hemophagocytic lymphohistiocytosis) disease status has a major impact in development of acute toxicities. The child in relapse or with progressive disease has an increased incidence of complications. The HPCT factors include the type of transplant (allogeneic or autologous), conditioning regimen (myeloablative or nonmyeloablative), regimen agents (chemotherapy, drugs, total body irradiation, and HPC source [related, unrelated, or umbilical cord]).

Acute toxicities: Nursing Impact



- Demands high level of skill
- Knowledge and expertise is vital
- Ability to connect the dots in respect to symptoms
- Demanding and rewarding, yet stressful
- Success of HPCT is directly related to the skill set of the nursing staff and mid-level providers



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Management of acute toxicities during HPCT has a significant impacts upon the healthcare team, particularly the nurses.

There is a demand for high level of skill and an ability to connect the dots in respect to symptoms. Knowledge and expertise is vital.

Acute toxicity management is demanding and rewarding, yet stressful. Success of HPCT is directly related to the skill set of the nursing staff and the mid-level providers.

Hematopoietic Progenitor Cell Transplantation: Cardiac Toxicities

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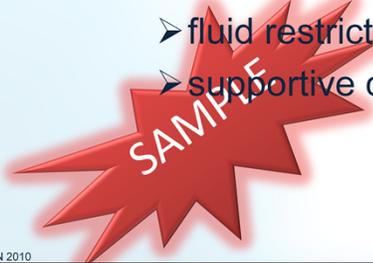


Several factors cause cardiac complications during hematopoietic progenitor cell transplantation (HPCT). Cardiac complications may be related to toxic effects of the conditioning regimen, infections, radiation and, graft-versus-host disease (GVHD). This module will discuss the symptoms and nursing interventions related to cardiac complications during HPCT.

Cardiac Damage: GVHD



- Rare
- Difficult to diagnose
- Cardiology consult
- Impaired function
- Treatment
 - high-dose steroids
 - fluid restriction
 - supportive care



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Cardiac damage from GVHD is rare and difficult to diagnose as symptoms resemble impaired myocardial contractile function.

Therapy is based on increased dosing of steroids, fluid restriction and supportive care. The cGVHD module discusses this toxicity in further detail.

Objectives



- List causes of fluid and electrolyte imbalances during hematopoietic progenitor cell transplantation (HPCT).
- Describe signs and symptoms of fluid and electrolyte imbalances during HPCT.
- Explain nursing assessment and interventions of fluid and electrolyte imbalances during HPCT.



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Fluid and Electrolyte Derangement
Sodium
Potassium
Calcium
Magnesium
Phosphorous
Glucose

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This next segment will detail fluid and electrolyte derangements.

Sodium: Hyponatremia



Cause	Excessive diaphoresis, capillary leak syndrome (CLS) GI losses (suction, vomiting, diarrhea), SIADH, pancreatitis and obstruction
Symptoms	Headache, irritability, fatigue, lethargy, confusion and seizures Abdominal cramps, muscle twitching, spasms and cramps Hypotension, tachycardia Nausea and vomiting
Diagnostics	↓ serum sodium ↓ serum chloride ↓ urine specific gravity ↑ Hct ↑ BUN/ Cr
Treatment	Correct cause Eliminate free water (diuresis, fluid restriction) Administer 3% saline (3-5 ml/kg over 20-60 min) if neurologic symptoms develop

Hyponatremia is decrease in serum Na concentration. It is caused by an excess of water relative to sodium. Common causes include diuretic use, diarrhea, capillary leak syndrome (CLS) and renal disease. Symptoms are primarily neurologic, due to an osmotic shift of water into brain cells causing edema, especially in an acute setting. Presentation includes headache, confusion, and stupor; seizures and coma may occur. Diagnosis is by measuring serum sodium, serum and urine electrolytes and osmolality . Treatment involves restricting water intake and promoting its loss, replacing any sodium deficit, and treating the cause.

Table adapted from: Hazinski, M. F. (Ed.). (2002). Manual of pediatric critical care. St. Louis, MO: Mosby Inc.

www.medscape.com

Hematopoietic Progenitor Cell Transplantation: Gastrointestinal toxicities

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Gastrointestinal (GI) system toxicities are common during hematopoietic progenitor cell transplantation (HPCT). Several factors cause GI complications. Gastrointestinal toxicities during HPCT may be related to toxic effects of conditioning regimen, infections, radiation, and graft-versus-host disease (GVHD). Gastrointestinal toxicities are a major cause of morbidity and death in HPCT patients. This module will discuss the symptoms and nursing interventions related to GI toxicities during HPCT.

aGVHD: Nursing management



- Supportive care
 - dietary restrictions
 - nothing by mouth
 - oral to IV meds
 - prevent infections
 - perirectal care
 - administer
 - immunosuppressive therapy
 - pain control
 - electrolyte supplementation
 - fluid replacement
 - hyperalimentation
 - antimicrobials
 - antispasmodics
 - transfusions
- Obtain stool cultures
- Prepare for diagnostic tests
- Educate the patient and family

Nursing management of aGVHD of the gut is mainly supportive care which includes dietary restrictions (nothing by mouth, oral, or IV meds), prevent infections, perirectal care, administer treatments (immunosuppressive therapy, pain control, electrolyte supplementation, fluid replacement, hyperalimentation, antimicrobials, antispasmodics, transfusions), obtain stool cultures, prepare for diagnostic tests, and educate the patient and family.

www.caridianbct.com/Images/platelets.jpg

Hematopoietic Progenitor Cell Transplantation: Hepatic Toxicities

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Hepatic complications are common during Hematopoietic Progenitor Cell Transplantation (HPCT). Hepatic complications during HPCT may be related to the toxic effects of the conditioning regimen, infections, radiation, and graft versus host disease (GvHD). This advanced module will discuss pathophysiology and hepatic complications diagnosis and management.

Liver Complications



- Morbidity and mortality
- Incidence 80%
- Complications
 - Transaminitis
 - Iron overload
 - Sinusoidal obstruction syndrome (SOS)
formerly known as veno-occlusive disease (SOS)
 - Graft versus host disease (GvHD)
 - Hepatitis
 - Fungal
 - Viral

Because of the liver's significant impact on homeostasis, hepatic complications are a major cause of morbidity and mortality during HPCT. The majority of HPCT patients experience liver dysfunction with variable etiology. The most frequent complications that occur during HPCT are transaminitis, sinusoidal obstruction syndrome (SOS) (formerly known as veno-occlusive disease), graft versus host disease (GvHD), and infectious hepatitis.

Increased Transaminitis: Workup (non GvHD)



- History and physical (H & P)
- Medication review
- Laboratory investigations
 - LFTs
 - Chemistries
 - PT/INR
 - Albumin
 - CBC
 - Hepatitis A, B, & C serologies
 - Iron & total iron-binding capacity (TIBC)
 - Ferritin
- Radiograph investigations
 - Ultrasound
 - CT
 - Magnetic resonance imaging (MRI)

The incidence of elevated transaminases (ALT & AST) occurs frequently during the HPCT process. As outlined in the previous slide, there are numerous reasons for the elevation.

Generally, damage to the liver will cause elevations in the liver enzymes. The diagnosis requires building a diagnosis on numerous pieces of information: Day post HPC infusion, the recipient's history, physical examination, laboratory studies and imaging. Most disease processes cause ALT to rise higher than AST.

This slide depicts the investigations that may be used in workup for transaminitis in a non-GvHD setting. Further diagnostic work up for infectious hepatitis will be discussed later in this module.

Hematopoietic Progenitor Cell Transplantation: Infections

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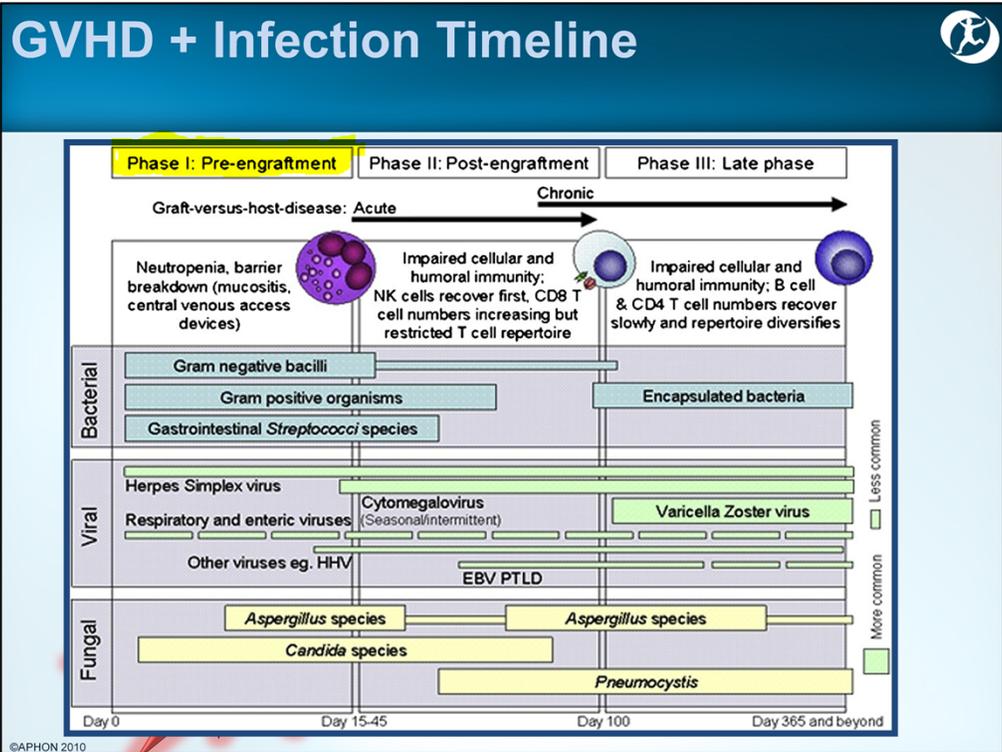


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Infections in the hematopoietic progenitor cell transplantation (HPCT) recipient remain the major cause of mortality. This module will address HPCT infectious complications.



We will discuss phase I (preengraftment) infections.

Tomblyn, M., Chiller, T., Einsele, H., Gress, R., Sepkowitz, K., Storek, J., Wingard, J., Young, J. & Boeckh, M. (2009). Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. *Biol Blood Marrow Transplant* 15: 1143-1238.

Postengraftment: Community Respiratory Viruses



Virus	Location	Clinical Symptoms	Onset
Respiratory syncytial virus	Pulmonary	Fever, dyspnea, hypoxia, rhinorrhea	Seasonal
Influenza A and B	Pulmonary	Fever, dyspnea, hypoxia, rhinorrhea	Seasonal
Parainfluenza (types 1, 2, and 3)	Pulmonary	Fever, dyspnea, hypoxia, rhinorrhea	Seasonal
Adenovirus	Pulmonary, GI, renal	Fever, hemorrhagic cystitis, rash, diarrhea	>30 days to 6 months
Rhinovirus	Pulmonary	Fever, dyspnea, hypoxia, rhinorrhea	Seasonal
Human metapneumovirus	Pulmonary	URI and flu-like symptoms	Seasonal

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This table provides an overview of the major community respiratory viruses: respiratory syncytial virus; influenza A and B; parainfluenza 1, 2, and 3; adenovirus; rhinovirus; and human metapneumovirus. The table further depicts the location of the virus, the clinical symptoms, and onset of each disease.



Ambulatory care of the Hematopoietic Progenitor Cell Transplantation (HPCT) patient and family starts with the initial referral from the primary care physician, the hematologist/oncologist (or patient self referral) and ends with referral back to the primary care physician. Visits to the ambulatory care clinic may be simple, with basic labs being drawn, or complex, with preparative regimens being administered, acute complications managed, or physical and psychosocial issues being addressed.

In many institutions, the patient is no longer admitted to the hospital for medical needs, but is managed as an outpatient in the ambulatory clinic. These challenges in ambulatory management require the HPCT service to incorporate all members of the multidisciplinary team into the HPCT process for positive outcomes.

This module will give an overview of ambulatory management of the pediatric HPCT patient. This module will focus on the unique role of the ambulatory nurse caring for the HPCT patient and family. Please refer to the assessment module for details about assessment and phone triage.

Ambulatory Care Setting: Ideal Components



- Blood bank
- Isolation capabilities
- Extended hours
- Privacy
- Emergency equipment
- Room for private discussion
- Procedure rooms
- Anesthesia coverage
- Interpreter staff
- Easy access to teaching materials
- Infusion space
- State-of-the-art monitoring equipment
- Physician coverage
- Quick laboratory turn-around
- Trained professional nursing staff
- Easy access to consultants
- Affordable housing nearby
- Intravenous (IV) pharmacy

The physical environment of the ambulatory setting is essential to positive outcomes for patient and family care. The ideal ambulatory setting includes the listed components. The ambulatory setting is a unique challenge because of the dynamic nature of the outpatient. Scheduling can be difficult related to unplanned and emergent clinic visits. The nurse, just like the inpatient nurse, must be flexible and prepared for anything.

Hematopoietic Progenitor Cell Transplantation: Acute Graft Versus Host Disease

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Numerous advances have been made in the field of hematopoietic progenitor cell transplantation (HPCT), providing many recipients a cure of disease. Allogeneic transplantation, although it can be a useful treatment modality for numerous diseases and disorders, is not without complications. Graft versus host disease (GVHD), an autoimmune disorder, is one of the most serious transplant-related complications after allogeneic HPCT.

The word *acute* is used to describe GVHD in relation to time. Acute GVHD (aGVHD) usually occurs within the first 100 days after allogeneic transplantation.

aGVHD: Risk Factors



- Human leukocyte antigen (HLA) disparity
- Hematopoietic progenitor cell (HPC) source
- Conditioning regimen
- Graft manipulation
- Donor age
- Sex match
- Viral status
- Infection
- Donor parity

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There are numerous risk factors associated with aGVHD.

The greater the disparity (HLA mismatch) between the recipient and the donor, the more significant the risk of aGVHD. Unrelated donor transplantation is associated with an increased incidence of aGVHD.

Peripheral blood HPC transplants are associated with an increased amount of GVHD. Umbilical cord blood is associated with a decreased incidence of GVHD when compared with traditional marrow transplantation.

The intensity of myeloablation from the conditioning regimen may affect the degree of GVHD.

T-cell depletion (removal or partial removal of the T cells) is associated with less GVHD.

The use of younger donors (younger than 30) is associated with less GVHD.

Sex-mismatched transplants, particularly female to male, have a higher incidence of GVHD.

Cytomegalovirus (CMV) seropositivity of the donor or recipient increases the risk of GVHD in the recipient.

Recipient infection (viral, bacterial, or fungal) escalates the risk of aGVHD. Human herpes virus 6 reactivation correlated with a higher risk for aGVHD II-IV but not CMV reactivation.

There is a suggestion that female donors who have a history of one or more pregnancies put the recipient at greater risk for GVHD as a result of alloimmunization.

Killer Ig-like receptor may lead to or be protective of developing aGVHD.

This is a picture of unrelated donor bone marrow HPCs.

Incidence of aGVHD



- Dependent on many factors
- Matched related donor 30% to 60%
- Matched unrelated donor 50% to 80%
- 30% develop aGVHD Grade III-IV
- Steroid-refractory aGVHD requiring a second-line therapy has a response rate of 30% to 50%, with poor overall survival



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Incidence of aGVHD is dependent on many factors: type of transplant, cell source, the risk factors listed on the previous slide.

The slide results were published in Current Opinion in Pediatrics 2009, 21:30-38 (Auletta and Cooke, 2009).

Hematopoietic Progenitor Cell Transplantation: Graft Versus Host Disease Pharmacology

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Topical Therapy



- Desonide
- Triamcinolone
- Fluocinonide
- Clobetasol
- Tacrolimus
- Pimecrolimus
- Hydrocortisone acetate
- Pramoxine HCL



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There are numerous topical agents available for the treatment of skin GVHD. Many are used in addition to systemic therapy. In some cases when there is a desire for graft-versus-leukemia effect, a transplant treatment may advocate the use of local therapy to avoid systemic therapy.

GVHD: Oral Therapy



Drug/Strength	Frequency	Special Considerations
Tacrolimus 0.1% ointment	Per prescribing guidelines	Area must be dried first, and medication is applied to the affected site; no food or drink for 30 minutes afterward. Ointments (petroleum jelly-based) are generally less effective than gels (alcohol-based) when used orally.
PreviDent 5000® (1.1% sodium fluoride) prescription-strength toothpaste	Per prescribing guidelines	Apply with toothbrush after normal oral hygiene regimen at night. Do not rinse. Do not eat or drink for 30 minutes after use.
Cevimeline 30-mg oral capsules	Per prescribing guidelines	None
Pilocarpine 5-mg tablets	Per prescribing guidelines	None
Cyclosporine 100 mg/ml oral solution	Per prescribing guidelines	No food or drink for 30 minutes afterward.

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Hematopoietic Progenitor Cell Transplantation: Immune Reconstitution

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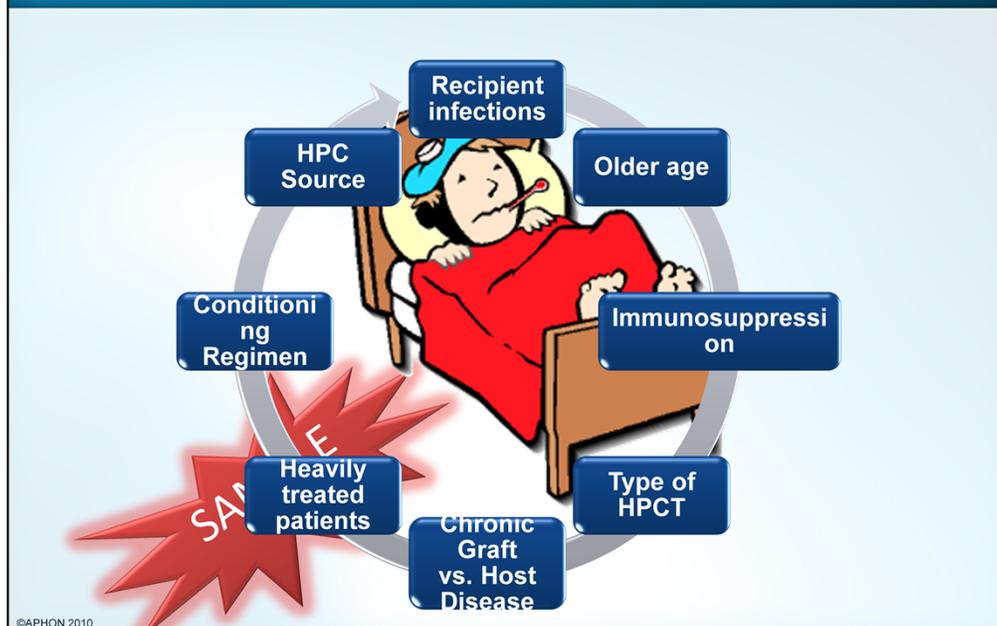
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The issue of post hematopoietic progenitor cell transplantation (HPCT) immune reconstitution is the subject of numerous studies, however much still remains to be learned. A basic knowledge of the immune system and transplantation is needed to understand immune reconstitution. This module will review the immune system and immune reconstitution post-BMT.

Contributing Factors to Immune Reconstitution



There are multiple contributing factors to immune reconstitution.

The HPC source (umbilical cord, bone marrow, or peripheral blood stem cells), HPCT recipient infections (cytomegalovirus, herpes simplex virus, Epstein Barr virus, human herpes virus-6), older age at the time of HPCT, immunosuppression (tacrolimus, cyclosporin, steroids), type of HPCT (autologous, allogeneic [related or unrelated]), the presences of chronic graft versus host disease, heavily treated patients and the conditioning regimen (myeloablative or reduced intensity).

Navigating the Hematopoietic Progenitor Cell Transplant Journey: Identifying Psychosocial Issues and Promoting Coping

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Hematopoietic progenitor cell transplant (HPCT) nurses demonstrate a strong foundation of knowledge and skills in the physical care of patients. Care is enhanced when nurses are well versed in addressing the psychosocial needs of the HPCT patients and their families. The issues faced by children, their adult caregivers, siblings and donors intersect, but each present us with unique challenges. The purpose of this module is to highlight psychosocial issues for HPCT patients and families at different points in treatment, discuss various coping mechanisms, and highlight some of the ways staff can support HPCT patients and families.

Stages in the HPCT Process: Building the Framework



- HPCT as a treatment option
- HPCT consultation
- Evaluation and preparation
- Hospitalization for HPCT
- Adaptation
- Preparation for discharge
- Recovery following hospitalization



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The process of HPCT involves a number of stages, from presenting HPCT as a treatment option to outpatient recovery. When considering the psychosocial issues for HPCT, it is important to recognize that what a particular individual and family faces will depend on a multitude of factors, especially where they are in the HPCT process. Utilizing an analogy of a journey, we will attempt to describe the many psychosocial issues patients and families face.

The stages in the transplant process are transplant as a treatment option, consultation with the HPCT medical team, evaluation and preparation for HPCT, hospital admission (preparative regimen, infusion day, engraftment and recovery), adaptation to hospitalization and acute complications, preparation for discharge, and recovery outside the hospital.



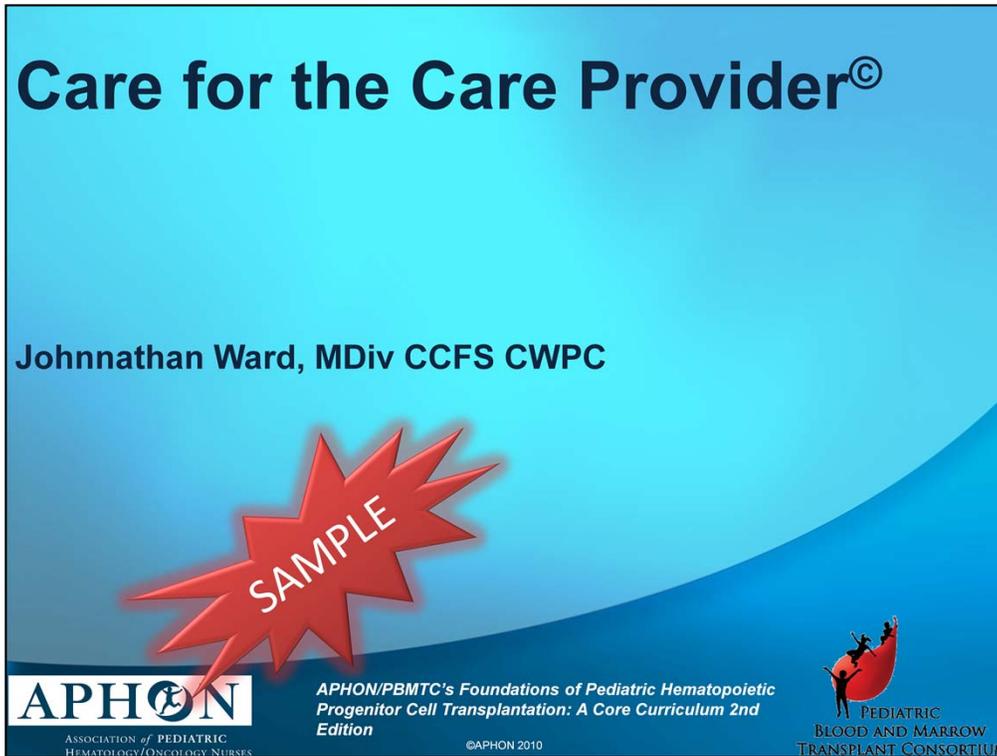
“When faced with little hope, 5% looks pretty good.”

- A Parent



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What inspires a parent to consent to a treatment with potentially fatal complications and no guarantees of success?



Professionals providing care for the hematopoietic progenitor cell transplant (HPCT) patient experience stress due to complex care needs. This module will discuss stress related to caring for pediatric HPCT patients with life-threatening conditions. A case study will be presented.

Caregiver Stress



“Caregiver stress can become dangerous to both the caregiver and the patient”



Wellness Matters 4 Life, LLC

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“Caregiver stress can become dangerous to both the caregiver and the patient”

Discussion question:

How can caregiver stress impact both the caregiver and patient care? (Instructor take some time to discuss this with students).

Possible answers:

unhealthy lifestyle for caregiver

judgment affected

mistakes such as medication errors

This quote was reprinted with permission from the National Brain Tumor Foundation. For more information, contact the National Brain Tumor Foundation at 800-934-2873 or visit www.braintumor.org

Hematopoietic Progenitor Cell Transplantation: Late Complications & Survivorship

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PEDIATRIC
BLOOD AND MARROW
TRANSPLANT CONSORTIUM

Hematopoietic progenitor cell transplant (HPCT) provides curative therapy for pediatric patients with malignancies, immunologic disorders, metabolic disorders and bone marrow failures. An increasing number of these children will survive into adulthood and are at risk for developing late complications.

Survival can come at the cost of late effects of treatment. These complications can be divided in to physical and psychosocial.

Delayed or late complications may be attributed to a combination of the transplant recipient's previous disease and therapy and the conditioning regimen.

Post-HPCT complications in the pediatric population are unique because of the dynamic nature of childhood development. Expectation of problems that may occur is necessary for anticipatory guidance, prevention and early detection and intervention when possible.

This module will review the long-term impact of HPCT on the pediatric patient.

Potential Long-Term Complications



- Chronic graft versus host disease (cGvHD)
- Infection/Immune reconstitution
- Pulmonary
- Endocrine
- Ocular
- Dental
- Cardiac
- Gastrointestinal
- Renal/Genitourinary
- Musculoskeletal
- Neurocognitive
- Skin
- Second malignancy
- Iron overload
- Auditory
- Psychosocial

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All body systems can be affected by HPCT long-term complications. This list is daunting. Each of these areas will be described in more detail throughout the remainder of the module.

We will start with physical complications and then psychosocial complications will be addressed.

The education of patient and families will be inclusive of all aspects of late effects.

Patient & Family Education



- Specific to disease & treatment received
- Inclusive of all possible late effect
- Teach specific markers/tests
- Educate about surveillance required
- Ensure appropriate follow up/transition to adult care
- Ongoing evaluation



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Each patient and family should be educated about the disease he/she had, what treatments they received and all potential side effects of each treatment. This teaching should be inclusive of all late effects even if the patient has not yet had any signs or symptoms. Patient and families should be taught what markers/tests are being evaluated to determine if they have a certain late effect. They should also be taught how often these markers or tests should be done. Follow-up should be given each visit and ongoing evaluation of all potential side effects should be done at each visit. When educating the patient and family about hypothyroidism, the signs and symptoms are reviewed. Because they can be such non-specific symptoms, it is important to remind the patient and family to report their concerns. For patients who demonstrate hypothyroidism, education should also include drug precautions and side effects.

Hypoadrenal: Education regarding cortisol deficiency focuses on the importance of maintaining strict adherence to a steroid taper regimen. Report low energy levels decreased stamina, lethargy, and fasting hypoglycemia. The patient and parent should be alerted to the importance of "stress dosing" of steroids in times of physiological stress. Growth deficiency-repeat measurements over time with consistent measurements/measurers, comparison to peers/siblings.

Gonadal Failure-education about "normal" and when to ask for referrals. Ocular-The nurse needs to review the warning signs for cataracts and remind families that any visual changes in the patient will warrant follow-up. Families also need to be reassured about the lens removal procedure.

Dental-Focus the education of the patient and family on healthy lifestyle behaviors that promote dental health, such as avoiding using tobacco products. Encourage the HPCT recipient to avoid a diet high in concentrated sugars. Reiterate the importance of daily oral care, including the proper use of a toothbrush, flossing and the use of mouthwashes.

Neurocog-The nurse is instrumental in empowering the family to advocate for their child. The patient and family should be encouraged to review test results with the school staff, and seek occupational, physical and speech therapies if warranted. Encourage early intervention programs, tutoring and use of local community resources.

Second mal-Education is based on the HPCT survivors risk of a second malignancy. Patients and families are instructed on the different types of second malignancies and the array of symptoms. GU-Nursing interventions focus on the education of the patient and family regarding GU late effects. The patient and family should include possible GU symptoms. The child with one kidney should avoid contact sports in order to prevent injury to the remaining kidney. The patient should be encouraged not to use NSAIDs due to renal compromise. Education should include the purpose of the medication treating the GU disorder, precautions and side effects. Education of the HPCT recipient regarding contact sports in children with a single kidney. Encourage the patient to report any urinary symptoms and attain prompt diagnosis and treatment. Instruct the HPCT recipient with kidney late effects against the use of non-steroidal anti-inflammatory medications and the use of any prescription or over the counter medications without consulting the health care team. Lastly the HPCT survivor needs reinforcement to continue lifelong compliance and follow up post transplantation.

GI-Nursing interventions focus on the education of the patient and family regarding GI late effects. Education of the HPCT recipient regarding dietary management is dependent on the cause of the GI-long term effects. In HPCT recipients with chronic malabsorption and malnutrition, a diet that is low fat, low residue gluten-free and lactose-free should be encouraged. The patient should be encouraged not to use alcohol and hepatotoxic medications. Education should include purpose of the medication treating the GI or liver disorder, precautions and side effects.

Card-The nurse provides the patient and family with information regarding cardiac complications post-HPCT. Cardiac education includes signs and symptoms of cardiac dysfunction. It also addresses healthy lifestyle behaviors (diet and exercise). The patient should be discouraged from using tobacco, alcohol or recreational drugs. Education should include any pharmacologic agents being used to address cardiac dysfunction. The patient and families need to know the importance of these drugs, the schedule and related side effects.

Pulm- Review the respiratory symptoms that are concerning, such as dyspnea, persistent cough, wheezing, exertional dyspnea, fatigue, cough, and decreased exercise tolerance. Educate the HPCT survivor regarding lifestyle habits that includes avoiding smoking, second hand smoke, recreational drugs, strong odors and chemicals. Reinforce the importance of receiving vaccinations. Some patients who are at risk for significant late pulmonary compromise may be on preventative or supportive medications. The purpose and prescription need to be reviewed in detail. The patient and family need to understand the implications of non-compliance to these medications.

Infection- When discussing the potential for late onset infection, the nurse will discuss the significance of prescribed prophylactic medications. (Example: The patient who is prescribed penicillin for functional asplenia post-HPCT.) The pediatric post-HPCT patient will require re-immunization. Patients and families need to understand that the patient is at risk until they have been re-immunized. Recommending continued good hygiene for infection prevention is a simple, but sometimes overlooked precaution. For adolescents who have undergone HPCT and are reintegrating to a "normal life," it is advisable to discuss safe sex practices for their protection.

Mus/skel-Nursing interventions focus on the education of the patient and family regarding musculoskeletal late effects. Education of the HPCT recipient includes healthy lifestyle behaviors (diet and exercise). The patient should have realistic expectations regarding their ability to participate in activities of daily living (ADL) as well as physical activity and sports. Lastly the HPCT survivor needs reinforcement to continue with lifelong follow-up post transplantation.

Hematopoietic Progenitor Cell Transplantation: Nutrition

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Nutritional complications are common during hematopoietic progenitor cell transplantation (HPCT). Several factors cause nutritional complications. Nutritional complications during HPCT may be related to toxic effects of the underlying disease, prior therapy, conditioning regimen, infections, radiation, and graft-versus-host disease. This module will discuss the symptoms and nursing interventions related to nutritional complications during HPCT.

Nutrition Assessment: Clinical Exam



- Visual or 'eyeball' whether child is under- or overweight
- Mouth
- Energy level
- Gastrointestinal symptoms
- Skin, nail, and hair assessment



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Oftentimes, you have to look at the patient to see if the growth charts really tell the whole story. Patients with more muscle mass may plot overweight in the BMI chart. Some may look thin or with excess body fat even though they plot normal in the chart. Look at the mouth for presence of ulcers or mucositis. Skin, nail, and hair assessments that show alterations of integrity may indicate poor nutrition.

Enteral Nutrition: Problems and Solutions



Problem	Solution
Mucositis	Supportive care Glutamine Palifermin
Gastric paresis	Pharmacological support with metochlopramide
Diarrhea	Infectious cause assessed Lomotil or Immodium
GVHD	Dependent on target organ Biopsy obtained Diagnosis made Treatment started
Nausea and vomiting	Major issue Pharmaceutical intervention Taper off anti-emetics Psychological support
Calorie intake	Determine calorie intake How to get there Half strength → full strength

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Achieving success in EN is not always easy; patients have complications. The most common problems and solutions are listed in this table.

- Mucositis:** The use of aggressive supportive care is essential. Many centers have adopted the use of glutamine or palifermin in mucositis prophylaxis.
 - Gastric paresis:** This process occurs in a substantial group of HPCT patients, particularly those with a total body irradiation containing conditioning regimen; the use of metochlopramide is beneficial.
 - Diarrhea:** This is a common issue during HPCT. The etiology of the diarrhea must be identified, and if infectious, treated accordingly. If a noninfectious etiology either lomotil or immodium can be used. Both drugs can be used in conjunction with metochlopramide, as their action is on different parts of the GI tract.
 - GVHD:** The impact of GVHD is dependent on the involved target organ. The patient will most likely need a biopsy for diagnosis. Once therapy is started and symptoms are diminishing, EN can be resumed.
 - Nausea and vomiting:** This is a major issue, as children and parents are worried about “throwing up the tube.” Pharmaceutical intervention is vital, and continuous administration of antiemetics is of great benefit in the success of EN. Subsequent tapering of the antiemetics until discontinued is helpful. Psychological support from child life and distraction therapies with art and music therapy work well.
- Calorie intake:** Once the proper amount of calories is determined, the methodology of how to ascertain the goal can be achieved by increasing increments every 2-3 hours, starting at half strength and advancing the concentration of the feed are helpful.