Fundamentals of haematopoetic stem cell transplantation

Key concepts

- Haematological and immunological principles of haematopoietic stem cell transplantation (HSCT).
- Donor histocompatibility.
- Types of HSCT.
- Diseases treatable by HSCT.
- Experience and impact of HSCT on various health domains.
- Prevention, detection, and management of common short and long term health alterations experienced by people undergoing HSCT.
- Acute and chronic graft-versus-host disease.
- Supportive care.
- Psychosocial impact on the individual and family.
- Ethical considerations.

Assumed knowledge and related information

- EdCaN module: The Biology of Cancer

Objectives

On completion of this supporting resource, you should be able to:

1. Discuss haematological and immunological principles of HSCT.
2. Explain the role of HSCT in the treatment of cancer.
3. Outline the various methods of HSCT.
4. Discuss the experience and impact of HSCT on the various domains of health.
5. Implement interventions to prevent, detect and manage common health alterations experienced by people undergoing HSCT.

Learning activities

At times, you will have learning activities to complete. Click on the learning activities button and a list of questions will pop up. The questions will relate to the content you've just read or the video you've just watched.

Resource links

Resource links are included throughout the resource. These links lead to interesting articles or websites, and are designed to encourage you to explore other available resources.

PDF of EdCaN module: Fundamentals of haematopoietic stem cell transplantation
You can download a PDF version of the module.

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Principles of transplantation

Haematopoietic stem cell transplantation in Australia

Since the first attempt at bone marrow transplantation in 1939, the procedure has become an accepted treatment for various haematologic deficiencies and malignant conditions. In 2014, 1901 transplants were performed in Australia and New Zealand, an increase of almost 4% over the previous year.17

In 2014, 1645 transplants were carried out at 40 hospitals in Australia:[2]

- 262 allogeneic - related donor
- 309 allogeneic - unrelated donor
- 1004 autologous single
- 34 autologous staged (two or more planned autologous infusions - counted as one transplant)
- greater proportion of male recipients – 60%
- 36% of recipients aged 60 and over.

The role of HSCT in cancer control

Haematopoietic stem cell transplantation (HSCT) has evolved over the past 20 years from experimental to first line therapy for many malignant and non-malignant diseases.[3]

In non-malignant diseases the role of transplantation is to replace defective marrow.

In malignant diseases, stem cell infusions rescue the marrow following disease-eradicating myelosuppressive therapy.

Due to advances in transplantation, long term experience, and ongoing clinical trials, recipient eligibility for transplant continues to expand. The list of indications for which transplant may be a standard treatment option continues to develop.[4] The three types of HSCT include allogeneic, autologous, and syngeneic.

Autologous transplants

Cells for autologous transplants are collected from the bone marrow or blood of an individual with the cancer is in remission or a state of minimal residual disease. The cryopreserved haematopoietic stem cells are reinfused to reconstitute the immune system.[5]

In Australia in 2014, the most common indications for autologous transplants in recipients aged over 16 years included:[17]

- multiple myeloma – 53.4%
- non-Hodgkin's lymphoma – 29.2%
- Hodgkin lymphoma – 5.2%.

The most common indications for autologous transplantation in recipients aged 0-15 in 2014 were:[17]

- neuroblastoma
- medulloblastoma
- primitive neuro-ectodermal tumour.

Allogeneic transplants

In allogeneic transplantation, the HSCs are obtained from a human leukocyte antigen-matched sibling, an unrelated volunteer donor, or cryopreserved umbilical cord blood. Improved understanding of the bone marrow microenvironment and chimerism has enabled the use of newer processes, such as non-myeloablative haematopoietic stem cell transplantation (NMHSCT).[6] Allogeneic transplants also lend an immune modulation effect on the individual with graft-versus-tumour effects.[7]

In Australia in 2014,the most common indications for allogeneic related donor transplants in recipients aged over 16 years included:[17]

- acute myeloid leukaemia – 40.6%

- acute lymphoblastic leukaemia – 12.9%
- non-Hodgkin's lymphoma – 8%
- myelodysplasia – 14.2%.

Similar indications were reported for allogeneic unrelated donor transplants aged over 16 years.[17]

In recipients aged 0-15 years, the most common indications for related and unrelated allogeneic transplantation in Australia in 2014 were:[17]

- acute lymphoblastic leukaemia
- acute myeloid leukaemia.

Syngeneic transplants

The source of the graft in syngeneic transplantation is an identical twin.[5]

Learning activity	
Completed ☐	1. Access the NCCN Practice Guidelines in Oncology (a free resource, but you must register and then click 'Remember me' to bypass the login page in future) and/or key Australian evidence based guidelines, and discuss recommendations regarding the role of HSCT in the management of: • multiple myeloma • acute myeloid leukaemia • chronic myelogenous leukaemia • myelodysplastic syndromes.

Haematopoiesis

In the multifaceted, multistep process of haematopoiesis, human blood cells are produced, regulated and maintained. Homeostasis is the balance between cellular growth and death, including human blood cells. Apoptosis is the mechanism by which homeostasis is achieved.[6]

Organs involved in formation of blood include the bone marrow, spleen, and liver. Haematopoiesis occurs in the flat bones, including the sternum, ribs, skull, pelvis, shoulders, vertebrae, and innominates.[6]

Central to the process of haematopoiesis is the pluripotent stem cell from which all variants of human cells initiate.[6] The earliest identifiable stem cell is called a colony-forming unit-blast cell (CFU-blast). It is capable of multilineage differentiation, as well as self-replication.[6] It is identified with a CD34 (luster of differentiation) marker.[5]

Cells that support immune function arise from pluripotent stem cells. Cells that have matured through the normal stages of haematopoiesis have specific functions involving infection control, oxygenation, coagulation, and haemostasis.[6]

Learning activities	
Completed	
☐	1. Access a current text and differentiate between the primitive cell lines progenitor cells and precursor cells.
☐	2. Outline the roles of the bone marrow, spleen, and liver in haematopoiesis.
☐	3. Access a current text and identify the normal cell count, lifespan, and function of the following blood cells: • Neutrophil • Eosinophil • Basophil • Monocyte / Macrophage • B lymphocyte • T lymphocyte • Erythrocyte • Thrombocyte.
☐	4. Access a current text and discuss the effects of the following on the marrow microenvironment, and the implications of these factors on the process of HSCT: • Ageing • Antineoplastic agents • Radiotherapy.

Transplant immunology

An individual's immunity protects their body against foreign substances. The immune system consists of nonspecific (natural) and specific (acquired) immunity, which interact with each other and have overlapping functions. The clinical implications of transplant immunology are apparent in the areas of human leukocyte antigen testing, immune modulation, immune reconstitution, donor selection, and the choices of source of stem cells.[6]

Human leukocyte antigen (HLA) typing

Donor tissue typing is based on human leukocyte antigen (HLA) typing, also called the major histocompatibility complex (MHC). There are Class I and Class II HLA / MHC located on human chromosome 6. Class I major antigens include A, B, and C. Class II includes DR, DQ, and DP.

HLA typing is generally performed through a search of 10 alleles - HLA A, B, C, DR, and DQ. Debate remains regarding the significance of other minor Class I antigens and HLA DP.[8]

Immune reconstitution

Conditioning regimens prior to HSCT alter an individual's immunity for months to several years post transplantation.[6]

In a recipient of an allogeneic HSCT, the establishment of the donor's immune system may provide a therapeutic graft-versus-tumour (GVT) effect. Negatively, it may also cause graft-versus-host disease (GVHD) and prolonged immune dysfunction.[9]

Natural killer (NK) cells and dendritic cells play an important role in activating T cells involved in GVT effect and graft-versus-host disease (GVHD).[8]

Learning activities	
Completed	Access a current text and the following resource • Emerging immunology of stem cell transplantation[8]
☐	1. Describe the roles of the body's nonspecific immune defenses: • Skin and mucous membrane defenses • Inflammatory response and phagocytosis • Interferons.
☐	2. Describe the components of and the roles of the body's specific immune defenses: • Humoral (antibody-mediated) immunity • Cell-mediated immunity.
☐	3. Summarise the implications of the body's nonspecific and specific immunity for HSCT.
☐	4. Summarise the role of cluster differentiation (CD) antigens and outline their role in HSCT.

☐	5. Outline the proposed role and function of dendritic cells and natural killer cells.
☐	6. Explain why there is a 25% chance that two siblings will be HLA-identical.
☐	7. Access the Australian Bone Marrow Donor Registry website and: • Outline the information and support a Specialist Cancer Nurse may provide to an individual newly diagnosed with acute leukaemia, and their family, about the process of identifying a histocompatible family member • Identify the services and support personnel who may help a family at this time, and outline their roles.

Sources of haematopoietic stem cells

The three options for HSCT include use of bone marrow (BM), peripheral blood stem cells (PBSC), and cord blood (CB). The biology of the graft and the immunological effects differ between the sources of stem cells.[8]

Bone marrow (BM)

- the first source of stem cells[8]
- harvested from the iliac crests of a donor under general anaesthetic[8]
- in Australia in 2012:[2]
    - bone marrow was the cell source for 14.16% (78/551) of allogeneic / syngeneic transplants
    - bone marrow was the source for <1% (1/1016) of autologous transplants.

Peripheral blood stem cells (PBSC)

- offers advantages over BM in collection procedure:[8]
    - no anaesthesia
    - less invasive procedure
    - no hospitalisation
- more chronic GVHD (cGVHD) after PBSC use with unrelated donor transplants for leukaemia[8]
- survival advantage with PBSC vs. BM[8]
- in Australia in 2012:[2]
    - peripheral blood was the cell source for 73.1% (403/551) of allogeneic / syngeneic transplants
    - peripheral blood was the source for >99% (1015/1016) of autologous transplants.

Cord blood (CB)

- increasing use in the last decade
- advantages include:[6, 8]
    - no apparent risk to donors
    - no prolonged screening process
    - immunologically immature T cells allow for cord blood to be transplanted in mismatched donors without the significant risk of GVHD.
- Disadvantages include:[6, 8]
    - prolonged immune reconstitution
    - low cell dose
    - potential for less GVT
    - limited long term data
    - multiple ethical, legal, and financial considerations remain.

In Australia in 2012:[2]

- cord blood was the cell source for 6.7% (37/551) of allogeneic / syngeneic transplants
- double cord blood was the cell source for 5.3% (29/551) of allogeneic / syngeneic transplants

- of the allogeneic cord blood transplants, 39 were in recipients aged 0-15 and 25 were in recipients aged over 16.

Learning activities	
Completed	
☐	1. Discuss circumstances where BM may be used rather than PBSC.
☐	2. Outline the components of an education session, including preparation, details of the procedure, and potential risks / effects for a donor undergoing: • PBSC collection • BM collection.
☐	3. Review the medical notes of a recipient of an autologous PBSC transplant, and: • Outline significant points in their treatment trajectory • Discuss how PBSC collection process differs in the context of autologous and allogeneic transplants.
☐	4. Access the ABMDR Cord Blood Information website, and summarise the key points to provide information to a person affected by cancer, and/or their relatives.

Donor considerations

Donor selection

Choice of donor depends on disease, histocompatibility, availability, informed consent, and medical competence.[10] Less than 30% of individuals have an HLA-identical sibling. In these circumstances, alternative donors, such as phenotypically matched, unrelated volunteers and partially matched family members, are considered.[9]

Ethnicity

Approximately 75% of Caucasian individuals can locate a suitable matched volunteer donor. Minor ethnic groups have lower rates of success. Such matched unrelated donors (MUD) are associated with significant complications, such as GVHD and prolonged and profound immunodeficiency.[9]

Physical factors

Other factors considered after HLA typing are donor characteristics such as:[8, 11]

- gender
- weight
- number of pregnancies
- overall health
- age
- Cytomegalovirus (CMV) negative serology (for CMV-negative recipients)
- ABO compatibility
- matched race.

Favourable donor characteristics are male gender, younger age, good size, and good health.[8]

Other considerations

In addition to assessment of the donor's physical suitability, the impact of the stem cell collection or harvest on the individual's lifestyle, and the relationship with the recipient should also be discussed. Unrelated donors also receive counselling prior to donation. A social worker may be involved to deal with stress and anxiety.[12]

Learning activities	
Completed ☐	1. Access a current text and National Marrow Donor Program HLA matching guidelines for unrelated adult donor hematopoietic cell transplants[11] , and describe the reported potential implications of the following donor characteristics: • Aged over 60 • Obesity (BMI greater than 30) • Female with a history of three pregnancies.

☐	2. Outline possible psychosocial issues that may impact on donors of haematopoietic stem cells: • Identify screening and assessment process to identify potential Issues • Discuss the concept of 'survivor's guilt' and how it may manifest • Discuss interventions to prevent and manage 'survivor's guilt'.
☐	3. Discuss why ethnic groups have lower rates of success in locating a fully matched donor when compared with Caucasians.

Recipient considerations

During the transplant evaluation process, potential recipients undergo physical and psychological assessments to determine eligibility for transplantation.[7] The transplant physician considers the individual's disease, risk factors, and reported survival data to determine appropriate disease management.

Factors that improve outcomes

Refinements in criteria for performing HSCTs have improved outcomes. Both disease and individual factors have been recognised as significant in minimising the risk of failure from toxicity and improving control of underlying disease.[13].

Disease factors associated with improved outcomes include:[13]:

- transplantation in individuals with chemotherapy-induced remission
- transplantation earlier in the course of the disease.

Australian ten-year survival probability data reinforce this. Recipients aged over 16 who received their first allogeneic related transplant in their first remission have a survival probability of 56%. Recipients with poor risk have a survival probability of 29%.[2]

Factors that increase risk

Individual factors that increase the risk associated with HSCT include:[13]

- advanced age of the individual
- significantly impaired ventilatory function
- abnormal hepatic function
- abnormal renal function
- presence of an active infection.

Potential autologous transplant recipients should have limited exposure to myelotoxic agents to avoid compromising stem-cell reserve prior to stem cell harvest.[14]

Learning activities	
Completed	
☐	1. Access current clinical guidelines and summarise components of the recipient evaluation.
☐	2. Access an individual's health record and describe the evaluation they underwent prior to transplantation.

Bone marrow registries

The major goal of an unrelated donor registry is to create a file of well-informed and well-selected volunteers, with the greatest likelihood of being suitable donors if chosen to donate. Deficiencies in this process may lead to a loss of time and money, impact quality and safety, and may impact on an individual's chances to receive a transplant.[12]

The World Marrow Donor Association (WMDA) has developed recommendations and eligibility criteria for the evaluation of volunteer donor health at recruitment and during later donor selection procedures. These recommendations promote international best practice in this area.[12, 15]

The recommendations include:

- sample screening questionnaire
- conditions leading to permanent deferral
- infectious diseases requiring a deferral period
- considerations associated with specific sexual partners
- conditions leading to temporary deferral
- prophylactic immunisations
- conditions requiring individual assessment.

The Australian Bone Marrow Donor Registry (ABMDR) is the organisation responsible for the recruitment of volunteer bone marrow/blood stem cell donors and the administrative management of the National Cord Blood Collection Network of public cord blood banks in Australia. Within Australia the registry network is comprised of:[16]

- Australian Red Cross Blood Service bone marrow donor centres
- Tissue typing laboratories
- Transplant centers
- Collection and apheresis centres
- AusCord cord blood banks.

The Australian Bone Marrow Transplant Recipient Registry (ABMTRR) records details of HSC transplants throughout Australasia. Transplant recipients are followed up annually for incidence of relapse, other major malignancy events, and death up until ten years post-transplant.[17]

Learning activities	
Completed	
☐	1. Access and read the ABMDR donor brochure.[18] Reflect on your feelings for or against becoming registered as a donor.
☐	2. Access the ABMDR Searching for a donor webpage, and • identify individuals in your facility who facilitate the donor search process • develop a summary of the unrelated donor search process for a recipient in your facility.
☐	3. Access Haematopoietic stem cell donor registries: World Marrow Donor Association recommendations for evaluation of donor health[12] and the updated WMDA Donor Medical Suitability Recommendations.

	Discuss how international agreements with the WMDA recommendations can lead to practice improvement internationally.

Ethical issues in HSCT

The Specialist Cancer Nurse (SCN) caring for individuals undergoing HSCT may experience a number of ethical issues in their roles as carer and advocate.

Eligibility for transplantation

The bioethical principle of benefit-burden states 'only medical treatments that provide more benefit than burden are ethically mandated'.[19] This concept may challenge a clinician's principles when individuals are offered HSCT as their only chance at cure or significant disease control.

Variables that may influence decision making and challenge ethical principles include an individual's age, toxicities, and treatment cost. Increased numbers of older individuals are undergoing HSCT with the advent of non-myeloablative transplants. Although there may be reduced toxicity associated with the conditioning, co-morbid conditions in the older person can make management equally complex.[19]

Issues related to religious or cultural beliefs need to be addressed prior to HSCT. For Jehovah's Witnesses, for example, non-acceptance of blood products may make HSCT an unacceptable treatment option and raise significant challenges to an individual's treatment journey.[19]

Informed consent

Where only one treatment alternative exists for a potential cure, such as HSCT, it has been proposed that a person's self-determination is constrained. This situation has implications when obtaining informed consent for recipients of HSCT.[19]

Veracity or telling the truth about the treatment and prognosis has been identified as a potential issue of concern in the process of informed consent. It may be a challenge for the health professional to ensure the recipient's wishes or interests are met and protected. Collaborative decision making has been identified as a means to overcome some of the challenges associated with informed consent in the HSCT setting.[19]

Donor issues

There is an ethical responsibility to inform the donor of the risks associated with donation of stem cells. Special considerations may be required when the donor is a child or minor. In the case of unrelated donors, strict guidelines are in place to protect the donor's and recipient's rights and confidentiality.[19]

Learning activities	
Completed ☐	1. Access SCT in Jehovah's Witnesses: the bloodless transplant[20] and: • Outline the challenges associated with managing treatment for a Jehovah's Witness

☐	• Discuss strategies to manage these challenges. 2. Access When parents refuse a sick teenager the right to give informed consent: the nurse's role[21] and The basis of informed consent for BMT patients[22], and: • Summarise the potential challenges to ensure informed consent for recipients of HSCT • Reflect on your own practice and describe a situation where the process of informed consent was challenging • Discuss how this situation was resolved or how it could have been improved.

Service delivery in HSCT

Innovative care delivery models have increased the use of ambulatory care services. A transplant program, however, requires inpatient care delivery to support intensive assessment and care requirements of the person undergoing HSCT.[23]

Guidelines and standards have been developed outlining the minimum requirements for:[24]

- facility resources
- required health professionals and service providers
- preparation of health professionals
- clinical services
- support services.

International standards have been developed by the Joint Accreditation Committee - International Society for Cellular Therapy (ISCT) and European Group for Blood and Marrow Transplantation (EBMT).[24]

JACIE[24] is a non-profit body established in 1998 for the purposes of assessment and accreditation in the field of HSCT. JACIE's primary aim is to promote high quality care and laboratory performance in haematopoietic stem cell collection, processing, and transplantation centres through an internationally recognised system of accreditation.[24]

The JACIE standards:[24]

- define the infrastructure required for all phases of the safe collection, processing, and administration of haematopoietic cells.
- require an ongoing assessment of these activities.
- do not prescribe the use of these therapies.
- require all clinical, collection, and processing facilities to evaluate and report clinical outcomes.

These Standards are based on the standards of the Foundation for the Accreditation of Cellular Therapy (FACT). The Standards extend and detail the pre-existing standards of the EBMT. Facilities have to meet certain minimum criteria detailed in the Standards to obtain accreditation, either for the entire program or just the portion that applies to the organisation.[24]

Other national and international organisations that promote best practice in HSCT through research, clinical standards and guidelines, regulation, and accreditation include:

- American Society for Blood and Marrow Transplantation[25]
- Australian Bone Marrow Donor Registry[26]
- Therapeutic Goods Administration[27]
- Australian and New Zealand Society of Blood Transfusion Specialists (ANZSBT)[28].

Learning activities	
Completed ☐	1. Access the FACT-JACIE International Standards for cellular therapy product collection, processing, and administration, and:

	• Summarise the recommendations for nurses working in HSCT units • Identify the minimum recommended policies and procedures required at your facility • Identify the Standard Operating Procedures manual in your facility.
☐	2. Identify the following health professionals and describe their role and function in the HSCT team: • Haematologists • Transplant coordinator • Registered nurses • Dietitian • Social worker • Pharmacist • Scientists (clinical laboratory staff).
☐	3. Identify the services that support a person to remain in the community post-transplant.

The transplant process

Pre-transplant workup

The role of the SCN in the pre-transplant period includes:[19]

- validating the individual's understanding of the plan and goal of care
- assisting the individual to formulate questions and giving additional information concerning the long term consequences of the planned therapy
- providing a detailed explanation of what the recipient may expect, including care requirements
- outlining the role of the carer and the commitment required.

Baseline assessment

A complete baseline nursing assessment is required prior to initiation of the conditioning regimen. Assessment is also needed at regular intervals throughout the transplant journey.

The SCN may identify risk factors that could trigger or exacerbate effects of the transplant. These may include:[29]

- previous treatment history
- responses to previous treatment
- perception of uncertainty and coping styles
- strategies for managing treatment effects.

Recipient and carer education

Prior to admission it is essential that recipients of HSCT and their carers receive thorough and individualised education. A number of existing resources are available online to people affected by cancer, providing information on the transplant procedure.

- Leukaemia Foundation website
- American Cancer Society patient information

Learning activities	
Completed ☐ ☐ ☐	1. Describe the assessment and education that the recipient receives in the pre-transplant period in your health care facility. 2. Outline the role and responsibilities of a carer that would be discussed with a recipient and their carer prior to transplantation. 3. Outline the evidence based information and education provided to a recipient and their carer regarding the following issues prior to admission: • Dietary restrictions • Visitor guidelines • Neutropaenic precautions • Bleeding precautions.

Harvesting and storage of stem cells

Bone marrow

Bone marrow is generally harvested from the posterior iliac crest, as either an inpatient or outpatient procedure. Marrow may also be aspirated from the anterior iliac crests and sternum if required. The amount required to achieve haematopoiesis is 10-15ml/kg of recipient body weight.[6]

Peripheral blood stem cells

Through a process of mobilisation, haematopoietic stem cells are relased from the bone marrow into the blood. Current mobilization strategies include the use of cytokines alone or cytokines combined with myelosuppressive antineoplastic agents. An ideal mobilisation regimen:[5]

- achieves adequate engraftment following autologous transplant
- has a low toxicity profile
- results in a minimal number of apheresis procedures.

Through the process of apheresis, whole blood is separated into its components and stem cells can be collected and stored. Venous access via the antecubital vein may be used. A dual-lumen central venous catheter may be needed if venous access is inadequate.[5]

Effects related to the collection procedure are usually well tolerated. They include:[5, 7]

- citrate toxicity leading to hypocalcaemia
- hypovolemia
- thrombocytopaenia.

Cord blood

Cord blood is harvested via a 16-gauge needle through the umbilical vein once the placenta has been delivered. The median volume harvested is 100ml.[7]

Cell processing

Prior to storage and/or administration, stem cells may be manipulated. They may be enriched with CD34+ cells or 'purged' by removing T lymphocytes or malignant cells.[29]

Processing of an HSCs includes sterility testing, blood typing and a reduction in fluid volume.[5]
Cells are cryopreserved until administration. Key principles of cryopreservation include:[5]

- reduce of the number of mature blood cells in the graft
- protect the cells from ice formation and dehydration during freezing using a cryoprotectant such as dimethylsufloxide or hydroxyethyl starch
- dilute cryoprotectant with saline or tissue culture media
- reduce the risk of cell injury by adding plasma protein to the graft

- cool at a controlled rate
- store at a temperature below -120°C in liquid nitrogen or mechanical freezers

Allogeneic stem cells are generally transfused into a recipient within 24 to 72 hours of collection and do not require cryopreservation.

Learning activities	
Completed	
☐	1. Outline the education that would be provided to a person undergoing a bone marrow harvest.
☐	2. Summarise the discharge education for a person following a bone marrow harvest.
☐	3. Outline the aetiology, assessment, and interventions to prevent and manage the following effects of peripheral blood stem cell harvest: • Citrate toxicity • Hypovolemia • Thrombocytopaenia.

Conditioning

Conditioning involves administration of a regimen of chemotherapy, radiation therapy, and immunosuppressive therapy in the days preceding infusion of stem cells. The days of conditioning are designated by negative or 'minus' numbers.[29]

Myeloablative chemoradiotherapy in conditioning regimens for autologous transplants aims to eradicate malignant disease.

Regimens for allogeneic conditioning can be myeloablative or non-myeloablative. The functions of the conditioning regimen in allogeneic transplantation are:[29]

- disease eradication
- host immunosuppression
- creation of space for the donor cells in the recipient marrow.

While there are standard existing protocols, selecting the appropriate conditioning regimen is a complex decision for the transplant physician. Factors that may be considered include:[29]

- ablative potency of the chemoradiotherapy
- immunosuppressive therapy
- disease-related factors
- recipient factors
- source or manipulation of stem cells
- pharmacologic and radiobiologic factors
- inpatient versus outpatient / ambulatory setting.

Learning activities	
Completed	
☐	1. Choose an autologous transplant conditioning regimen and complete the following: • Outline the indications • Identify the chemoradiotherapy agents in the protocol • Outline the information and supportive care provided to a recipient of the transplant • Discuss interventions to prevent and manage potential immediate effects of the conditioning regimen.
☐	2. Choose an allogeneic transplant conditioning regimen and complete the following: • Outline the indications • Identify the chemoradiotherapy agents in the protocol • Outline the information and supportive care provided to a recipient of the transplant • Discuss interventions to prevent and manage potential immediate effects of the conditioning regimen.

Transfusion of BM / PBSC

Stem cell infusion occurs on day 0. The recipient receives hydration and premedication according to their protocol, which may include:[7]

- lorazepam
- diphenhydramine hydrochloride
- hydrocortisone
- paracetamol
- frusemide
- methylprednisolone.

Frozen stem cells are thawed and quickly infused via a central venous access device. The recipient may experience a number of effects of the stem cell infusion related to the DMSO, lysis of red blood cells, volume of infusate and the coldness of the thawed cells:[7]

- nausea and vomiting
- haemoglobinuria
- elevated serum creatinine
- elevated serum bilirubin
- cardiovascular effects
- chills and fever
- anaphylactic reaction.

Learning activities	
Completed	
☐	1. Review an autologous transplant protocol and explain the rationale for processes on day 0 for the recipients.
☐	2. Review an allogeneic transplant protocol and explain the rationale for processes on day 0 for the recipients.
☐	3. Review your local protocol for stem cell infusion and conduct a teaching session with a novice nurse using the protocol.
☐	4. Identify the signs and symptoms of anaphylactic reaction during stem cell infusion.
☐	5. Discuss interventions to prevent and manage an anaphylactic reaction during stem cell infusion.
☐	6. Outline the implications of a blood type incompatibility between the donor and recipient and interventions to reduce adverse effects in: • Minor ABO mismatch • Major ABO mismatch.
☐	7. Outline your response as an SCN for a recipient who complains of 'black urine' six hours post stem cell infusion.

Engraftment and recovery

HSC engraftment and production of normal blood cells occur approximately 7-20 days post transplantation.[10,30] During this period the recipient requires comprehensive assessment and monitoring, physical care, and psychosocial and spiritual support.

Successful engraftment of transplanted stem cells depends on the quality and quantity of stem cells and the integrity of the marrow's microenvironment.[6]

Haematopoietic and immunological recovery occur at variable speeds and are influenced by a number of factors:[7]

- the nature and status of the primary disease
- previously administered chemotherapy and radiation
- the type of preparative regimen
- the type of GVHD prophylaxis
- viral complications
- the use of antiviral agents.

Lack of initial engraftment of donor cells, or loss of donor cells after initial engraftment, is termed graft failure or graft rejection.[31] These conditions occur in less than 5% of recipients and are rare after matched-sibling transplants.[31]

Learning activities	
Completed	
☐	1. Access Mixed chimerism in SCT: conflict or peaceful coexistence?[32] and: • Define the term chimerism • Summarise the implications of an individual's chimeric state following HSCT.
☐	2. For each of the following drugs commonly used in the acute transplant period: • Cyclosporine • Tacrolimus • Fluconazole • Acyclovir • Methotrexate • Cotrimoxazole • Intragam • G-CSF a. identify the classification of the drug b. describe the indication for the drug c. discuss potential short and long term effects associated with the drug d. explain the nursing interventions to prevent, detect early, and manage these effects e. identify other nursing considerations associated with administering these drugs.

☐	3. Access a current text and identify the average length of time to engraftment for: • Autologous transplants • Allogeneic transplants • Non-myeloablative allogeneic transplants.
☐	4. Access Graft failure after allogeneic hematopoietic cell transplantation[31] and: • Summarise the risk factors for graft failure • Outline methods to prevent and manage graft failure.
☐	5. Discuss common psychosocial concerns in the immediate post-transplant period and nursing responses to these.

Acute effects of HSCT

Potential early effects of HSCT, requiring astute nursing assessment and management, include:[7, 11]

- mucositis
- infection
- veno-occlusive disease
- ongoing effects of the conditioning regimen (nausea, vomiting, diarrhoea, haemorrhagic cystitis).

Complications that may occur 30 to 100 days post allogeneic transplant include:[7]

- acute GVHD
- interstitial pneumonia (CMV and idiopathic)
- varicella zoster virus
- bacteremia
- herpes simplex virus
- restrictive lung disease
- disseminated fungal infection.

Care requirements of the recipient during the acute phase include:[7]

- thorough assessments
- blood tests
- blood product transfusion
- nutritional, antibiotic, immunoglobulin, and intravenous fluid support
- symptom management
- skin biopsies
- bone marrow biopsies and aspirations
- close monitoring of medication administration and drug levels
- care of the central venous access device
- psychosocial support.

There are significant risks to day 100 post-transplant. The cumulative incidence of transplant related mortality (i.e. deaths other than those from relapse or persistent disease) for allogeneic transplant recipients in Australia and New Zealand in 2011 was 9.3% at 100 days post-transplant.[2] In autologous transplant recipients, this figure was 1.8% mortality at 100 days post-transplant.[2]

Learning activities	
Completed	
☐	1. Access a current text and Nausea and vomiting with high-dose chemotherapy and stem cell rescue therapy: a review of antiemetic regimens[33] and summarise the assessment and management of nausea and vomiting in people during HSCT.
☐	2. Access a current evidence based guidelines and Palifermin reduces incidence and severity of oral mucositis in allogeneic stem-cell transplant recipients[34] and summarise the assessment and management of oral mucositis in people following HSCT.

☐	3. Access a current text and Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies[35] and: • Define hepatic veno-occlusive disease • Identify risk factors for VOD • Identify signs and symptoms of VOD • Identify nursing and medical interventions to prevent and manage VOD.
☐	4. Access a current text and the following resources: • Graft-versus-host disease in oncology nursing practice[36] • GVHD: a continuing barrier to the safety of allogeneic transplantation[37] • Corticosteroids for preventing graft-versus-host disease after allogeneic myeloablative stem cell transplantation[38] (free resource, but you must register and login to access it) and: • Describe the pathology of acute graft-versus-host disease • Identify the clinical manifestations of acute graft-versus-host disease • Summarise approaches to prevent and manage acute GVHD.
☐	5. Access Pain syndromes in the setting of haematopoietic stem cell transplantation for haematological malignancies[39] and: • Summarise the pain syndromes experienced by the people following HSCT • Discuss implications of HSCT on pain management.
☐	6. Summarise the indications for blood product support in the post-transplant period.
☐	7. Outline the rationale for the following associated with blood product administration following HSCT: • Irradiation • Leukocyte reduction • CMV assessment.

Discharge and follow up care

The period of hospitalisation for recipients of transplantation varies according to their condition, the type of transplant, and protocol. Individual transplant centres vary in their criteria for discharge from the acute care setting.[7]

Critical verbal and written discharge instructions to the recipient and their carers prior to discharge should include:[7]

- signs and symptoms to report to the transplant centre
- bleeding precautions
- infection control practices
- central venous access device care
- dietary restrictions
- medical instructions
- follow up care and appointments
- what to do in an emergency.

Transplant recipients still have special health care needs following discharge. A treatment and communication plan is required to ensure appropriate short and long term monitoring.

Recommended screening and preventive practices for transplant recipients have been developed by a consensus panel formed by members of:

- the Center for International Blood and Marrow Transplant Research (CIBMTR)
- the European Group for Blood and Marrow Transplantation (EBMT)
- the American Society for Blood and Marrow Transplantation (ASBMT).

The National Marrow Donor Program (NMDP), in partnership with these organisations, has developed Recommended post-transplant care guidelines.[40] Recipients and health care professionals can use these guidelines to schedule long term follow up care after a marrow, peripheral blood stem cell, or cord blood transplant.[41]

Learning activities	
Completed	
☐	1. Outline common criteria for discharge following transplantation in your practice setting.
☐	2. Summarise the advice and information resources you would provide to a recipient and carer regarding the following possible scenarios post discharge: • Presence of a temperature greater than 38ºC • Diarrhoea for three days • Redness and pain at Hickman site.
☐	3. Identify the recommended tests and procedures for recipients' six-month, one-year, and annual post-transplant check-ups in your facility and compare these to the Recommended post-transplant care guidelines[40] for:

☐	• Autologous recipients • Allogeneic recipients. 4. Discuss the community and health care facility resources that support the transplant recipient and their carer following discharge.

Chronic effects

Chronic effects may loosely be termed those that occur after day +100. Recipients are at risk of complications related to:

- organ damage from the conditioning regimen
- chronic GVHD
- immune dysfunction and effects of immunosuppressive therapy.

Quality of life

While many HSCT recipients have a good quality of life at one year and have resumed part or full time employment, a significant proportion of survivors experience persistent anxiety and depressive symptoms, fatigue, sexual dysfunction, and fertility concerns.[42]

Chronic graft-versus-host disease

Chronic GVHD (cGVHD) is a syndrome of immune dysfunction that results in immunodeficiency and autoimmunity. cGVHD has been reported in at least 30-50% of recipients of transplants from HLA-matched siblings, and at least 60-70% of recipients from unrelated donors.[43]

Any organ may be involved and many symptoms resemble those of spontaneously occurring autoimmune disorders. The skin, liver, and mouth are the most frequent targets. Opportunistic infections are common, including invasive fungal infections and Pneumocystis jiroveci pneumonia. Decreased quality of life and depression have also been associated with cGVHD.[43]

Infections

Transplant recipients, especially allogeneic recipients with cGVHD, have an increased risk of infection for up to five years after transplantation. Contributing factors include persistent hypogammaglobinaemia, impaired cellular immunity, and splenic hypofunction.[30]

Recurrent sinopulmonary infections (sinusitis, pneumonia, bronchitis) are common in the first two years.

Reactivation of latent varicella zoster virus occurs in almost 50% of survivors.

Reactivation of cytomegalovirus (CMV) is most common in allogeneic recipients who are taking corticosteroids for GVHD.

Antibody titres to vaccine-preventable diseases decline during the first four years after transplantation, requiring revaccination.[30]

Causes of death

In recipients of allogeneic transplants carried out in Australia and New Zealand between 1998 and 2011, the most common primary causes of death in the first year included:[2]

- relapse / recurrence / persistent disease – 34.1%
- infection - 19.1%
- graft-versus-host disease - 15.7%
- multiple organ failure – 5.3%.
- interstitial pneumonitis – 3.7%.

In recipients of autologous transplants, the primary causes of death in the first year included:[2]

- relapse / progression / persistent disease – 72.6%
- infection – 9.3%.

The majority of deaths in the second year post allogeneic transplantation in Australia and New Zealand between 1998 and 2007 were caused by:[2]

- relapse / recurrence / persistent disease– 59.7%
- infection - 16.5%
- graft-versus-host disease – 8.4%.

The majority of deaths in the second year after autologous transplantation were caused by:[2]

- relapse / progression / persistent disease – 78.3%
- infection – 4.3%
- new malignancy – 1.9%.

Learning activities	
Completed	
☐	1. Access a current text and/or literature and watch the Coping with chronic graft-versus-host disease presentation[44], and: • Distinguish between acute and chronic graft-versus-host disease • Describe the pathology of chronic graft-versus-host disease • Identify the clinical manifestations of chronic graft-versus-host disease • Outline the treatment options for chronic graft-versus-host disease • Review common psychosocial experiences for the individual with graft-versus-host disease • Discuss the role of the SCN in the functional and psychosocial support of the individual with graft-versus-host disease.
☐	2. Identify the pharmacological approaches used prophylactically in the management of infection risk in transplant recipients post discharge and explain the rationale for the use of the drug / strategy.
☐	3. Discuss the implications of a diagnosis of herpes zoster (shingles) in a transplant recipient, considering: • Infection control • Symptom management

☐	• Occupational health and safety. 4. Access Hematopoietic stem cell transplantation: a primer for the primary care physician[45] and: • Discuss the role of vaccination in recipients after allogeneic and autologous HSCT • Outline the suggested schedule of vaccinations.

Late effects

With the increased use of HSCT there is a rising population of survivors worldwide. Lifetime surveillance and management of transplant recipients is necessary to ensure ongoing quality of life and longevity. Key supportive care needs identified in HSCT survivors include fatigue, psychological distress, occupational and financial issues, and sexuality and fertility concerns.[46]

There are numerous models of survivorship care. Essential features of high quality services include comprehensiveness, a coordinated approach, and individualised, holistic care provision.[47] Long term follow-up should include assessment of psychological symptoms, quality of life, sexual function, fertility, and inquiring into the individual's personal support network, in addition to screening for major organ dysfunction and second malignancies.[46]

Potential late effects

The late effects summarised in this section are those experienced 5 or more years after HSCT.[48]

Ophthalmologic late effects

- Sicca syndrome (dry eye)
- cataracts are a common late effect, often related to total body irradiation or steroid use.

Pulmonary late effects

- ongoing restrictive or obstructive changes related to infections and pulmonary complications within two years of HSCT
- conditions include chronic bronchitis, hepatopulmonary syndrome, bronchiolitis obliterans, pulmonary fibrosis, and idiopathic pneumonia syndrome.

Endocrine late effects

- gonadal dysfunction
- ovarian failure
- thyroid dysfunction
- growth hormone deficiency.

Gastrointestinal late effects

- dry mucous membranes.

Musculoskeletal late effects

- avascular necrosis
- diminished bone mineral density
- osteochondromas.

Neurocognitive late effects

- cognitive dysfunction.

Secondary malignant neoplasm

A devastating late effect of HSCT is the development of a secondary malignant neoplasm (SMN). In the first decade after HSCT, the recipient is at risk of:

- post-transplant lymphoproliferative disorders (PTLD)
- myelodysplasia (MDS)
- acute myeloid leukaemia (AML).

Learning activities	
Completed	
☐	1. Access What constitutes ideal survivorship care?[49] and Nurse-led survivorship care[50], and: • Summarise the principles of optimal survivorship care • Describe potential roles for the SCN in survivorship care of the individual post HSCT • Outline barriers to optimal survivorship care • Discuss recommendations to improve survivorship care.
☐	2. Access NMDP Long-term survival guidelines - recommended post-transplant care[51], and: • Identify the yearly assessments and tests required of the recipient of an allogeneic transplant at five years post-transplant • Discuss the potential psychosocial impact of long term follow up.
☐	3. Access a current text and Late effects in survivors of Hodgkin and Non-Hodgkin Lymphoma treated with autologous hematopoietic cell transplantation: a report from the bone marrow transplant survivor study[52], and: • Identify three long term issues (excluding graft-versus-host disease) experienced by individuals post HSCT • Summarise the evidence regarding the incidence and impact of each issue • Discuss the potential role of the SCN pre and post HSCT in the counselling, education, early identification, and management of these long term issues.

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