Hematopoietic Stem Cell Transplantation

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Contents

10.1 Principles of Treatment

The purpose of hematopoietic stem cell transplantation (HSCT) is to replace diseased, damaged, or absent hematopoietic stem cells with healthy hematopoietic stem cells. In general, allogeneic transplants are used when the hematopoietic stem cells are diseased (e.g., leukemia), damaged (e.g., sickle cell disease), or absent (e.g., severe immunodeficiency disease). Autologous transplants are used to provide stem cell rescue after higher doses of chemotherapy or radiation therapy (e.g., solid tumors).

Higher doses of chemotherapy and radiation therapy can cause dose-limiting myelosuppression. Infusing healthy stem cells allows the bone marrow to recover after intensive therapy. In the allogeneic setting, the new immune system from the donor may be effective in preventing disease recurrence by providing a graft-versus-tumor effect.

HSCT is an important treatment modality for children with aggressive malignancies in first remission or those who have recurrent disease.

Types of HSCT include the following (see Table 1):

- Allogeneic: Stem cells are collected from someone other than the recipient. These donor cells can be obtained from a variety of donor sources. A matched related donor is a family member, usually a sibling, with a 6/6 antigen match. A mismatched related donor is a family member, usually a sibling or parent, with a 3/6, 4/6, or 5/6 antigen match. A matched unrelated donor is one who is not genetically related to the recipient, with a 5/6 or 6/6 antigen match.

Table 10.1. Comparison of advantages and disadvantages of types of HSCT and different donor sources

Type of HSCT	Advantages	Disadvantages
Allogeneic		
Matched related	Healthy source of cells Easy access to donor	Some risk of GvHD 30% likelihood of sibling match
Mismatched related	Healthy source of cells Easy access to donor Availability of donor for most patients	Greater risk of GvHD Risk of graft failure
Matched unrelated	Healthy source of cells	Risk of GvHD 3–6 month waiting period for donor procurement Limited ethnic minority donors Expensive donor charges
Autologous	Easy access to donor No GvHD	No graft versus tumor effect Possible tumor contamination
Syngeneic	Healthy source of cells	Some risk of GvHD
Donor Source	Advantages	Disadvantages
Bone marrow	Well-tested collection method	General anesthesia risks Pain at harvest site
Peripheral blood	Faster engraftment	Venous access
Cord blood	Easy procurement of cells Decreased chance of viral transmission	Limited number of cells per unit Potential transmission of genetic diseases Costs for cryopreservation and storage

- Autologous: Stem cells are collected (or harvested) from the recipient
- Syngeneic: Stem cells are collected from a donor who is an identical twin of the recipient

If bone marrow is the donor source, the stem cells are collected directly from the bone marrow space, with the posterior iliac crest being the most common harvest site. The collection is done in the operating room, and the donor will usually receive general anesthesia for the procedure. If peripheral blood is used, the stem cells are collected by pheresis, usually in an outpatient setting. Temporary pheresis catheters may be placed prior to the procedure when venous access is difficult. Stem cells may also be collected directly from the umbilical cord at the time of birth. These cells are then cryopreserved (frozen) and stored for use at a later time.

Human leukocyte antigens (HLA) are a complex series of proteins on the surface of human leukocytes used for identifying a donor match (Fig. 10.1). These proteins, called antigens, make up the major histocompatibility complex, which helps the body recognize foreign proteins and cells. One set of antigens is inherited from each parent; therefore, a biological parent will be at least a 3/6 match for a child. The antigens of primary concern for HLA typing are A, B, and DR. The more disparity that exists between the donor and the recipient, the greater the risk of graft versus host disease (GvHD) and graft failure. HSCT is used for a variety of malignant and nonmalignant diseases (Table 10.2).

Figure 10.1
Example of HLA typing

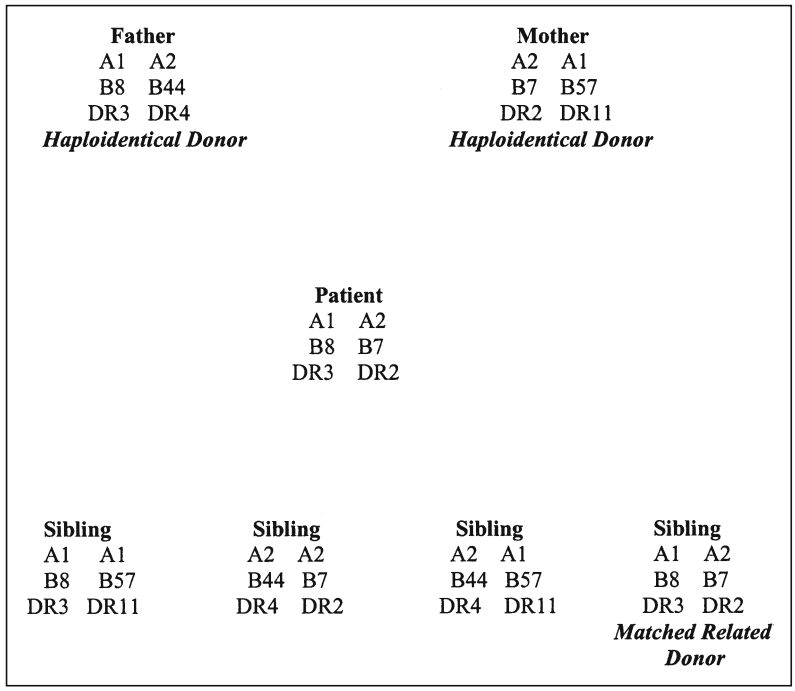

Table 10.2. Diseases for which HSCT is a treatment option (from Forte and Norville, 1998)

Disease	Rationale for hematopoietic stem cell transplantation
Leukemias, lymphomas	Chemotherapy, with or without total body irradiation, is used to eradicate tumor cells and to make room for engraftment of healthy cells. Irradiation is often used in mismatched and unrelated transplants.
Solid tumors: neuroblastoma, sarcoma, brain tumor	High doses of chemotherapy or radiation therapy are given to kill tumor cells. An autologous "rescue" is given to prevent prolonged myelosuppression.
Hematologic diseases: thalassemia, sickle-cell disease, severe aplastic anemia, Fanconi's anemia	Chemotherapy is given to eradicate cells in the bone marrow and to make space for engraftment of healthy allogeneic cells. The new donor cells will produce normal white cells, red cells, and platelets.
Immunodeficiency diseases: Wiskott-Aldrich syndrome, severe combined immunodeficiency syndrome (SCIDS), cartilage-hair hypoplasia	Chemotherapy is given to eradicate cells in the bone marrow and to make space for engraftment of healthy allogeneic cells. In the case of SCIDS, chemotherapy may not always be used.
Genetic diseases: adrenoleukodystrophy, metachromatic leukodystrophy, Hurler's syndrome	Chemotherapy is given to eradicate cells in the bone marrow. Donor cells, which will eventually produce the deficient enzyme, are infused.

10.2 Description of Treatment

HSCT can be divided into three phases: pretransplant, transplant, and post-transplant. The pretransplant phase includes donor and recipient evaluation and administration of a conditioning regimen (chemotherapy agents selected for specific activity). Day 0, the day of stem cell infusion, constitutes the transplant phase. Donor stem cells collected on this day are administered as a fresh product infusion. Donor cells collected prior to the initiation of conditioning are cryopreserved for infusion on Day 0. During the post-transplant or engraftment phase, the recipient is monitored for side effects of the conditioning regimen, complications of the transplant, and engraftment, which is the term used to indicate that the donor cells have migrated to and are repopulating the bone marrow space.

Pretransplant evaluation of the donor assures healthy stem cells and a donor who is able to tolerate the collection procedure. The age range of donors varies from infancy (3–4 months) to 65 years. The donor evaluation should include physical examination, complete health history for genetic disorders, and serological testing that includes CBC with differential, confirmatory HLA typing, ABO cross-matching, chemistry profile, coagulation screen, infectious disease testing, and a pregnancy test (if appropriate). Donors may be offered an opportunity to donate, if needed, an autologous unit of blood prior to collection of stem cells for autotransfusion.

The donor should have an opportunity to discuss issues such as testing procedures, health risks, and psychosocial sequelae with appropriate healthcare providers. These issues are especially important in the case of child donors. Consultation with child life specialists, social workers, and clergy may be beneficial and make the procedure less stressful and easier to tolerate.

The purpose of the recipient evaluation is to determine disease status and identify any underlying medical issues such as organ dysfunction or infections that could pose additional risks to the recipient. The recipient will have a more extensive evaluation than the donor. In addition to the studies listed above, the evaluation should include an assessment of the recipient's disease status, which will depend on the type of disease and the areas of previous involvement or treatment. These studies may include diagnostic scans (e.g., CT, MRI) as well as bone marrow aspirate/biopsy and lumbar puncture. Studies useful in evaluating organ dysfunction include chest x-ray, echocardiogram, pulmonary function tests (if age-appropriate), creatinine clearance or glomerular filtration rate, and dental exam. An audiogram may be ordered for patients who have a history of hearing loss or have previously received ototoxic agents. An ophthalmology exam may be done if the recipient is to receive total body irradiation (TBI).

Baseline monitoring for late effects might include baseline neuropsychological testing, endocrine function studies, and bone scans. A central venous access device will be placed, and information regarding sperm banking and egg harvesting should be provided to age-appropriate patients.

Conditioning (preparative) regimens are used to prepare the bone marrow space for the incoming graft, immunosuppress the recipient to prevent GvHD, and eradicate tumor cells when treating a malignant disease. In general, the conditioning regimen is given for 4–10 days prior to the stem cell infusion. The conditioning regimen selection depends on the disease being treated and the type of HSCT.

Conditioning regimens can include chemotherapy, radiation therapy, and immunotherapy. Chemotherapy is the backbone of the conditioning regimen and is used for most HSCT. Commonly used agents include cyclophosphamide, busulfan, cytarabine, melphalan, thiotepa, cisplatin, carboplatin, and etoposide. Radiation therapy in the form of TBI provides immunosuppression as well as treatment for sanctuary sites (central nervous system and testes). TBI is usually delivered in fractionated doses twice a day for 4–5 days. Local control radiation therapy may be given before or after transplant to patients with a history of central nervous system disease. Immunotherapy includes agents such as antithymocyte globulin (ATG) and monoclonal antibodies, such as Campath and CD45 antibody. These agents are usually given once a day for 3–4 days and are used to bind with and destroy recipient circulating T-lymphocytes

in an attempt to decrease the risk of nonengraftment and GvHD.

10.2.1 Stem Cell Collection (Harvest)

Hematopoietic stem cells are immature progenitor cells that mature in the bone marrow space. After differentiation and maturation, they are released into the peripheral circulation as mature erythrocytes, lymphocytes, and thrombocytes. Stem cells can be obtained from the bone marrow, peripheral circulation, and cord blood. Stem cells from the bone marrow are most often collected under general anesthesia from the posterior iliac crest. The cells are placed in a sterile collection system, mixed with heparin, and filtered to remove bone spicules, fat globules, and blood clots.

Peripheral stem cells are collected by pheresis. Stem cells are mobilized into the peripheral circulation using granulocyte colony-stimulating factor (G-CSF) or chemotherapy (for autologous HSCT). Using a pheresis machine and large venous catheters, the desired stem cells are selected and removed from the peripheral blood based on weight. The remaining cells (red cells, platelets, and plasma) are then reinfused into the donor. The cells are placed in a sterile collection system, mixed with heparin, filtered, and mixed with a preservative prior to being cryopreserved. Cord blood stem cells are collected from a newborn's cord and placenta immediately after birth and cryopreserved for possible use at a later time.

Stem cell processing can include buffy-coating to deplete volume or erythrocyte contamination and purging to remove any remaining tumor cells. T-cell depletion and $CD34^+$ selection (collection of specific progenitor cells) are techniques used to reduce the number of T-lymphocytes in the final product.

Stem cell infusion is similar to a blood product transfusion, and the patient and family often perceive it as anticlimactic. Stem cells are infused through a central line and should not be filtered or irradiated. Side effects associated with the HCST are listed in Table 10.3. Fresh stem cell products are most often

Table 10.3. Common side effects of hematopoietic stem cell infusions

Type of product	Side effect	Nursing assessment	Nursing interventions
Fresh stem cells	Allergic reaction	Obtain baseline vital signs (VS) and breath sounds Assess skin for evidence of flushing, itching and urticaria	Premedicate with antihistamine, corticosteroid, and antipyretic Monitor VS and breath sounds frequently during and immediately after infusion per institutional policy
	Hemolytic transfusion reaction	Assess ABO compatibility of donor and recipient	Administer pre- and post-hydration fluids for ABO incompatibility Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion Monitor for fever, chills, chest or back pain, dark urine, dyspnea, tachycardia, hypotension, shock
	Fluid overload	Assess baseline weight and fluid status Assess baseline breath sounds and pulse oximetry	Monitor fluid status during and immediately after infusion Monitor for cough, dyspnea, decreased oxygen saturation, hypertension, tachycardia, edema Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion

Table 10.3. (Continued)

Type of product	Side effect	Nursing assessment	Nursing interventions
	Micropulmonary emboli	Assess preinfusion VS, breath sounds and pulse oximetry	Monitor respiratory rate and pulse oximetry during infusion Monitor for dyspnea, decreased oxygen saturation, sudden severe headache or chest pain
	Infection	Assess baseline VS, including temperature	Monitor temperature frequently during infusion Administer antipyretic for elevated temperature Obtain sample of product and blood sample from patient for cultures
Preserved stem cells	Bad taste in mouth (due to DMSO) Nausea and vomiting		Administer antiemetics prior to infusion Offer hard candy or chewing gum if patient not sedated
	Arrhythmia and hypertension	Assess baseline VS and EKG	Monitor VS and EKG during and immediately after infusion Administer antihypertensive and diuretic
	Hemoglobinuria		Administer pre- and post-hydration fluids Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion
	Allergic reaction	Obtain baseline VS and breath sounds Assess skin for evidence of flushing, itching and urticaria	Premedicate with antihistamine, corticosteroid and antipyretic Monitor VS and breath sounds frequently during and immediately after infusion per institutional policy
	Fluid overload	Assess baseline weight and fluid status Assess baseline breath sounds and pulse oximetry	Monitor fluid status during and immediately after infusion Monitor for cough, dyspnea, decreased oxygen saturation, hypertension, tachycardia, edema Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion
	Micropulmonary emboli	Assess preinfusion VS, breath sounds and pulse oximetry	Monitor respiratory rate and pulse oximetry during infusion Monitor for dyspnea, decreased oxygen saturation, sudden severe headache, or chest pain
	Infection	Assess baseline VS, including temperature	Monitor temperature frequently during infusion Obtain sample of product and blood sample from patient for cultures Administer antipyretic for elevated temperature

Table 10.4. Timing of potential complications associated with HSCT (adapted from Fort and Norville, 1998)

Early (conditioning to engraftment)	Intermediate (engraftment to first 100 days)	Late (after 100 days)
Bone marrow suppression	Infections	Immunosuppression
Nausea, vomiting, diarrhea, anorexia, mucositis	Acute GvHD	Chronic GvHD
Parotitis	Graft failure	Infections
Infections	Interstitial pneumonitis	Endocrine dysfunction
Skin erythema		Cataracts
Capillary leak syndrome		Disease recurrence
Acute renal insufficiency		Secondary malignancies
Hemorrhagic cystitis		
Veno-occlusive disease		
Seizures		

used for allogeneic transplants, which are generally infused within 48 hours of collection. The stem cell product is infused over 2–4 hours as a slow intravenous (IV) infusion. Red cell or volume depletion prior to infusion is dependent on the donor and recipient's ABO status and the volume of donor cells collected compared to the recipient's body weight.

Stem cells collected from any donor source can be frozen and infused at a later time. In general, frozen stem cells are most often used for autologous transplants. To minimize the destruction of red cells during the freezing and thawing processes, a preservative (dimethyl sulfoxide, DMSO) is added to the stem cell product. DMSO has a garlic-like odor that is excreted from the lungs of the recipient for 24–48 hours after the stem cell infusion. DMSO infusion can cause transient cardiac arrhythmias, most commonly bradycardia, and hypertension. For this reason, many institutions require cardiac monitoring during and immediately after the infusion. Once the product is thawed, a rapid IV infusion is recommended.

10.3 Potential Side Effects

Side effects and complications associated with HSCT can occur at any time during the transplant process (Table 10.4). The side effects commonly associated with the conditioning regimen and time period to engraftment tend to occur early, within the first few weeks of transplant. Side effects that occur from the time of engraftment and during the first 100 days thereafter usually result from the conditioning regimen, prolonged immunosuppression, or early engraftment. Complications occurring 100 days or more after transplant are categorized as late effects.

10.3.1 Early Side Effects

Early side effects of the conditioning regimen can include bone marrow suppression, nausea, vomiting, diarrhea, anorexia, mucositis, parotitis, skin erythema, infections, capillary leak syndrome, acute renal insufficiency, veno-occlusive disease, and seizures. Bone marrow suppression typically occurs 7–10 days after the conditioning regimen begins. Fully ablative conditioning regimens will eradicate all cell lines in the bone marrow, causing anemia, thrombocytopenia, and neutropenia, with an absolute neutrophil count (ANC) of 0. Bone marrow suppression is prolonged and will continue until engraftment occurs. The timing of engraftment is affected by the conditioning regimen administered, the stem cell source, manipulation of the cells, the recipient's past history of prior chemotherapy, and the recipient's clinical condition. An ANC of 500 and a platelet count of

20,000 mm^2 without transfusions indicate engraftment. The average time to engraftment is, in general, 14–28 days. Typically, platelets are the last cell line to become self-sustaining. As red cells engraft, the recipient's blood type will change to that of the donor when ABO differences are present.

Transfusions of leukocyte-depleted and irradiated red blood cells are often administered when hemoglobin levels fall below 8 g/dl. Leukocyte depletion minimizes the risk of viral contamination, particularly cytomegalovirus (CMV). Irradiation reduces the risk of GvHD from transfused blood products by eliminating the immunocompetent lymphocytes in the product without compromising its functional qualities (Ryan et al., 2002). There is a potential for cardiac and respiratory compromise associated with hemoglobin levels less than 7 g/dl.

Side effects of anemia include fatigue, irritability, pallor, tachycardia, shortness of breath, and dizziness. The administration of blood products or supplemental oxygen may be required. During transfusion, monitor for signs and symptoms of adverse effects.

The risk of bleeding is increased when the platelet count is <20,000 mm^2. The nurses must assess for signs and symptoms of bleeding or blood loss, including bruising, petechiae, epistaxis, or oozing from the gums or central venous line. If transfusion is required, platelet products should be leukocyte-depleted and irradiated.

When the ANC falls below 500 cells/mm^3, patients are at a significantly increased risk of infection. Physical examination should include detailed inspection of the mouth, rectum, IV sites, and all wounds for evidence of infection. Symptoms including dysuria, sore throat, cough, and rectal pain are particularly worrisome in the neutropenic patient.

Gastrointestinal toxicity in the form of nausea and vomiting can begin within the first 24 hours of starting the conditioning regimen and can continue for several days after the transplant. Antibiotics, infections, and mucositis can exacerbate vomiting. Diarrhea can occur anytime during the conditioning regimen and last as long as 2 weeks after the transplant. Although chemotherapy is the usual cause of diarrhea during this time period, an infectious cause must be excluded. Mucositis usually peaks 7–14 days after the start of the conditioning regimen and resolves as engraftment (return of WBCs) occurs. Anorexia often accompanies the nausea, vomiting, diarrhea, and mucositis and can continue for several months after the transplant, especially in adolescent and young adult patients.

Supportive care for gastrointestinal symptoms includes administering antiemetics on a scheduled basis, as well as nutritional supplements, fluids, and total parenteral nutrition. Meticulous oral hygiene, perirectal hygiene, and skin care to prevent skin breakdown and secondary infections are necessary. Blood and stool cultures may be needed to isolate infectious agents. Pain assessment must be performed each shift and more often if the child is in pain. Oral or IV analgesics, preferably patient-controlled analgesia, may be required for mucositis pain.

Parotitis, inflammation of the parotid gland, usually occurs after the first or second dose of TBI. Common complaints are bilateral swelling and pain in the jaws. This side effect is self-limited, often lasting only a day or two. Applying warm compresses externally to the jaw and administering mild analgesics will usually provide relief.

Skin erythema, darkening, and dryness is not uncommon after TBI. This condition is most often mild and typically responds to moisturizing lotions, creams, and gels. A head-to-toe skin assessment is required daily. To prevent additional skin damage, patients need to be instructed not to use oil-based skin products while receiving TBI.

Infections during the early phase of transplant are a result of neutropenia, immunosuppression, and alterations in mucosal integrity and indwelling central lines. Patients are susceptible to bacterial, viral, and fungal infections. Common bacterial pathogens are *E. coli*, *Klebsiella*, *Pseudomonas, Staphylococcus aureus,* and coagulase-negative *Staphylococcus*. Reactivation of herpes simplex virus (HSV) is the predominant viral pathogen complicating mucositis during this time period. *Candida* spp. can infect the gastrointestinal tract, complicate toxicities, and secondarily infect other wounds and IV sites.

Prevention of infections is multifactorial and includes handwashing, limits on the number of visitors, high-energy particulate air (HEPA) filter systems,

prophylactic antimicrobials, and administration of CMV-negative blood to CMV-seronegative recipients. A combination of broad-spectrum antibiotics is given from initiation of the conditioning regimen until engraftment as common prophylaxis against bacterial infections. Acyclovir or valacyclovir prophylaxis can reduce the risk of HSV reactivation. Fluconazole, voriconazole, or low-dose amphotericin is effective prophylaxis against fungal infections. Although controversial, intravenous immunoglobulin (IVIG) therapy is administered every 2–4 weeks to provide passive immunity.

Other interventions include monitoring the patient for fever and other signs of infection, obtaining blood and urine cultures at the onset of fever before starting antibiotics, drawing blood cultures daily for subsequent fevers, and obtaining other diagnostic studies (e.g., chest x-ray, CT) as appropriate. Patients who continue to be febrile after 3–5 days should receive treatment doses of amphotericin.

Hemorrhagic cystitis can occur within 24 hours of administration of chemotherapy and as late as several months after HSCT. The primary causes of hemorrhagic cystitis include cyclophosphamide, radiation therapy, and viruses. The active metabolite of cyclophosphamide, when allowed to remain in contact with the bladder mucosa, will cause irritation and bleeding. Viruses that can cause this complication include adenovirus, CMV, and BK virus.

Signs and symptoms of hemorrhagic cystitis include hematuria (microscopic or gross), urinary frequency, dysuria, suprapubic pain, and bladder spasms. A bladder ultrasound and urine cultures for bacteria and viruses are used for diagnosis.

Management includes pre- and post-hydration fluids and mesna for cyclophosphamide administration, placement of a Foley catheter or continuous bladder irrigation, and platelet transfusions.

If a urinary catheter has not been placed, the child must void at least every 1–2 hours during, and for 24 hours after, each dose of cyclophosphamide. Strict measuring of intake and output must be done in addition to platelet counts, coagulation studies, and close monitoring for microscopic hematuria. Administering blood products and providing pain control are other necessary supportive care measures.

Acute renal failure and nephritis are frequent complications after HSCT. Radiation therapy, immunosuppressive agents, and virus and bacterial toxins can cause nephritis. Acute renal failure can result from nephrotoxic drugs, infection, and inadequate renal perfusion.

Common symptoms of renal toxicity include increased weight, edema, decreased urine output, hypertension, elevated creatinine and BUN, and altered sensorium.

Medical management includes administration of diuretics, antihypertensives, vasopressors, and dialysis. Blood chemistries need to be monitored daily, and blood levels of nephrotoxic medications (e.g., cyclosporine, tacrolimus, vancomycin, gentamicin) must be checked until the appropriate dose level is reached and then routinely. Dose and frequency of nephrotoxic medications need to be adjusted as ordered, and renal doses of dopamine are given to promote renal perfusion.

Capillary leak syndrome, a shift of intravascular fluid into the extravascular space, often occurs 7–14 days after HSCT. Tissue damage from the conditioning regimen causes the release of cytokines that cause a capillary permeability. This permeability can lead to weight gain, fluid retention, ascites, cough, shortness of breath, and pulmonary edema. The child must be assessed for signs and symptoms of fluid overload, including weight gain, hypertension, abnormal breath sounds, and intake that is greater than output.

Veno-occlusive disease (VOD) results from the high-dose chemotherapy and radiation therapy administered during the conditioning regimen. The small vessels and central vein of the liver become occluded, causing congestion, venous outflow obstruction, and eventual hepatocyte damage. Onset is usually 7–21 days after transplant. The clinical features of VOD include weight gain, right upper quadrant pain, hepatomegaly, elevated serum bilirubin, ascites, and encephalopathy. Management includes maintaining fluid and electrolyte balance by strictly monitoring intake and output, obtaining accurate daily weights and measuring abdominal girth every shift, minimizing the adverse effects of ascites by restricting oral and IV fluids and administering diuretics and pain medications, adjusting medications to reflect hepatic

and renal function, avoiding compounding encephalopathy with medications that alter mental status, and preventing bleeding.

Neurotoxicity can occur anytime during the transplant process. Seizures can result from medication toxicity, infection, hemorrhage, hypertension, and electrolyte abnormalities. In the early phase of transplant, high levels of chemotherapeutic agents (busulfan) and immunosuppressive agents (cyclosporine, tacrolimus) can cause seizures. Cyclosporine and tacrolimus can also cause tremors and peripheral neuropathy. Monitoring blood levels and adjusting doses can prevent and minimize these side effects.

10.3.2 Intermediate Side Effects

Intermediate side effects and complications of HSCT can include infections, graft failure, acute GvHD, and interstitial pneumonitis. Infections during this phase are more common and more severe for allogeneic patients than autologous patients as a result of impaired cell-mediated and humoral immunity, immunosuppressive therapy to prevent GvHD, and the presence of indwelling lines. Common pathogens include gram-negative bacteria (*E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*), gram-positive bacteria (*Staphylococcus aureus,* coagulase-negative *Staphylococcus, Streptococcus pneumoniae*), fungus (*Candida*, *Aspergillus*), and viruses (adenovirus, CMV).

Predisposing factors associated with infections during this period include neutropenia, central venous lines, immunosuppressive therapy, and GvHD.

Strategies to prevent or minimize the risk of infections include handwashing, HEPA filtration, low-bacterial diets, avoidance of crowded places, and antibacterial, antifungal, and antiviral prophylaxis. Antibacterial and antifungal (fluconazole, low-dose amphotericin B) prophylaxis continues until engraftment (defined as an ANC >500 for 3 consecutive days).

CMV infection is a life-threatening infection that usually occurs within the first 2 months post-transplant. Most centers will provide some form of prophylaxis when the recipient or donor is CMV-seropositive pretransplant, either ganciclovir IV from engraftment through 100 days post-transplant or CMV antigenemia monitoring with ganciclovir treatment when virus is detected. Additional strategies to prevent CMV infection include administration of leukocyte-depleted blood products and CMV-seronegative blood products to seronegative recipients. IVIG may also be given to provide passive immunity during this phase of HSCT.

Treatment is aimed at specific pathogens causing infections. Initial treatment usually includes broad-spectrum antibiotics, followed by specific antimicrobials based on culture and sensitivity results. Treatment of CMV infection can include ganciclovir and IVIG, foscarnet, and cidofovir.

Acute GvHD (AGvHD) is an immune-mediated response in which the immunocompetent donor T-cells recognize the host (recipient) antigens as foreign and mount an attack. It is the consequence of alloreactivity between the donor and recipient. The immunocompetent donor T-cells recognize the alloantigens (major and minor histocompatibility antigens) of the recipient and become activated, which leads to further expansion of alloreactive T-cells. This leads to the release of cytokines, recruitment of other immune system effector cells, and eventual tissue damage.

Incidence and severity depend on the type of transplant and the degree of HLA disparity between the donor and recipient. The recipient's age, the number of T-cells transfused, and the GvHD prophylaxis used are additional risk factors. The onset of AGvHD usually coincides with engraftment and occurs within the first 100 days of transplant.

Clinical presentation typically involves one of three targeted organs: the skin, liver, or gut. Diagnosis can be made clinically based on symptoms and laboratory values. However, tissue biopsy is required for definitive diagnosis. Individual organ involvement is staged for severity, and an overall grade is assigned based on severity and combined organ involvement. Skin AGvHD is the most common initial presenting manifestation. The rash begins as a macular erythematous rash of the palms and soles. It can progress to a maculopapular erythematous rash on the trunk and extremities to bullae and generalized desquamation. Pruritus and pain are common associated symptoms (Table 10.5).

Table 10.5. Acute GvHD stage and grading systems

Staging of individual organ system(s)				
Organ	**Stage**	**Description**		
Skin	+1	Maculopapular (M-P) eruption over <25% of body area		
	+2	Maculopapular eruption over 25–50% of body area		
	+3	Generalized erythroderma		
	+4	Generalized erythroderma with bullous formation and often with desquamation		
Liver	+1	Bilirubin 2.0–3.0 mg/dl; SGOT 150–750 IU		
	+2	Bilirubin 3.1–6.0 mg/dl		
	+3	Bilirubin 6.1–15.0 mg/dl		
	+4	Bilirubin >15.0 mg/dl		
Gut	+1	Diarrhea >30 ml/kg or >500 ml/day		
	+2	Diarrhea >60 ml/kg or >1,000 ml/day		
	+3	Diarrhea >90 ml/kg or >1,500 ml/day		
	+4	Diarrhea >90 ml/kg or >2,000 ml/day; or severe abdominal pain and bleeding with or without ileus		
Overall grading of acute GvHD				
Grade	**Skin staging**	**Liver staging**		**Gut staging**
I	+1 to +2	0		0
II	+1 to +3	+1	and/or	+1
III	+2 to +3	+2 to +4	and/or	+2 to +3
IV	+2 to +4	+2 to +4	and/or	+2 to +4

Liver AGvHD causes degeneration of mucosa and small bile ducts and results in hepatitis-like symptoms (fatigue, abnormal liver function tests, right upper quadrant pain, hepatomegaly, jaundice, and pruritus). Increased bilirubin and alkaline phosphatase levels are the earliest and most common abnormalities noted.

Gut AGvHD is characterized by diarrhea and abdominal cramping, which can progress to severe ileus. Degeneration of the mucosal lining of the GI tract results in green, watery, guaiac-positive diarrhea; abdominal discomfort; nausea; vomiting; anorexia; malabsorption; and ascites. Both the upper and lower GI tract can be involved.

Prevention remains the key to effective management of AGvHD. Prevention strategies are aimed at preventing the activation of T-cells and depleting mature alloreactive T-cells from donor grafts. Cyclosporine, used in combination with other immunosuppressive agents, has been standard GvHD prophylaxis, but tacrolimus is being used instead of cyclosporine for unrelated and mismatched transplants because it has proven to be superior to cyclosporine in this group of patients (Ryan et al., 2002). New monoclonal antibodies, Campath and CD45 antibody, are being incorporated into conditioning regimens as GvHD prophylaxis. T-cell depletion, monoclonal antibodies, and $CD34^+$ selection are successful strategies to deplete alloreactive T-cells from donor grafts.

Treatment consists of adding corticosteroids and continuing cyclosporine or tacrolimus (Table 10.6). Antithymocyte globulin and newer monoclonal antibodies are added in cases of steroid-resistant or severe AGvHD.

Table 10.6. Agents used to prevent and treat GvHD (from Forte, 1997)

	Mechanism	Toxicities
Cyclosporine (Sandimmune)	Blocks synthesis of IL-2, suppresses development of cytotoxic T-lymphocytes	Renal toxicity, hypertension, magnesium wasting, hyperkalemia, tremors, seizures, gingival hypertrophy, hirsutism, cortical blindness
FK506 (Prograf)	Is similar to cyclosporine	Are similar to those associated with cyclosporine, hyperglycemia
Methotrexate (Mexate)	Inhibits DNA synthesis by competitively binding with dihydrofolate reductase	Renal toxicity, liver toxicity, mucositis
Glucocorticoids	Prevents production and release of IL-1 from macrophages	Myelosuppression, mood swings, hypertension, hyperglycemia, GI bleeding, osteoporosis, acne, cushingoid syndrome
Antithymocyte globulin (ATG) (an immune globulin)	Acts against human thymocytes	Fever, chills, rash, anaphylaxis, serum sickness
OKT3 (Orthoclone) (a monoclonal antibody)	Is specific for circulating CD3 T-cells	First-dose reaction: fever, chills, diarrhea, dizziness, chest pain, wheezing, tremor
Thalidomide	Decreases the number of helper T-cells and increases the number of suppressor T-cells	Peripheral neuropathies, constipation, sedation
Hydroxychloroquine (Plaquenil)	Reduces secretion of IL-1, IL-6, and tumor necrosis factor	Ocular toxicity, nausea, diarrhea, rash, photosensitivity

Graft failure or rejection occurs when the donor graft is not sustained in the recipient. This complication is relatively uncommon in allogeneic HSCT, with an incidence of approximately 1% with HLA-matched donors and 5–10% with mismatched donors (Guinan et al., 2002). Graft failure can occur when the stem cell dose is too low, the recipient marrow is not completely ablated, or the immunosuppression is inadequate. Infections and tumor recurrence can also cause graft failure. Treatment may include increased immunosuppression or infusion of donor T-lymphocytes.

Interstitial pneumonitis is the leading cause of respiratory failure in HSCT patients. It can result from infection or toxicity of the conditioning regimen. Idiopathic pneumonitis is a noninfectious interstitial pneumonia that often follows engraftment, strongly suggesting an immunologic response involved in the process. Clinical features include dyspnea, nonproductive cough, hypoxia, diffuse alveolar damage, and nonlobar infiltrates on x-ray. The mortality rate for this complication is extremely high despite aggressive treatment with antimicrobials, blood products, steroids, and ventilatory support (Ryan et al., 2002).

10.3.3 Late Side Effects

Late side effects and complications can include immunosuppression and infections, chronic GvHD, endocrine dysfunction, cataracts, disease recurrence, and secondary malignancies. Immunosuppression and infections remain a risk during this time despite neutrophil engraftment. Both cellular and humoral immunity remain depressed until full immune reconstitution occurs. This delayed immune recovery can lead to acute and chronic infections and nutritional deficits (Guinan et al., 2002; Ryan et al., 2002).

Table 10.7. Prophylaxis for PCP

Age	Primary recommendation	Second alternative
Infants (1–12 months)	* TMP-SMZ (150/750 mg/m^2) by mouth twice daily for 3 consecutive days	Dapsone (infants >1 month) 2 mg/kg by mouth daily
Children (>12 months)	TMP-SMZ (150/750 mg/m^2) by mouth twice daily for 3 consecutive days	Dapsone 2 mg/kg by mouth daily, maximum 100 mg by mouth daily
Adolescents	TPM-SMZ (160 mg/800 mg) by mouth three times a week	Dapsone 100 mg by mouth daily

* prophylaxis – sulfomethoxazole/trimethoprim/co-trimoxazole

Several factors contribute to this protracted impaired immunity: patient and donor age, conditioning regimen used, degree of HLA disparity between donor and recipient, presence of GvHD, presence of infection, and type of post-transplant immunosuppression used.

Common post-transplant infections include *Pneumocystis jiroveci* (formerly called *Pneumocystis carinii*), varicella-zoster, CMV, adenovirus, and Epstein-Barr virus lymphoproliferative disease. Management includes *Pneumocystis jiroveci* prophylaxis for 1 year post-transplant (Table 10.7) and frequent monitoring for evidence of infections and immune recovery.

Chronic GvHD (CGvHD) is a chronic autoimmune syndrome that resembles collagen vascular diseases such as scleroderma and systemic lupus erythematosus. The primary effect of CGvHD is the epithelial cell damage to tissue that can lead to fibrosis and atrophy. Chronic GvHD targets the same organs as AGvHD – the skin, liver, and gut – however, it may affect others as well, such as the eyes and lungs. The secondary effect of marked immunosuppression has a significant impact on morbidity and mortality post-transplant.

Risk factors for CGvHD include prior AGvHD, donor and recipient HLA disparity, and increasing patient age. The decreased incidence over the last decade can be attributed to improved HLA matching and effective AGvHD prevention. Chronic GvHD can occur as progression of acute GvHD, follow a period of quiescence after acute GvHD, or occur as de novo disease. Historically, GvHD that occurs 100 days after transplant is considered chronic. The increased use of donor T-lymphocytes in the post-transplant period requires careful assessment and diagnosis of GvHD symptoms.

Clinical presentation is remarkable for sicca syndrome, extreme dryness of mucous membranes and tissues, and infections (Table 10.8). Diagnosis can be made clinically based on symptoms and laboratory values. However, tissue biopsy is required for definitive diagnosis. Chronic GvHD is graded as limited or extensive: Limited is described as localized skin involvement and/or hepatic dysfunction, and extensive is described as generalized skin involvement with multiorgan involvement.

Treatment consists of immunosuppression with many of the same agents used to treat AGvHD (Table 10.6). Initial treatment usually includes cyclosporine or tacrolimus and steroids that are slowly tapered over several months. Several newer agents are now available. For severe CGvHD of the skin, both psoralen and ultraviolet radiation (PUVA) and extracorporeal photopheresis have been beneficial.

Endocrine dysfunction may present as growth failure, thyroid dysfunction, ovarian dysfunction, or testicular dysfunction. Risk factors include TBI and long-term steroid therapy, although fractionated TBI has decreased the incidence of hypothyroidism to 10% (Guinan et al., 2002). Treatment includes thyroid replacement therapy and growth hormone therapy, respectively, for thyroid dysfunction and growth delays. Females who have chemotherapy after puberty have more permanent infertility and menopausal symptoms than those treated before puberty. Testic-

Table 10.8. Chronic GvHD: clinical effects and nursing interventions

Organ/system involved	Clinical effects	Nursing interventions
Skin	Itching, burning, scleroderma, ulcerations, hyperpigmentation, erythema, dryness Erythema can be activated by sun exposure	Teach patient to use skin moisturizers and nondrying, nonabrasive soaps Teach patient to protect skin from sunlight and avoid prolonged sun exposure; emphasize need to use sunscreens
	Alopecia, nail ridging, joint contractures	Apply topical steroid creams to relieve itching and/or burning Provide range of motion exercises Practice specific exercise regimens recommended by PT/OT to prevent contractures
Liver	Obstructive jaundice	Monitor liver function tests
	Cirrhosis with esophageal varices and hepatic failure	Teach patient low-fat diet, if indicated
GI tract	Xerostomia, stomatitis, ulcerations, lichen planus-like striae and plaques, taste changes, dysphagia, retrosternal pain, diarrhea, malabsorption	Promote oral hygiene and regular dental follow-up Encourage use of artificial saliva or alkaline-saline mouthwash to relieve oral dryness Provide lanolin for lip moisturizing Provide nutritional counseling and dietary referral Monitor weights
Eyes	Decreased tear production Burning, photophobia, itching, sensation of grittiness in eyes	Promote regular ophthalmology exams Provide artificial tears to relieve ocular dryness Suggest use of sunglasses to decrease discomfort of photophobia
Lungs	Obstructive and restrictive lung changes	Provide chest PT and incentive spirometer, if indicated
	Cough, dyspnea, pneumothorax	Monitor pulmonary function tests on a regular basis
Immunosuppression	Increased risk of infection Slowed immune recovery	Maintain measures to prevent infections Promote good general hygiene Administer immunosuppressive therapy and monitor for side effects Monitor compliance with infection prophylaxis medications

ular dysfunction includes sterility, azoospermia, and premature ejaculation in males treated with TBI. Regardless of age, TBI may result in primary gonadal failure in both genders. Treatment may include hormone replacement therapy.

Cataracts, usually posterior and bilateral, can occur several years post-transplant in patients who receive TBI. Fractionated TBI has significantly reduced the incidence. Treatment is surgical removal of the cataracts.

Disease recurrence remains the primary cause of treatment failure after autologous and allogeneic HSCT. Patients at increased risk for relapse include those with high-risk diseases, poor response to initial therapy, unfavorable cytogenetic abnormalities, and significant disease/tumor burden at time of trans-

plant. Treatment can include donor lymphocyte infusions, second transplants, and discontinuing immunosuppressive therapy.

Secondary malignancies are potential problems for both autologous and allogeneic transplant recipients. High-dose chemotherapy, TBI, and immunosuppression are the primary etiologies. Myelodysplastic syndrome and leukemia occur at an incidence of 4–20% at 5–6 years after autologous transplant. Patients receiving an allogeneic transplant are at risk of developing post-transplant lymphoproliferative disease, which can occur within 6 months after transplant, and a variety of solid tumors at an incidence rate eight times higher than the normal (Guinan et al., 2002).

10.4 Special Considerations

Discharge planning and teaching become focused once engraftment begins. Discharge can be anticipated once engraftment has occurred. Engraftment is generally defined as an ANC >500 for 3 consecutive days. In general, patients are required to remain in close proximity to the transplant center for the first 100 days after allogeneic transplant. Autologous transplant patients may be referred to their primary physician once engraftment has occurred and HSCT complications have resolved.

General discharge criteria include the following:

- ANC >500
- Afebrile for 24 hours
- Able to take oral medications
- Oral intake of calories and fluids is 50% of nutritional needs
- Patient is on total parenteral nutrition or nasogastric feedings
- Any transplant complications are resolved or controlled
- Primary caregiver is able to care for central venous line and provide any nutritional support that is needed.

Instructions to patient and caregiver should include the following topics:

- Infection control practices: handwashing, social isolation, face masks, temperature monitoring, and avoidance of new pets and plants
- Activities of daily living: diet, personal hygiene, mouth care, sun exposure, exercise, and school reentry
- Central line care and parenteral medication administration
- Importance of oral medication compliance
- Reportable signs and symptoms: fever, cough, rash, vomiting, diarrhea, bleeding, pain, and inability to take oral medications.

Outpatient follow-up will be tailored to the patient's needs. The frequency of clinic appointments is based on type of transplant, engraftment status, and unresolved complications. Regular monitoring will include physical assessment, routine blood counts, serum chemistries and medication levels (cyclosporine and tacrolimus), symptom and toxicity management, medication compliance, and nutritional assessment.

Annual evaluations of recipients of allogeneic transplants are required for monitoring engraftment status and assessing for late effects. Typical tests performed on an annual basis include

- Complete blood count with differential
- Serum chemistries
- Immunoglobulin levels
- Immune function tests
- Endocrine function tests
- Pulmonary function tests
- Cardiac function tests
- Ophthalmologic examination
- Renal function tests
- Neuropsychological evaluation.

Psychosocial issues faced by patients and their families are numerous, with different issues presenting during each stage of transplant. Some of these include prolonged hospitalization, emotional isolation from family and friends, role changes within the family dynamics, invasive medical procedures, treatment-related side effects and complications, fear of relapse, and financial concerns. All of these can have a significant impact on the quality of life experienced

by the patient and the entire family. Consequently, a diverse multidisciplinary team of healthcare providers is required to assist the patient and family in successfully dealing with these issues.

10.5 Future Perspectives

Future direction in HSCT will consist of optimizing graft versus leukemia (GvL) effects, minimizing toxicity, engineering more precise grafts, moving to outpatient procedures, and combining stem cell transplantation with gene therapy.

GvL is an immune response to donor cells against recipient leukemia. There is evidence for GvL effect with the infusion of unmanipulated donor lymphocytes to relapsed patients after allogeneic HSCT. The future holds identification of minor antigens and their roles in GvL and GvHD.

Minimizing regimen-related toxicity would broaden the use of HSCT to nontraditional disorders such as autoimmune and degenerative diseases and improve long-term survival of transplant recipients. Monoclonal antibodies, such as Campath, CD45, and Rituxan, are being incorporated into conditioning regimens to substitute in part or in whole for the traditional cytotoxic and immunosuppressive drugs currently used. Many centers are developing submyeloablative conditioning regimens with less toxic chemotherapy. The use of adoptive immunotherapy in the form of cytotoxic T-lymphocytes has been demonstrated to prevent and treat transplant infections and post-transplant lymphoproliferative disorders.

T-cell depletion and $CD34^+$ selection are examples of more precise graft engineering to reduce complications such as graft failure and GvHD. Further identification of minor antigens could lead to more selective T-cell depletion techniques that might allow GvHD prevention without significant loss of GVL effect.

Several centers are exploring the possibility of providing stem cell transplants in the outpatient arena. This could have a significant impact on length of hospitalization and financial costs of HSCT in the future. As technology and basic science advance, HSCT will be combined with gene therapy as a vehicle for gene insertion, which will enhance applicability of stem cell transplantation, provide less toxic therapy, and improve survival.

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