

## CJON WRITING MENTORSHIP PROGRAM ARTICLE

# Hematopoietic Stem Cell Transplantation: Implications for Critical Care Nurses

Marlon G. Saria, MSN, RN, AOCNS, and Tracy K. Gosselin-Acomb, RN, MSN, AOCN®

Hematopoietic stem cell transplantation (HSCT) is being used increasingly in the treatment of malignant and nonmalignant diseases. The treatment modality has been proven effective but is not without risks. Studies consistently have identified the need for advanced supportive care (e.g., multiple organ dysfunction, vasopressor use, mechanical ventilation) as a negative prognostic indicator in patients who have received HSCT. Among patients who have received HSCT, 15%–40% require critical care monitoring or advanced support. Nurses on intensive care units can positively impact outcomes for transplant recipients when they possess the specialized skills to recognize and promptly intervene when transplant-related complications arise. This article will provide a basic overview of the HSCT process and outline the complications that may necessitate transfer to a higher level of care for specialized skills and equipment in the intensive care setting.

**T**he growth of hematopoietic stem cell transplantation (HSCT) programs in the United States has presented unique challenges to the nursing profession, which already is overly burdened. Issues such as an increased need for specialty education and training, integration of specialties, and inadequate staffing complicate the basic clinical concerns. The issues are directly related to increased patient acuity and complexity of treatment regimens. One of the challenges emerging in medical centers and institutions with smaller transplant programs is the provision of care for critically ill HSCT recipients by nononcology critical care nurses. Although many cancer centers take pride in the fact that every nurse on every unit is an oncology nurse, general intensive care units (ICUs) commonly receive and provide care for HSCT recipients in medical centers that are not dedicated to the care of patients with cancer. ICU nurses in nonspecialized hospitals may be experienced critical care nurses but have little or no knowledge of the specialized care needed by patients receiving HSCT. The aim of this article is to provide a basic overview of the HSCT process and to outline the complications that may necessitate transfer to a higher level of care and the specialized skills and equipment in the intensive care setting.

## Overview

The term HSCT is used increasingly by medical professionals to refer to the procedure previously known as bone marrow transplantation to be inclusive of the multiple sources of donor stem cells available for transplantation: bone marrow, peripheral blood, and cord blood. The traditional classification of HSCT is based on the relationship of the donor to the patient. Stem cells used in an autologous transplant are harvested from a patient's own marrow or peripheral blood, a syngeneic transplant uses stem cells from an identical twin, and an allogeneic transplant

### At a Glance

- ◆ Critical care monitoring or advanced support may be unavoidable for some patients receiving hematopoietic stem cell transplantation (HSCT).
- ◆ Care of critically ill patients undergoing HSCT presents a unique challenge to healthcare professionals.
- ◆ Early recognition and prompt intervention for HSCT-related complications can positively impact outcomes of care.

uses stem cells from a human leukocyte antigen- (HLA-) identical or closely matched sibling or an unrelated donor.

The list of indications for HSCT has been expanding gradually. The goal of HSCT for patients with malignancy is to rescue their marrow from the toxic effects of chemotherapy, with or without total body irradiation (TBI), permitting the administration of higher and potentially more curative doses of chemotherapy. In contrast, the goal of HSCT in patients with nonmalignant diseases is to replace nonfunctional or failed marrow (Kotloff, Ahya, & Crawford, 2004; Resnick, Shapira, & Slavin, 2005; Shaffer &

---

Marlon G. Saria, MSN, RN, AOCNS, is an oncology clinical nurse specialist at the University of California, San Diego Medical Center; and Tracy K. Gosselin-Acomb, RN, MSN, AOCN®, is the director of oncology services at Duke University Hospital in Durham, NC. The authors were participants in the 2005 *CJON* Writing Mentorship Program, which was underwritten through an unrestricted educational grant by Amgen Inc. No significant financial relationship to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society. (Submitted March 2006. Accepted for publication April 12, 2006.)

Digital Object Identifier: 10.1188/07.CJON.53-63

Wilson, 1993). Malignant and nonmalignant disorders commonly treated with HSCT are listed in Table 1. Patients are eligible for HSCT when they meet physical and psychological criteria set forth by the multidisciplinary transplant team. The HSCT process includes stem cell harvest, high-dose radiation and/or chemotherapy administration, stem cell infusion, and recovery.

## Hematopoietic Stem Cell Transplantation Procedure

### Conditioning Regimens

Prior to stem cell infusion, patients receive high doses of chemotherapy with or without TBI, also known as the conditioning or preparative regimen, to eradicate the disease, suppress the

bone marrow, and prevent rejection of donor stem cells (Kotloff, et al., 2004; Shivnan, Shelton, & Onners, 1996). The intensity of conditioning regimens and the associated increases in the incidence and severity of complications, not to mention the dramatic reduction in quality of life, have preempted the development of a relatively newer modality of HSCT, known as nonmyeloablative stem cell transplantation (Diaconescu et al., 2004). The modality reduces the intensity of conditioning regimens to a level that still allows reconstitution of the immune system but may not be adequate to eradicate the disease (Resnick et al., 2005). The common conditioning regimens and indications used for myeloablative and nonmyeloablative procedures are listed in Table 2. Nursing care during the conditioning phase is focused on the prevention, early recognition, and prompt management of treatment-related toxicities.

### Growth Factors

As mentioned earlier, bone marrow suppression is an intended outcome toxicity of the conditioning regimens for HSCT; therefore, severe neutropenia is to be expected during the course of transplantation (West & Mitchell, 2004). Use of a hematopoietic growth factor is recommended to hasten hematopoietic recovery time, lower infection rates, decrease length of stay, and possibly reduce costs (Ozer et al., 2000; West & Mitchell). Keratinocyte growth factor, a novel agent used to reduce the duration and severity of oral mucositis following high-dose chemotherapy and radiotherapy (Spielberger et al., 2004), is the latest addition to supportive therapy agents for patients undergoing HSCT. Nursing care of patients receiving growth factors includes timely administration and recognition and management of side effects, including bone pain, flu-like symptoms, pain at injection site, hypertension, and myalgia.

### Immunosuppressive Therapy

Immunosuppressive therapy is indicated for the prevention and treatment of graft-versus-host disease (GVHD). GVHD is an immunologic reaction between a patient (host) and grafted stem cells and is a serious complication related to allogeneic HSCT. The treatment goal is to partially suppress donors' immunity to prevent GVHD while maximizing benefit from graft-versus-tumor effect (Bevans & Shelburne, 2004). Corticosteroids, cyclosporine (Sandimmune®, Novartis Pharmaceuticals, East Hanover, NJ), tacrolimus (Prograf®, Fujisawa Healthcare Inc., Deerfield, IL), mycophenolate mofetil (CellCept®, Hoffmann LaRoche Inc., Nutley, NJ), and methotrexate are the most common immunosuppressants used in the HSCT setting. Widely varying formulations, bioavailability, narrow therapeutic levels, and multiple drug interactions can result in increased toxicities from high serum concentrations of immunosuppressive agents. Graft failure from subtherapeutic levels also can occur (Leather, 2004). Table 3 summarizes the nursing implications for some of the common drugs used in the HSCT setting.

### Antimicrobials

Patients undergoing HSCT are severely immunocompromised because of several factors: the disease process (malignant or nonmalignant); conditioning regimens, which ablate bone marrow; and immunosuppressive therapy used to prevent and treat GVHD.

**Table 1. Indications for Hematopoietic Stem Cell Transplantation (HSCT)**

TYPE OF DISEASE	AUTOLOGOUS HSCT	ALLOGENEIC HSCT
<b>Malignant</b>		
Hematologic malignancies	Hodgkin disease	Acute lymphocytic leukemia
	Non-Hodgkin lymphoma	Acute myelogenous leukemia
Solid tumors	Multiple myeloma	Chronic myelogenous leukemia
	Neuroblastoma	Myelodysplastic syndrome
	Sarcoma	Non-Hodgkin lymphoma
Germ cell tumor		–
<b>Nonmalignant</b>		
Hematologic	–	Severe aplastic anemia
		Fanconi anemia
		Thalassemia
		Sickle cell disease
		Diamond Blackfan anemia
		Chediak-Higashi syndrome
		Chronic granulomatous disease
Immunodeficiency	–	Congenital neutropenia
		Severe combined immunodeficiency disease
		Wiskott-Aldrich syndrome
Genetic	–	Functional T-cell deficiency
		Adrenoleukodystrophy
		Metachromatic leukodystrophy
Miscellaneous	–	Hurler syndrome
		Hunter disease
		Gaucher syndrome
	Osteoporosis	
	Langerhan cell histiocytosis	
	Glycogen storage diseases	

*Note.* From "Basic Concepts of Transplantation" (p. 15), by D. Niess and K. Duffy in S. Ezzone (Ed.), *Hematopoietic Stem Cell Transplantation: A Manual for Nursing Practice*, 2004, Pittsburgh, PA: Oncology Nursing Society. Copyright 2004 by the Oncology Nursing Society. Reprinted with permission.

**Table 2. Common Conditioning Regimens and Indications<sup>a</sup>**

ABBREVIATION	REGIMEN/AGENTS	INDICATIONS/DISEASE
Cy/TBI	Cyclophosphamide and total body irradiation	Acute myelogenous leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma
TBI/VP	Total body irradiation and etoposide	Acute myelogenous leukemia, acute lymphocytic leukemia, non-Hodgkin lymphoma, and Hodgkin disease
Bu/Cy	Busulfan and cyclophosphamide	Acute myelogenous leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma
Bu/Cy/VP	Busulfan, cyclophosphamide, and etoposide	Acute myelogenous leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma
Cy	Cyclophosphamide	Severe aplastic anemia
Cy/ATG	Cyclophosphamide and antithymocyte globulin	Severe aplastic anemia
TBI/Mel	Total body irradiation and melphalan	Multiple myeloma
Mel	Melphalan	Multiple myeloma and nonmyeloablative stem cell transplant <sup>b</sup>
CTCb	Cyclophosphamide, thiopeta, and carboplatin	Breast cancer
CT	Cyclophosphamide and thiopeta	Breast cancer
CEC	Cyclophosphamide, etoposide, and carboplatin	Breast cancer and solid tumors
CBV	Cyclophosphamide, carmustine, and etoposide	Non-Hodgkin lymphoma and Hodgkin disease
BEAM	Carmustine, etoposide, cytarabine, and melphalan	Non-Hodgkin lymphoma and Hodgkin disease
MCC	Mitoxantrone, carboplatin, and cyclophosphamide	Ovarian cancer
TBI	Total body irradiation	Nonmyeloablative stem cell transplant <sup>b</sup>
Fludara/Bu/ATG	Fludarabine, busulfan, and antithymocyte globulin	Nonmyeloablative stem cell transplant <sup>b</sup>
Fludara/Cy	Fludarabine and cyclophosphamide	Nonmyeloablative stem cell transplant <sup>b</sup>
Fludara/Cy/ATG	Fludarabine, cyclophosphamide, and antithymocyte globulin	Nonmyeloablative stem cell transplant <sup>b</sup>
Fludara/Mel	Fludarabine and melphalan	Nonmyeloablative stem cell transplant <sup>b</sup>

<sup>a</sup> This list is not all inclusive and serves only as examples of conditioning regimens.

<sup>b</sup> These agents currently are used in clinical trials.

*Note.* From "Transplant Course" (p. 44), by F. McAdams and M. Burgunder in S. Ezzone (Ed.), *Hematopoietic Stem Cell Transplantation: A Manual for Nursing Practice*, 2004, Pittsburgh, PA: Oncology Nursing Society. Copyright 2004 by the Oncology Nursing Society. Reprinted with permission.

Therefore, patients are susceptible to severe infections. Life-threatening infections have remained a leading cause of morbidity among HSCT recipients and have accounted for approximately 20% of deaths, most of which generally occur in the first 100 days after transplantation (Zuccotti, Strasfeld, & Weinstock, 2005). The role of prophylactic antibiotics long has been established, although the most appropriate agents and the duration of therapy still are subjects of much discussion (Trifilio, Verma, & Mehta, 2004). Selection of a prophylactic agent should consider institutional susceptibility profiles and the spectrum of organisms that must be covered (West & Mitchell, 2004).

**Bacterial infections:** More common during the neutropenic phase after conditioning regimens, bacterial infections may be acquired at any point during the HSCT process. Primary sources of bacterial infection include central venous catheters, mouth flora, and gut flora. Decisions regarding the use of prophylactic antibacterial agents must take into consideration the benefits of prevention of infection against the consequences of organisms developing resistance (Sullivan et al., 2001).

**Fungal infections:** Fungal infections occurring in patients undergoing HSCT can be grouped into three general categories: invasive infection (*Candida* and *Aspergillus* species), geographically restricted systemic mycoses (*Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*), and invasive infections of newly emerging fungi (*Fusarium*, *Paecilomyces*, the *Zygomycetes* [includes mucor species], *Scedosporium*,

*Scopulariopsis*, and *Dactylaria*). Antifungals are used in three ways to prevent diseases: prophylactic (general prevention), empiric (e.g., febrile neutropenic patient with negative clinical and laboratory findings), and preemptive (high risk for life-threatening infection prior to onset of clinically recognizable disease) (Sullivan et al., 2001).

**Protozoal infections:** Included in this category are *Pneumocystis carinii* pneumonia and toxoplasma gondii. Prophylaxis against *Pneumocystis carinii* pneumonia using trimethoprim-sulfamethoxazole as the preferred agent is recommended for all allogeneic HSCT recipients (Sullivan et al., 2001).

**Viral infections:** Common viral infections after HSCT include cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, and the respiratory viruses (respiratory syncytial viruses, parainfluenza viruses, influenza viruses, and adenovirus). Recommendations include the use of prophylactic or preemptive agents for high-risk and/or seropositive individuals to prevent disease or disease recurrence (Sullivan et al., 2001).

## Critical Care Complications of Transplantation

Recipients of HSCT usually require critical care monitoring or advanced support. A 2003 review by Afessa, Tefferi, Dunn, Litzow, and Peters reported admission rates to the ICU ranging

**Table 3. Nursing Implications of Selected Drugs Used in Hematopoietic Stem Cell Transplantation**

AGENT OR DRUG	NURSING IMPLICATIONS
<b>Immunosuppressants</b>	
Tacrolimus	<ul style="list-style-type: none"> <li>• Therapeutic range is 5–15 ng/ml.</li> <li>• Azole antifungals, calcium channel blockers, theophylline, and macrolide antibiotics may increase tacrolimus levels, leading to increased toxicity.</li> <li>• Phenobarbital, phenytoin, rifampin, and St. John's wort may decrease tacrolimus levels, leading to graft-versus-host disease (GVHD).</li> </ul>
Cyclosporine	<ul style="list-style-type: none"> <li>• Minimum concentration or predose trough level: 75–300 ng/ml</li> <li>• Coadministration with sirolimus significantly increases peak concentration of sirolimus; have a four-hour interval between doses.</li> <li>• Azole antifungals, calcium channel blockers, fluoroquinolones, and macrolide antibiotics may increase cyclosporine levels, leading to toxicity.</li> <li>• Carbamazepine, phenytoin, rifampin, and St. John's wort may decrease cyclosporine levels, leading to GVHD.</li> </ul>
Sirolimus	<ul style="list-style-type: none"> <li>• Target concentrations               <ul style="list-style-type: none"> <li>– With tacrolimus or cyclosporine: 5–10 ng/ml</li> <li>– Without tacrolimus or cyclosporine: 10–12 ng/ml</li> </ul> </li> <li>• Administer four hours after administration of cyclosporine.</li> </ul>
<b>Antifungal Therapy</b>	
Fluconazole	<ul style="list-style-type: none"> <li>• Drug interactions with tacrolimus and cyclosporine are more likely to occur at doses higher than 200 mg per day.</li> <li>• Rifampin shortens the half-life of fluconazole.</li> <li>• Phenytoin toxicity may occur when coadministered with fluconazole at doses higher than 200 mg per day.</li> <li>• Fluconazole inhibits metabolism of warfarin, requiring frequent monitoring of International Normalized Ratio in the first few days of concomitant administration.</li> </ul>
Itraconazole	<ul style="list-style-type: none"> <li>• Serum concentrations of higher than 500 ng/ml are required to prevent invasive fungal infection.</li> <li>• Drugs that decrease plasma concentration of itraconazole include carbamazepine, phenobarbital, phenytoin, isoniazid, rifampin, and rifabutin.</li> <li>• Itraconazole may increase serum concentration of tacrolimus, cyclosporine, sirolimus, and warfarin.</li> <li>• Case reports have reported increased concentrations (leading to greater toxicities) of antineoplastics (e.g., vinca alkaloids, busulfan, ifosfamide, cyclophosphamide, epipodophyllotoxins) when coadministered with itraconazole.</li> </ul>
Voriconazole	<ul style="list-style-type: none"> <li>• Concurrent administration with the following agents is contraindicated: sirolimus, ergot alkaloids, terfenadine, astemizole, cisapride, pimozone, quinidine, rifampin, and rifabutin.</li> </ul>
<b>Echinocandins</b>	
Caspofungin	<ul style="list-style-type: none"> <li>• May decrease plasma concentration of tacrolimus, necessitating an increase in tacrolimus dose</li> <li>• Concomitant administration of caspofungin with cyclosporine is not recommended.</li> </ul>

*Note.* Based on information from Leather, 2004; Srinivas et al., 2005.

from 15%–40% of all HSCT recipients. HSCT-related complications were classified by Scott, Morgan, Durrant, and Boots (2002) according to etiology: (a) conditioning regimen–related toxicity, (b) immunosuppression, (c) donor cell–mediated toxicity, (d) recipient cell–mediated toxicity, and (e) relapse of underlying malignancy. Complications also may be classified according to the time they occur in the HSCT continuum: (a) preengraftment, usually from the start of the conditioning regimen to approximately day 30; (b) early after engraftment (i.e., neutrophil recovery that continues until B- and T-lymphocyte recovery is apparent), which usually is from day 30–100; and (c) late after the transplantation phase, occurring more than 100 days after stem cell reinfusion (Pallera & Schwartzberg, 2004). Figure 1 presents a chronology of the complications of HSCT.

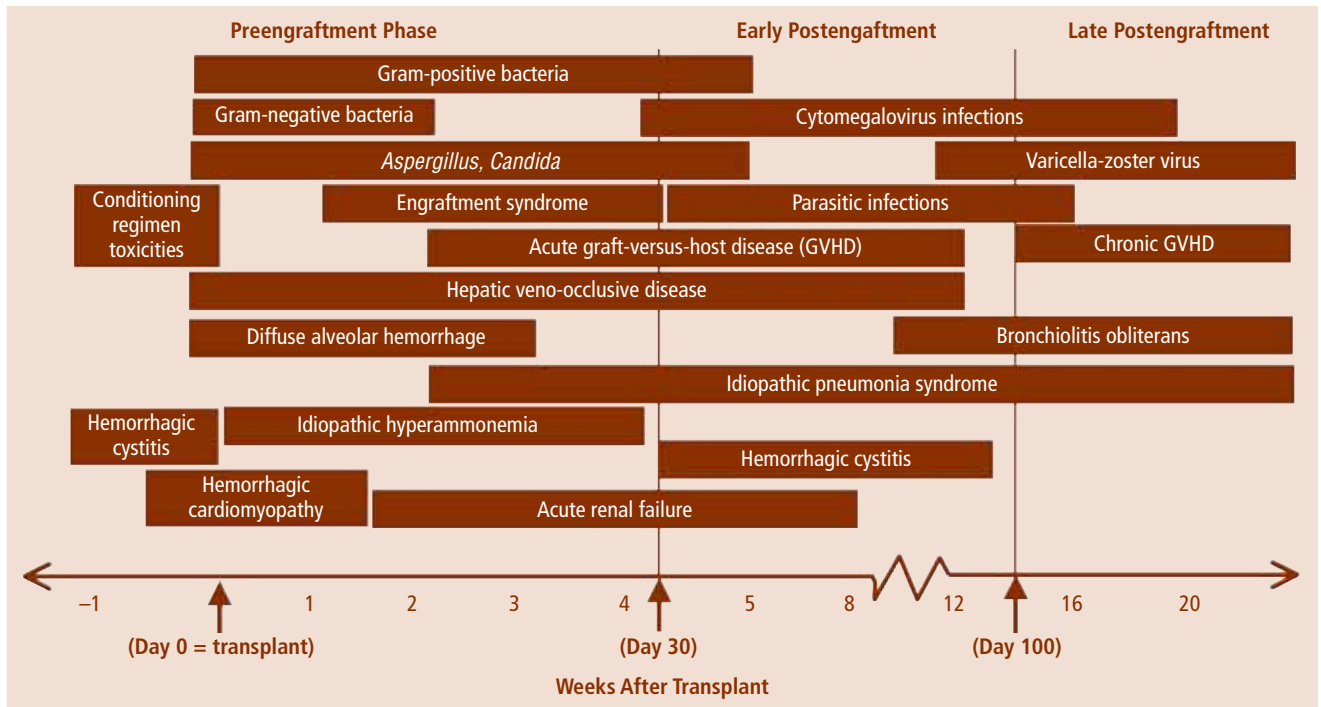
### Infectious Complications

Although the highest risk for infections during the course of HSCT is during the obligatory period of neutropenia, infectious complications may arise at any point during preengraftment, early after engraftment, and well into the late postengraftment

phase (Wujcik, Ballard, & Camp-Sorrell, 1994). Clinical signs of infection in patients undergoing HSCT may be very subtle. Prompt recognition is key to preventing the sudden and rapid deterioration of patients' clinical condition.

**Sepsis:** Sepsis, a life-threatening consequence of documented infection, presents when two or more of the following parameters are met: (a) temperature greater than 100.4°F or 38°C, (b) heart rate greater than 90 beats per minute, (c) respiratory rate greater than 20 breaths per minute, and (d) white blood cell count greater than 12,000 or less than 4,000 or greater than 10% bands (Gobel, 2005). Shorr, Moores, Edenfield, Christie, and Fitzpatrick (1999) identified sepsis as the most frequent reason for intubation in a prospective data review of 17 patients requiring intubation in a cohort of 159. Studies by Jackson et al. (1998) and Soubani et al. (2004) listed sepsis as the second leading cause of ICU admission, second only to pulmonary complications. A study conducted by Price, Thall, Kish, Shannon, and Andersson (1998) listed sepsis as the third cause of ICU admission, preceded by pulmonary and cardiac etiologies.





**Figure 1. Chronology of Hematopoietic Stem Cell Transplant Complications**

*Note.* Based on information from Khurshid & Anderson, 2002; Leger & Nevill, 2004; Shivnan et al., 1996.

**Bacterial pneumonia:** Bacterial pneumonia is seen primarily during the preengraftment period of obligatory severe neutropenia. Although fever often is the presenting symptom in neutropenic patients, fever and chest x-ray abnormalities may be absent. Prompt initiation of broad-spectrum antibiotics with antipseudomonal activity is necessary in all probable cases of bacterial pneumonia and in febrile neutropenic patients without a consistent site of infection (Kotloff et al., 2004).

**Cytomegalovirus:** Cytomegalovirus significantly contributes to morbidity and mortality in patients undergoing HSCT, particularly those who receive allogeneic transplants. Pneumonitis is the most common manifestation that requires advanced support (Barnes & Stallard, 2001). Cytomegalovirus pneumonitis typically is demonstrated by nonproductive cough, fever, and hypoxemia, which may deteriorate rapidly to respiratory failure. Mechanical ventilation, when indicated, uses high levels of inspired oxygen and positive end-expiratory pressure (Shaffer & Wilson, 1993). In the not-so-distant past, death almost always was certain with diagnosis of cytomegalovirus pneumonitis; however, survival rates are improving with the advent of combination treatment with ganciclovir (Cytovene®, Hoffmann LaRoche Inc.) and cytomegalovirus immunoglobulin (Thymoglobulin®, Genzyme Corp., Cambridge, MA) (Kotloff et al., 2004).

**Aspergillosis:** One of the most catastrophic complications of HSCT is invasive aspergillosis, a risk often identified with recipients of allogeneic transplants but which may occur in those receiving autologous transplants. In most cases, invasive aspergillosis is confined to the lungs; however, sinus and central nervous system involvement is reported with some frequency (Kotloff et al., 2004). Three factors play a crucial role in the development of aspergillosis in patients undergoing HSCT: disruption in the mu-

cocutaneous barrier to infection, environmental exposure to the pathogen, and immunosuppression (Sullivan et al., 2001). Clinical presentation includes cough, dyspnea, pleuritic chest pain, and hemoptysis. Seizures and hemiparesis are early warning signs of central nervous system involvement (Kotloff et al.).

### Engraftment Syndrome

Engraftment syndrome is a poorly understood cluster of symptoms that occurs during the neutrophil recovery phase (periengraftment period) of allogeneic and autologous HSCT and has been described only recently (Gorak et al., 2005). The heterogeneity of clinical findings and the lack of consistent diagnostic criteria have led to incongruous reports on its incidence and risk factors (Maiolino et al., 2003). The release of proinflammatory cytokines, including interleukin-1, tumor necrosis factor  $\alpha$ , and interferon  $\gamma$ , as a consequence of tissue injury from intense conditioning regimens or from recovering neutrophils is implicated in the pathogenesis of engraftment syndrome (Gorak et al.). Although the clinical features of engraftment syndrome vary widely, consistent descriptions include noninfectious fever associated with skin rash, weight gain, diarrhea, and pulmonary infiltrates (Capizzi et al., 2001; Gorak et al.; Maiolino et al.). Early recognition of the syndrome is crucial to avoid indiscriminate use of antibiotic therapy for presumed infectious complications and to initiate steroid therapy promptly, which has been found to be beneficial for patients with engraftment syndrome (Capizzi et al.).

### Graft-Versus-Host Disease

Deeg (2003) defined GVHD as “the clinical manifestation of the attempts of two immune systems, donor and recipient, to

defend their identities” (p. 15) and used the analogy of war to describe the confrontation between the two systems. A literature review by Pallera and Schwartzberg (2004) revealed that significant GVHD occurs in 25%–70% of HLA-matched allogeneic transplant recipients (related or unrelated), and the incidence increases with age. GVHD may be acute or chronic and is distinguished not only by onset of manifestations in relation to the date of the transplant but also by clinical manifestations. Acute GVHD is characterized by inflammation of the skin, liver, and colon as evidenced by rash, diarrhea, and jaundice; it develops in the first three months of HSCT. Chronic GVHD is characterized by dryness of mucous membranes and fibrotic complications that may involve multiple organs; it develops three months after HSCT (Mielcarek et al., 2003).

**Acute graft-versus-host disease:** The clinical manifestations of acute GVHD include rash, mucosal shedding, subsequent diarrhea, and biliary stasis (Jaksch & Mattsson, 2005). The manifestations reveal tissue injury in the three target organs of the disease: the skin, intestinal mucosa, and liver, which share the feature of being exposed to the environment, with the skin and the gut as protective barriers and the liver as the first line of defense outside the gut (Ferrara & Yanik, 2005). Grading of acute GVHD conforms to the criteria listed in Tables 4 and 5.

Glucocorticoids remain the backbone of treatment for acute GVHD, and other immunosuppressant agents such as cyclosporine (Sandimmune), tacrolimus (Prograf), and methotrexate are being used as part of prophylactic strategies. Agents such as sirolimus (Rapamune®, Wyeth Pharmaceuticals Inc., Madison,

**Table 5. Severity of Acute Graft-Versus-Host Disease**

OVERALL GRADE	SKIN GRADE	LIVER GRADE	GASTROINTESTINAL TRACT GRADE
0	0	0	0
1	1 or 2	0	0
2	1, 2, or 3	1	1
3	2 or 3	2 or 3	2 or 3
4	2, 3, or 4	2, 3, or 4	2, 3, or 4

*Note.* From “Managing the Toxicity of Hematopoietic Stem Cell Transplant,” by A. Pallera and L. Schwartzberg, 2004, *Journal of Supportive Oncology*, 2, p. 228. Copyright 2004 by Elsevier Inc. Reprinted with permission.

NJ), thalidomide (Thalomid®, Celgene Corporation, Warren, NJ), antithymocyte globulin (Thymoglobulin), azathioprine (Imuran®, Prometheus Laboratories, Inc., San Diego, CA), photophoresis, psoralen with ultraviolet A therapy, hydroxychloroquine (Plaquenil®, Sanofi-Synthelabo Inc., New York, NY), rituximab (Rituxan®, Genentech, Inc., South San Francisco, CA), daclizumab (Zenapax®, Hoffmann LaRoche Inc.), infliximab (Remicade®, Centocor Inc., Malvern, PA), and pentostatin (Nipent®, Supergen Inc., San Ramon, CA) have been used in the management of steroid-refractory GVHD with varying success rates (Pallera & Schwartzberg, 2004). Use of these agents varies according to institutions with consideration to physician and patient preferences.

**Chronic graft-versus-host disease:** In contrast to the pathogenesis of acute GVHD, the pathogenesis of chronic GVHD is poorly understood. Chronic GVHD may develop as an extension of acute GVHD (progressive onset), after acute GVHD resolution (quiescent onset), or without acute GVHD (de novo onset) (Kansu, 2004). A 2001 survey of transplant centers participating in the International Bone Marrow Transplant Registry revealed variations in establishing diagnosis of chronic GVHD based on clinical presentation and discrepancies in the use of diagnostic tests (Lee et al., 2002). Figure 2 classifies chronic GVHD as either limited or extensive based on clinical and pathologic presentation. Management of chronic GVHD incorporates the same therapies used for the treatment of acute GVHD. Systemic therapy using a combination of cyclosporine and prednisone is the first-line treatment used most widely by transplant centers. For patients refractory to steroids, tacrolimus has been used with mycophenolate mofetil as salvage therapy.

### Hepatic Veno-Occlusive Disease

The clinical diagnosis of hepatic veno-occlusive disease is considered one of the complications commonly associated with HSCT and is based on the classic triad of weight gain, painful hepatomegaly, and jaundice (Wadleigh, Ho, Momtaz, & Richardson, 2003). Hepatic veno-occlusive disease is a direct result of endothelial cell damage and cytokine release from high-dose chemotherapy that activates the coagulation cascade, leading to occlusion and constriction in the hepatic vasculature, eventually causing hepatic outflow obstruction, portal hypertension, hepatocyte necrosis, and parenchymal fibrosis (Coppell, Brown, & Perry, 2003).

**Table 4. Grading of Acute Graft-Versus-Host Disease: Severity of Individual Organ Involvement**

ORGAN AND GRADE	DESCRIPTION
<b>Skin</b>	
+1	A maculopapular eruption involving less than 25% of the body surface
+2	A maculopapular eruption involving 25%–50% of the body surface
+3	Generalized erythroderma
+4	Generalized erythroderma with bullous formation, often with desquamation
<b>Liver</b>	
+1	Moderate increase of serum glutamic-oxaloacetic transaminase (150–750 IU) and/or bilirubin (2.0–3.0 mg/dl)
+2	Bilirubin increase (3.1–5.9 mg/dl)
+3	Bilirubin increase (6.0–14.9 mg/dl)
+4	Bilirubin increase >15 mg/dl
<b>Gastrointestinal Tract</b>	
+1	Stool > 500 ml per day
+2	Stool > 1,000 ml per day
+3	Stool > 1,500 ml per day
+4	Stool > 2,000 ml per day or severe abdominal pain, with or without ileus

*Note.* From “Managing the Toxicity of Hematopoietic Stem Cell Transplant,” by A. Pallera and L. Schwartzberg, 2004, *Journal of Supportive Oncology*, 2, p. 228. Copyright 2004 by Elsevier Inc. Reprinted with permission.

### Limited Chronic GVHD

Either or both:

- Localized skin involvement
- Hepatic dysfunction from chronic GVHD

### Extensive Chronic GVHD

Either:

- Generalized skin involvement
- Localized skin involvement and/or hepatic dysfunction from chronic GVHD

Plus one or more of the following:

- Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis or involvement of eye (Schirmer's test with less than 5 mm wetting)
- Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy
- Involvement of any other target organ

## Figure 2. Clinical-Pathologic Classification of Chronic Graft-Versus-Host Disease (GVHD)

*Note.* From "Managing the Toxicity of Hematopoietic Stem Cell Transplant," by A. Pallera and L. Schwartzberg, 2004, *Journal of Supportive Oncology*, 2, p. 229. Copyright 2004 by Elsevier Inc. Reprinted with permission.

Clinical presentation of the disease usually is heralded by asymptomatic weight gain because of water and sodium retention, followed by progressive hyperbilirubinemia. Severe right-upper-quadrant pain necessitating the use of narcotics usually is the first symptom of the disease, which also distinguishes hepatic veno-occlusive disease from GVHD and fungal infections. Subsequent physical examination usually reveals hepatomegaly and ascites, with resultant weight gain being refractory to conventional diuretics. Clinical manifestations also may include thrombocytopenia refractory to platelet transfusions, coagulation factor deficiencies, and prolonged prothrombin time. Severe encephalopathy progressing to coma may be seen in very serious cases. Liver biopsy, although considered the gold standard in the diagnosis of hepatic veno-occlusive disease, may be contraindicated in most patients because of severe thrombocytopenia; as such, clinicians must rely heavily on clinical findings to establish diagnosis (Kumar, DeLeve, Kamath, & Tefferi, 2003). The diagnostic criteria for hepatic veno-occlusive disease are summarized in Figure 3, and the classification system for severity of disease is summarized in Figure 4.

Prevention of hepatic veno-occlusive disease is the most effective management strategy because treatment has continued to be elusive. Recognizing and altering risk factors, such as reducing chemotherapy doses, fractionating TBI, and using nonmyeloablative HSCT, may reduce the incidence of hepatic veno-occlusive disease. The use of prophylactic, low-dose, unfractionated heparin may aggravate bleeding; low-molecular-weight heparin, although promising, has yet to be subjected to further clinical trials. A retrospective study of 462 adult patients receiving HSCT revealed that low-molecular-weight heparin was more effective than unfractionated heparin, with or without prostaglandin E<sub>1</sub>, in preventing hepatic veno-occlusive disease (Simon et al., 2001). Ursodeoxycholic acid (Actigall®, Watson Pharmaceuticals, Corona, CA) is thought to protect he-

patocytes from cholestasis but failed to demonstrate any benefit in one study (Coppell et al., 2003). A newer agent, defibrotide, a fibrinolytic and antithrombotic agent, is currently in a phase II clinical trial and has shown positive results (National Institutes of Health, 2004).

## Respiratory Complications

Respiratory complications, including infectious and noninfectious etiologies, are of major concern in the HSCT population, with an incidence as high as 60% reported in the literature and as much as one-third of patients requiring intensive care support (Kotloff et al., 2004; Shivan et al., 1996). In addition, respiratory complications have been reported to be the most common cause of mortality in HSCT patients in postmortem reviews of pulmonary findings by Roychowdhury et al. (2005) and Sharma et al. (2005). Categorically, respiratory failure has been reported as the most common cause of critical illness, with incidence reports as high as 66%, followed by sepsis with hypotension in 10% of HSCT patients (Jackson et al., 1998; Kotloff et al., 2004). In another review, conducted by Benoit, Vandewoude, Decruyenaere, Hoste, and Colardyn (2003), the mortality rate for patients who had undergone allogeneic HSCT and subsequently developed respiratory failure requiring mechanical ventilation was 83%–97%. Common noninfectious respiratory complications include diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, bronchiolitis obliterans, and pulmonary fibrosis.

**Diffuse alveolar hemorrhage:** Diffuse alveolar hemorrhage is an infrequent, noninfectious respiratory complication of

### Seattle Criteria

Development of at least two of the three following clinical features before day 30 after transplantation:

- Jaundice
- Hepatomegaly with right-upper-quadrant pain
- Ascites and/or unexplained weight gain

### Baltimore Criteria

Development of hyperbilirubinemia with serum bilirubin > 2 mg/dl within 21 days after transplantation and at least two of the following clinical signs and symptoms:

- Hepatomegaly, which may be painful
- Weight gain > 5% from baseline
- Ascites

### Modified Seattle Criteria

Development of at least two of the three following clinical features within 20 days after transplantation:

- Hyperbilirubinemia with serum bilirubin > 2 mg/dl
- Hepatomegaly with right-upper-quadrant pain
- Weight gain > 2% from baseline body weight because of fluid accumulation.

## Figure 3. Diagnostic Criteria for Veno-Occlusive Disease

*Note.* From "Hepatic Veno-Occlusive Disease (Sinusoidal Obstruction Syndrome) After Hematopoietic Stem Cell Transplantation," by S. Kumar, L. DeLeve, P. Kamath, and A. Tefferi, 2003, *Mayo Clinic Proceedings*, 78, p. 593. Copyright 2003 by Mayo Foundation for Medical Education and Research. Reprinted with permission.

### Mild

- Patient has no adverse effects from liver disease.
- Patient requires no treatment of veno-occlusive disease.
- Illness is self-limited.

### Moderate

- Patient has an adverse effect from liver disease.
- Patient requires treatment of veno-occlusive disease (such as diuretics for fluid retention or medication to relieve pain from hepatomegaly).

### Severe

- Signs and symptoms of veno-occlusive disease do not resolve by day 100.
- Patient dies of complications directly attributable to veno-occlusive disease.

## Figure 4. Classification System for Severity of Veno-Occlusive Disease

*Note.* From "Hepatic Veno-Occlusive Disease (Sinusoidal Obstruction Syndrome) After Hematopoietic Stem Cell Transplantation," by S. Kumar, L. DeLeve, P. Kamath, and A. Tefferi, 2003, *Mayo Clinic Proceedings*, 78, p. 594. Copyright 2003 by Mayo Foundation for Medical Education and Research. Reprinted with permission.

HSCT, with incidence rates ranging from 1%–5% and 3%–7% in the autologous and allogeneic transplant settings, respectively (Weisdorf, 2003). Survival rates are dismal at less than 33% (Weisdorf), which reflects the 70%–100% mortality rate reported by Raptis et al. (1999). Bronchoscopy establishes the diagnosis of diffuse alveolar hemorrhage, a hemorrhagic syndrome characterized by cough or dyspnea, respiratory compromise, and radiographic evidence of unilateral or bilateral alveolar infiltrates, often associated with fever without evidence of infection occurring two to three weeks after HSCT (Lewis, DeFor, & Weisdorf, 2000). Admission to the ICU and mechanical ventilation are almost always necessary in the management of diffuse alveolar hemorrhage (Kotloff et al., 2004). Management also includes measures to reduce alveolar filling and pulmonary edema, as well as administration of high-dose steroids in an attempt to reduce potential acute inflammatory response thought to be the pathophysiologic mechanism behind the syndrome (Raptis et al.; Weisdorf).

**Idiopathic pneumonia syndrome:** The diagnosis of idiopathic pneumonia syndrome, pathologically defined by the presence of noninfectious interstitial and alveolar pneumonitis and interstitial fibrosis that leads to alveolar congestion and decreased lung compliance, usually is one of exclusion (Shankar & Cohen, 2001). Clinical manifestations vary from asymptomatic to acute respiratory distress syndrome and usually include

**Table 6. Organ-Specific Treatment-Related Toxicities of Hematopoietic Stem Cell Transplantation**

SPECIFIC TOXICITIES	CLINICAL PRESENTATION	MANAGEMENT
<b>Gastrointestinal System</b> Neutropenic enterocolitis: necrotizing inflammation of the cecum, colon, and terminal part of the ileum occurring at the end of 7–10 days after the completion of chemotherapy	Fever, abdominal pain, and diarrhea during the neutropenic phase	Conservative management includes bowel rest, fluid resuscitation, broad-spectrum antibiotics, antimycotic drugs, and granulocyte macrophage–colony-stimulating factors.
<b>Cardiac System</b> Antracycline-induced cardiomyopathy	Chronic weight gain, peripheral edema, tachycardia, dyspnea on exertion, orthopnea, and adventitious breath sounds	Supportive care involves fluid management, diuretics, and digitalis.
Cyclophosphamide toxicity	Hemorrhagic myocardial necrosis, pericardial effusion and tamponade, and fibrinous pericarditis	–
<b>Renal System</b> Nephrotoxicity may be caused by acute tubular necrosis from nephrotoxins or secondary to tumor cell lysis.	Elevated serum creatinine	Fluid and electrolyte management
Hemorrhagic cystitis: following treatment with high-dose ifosfamide or cyclophosphamide	Hematuria	Prophylactic measures include hyperhydration and administration of mesna. Treatment includes aggressive hydration, diuresis, and bladder antispasmodics.
<b>Neurologic System</b> Encephalopathy may be caused by conditioning regimen, immunosuppressive drugs, infections, or cerebrovascular events.	Subtle mental status changes to seizures	Prophylactic treatment with phenytoin when high-risk drugs are given (e.g., high-dose busulfan), close monitoring of drug levels, and blood pressure management
Idiopathic hyperammonemia	Acute-onset lethargy, confusion, tachypnea, vomiting with rapid progression to coma, and death	Hemodialysis

*Note.* Based on information from Pallera & Schwartzberg, 2004; Shaffer & Wilson, 1993; Wach et al., 2004.



dyspnea, nonproductive cough, hypoxemia, tachypnea, and diffuse radiographic infiltrates (Khurshid & Anderson, 2002). The syndrome occurs 42–49 days after HSCT in approximately 12% of allogeneic transplant patients (Khurshid & Anderson) and carries a mortality rate as high as 82% (Kantrow, Hackman, Boeckh, Myerson, & Crawford, 1997). Diagnosis is established by bronchioalveolar lavage. Until effective prophylactic or treatment strategies are identified, most patients succumb to respiratory failure or complications related to superimposed infections (Khurshid & Anderson).

**Bronchiolitis obliterans:** Bronchiolitis obliterans is an obstructive pulmonary disease affecting 10%–15% of HSCT recipients with chronic GVHD during the first year after transplantation. The insidious onset of bronchiolitis obliterans often is characterized by the absence of respiratory symptoms with normal-appearing or hyperinflated lungs on x-ray (Dudek, Mahaseth, DeFor, & Weisdorf, 2003). Commonly observed clinical indicators include recurrent sinusitis and bronchitis, with a persistent, unexplained cough as the usual presenting symptom. Pulmonary function tests that reveal bronchodilator-resistant airway obstruction establishes diagnosis (Rabitsch et al., 2001). The disease often is refractory to treatment, and patients who do not respond to immunosuppressive therapy have a grave prognosis (Rabitsch et al.). Patients who meet rigid criteria (cured of underlying disease warranting HSCT and absence of comorbidities) may be offered lung transplantation (Kotloff et al., 2004) as an option to manage the disease.

## Conclusion

Admission to the ICU is inevitable for some HSCT recipients. Hemodynamic monitoring, electrocardiography monitoring, ventilatory support, and continuous electrolyte replacement therapy are but some of the treatment modalities that cannot always be supported on a bone marrow transplant unit. Nurses can positively impact outcomes and decrease ICU admissions through early recognition of and intervention for complications expected throughout the course of transplantation. The complications presented in this article are not all inclusive of the toxicities related to HSCT. Table 6 lists other treatment-related toxicities that may be expected in the transplant setting.

The care of critically ill patients undergoing HSCT is laden with challenges, including the lack of proven therapeutic strategies to manage a number of transplant-related complications, dilemmas in completing diagnostic procedures (comorbid conditions preclude the performance of invasive diagnostic techniques), and conflicts that arise from the difference in perception of patient survivability. Proper identification of patients who would benefit from ICU support has continued to be elusive; prognostic indicators, such as the Acute Physiology and Chronic Health Evaluation, Simplified Acute Physiology Scale, Sequential Organ Failure Assessment, and Mortality Probability Model, have not been validated in the HSCT setting (Benoit et al., 2003; Price et al., 1998; Silfvast, Pettila, Ihalainen, & Elonen, 2003). Rubenfeld and Crawford's (1996) proposal for evidence-based guidelines for initiation of mechanical ventilation after HSCT is the only existing document, to the authors' knowledge, that addresses the issues associated with futility of mechanical ventilation in the HSCT setting (see Figure 5).

- I. The goal of bone marrow transplantation is to cure the underlying condition and return the patient to an acceptable quality of life. When these goals are no longer attainable or at the request of a suitably informed patient or surrogate, further intensive life support should cease.
- II. All bone marrow transplant recipients, their surrogates, and involved physicians and nurses should participate in the informed consent for transplantation. As part of this informed consent, an estimate of the patient's risk for requiring mechanical ventilation and developing hepatic veno-occlusive disease should be conveyed in simple language.
- III. The outcomes for mechanically ventilated patients should be presented. Individual institutions that have formally collected prognostic data from samples of similar size may substitute their experience in this section.
  - A. Approximately 6% of patients survive for 30 days after extubation and are discharged from the hospital. Half of these survivors live for more than two years.
  - B. Patients who are mechanically ventilated, develop lung injury, and either receive vasopressors or develop hepatic and renal insufficiency (as previously defined) do not survive (as estimated in 398 similar patients at the Fred Hutchinson Cancer Research Center).
  - C. Patients without this combination of risk factors have a survival rate of about 13%.
- IV. The following conditions make the goals of bone marrow transplantation, specified in (I), unattainable: massive intracranial hemorrhage, tumor relapse despite transplantation, and fungal infection with progressive graft-versus-host disease requiring immunosuppression.
- V. The presumption is that patients who fulfill the criteria in (IIIB) or (IV) will not receive prolonged life support because the goals of transplantation specified in (I) would no longer be attainable. Patients and surrogates who do not agree with this standard of care should be encouraged to discuss their concerns at the time of informed consent for the transplantation.
- VI. The guidelines are not meant to be rigid. Patients who enter an approved experimental trial to improve the outcome of critical illness in bone marrow transplant recipients may be exempted. When care deviates from this guideline, review by an institutional committee should be initiated. The committee should review the case in a timely fashion and ensure that those involved have communicated the outcome data fairly and heard all opinions. Most cases should be able to be resolved by discussion, appeal to the data, and referral to the informed consent. Intensive care may be continued if the reasons to do so are compelling (for example, rapid clinical improvement during the review period), although the expectation of survival for 30 days after extubation and hospital discharge is unchanged.

### Figure 5. Proposed Guidelines for Mechanical Ventilation After Hematopoietic Stem Cell Transplantation

*Note.* From "Withdrawing Life Support From Mechanically Ventilated Recipients of Bone Marrow Transplants," by G.D. Rubenfeld and S.W. Crawford, 1996, *Annals of Internal Medicine*, 125, pp. 625–633 (Appendix). Copyright 1996 by the American College of Physicians. Reprinted with permission.

The development of novel therapies to prevent and manage treatment-related complications is the silver lining behind the dismal prognosis for HSCT recipients who require critical care. The growing amount of outcomes data continues to add to the body of knowledge. Transplant nurses and critical care nurses working with transplant recipients must continue collaborative efforts to improve outcomes in the HSCT recipient population.

**Author Contact:** Marlon G. Saria, MSN, RN, AOCNS, can be reached at msaria@ucsd.edu, with copy to editor at CJONEditor@ons.org.

## References

- Afessa, B., Tefferi, A., Dunn, W.F., Litzow, M.R., & Peters, S.G. (2003). Intensive care unit support and Acute Physiology and Chronic Health Evaluation III performance in hematopoietic stem cell transplant recipients. *Critical Care Medicine, 31*, 1715-1721.
- Barnes, R.A., & Stallard, N. (2001). Severe infections after bone marrow transplantation. *Current Opinion in Critical Care, 7*, 362-366.
- Benoit, D.D., Vandewoude, K.H., Decruyenaere, J.M., Hoste, E.A., & Colardyn, F.A. (2003). Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. *Critical Care Medicine, 31*, 104-112.
- Bevans, M., & Shelburne, N. (2004). Hematopoietic stem cell transplantation. *Clinical Journal of Oncology Nursing, 8*, 541-543.
- Capizzi, S.A., Kumar, S., Huneke, N.E., Gertz, M.A., Inwards, D.J., Litzow, M.R., et al. (2001). Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. *Bone Marrow Transplantation, 27*, 1299-1303.
- Coppell, J.A., Brown, S.A., & Perry, D.J. (2003). Venous-occlusive disease: Cytokines, genetics, and haemostasis. *Blood Reviews, 17*, 63-70.
- Deeg, H.J. (2003). New strategies for prevention and treatment of graft-versus-host disease and for induction of graft-versus-leukemia effects. *International Journal of Hematology, 77*, 15-21.
- Diaconescu, R., Flowers, C.R., Storer, B., Sorror, M.L., Maris, M.B., Maloney, D.G., et al. (2004). Morbidity and mortality with non-myeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood, 104*, 1550-1558.
- Dudek, A.Z., Mahaseth, H., DeFor, T.E., & Weisdorf, D.J. (2003). Bronchiolitis obliterans in chronic graft-versus-host disease: Analysis of risk factors and treatment outcomes. *Biology of Blood and Marrow Transplantation, 9*, 657-666.
- Ferrara, J.L., & Yanik, G. (2005). Acute graft versus host disease: Pathophysiology, risk factors, and prevention strategies. *Clinical Advances in Hematology and Oncology, 3*, 415-419, 428.
- Gobel, B. (2005). Metabolic emergencies. In J.K. Itano & K.N. Taoka (Eds.), *Core curriculum for oncology nursing* (4th ed., pp. 383-421). Pittsburgh, PA: Oncology Nursing Society.
- Gorak, E., Geller, N., Srinivasan, R., Espinoza-Delgado, I., Donohue, T., Barrett, A.J., et al. (2005). Engraftment syndrome after nonmyeloablative allogeneic hematopoietic stem cell transplantation: Incidence and effects on survival. *Biology of Blood and Marrow Transplantation, 11*, 542-550.
- Jackson, S.R., Tweeddale, M.G., Barnett, M.J., Spinelli, J.J., Sutherland, H.J., Reece, D.E., et al. (1998). Admission of bone marrow transplant recipients to the intensive care unit: Outcome, survival and prognostic factors. *Bone Marrow Transplantation, 21*, 697-704.
- Jaksch, M., & Mattsson, J. (2005). The pathophysiology of acute graft-versus-host disease. *Scandinavian Journal of Immunology, 61*, 398-409.
- Kansu, E. (2004). The pathophysiology of chronic graft-versus-host disease. *International Journal of Hematology, 79*, 209-215.
- Kantrow, S.P., Hackman, R.C., Boeckh, M., Myerson, D., & Crawford, S.W. (1997). Idiopathic pneumonia syndrome: Changing spectrum of lung injury after marrow transplantation. *Transplantation, 63*, 1079-1086.
- Khurshid, I., & Anderson, L.C. (2002). Non-infectious pulmonary complications after bone marrow transplantation. *Postgraduate Medical Journal, 78*, 257-262.
- Kotloff, R.M., Ahya, V.N., & Crawford, S.W. (2004). Pulmonary complications of solid organ and hematopoietic stem cell transplantation. *American Journal of Respiratory and Critical Care Medicine, 170*, 22-48.
- Kumar, S., DeLeve, L.D., Kamath, P.S., & Tefferi, A. (2003). Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. *Mayo Clinic Proceedings, 78*, 589-598.
- Leather, H. (2004). Drug interactions in the hematopoietic stem cell transplant (HSCT) recipient: What every transplant needs to know. *Bone Marrow Transplantation, 33*, 137-152.
- Lee, S.J., Vogelsang, G., Gilman, A., Weisdorf, D.J., Pavletic, S., Antin, J.H., et al. (2002). A survey of diagnosis, management, and grading of chronic GVHD. *Biology of Blood and Marrow Transplantation, 8*, 32-39.
- Leger, C.S., & Nevill, T.J. (2004). Hematopoietic stem cell transplantation: A primer for the primary care physician. *Canadian Medical Association Journal, 170*, 1569-1577.
- Lewis, I.D., DeFor, T., & Weisdorf, D.J. (2000). Increasing incidence of diffuse alveolar hemorrhage following allogeneic bone marrow transplantation: Cryptic etiology and uncertain therapy. *Bone Marrow Transplantation, 26*, 539-543.
- Maiolino, A., Biasoli, I., Lima, J., Portugal, A.C., Pulcheri, W., & Nucci, M. (2003). Engraftment syndrome following autologous hematopoietic stem cell transplantation: Definition of diagnostic criteria. *Bone Marrow Transplantation, 31*, 393-397.
- Mielcarek, M., Martin, P.J., Leisenring, W., Flowers, M.E., Maloney, D.G., Sandmaier, B.M., et al. (2003). Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood, 102*, 756-762.
- National Institutes of Health. (2004). Defibrotide in treating patients with liver damage following peripheral stem cell transplantation. Retrieved November 15, 2005, from <http://www.clinicaltrials.gov/ct/show/NCT00003966>
- Ozer, H., Armitage, J.O., Bennett, C.L., Crawford, J., Demetri, G.D., Pizzo, P.A., et al. (2000). 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. *Journal of Clinical Oncology, 18*, 3558-3585.
- Pallera, A.M., & Schwartzberg, L.S. (2004). Managing the toxicity of hematopoietic stem cell transplant. *Journal of Supportive Oncology, 2*, 223-237.
- Price, K.J., Thall, P.F., Kish, S.K., Shannon, V.R., & Andersson, B.S. (1998). Prognostic indicators for blood and marrow transplant patients admitted to an intensive care unit. *American Journal of Respiratory and Critical Care Medicine, 158*, 876-884.
- Rabitsch, W., Deviatko, E., Keil, F., Herold, C., Dekan, G., Greinix, H., et al. (2001). Successful lung transplantation for bronchiolitis obliterans after allogeneic marrow transplantation. *Transplantation, 71*, 1341-1343.

- Raptis, A., Mavroudis, D., Suffredini, A., Molldrem, J., Van Rhee, F., Childs, R., et al. (1999). High-dose corticosteroid therapy for diffuse alveolar hemorrhage in allogeneic bone marrow stem cell transplant recipients. *Bone Marrow Transplantation*, *24*, 879-883.
- Resnick, I.B., Shapira, M.Y., & Slavin, S. (2005). Nonmyeloablative stem cell transplantation and cell therapy for malignant and non-malignant diseases. *Transplant Immunology*, *14*, 207-219.
- Roychowdhury, M., Pambuccian, S.E., Aslan, D.L., Jessurun, J., Rose, A.G., Manivel, J.C., et al. (2005). Pulmonary complications after bone marrow transplantation: An autopsy study from a large transplantation center. *Archives of Pathology and Laboratory Medicine*, *129*, 366-371.
- Rubinfeld, G.D., & Crawford, S.W. (1996). Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: A case for evidence-based guidelines. *Annals of Internal Medicine*, *125*, 625-633.
- Scott, P.H., Morgan, T.J., Durrant, S., & Boots, R.J. (2002). Survival following mechanical ventilation of recipients of bone marrow transplants and peripheral blood stem cell transplants. *Anaesthesia and Intensive Care*, *30*, 289-294.
- Shaffer, S., & Wilson, J.N. (1993). Bone marrow transplantation: Critical care implications. *Critical Care Nursing Clinics of North America*, *5*, 531-542.
- Shankar, G., & Cohen, D. (2001). Idiopathic pneumonia syndrome after bone marrow transplantation: The role of pre-transplant radiation conditioning and local cytokine dysregulation in promoting lung inflammation and fibrosis. *International Journal of Experimental Pathology*, *82*, 101-113.
- Sharma, S., Nadrous, H.F., Peters, S.G., Tefferi, A., Litzow, M.R., Aubry, M.C., et al. (2005). Pulmonary complications in adult blood and marrow transplant recipients: Autopsy findings. *Chest*, *128*, 1385-1392.
- Shivnan, J., Shelton, B.K., & Onners, B.K. (1996). Bone marrow transplantation: Issues for critical care nurses. *AACN Clinical Issues*, *7*, 95-108.
- Shorr, A.F., Moores, L.K., Edenfield, W.J., Christie, R.J., & Fitzpatrick, T.M. (1999). Mechanical ventilation in hematopoietic stem cell transplantation: Can we effectively predict outcomes? *Chest*, *116*, 1012-1018.
- Silfvast, T., Pettila, V., Ihalainen, A., & Elonen, E. (2003). Multiple organ failure and outcome of critically ill patients with haematological malignancy. *Acta Anaesthesiologica Scandinavica*, *47*, 301-306.
- Simon, M., Hahn, T., Ford, L.A., Anderson, B., Swinnich, D., Baer, M.R., et al. (2001). Retrospective multivariate analysis of hepatic veno-occlusive disease after blood or marrow transplantation: Possible beneficial use of low molecular weight heparin. *Bone Marrow Transplantation*, *27*, 627-633.
- Soubani, A.O., Kseibi, E., Bander, J.J., Klein, J.L., Khanchandani, G., Ahmed, H.P., et al. (2004). Outcome and prognostic factors of hematopoietic stem cell transplantation recipients admitted to a medical ICU. *Chest*, *126*, 1604-1611.
- Spielberger, R., Stiff, P., Bensinger, W., Gentile, T., Weisdorf, D., Kewalramani, T., et al. (2004). Palifermin for oral mucositis after intensive therapy for hematologic cancers. *New England Journal of Medicine*, *351*, 2590-2598.
- Srinivas, T.R., Meier-Kriesche, H.U., & Kaplan, B. (2005). Pharmacokinetic principles of immunosuppressive drugs. *American Journal of Transplantation*, *5*, 207-217.
- Sullivan, K.M., Dykewicz, C.A., Longworth, D.L., Boeckh, M., Baden, L.R., Rubin, R.H., et al. (2001). Preventing opportunistic infections after hematopoietic stem cell transplantation: The Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation practice guidelines and beyond. *Hematology*, 392-421.
- Trifilio, S., Verma, A., & Mehta, J. (2004). Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: Heterogeneity of current clinical practice. *Bone Marrow Transplantation*, *33*, 735-739.
- Wach, M., Dmoszynska, A., Wasik-Szczepanek, E., Pozarowski, A., Drop, A., & Szczepanek, D. (2004). Neutropenic enterocolitis: A serious complication during the treatment of acute leukemias. *Annals of Hematology*, *83*, 522-526.
- Wadleigh, M., Ho, V., Momtaz, P., & Richardson, P. (2003). Hepatic veno-occlusive disease: Pathogenesis, diagnosis and treatment. *Current Opinion in Hematology*, *10*, 451-462.
- Weisdorf, D.J. (2003). Diffuse alveolar hemorrhage: An evolving problem? *Leukemia*, *17*, 1049-1050.
- West, F., & Mitchell, S.A. (2004). Evidence-based guidelines for the management of neutropenia following outpatient hematopoietic stem cell transplantation. *Clinical Journal of Oncology Nursing*, *8*, 601-613.
- Wujcik, D., Ballard, B., & Camp-Sorrell, D. (1994). Selected complications of allogeneic bone marrow transplantation. *Seminars in Oncology Nursing*, *10*, 28-41.
- Zuccotti, G., Strasfeld, L., & Weinstock, D.M. (2005). New agents for the prevention of opportunistic infections in haematopoietic stem cell transplant recipients. *Expert Opinion on Pharmacotherapy*, *6*, 1669-1679.

Receive continuing nursing education credit for reading this article and taking a brief quiz. See the Continuing Nursing Education in this issue for more information.