With increasing frequency, oncology nurses are providing long-term care to hematopoietic stem cell transplantation (HSCT) recipients in nontransplantation settings. This may be a result of more patients receiving HSCTs, recipients living longer, and recipients’ desire to return to their hometowns as soon as possible. Although critical to patients’ initial recovery after HSCT, immune reconstitution also must remain a priority of oncology nursing care long beyond the date of discharge from a transplantation center. As patients resume their normal lives, oncology nurses need to be diligent in assessment and education to facilitate the ultimate goal, a safe life after HSCT. This article provides concise details about the short- and long-term immunologic effects of HSCT and focuses on the long-standing threat of opportunistic infections that can persist months and years after HSCT.

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many disorders, such as hematologic and oncologic malignancies as well as immunologic and metabolic disorders (Ault & Lazarus, 2005; Wingard, Vogelsang, & Deeg, 2002). With the use of hematopoietic growth factors, peripheral blood stem cells, and nonmyeloablative (NM) conditioning regimens, the morbidity and mortality of allogeneic HSCT have decreased, whereas the frequency of transplantations has increased. Yet, despite the advances, dysfunctional immune reconstitution after transplantation continues to affect optimal patient outcomes.

Immune reconstitution can be defined as the recovery of antigen-specific T-cell function, production of cytokines, and cooperation with B lymphocytes in antibody productions (Alcoser & Burchett, 1999). Numerous transplant-related factors impact immune reconstitution. Immunologic recovery after transplantation occurs in three distinct phases (see Figure 1), during which the pathogens causing the most frequently occurring opportunistic infections can differ (Spitzer, Boeckh, & Nash, 2003).

Infection is the leading nonrelapse cause of mortality among allogeneic transplantation recipients (Center for International Blood and Marrow Transplant Research, 2005). Infections can and do occur at any time during the transplantation process, even when hematologic recovery has occurred but immunodeficiency still persists (Leather & Wingard, 2001).

Because oncology nursing care is needed for patients who have received allogeneic HSCT far beyond initial hospitalization, this article aims to increase awareness of the possible long-term immunodeficiency patients may have, the factors influencing the immunodeficiency, and the risk of possible infections. Nurses play an important role in patient education, identification of symptoms, and patient compliance with prophylactic medications.

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Factors Affecting Immune Reconstitution

The immune system has two components, innate and adaptive. The innate system is the one with which people are born, and the adaptive immune system is acquired throughout people’s lifetimes. The innate system includes anatomic barriers such as the skin and mucosa, along with cytokines, natural killer (NK) and phagocytic cells, and acute-phase proteins (Shames & Kishiyama, 2000). The adaptive immune system includes the cellular and humoral systems (Shames & Kishiyama).

The cellular immune system is composed predominantly of T lymphocytes. Three primary types of T lymphocytes exist, all with specific roles (see Figure 2). The chief function of the cellular immune system is to respond to and kill antigens such as viruses and to aid or inhibit B-lymphocyte function (McKenny & Salerno, 2001). The humoral system is comprised of B lymphocytes that, together with T lymphocytes, make antibodies, the immunoglobulins that combine with antigens to initiate immune responses (Shames & Kishiyama, 2000).

Immune Recovery: Cellular Immunity

In the absence of graft-versus-host disease (GVHD), the total T-lymphocyte count usually returns to normal three months after transplantation. The normal ratio of CD4+ helper T cells to CD8+ suppressor T cells is 2:1 (Alcoser & Burchett, 1999). Studies consistently have shown that levels of CD8+ T cells return to normal by day 100; however, CD4+ T lymphocytes do not return to normal until the second half of the first year (Shenoy et al., 1999). In fact, CD4+ levels can remain below normal limits for more than two years after transplantation, resulting in a reversal of the CD4+ to CD8+ ratio, which can persist for as many as five years after bone marrow transplantation (BMT) (Fujimaki et al., 2001).

Immune Recovery: Humoral Immunity

Humoral reconstitution can be viewed as triphasic, with barely detectable counts from the time of transplantation until three to six months after transplantation; rapidly increasing B-cell counts, leading to above-normal levels 6–24 months after transplantation; and subsequent normalization, typically during the following years (Paloczi, 2000). Serum immunoglobulins may return to normal by four months after transplantation but may be misleading because immunoglobulins are not always functional, especially when GVHD is present (Alcoser & Burchett, 1999). Deficiency in B-lymphocyte function is recognized in the setting of chronic GVHD, which is thought to be the result of the immunosuppressive nature of GVHD process (Abrahamsen et al., 2005). In addition, the use of immunosuppressive medications to treat chronic GVHD further negatively impacts B-lymphocyte function. B-lymphocyte function relies on adequate T-cell function; therefore, when T-lymphocyte function is impaired, so is B-lymphocyte function (Paloczi).

Factors influencing immune reconstitution after allogeneic HSCT include the age of the recipient, the conditioning regimen (e.g., myeloablative, NM), GVHD status, immunosuppressive medications, the source of hematopoietic stem cells (i.e., peripheral blood stem cells [PBSCs], bone marrow, umbilical cord blood) (Auletta & Lazarus, 2005), and the donor’s age and gender (Azuma, Hirayama, Yamamoto, & Komada, 2002; Kolman et al., 2001).

The thymus produces T lymphocytes and is the site of initial T-lymphocyte differentiation (Shames & Kishiyama, 2000), a crucial factor in immune reconstitution (Fallen et al., 2003). Advancing age leads to decreased thymic function and slower naïve T-cell reconstitution, thereby negatively impacting immune reconstitution (Fallen et al.).

Myeloablative Versus Nonmyeloablative Conditioning Regimens

NM conditioning regimens employ the use of lower doses of chemotherapy that allow for recovery of a recipient’s own immune system. The use of NM conditioning regimens decreases the rate of chemotherapy-related toxicities and primarily relies on the development of GVHD for the control of the malignancy being treated. In contrast, myeloablative conditioning regimens use high doses of chemotherapy with or without radiation therapy to completely destroy or myeloablate a recipient’s bone marrow, allowing for replacement by a new immune system.

The use of NM conditioning regimens is relatively recent; therefore, few studies have compared the immune reconstitution of myeloablative versus NM allogeneic HSCTs. Small sample
sizes and different conditioning regimens hinder decisive conclusions. Of two studies that used similar conditioning for NM transplantsations, Saito et al. (2003) showed that patients receiving NM therapy had delayed lymphocyte reconstitution compared to those receiving conventional HSCT. In contrast, Morecki et al. (2001) showed that stem cell reconstitution after NM transplantation resulted in faster immune reconstitution. Although studies comparing myeloablative versus NM transplantsations have limitations, they consistently have shown a decrease in bacterial infections soon after transplantation in NM recipients (Busca et al., 2003; Junghanss & Marr, 2002). However, the rate of fungal infections is consistent between the two groups in the late post-transplantation phase (Junghanss & Marr).

Graft-Versus-Host Disease

GVHD is a clinical syndrome resulting from immunocompetent lymphocytes infused with donor stem cells recognizing antigens in the host as foreign and initiating an immunologic reaction (Forman, 2003). The occurrence and treatment of GVHD can lead to profound deficiencies of cell-mediated and humoral immunity (Leather & Wingard, 2001). Chronic GVHD occurring more than 100 days after transplantation negatively impacts the rate of immune reconstitution through various mechanisms.

1. Chronic GVHD decreases production of CD4+ helper T lymphocytes that are necessary for regulation of T- and B-lymphocyte regulation (Maury et al., 2001).

2. Chronic GVHD increases CD8+ suppressor T lymphocytes that suppress T- and B-lymphocyte response (Parkman & Weinberg, 1999).

3. Chronic GVHD diminishes hosts’ ability to mount an antigen-specific T-lymphocyte response and to produce specific antibodies (Parkman & Weinberg, 2000).

4. Chronic GVHD selects thymic and nonthymic sites as target organs, thereby negatively impacting T-lymphocyte maturation (Fallen et al., 2003; Paloczi, 2000).

Therefore, nurses caring for recipients of allogeneic HSCTs must be cognizant of the fact that immunodeficiency and increased risk for developing infections remain prevalent in patients with chronic GVHD many months after transplantation.

Immunosuppressive Therapy

The primary mechanism of action of many immunosuppressive agents used in the transplantation setting is acting directly on the T lymphocytes or the cytokines that control them. For example, cyclosporine and tacrolimus, two commonly used immunosuppressives, inhibit interleukin-2 production, which is required for T-cell responses (Alcoser & Burchett, 1999). Glucocorticoids, commonly used in the treatment of GVHD, negatively impact immune reconstitution by suppressing cellular immunity (Franchimont, 2004) and impairing effective functioning of phagocytic cells (Leather & Wingard, 2001).

Peripheral Blood Stem Cells Versus Bone Marrow

Allogeneic transplantation can be provided by a traditional infusion of harvested bone marrow cells or by a more recently developed procedure using harvested PBSCs. PBSCs are hematopoietic or parent cells made by the bone marrow which differentiate into platelets, red blood cells, and white blood cells. Overproduction of PBSCs is stimulated via the use of growth factors such as granulocyte–colony-stimulating factor. PBSCs then are harvested via apheresis. Both bone marrow and PBSC are infused via IV into the recipient.

Studies comparing transplantations with PBSCs and bone marrow have shown that the use of PBSCs leads to faster engraftment of granulocytes and lymphocytes, whereas B cells and NK cell reconstitution are similar with bone marrow and PBSCs (Storeck et al., 2001). Faster engraftment may occur because infused PBSCs contain more lymphocytes and monocytes (Shenoy et al., 1999). However, recipients of PBSC have greater rates of late-onset chronic GVHD and higher incidence of fungal and viral infections (Anderson et al., 2003). A meta-analysis of nine randomized clinical trials revealed statistically significant faster engraftment of neutrophils and platelets, an increased incidence of grade 3–4 acute GVHD, and increased incidence of overall chronic GVHD with PBSCs when compared with bone marrow (Stem Cell Trialists’ Collaborative Group, 2005).

Age and Gender of Donor

In a retrospective study of 6,978 volunteer BMT donors identified by the National Marrow Donor Program, the age and gender of the donors were identified as the two most important donor characteristics that influence HSCT recipient outcome (Kollman et al., 2001). Age of the donor was inversely correlated with overall and disease-free survival. As age increased, so did the incidence of GVHD. Recipients of donor stem cells from females who had multiple pregnancies also had an increased incidence of GVHD (Kollman et al.).

Clinical Significance of Delayed Immune Reconstitution

The most crucial consequence of delayed immune reconstitution is the risk of developing opportunistic infections. Quantitative recovery of innate and adaptive immunity does not always correlate with qualitative cellular function, as seen when normal absolute lymphocyte counts occur prior to normalization of lymphocyte function (Auletta & Lazarus, 2005). The phenomenon is an important consideration when caring for patients who have normal counts but persistent opportunistic infections.

Factors and pathogens that cause opportunistic infections vary at different stages after transplantation (Yoo et al., 2004). During the pre-engraftment stage, recipients are most prone to bacterial and fungal infections as a result of granulocytopenia and altered integrity of anatomic barriers, such as the skin and mucosa. In the postengraftment and late phases of allogeneic HSCT, recipients are at increased risk for bacterial, fungal, and viral infections as a result of cellular and humoral immune dysfunction (Yoo et al.). Although the risk of infection may be similar throughout the continuum of HSCT recovery, the causative pathogens may differ, as seen in Figure 3 (Spitzer et al., 2003).
According to data from the Center for International Blood and Marrow Transplant Research (2005) and as displayed in Figure 4, infection was the leading cause of non-relapse-related deaths in allogeneic HSCT. This fact is highlighted in a European Group for Blood and Marrow Transplantation analysis of cause of death after allogeneic HSCT (Gratwohl et al., 2005). The study analyzed 14,403 recipients with early leukemia from 1980–2001. The report found that, although transplantation-related mortality is decreasing, the risk of death resulting from infection remains problematic. The study found that the median time to infection-related death was three months, 25% of infectious deaths took place within two months after HSCT, 25% occurred after seven months, and 10% occurred after one year. The study exemplifies the need for diligent monitoring of transplantation recipients not only in the pre-engraftment phase but also during the postengraftment and late phases of the transplantation process.

### Infections During the Postengraftment Period

The postengraftment stage (i.e., 30–100 days) is characterized by hematologic reconstitution combined with impaired cellular and humoral immunity (Pallera & Schwartzberg, 2004) in addition to potential disturbance in granulocyte function (Einsele et al., 2003).

Patients remain at risk for bacterial, viral, and fungal infections. In fact, 74% of all allogeneic HSCT recipients develop infections after day 50 (Einsele et al., 2003).

#### Viral Infections

Patients are susceptible to numerous viruses, including respiratory syncytial virus, adenovirus, and Epstein-Barr virus, which can cause post-transplantation lymphoproliferative disease.

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**Figure 3. Prevalent Infections After Hematopoietic Stem Cell Transplantation**

However, cytomegalovirus (CMV) is the most common and is one of the primary causes of infection-associated mortality after allogeneic HSCT (Einsele et al., 2003). Patients who are most at risk for developing CMV infection are seropositive recipients, seronegative recipients who received cells from a seropositive donors, and those receiving corticosteroids for GVHD (Campbell & Moravec, 2000). CMV infections commonly manifest as pneumonia, gastroenteritis, hepatitis, and retinitis (Einsele et al.).

Fungal Infections

Patients most at risk for developing fungal infections during the postengraftment phase are those with GVHD receiving treatment with corticosteroids (Leather & Wingard, 2001). Candida and Aspergillus species are the most common pathogens causing systemic fungemia in patients after allogeneic HSCT (Einsele et al., 2003). Candida infections are most prevalent when mucosal damage of the gastrointestinal tract is present (Leather & Wingard). Aspergillus is an airborne pathogen, and the portals of entry often are the nasal passages and respiratory tract (Leather & Wingard). Aspergillus may manifest as a fever that is unresponsive to broad-spectrum antibiotics (Einsele et al.) or as sinus or respiratory symptoms (Leather & Wingard).

Bacterial Infections

HSCT recipients frequently are discharged home with an indwelling vascular access device in situ. Those with such a device are at increased risk for gram-positive and gram-negative infections, with Staphylococcus epidermidis being the most common pathogen (Leather & Wingard, 2001).

Parasitic Viruses

Pneumocystis carinii (PCP), or Pneumocystis jiroveci as it is classified now (Kruger et al., 2005), can cause atypical and lethal pneumonia in immunocompromised patients who do not receive adequate prophylaxis (Shapiro, Davison, & Rust, 1997). Compliance with prophylaxis such as bactrim has led to PCP becoming an uncommon complication of transplantation, resulting in less than a 0.2% incidence (Boeckh, 2003).

Infections During the Late Phase

In the late post-transplantation period (>100 days) in the absence of GVHD, immune reconstitution usually is advanced (Einsele et al., 2003). However, patients with GVHD continue to experience cellular and humoral immunodeficiency (Einsele et al.). Patients are at an increased risk for developing encapsulated bacterial infections and experiencing reactivation of varicella zoster in addition to developing the infections mentioned previously (Kruger et al., 2005). Encapsulated bacteria, such as Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococci, and gram-negative bacteria such as the Pseudomonas species, can cause pneumonias (Campbell & Moravec, 2000).

Varicella zoster virus reactivation usually manifests as patches of raised erythematous papules that develop into vesicles (Shapiro et al., 1997). It generally occurs during the five months after transplantation; however, allogeneic recipients are at risk for varicella infection for two years or longer after transplantation (Leather & Wingard, 2001).

Nursing Implications

Infections are a leading cause of mortality in allogeneic stem cell transplantation. Because infections continue to occur after pre-engraftment, patients must remain diligent in following guidelines aimed at preventing opportunistic infections.

Figure 4. Causes of Death After Transplants Performed in 1996–2000

Oncology nurses caring for transplantation recipients can follow two recommendations that will positively affect the care of their patients.

Primarily, nurses should become familiar with established guidelines for the management of patients who have received allogeneic HSCT and prophylaxis of opportunistic infections. Figure 5 is a brief summary of some of the guidelines developed by the Centers for Disease Control and Prevention, Infectious Disease Society of America, and American Society of Blood and Marrow Transplantation (2000). Note that the information provided includes guidelines only; each transplantation institution will have its own protocols for post-transplantation care management. When people in the community who have received HSCT are being cared for, effective communication between transplantation facilities and community practices is important.

In addition, oncology nurses should assess patients’ risk of and monitor for developing opportunistic infections. By becoming familiar with the opportunistic infections that patients are most susceptible to and recommendations regarding prophylactic measures, oncology nurses will be well prepared to offer scientifically sound patient education.

In determining patients’ risk, nurses can ask several questions.

- What type of allogeneic transplantation did the patient receive—NM or myeloablative?
- What was the conditioning regimen?
- Who was the donor? A family member? A full match? Male or female?
- How old was the donor?
- Does the patient have GVHD?
- What is the CMV status of the patient and the donor?
- Is the patient receiving immunosuppression medications?
- Should the patient be taking prophylactic antimicrobials?
- Are the blood products leukoreduced and CMV appropriate?
- Does the patient require reimmunization with childhood vaccinations?

**Prevention of Bacterial Infections**
- Strict hand washing
- Pneumococcal vaccination 12 and 24 months after transplantation
- Antimicrobial prophylaxis in patients with chronic graft-versus-host disease (GVHD)

**Prevention of Viral Infections**
- Cytomegalovirus (CMV)
  - No sharing of cups and utensils
  - Latex condoms during sexual intercourse if CMV status is discordant
  - CMV-negative recipients should receive seronegative, leukocyte-reduced blood products.
  - Recipients at risk should begin a prevention program from engraftment to day 100.
  - Screen for CMV antigenemia at least weekly from day 10–day 100.
  - Commence gancyclovir if antigenemia is positive.
- Community respiratory virus
  - Influenza vaccination for all family members and close contacts
  - Influenza vaccination not recommended for recipient
- Herpes virus
  - Test recipients’ immunoglobulin G (IgG) status.
  - Seronegative patients should practice safe hygiene and frequent hand washing and avoid sharing utensils.
  - No prophylaxis after engraftment is recommended.
- Varicella zoster virus (VZV)
  - Test recipients’ IgG status.
  - Vaccinate family members and close contacts who are VZV and IgG negative.
  - No prophylaxis after engraftment is recommended.

**Prevention of Fungal Infections**
- Frequent hand washing to prevent spread of *Candida*
- Fluconazole prophylaxis against yeast infections
- Avoid soil, areas of high dust exposure (e.g., construction sites), and foods that contain molds (e.g., blue cheese).

**Prevention of Protozoal Infections**
- Prophylaxis with bactrim, dapsone, or inhaled pentamidine from engraftment to at least six months after transplantation
- Prophylaxis to continue in the presence of immunosuppressive drugs and GVHD

**Conclusions**

The Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society of Blood and Marrow Transplantation (2000) issued a comprehensive, 128-page document with recommendations for strategies for safe living after HSCT that can be located at www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm. Numerous issues are addressed, including recommendations for safe sex, food, hygiene, and pets.

The evidence supporting the recommendations varies in scientific strength. Each transplantation center will implement its own criteria for post-transplantation care management, which usually is based on the guidelines of the Centers for Disease Control and Prevention. The Fred Hutchinson Cancer Research Center has published general long-term follow-up guidelines for adult patients at www.fhcrc.org/science/clinical/ltfu/patient. In addition to locating recommendations about routine health care, special tests, cancer risks and protection, vaccinations, risks of infection, and prednisone, oncology nurses also can find examples of food and water safety as well as diet and nutrition guidelines at the same Web site, in addition to recommendations for pediatric patients.

Although many research studies focus on various treatments, engraftment, immune reconstitution, morbidity, and mortality at the time of HSCT, a tremendous need exists for scientifically sound research in care following discharge from a transplantation center. Quality of life, morbidity, and mortality outcomes of studies comparing controversial, conflicting, or nonscientifically based recommendations will be the foundation for the evidence-based practice guidelines of the future.
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