

Preventing and Managing Infections in Neutropenic Stem Cell Transplantation Recipients: Evidence-Based Review

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The number of hematopoietic stem cell transplantations (HSCTs) performed annually is increasing. Although general survival rates have risen since 1990, mortality and morbidity from preventable complications can be improved. As a result, this article will review developments in preventing and managing infections in neutropenic HSCT recipients.

In the history of medicine, technical advances often have preceded scientific research, as in the case of hematopoietic stem cell transplantation (HSCT). Developments in the related fields of supportive care, including transfusion medicine and antibiotics, histocompatibility testing, conditioning regimens, and management of complications, enabled the advancement of the science of transplantation (Wingard, 2007). Techniques used in stem cell collection have been enhanced by the development of more efficient blood cell separators, whereas advances in pharmacology dramatically improved cell mobilization techniques and management of treatment-related toxicities. Clinical management of the complications of transplantation continuously evolves in response to breakthroughs in diagnostic techniques and pharmacologic interventions. The significant discoveries have contributed to better outcomes reported in the transplantation literature. Despite unparalleled growth in the field of transplantation, improvements are needed as treatment-related mortality and morbidity remain a concern for recipients, practitioners, and scientists.

Infection is a major source of treatment-related mortality and morbidity in patients with cancer receiving HSCT (Munshi & Montgomery, 2000). Infection has been reported as the leading cause of non-relapse mortality among allogeneic HSCT recipients (Laffan & Biedrzycki, 2006).

Causes of death in the first 100 days post-transplantation are mainly related to the primary disease, graft-versus-host disease, infection, and end-organ damage. From 2003–2008, fewer deaths related to primary disease (35%) were reported among unrelated donor transplantations; however, infection-related deaths are higher in this group (17%) compared to human leukocyte antigen-identical sibling or autologous transplantations (Pasquini & Wang, 2010).

The risk of developing a life-threatening infection is associated primarily with the obligatory period of neutropenia that follows the myelosuppressive conditioning regimen used in preparing for transplantation. Prompt recognition of and reaction to potential infection may define success in managing neutropenia and reducing mortality and morbidity in this population (de Naurois et al., 2010). To date, strategies to reduce the risks and manage the complications of neutropenia include nonpharmacologic interventions such as environmental manipulation and lifestyle modifications (neutropenic precautions) and pharmacologic interventions with the use of antibiotics and colony-stimulating

growth factors. The interventions have been widely investigated, but any improvement has been modest at best.

Neutropenia: A Necessary Evil

Human bone marrow transplantation began in 1957 when laboratory workers who were exposed to radiation during the Vinca nuclear reactor incident were treated with allogeneic bone marrow (Wingard, 2007). In 2009, more than 32,000 autologous and 26,000 allogeneic transplantations were performed worldwide. Of those, almost 12,000 autologous and 7,000 allogeneic transplantations were performed in the United States (Pasquini & Wang, 2010).

HSCT is considered by many as a supportive therapy that permits the use of lethal doses of chemotherapy and radiation therapy for malignant diseases. In 2008, the most common indication in North America were plasma cell disorders and lymphomas, accounting for 60% of all transplantations. Less than 3% of transplantations were performed for nonmalignant diseases (Pasquini & Wang, 2010).

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The conditioning regimen, consisting of high-dose chemotherapy or radiation therapy or a combination of both, is given prior to stem cell infusion to eradicate the malignancy, create space in the marrow, and suppress the immune system to prevent rejection of donor stem cells (Saria & Gosselin-Acomb, 2007). Therefore, neutropenia is a necessary consequence of bone marrow ablation.

Patients receiving a standard conditioning regimen undergo a phase of neutropenia, thereby increasing their risk for developing life-threatening infections during that time (Menichetti, 2010). Those who develop an infection are expected to extend their hospital stay by an average of seven more days and incur an additional \$14,800 in medical costs (Shelton, 2003).

Nursing research on cancer treatment-related neutropenia has largely focused on environmental manipulation, lifestyle modifications, and quality-of-life issues. Nursing literature on preventing complications of neutropenia includes reports about appropriate care of vascular access devices, inpatient infection control procedures, protective isolation, prompt recognition of symptoms, and patient and family education. Literature on the nursing management of neutropenia consists mostly of quality improvement projects that evaluate prophylactic use of growth factors and timely administration of antibiotics. In clinical practice, although 80% of the respondents to a survey reported using clinical practice guidelines for risk assessment, management, and patient education in chemotherapy-induced neutropenia and febrile neutropenia, 61% did not recognize that patients who are receiving their first cycle of chemotherapy are at greater risk for developing neutropenia (Nirenberg, Reame, Cato, & Larson, 2010).

Literature Review

Neutropenia is operationally defined as an absolute neutrophil count lower than 2,000 cells/mm³. Susceptibility to infection increases as the count drops below 500 cells/mm³ or the duration of the neutropenia is prolonged (National Cancer Institute Cancer Therapy Evaluation Program, 2009; National Comprehensive Cancer Network [NCCN], 2005). Neutrophils account for 60% of the circulating blood cells and play a vital role in the body's innate immune response against pathogens,

particularly bacterial and fungal organisms (Abbas & Lichtman, 2006; Nirenberg et al., 2006a). Although neutrophils are produced at a rate of 100 billion cells per day, the cells require almost 12 days to mature in the bone marrow and they have a relatively short life span of about 12 hours in circulation (Dailey, 2002; Petruzzelli, 2003). Proliferation and maturation of neutrophils depend on the presence of granulocyte-colony-stimulating factors (G-CSF), granulocyte macrophage-colony-stimulating factor (GM-CSF), and other cytokines (Petruzzelli, 2003).

Cancer chemotherapy and radiation therapy, such as those used in the HSCT setting, suppress the normal production and subsequent availability of neutrophils to phagocytize foreign microbes, ultimately increasing susceptibility to infection (Abbas & Lichtman, 2006; Nirenberg et al., 2006a). Incidence of infections post-transplantation range from 15%–60% depending on several factors including preexisting disease or condition, type of infection, source of stem cells, conditioning regimen, and type of transplantation (Smith & Wright-Kanuth, 2001). Mortality rates in adults with febrile neutropenia range from 4%–10%, with unacceptably high rates being reported for patients with acute leukemia (70%–75%) and solid tumors (50%) with an identified infection secondary to neutropenia (Nirenberg, Mulhearn, Lin, & Larson, 2004; Vidal et al., 2004). Preventing complications of neutropenia is key to avoiding devastating results in HSCT.

HSCT recipients will experience a period of neutropenia that lasts for about 10–30 days (West & Mitchell, 2004). In addition to the myelosuppressive effects of the conditioning regimen, factors such as immunosuppressive therapy for graft-versus-host disease prevention, previous infections, underlying malignancies, and malnutrition place transplantation recipients at a higher risk for developing neutropenia. The types of infectious complications that may occur correspond to the specific immunologic deficiency that accompanies each phase of the transplantation process relative to engraftment (West & Mitchell, 2004). During the pre-engraftment phase (defined by convention as the first 30 days following stem cell infusion), bacterial infections predominate, along with fungal infections for patients with prolonged neutropenia (Afessa & Pe-

ters, 2006; De Bock & Middelheim, 2000; Smith & Wright-Kanuth, 2001). In the midrecovery phase, typically occurring from 30–100 days post-transplantation, viral and fungal infections are more commonly observed (De Bock & Middelheim, 2000). During late recovery phase (more than 100 days post-transplantation), the risk for developing invasive fungal infections in addition to viral and bacterial infections is higher in patients with chronic graft-versus-host disease (De Bock & Middelheim, 2000).

Prophylactic Interventions and Growth Factors

Reports from a systematic review of 17 randomized, controlled trials (N = 3,493) of the effect of primary prophylaxis with G-CSF on febrile neutropenia and mortality in adult patients receiving standard chemotherapy revealed results that were in favor of colony-stimulating factors (Kuderer, Dale, Crawford, & Lyman, 2007). The meta-analysis reported the statistical significance of the efficacy of colony-stimulating factors in reducing the risk of febrile neutropenia as well as infection-related mortality and early death.

The results of the studies prompted the American Society of Clinical Oncology and NCCN to make a recommendation on primary and secondary prophylactic administration of colony-stimulating factors in patients at high risk outside of the HSCT setting (Smith et al., 2006; Wilson & Gardner, 2007). However, emerging data from clinical practice indicate that patients often receive abbreviated courses of G-CSF that deviate from the recommendations; therefore, patients do not receive full protection from febrile neutropenia (Aapro, Crawford, & Kamioner, 2010). Lyman (2011) compared international clinical practice guidelines for the prevention of febrile neutropenia using myeloid growth factors and concluded that new information relating to efficacy and risk of second malignancies are likely to alter future guideline recommendations in the non-transplantation setting. Studies evaluating the use of G-CSF in the transplantation setting favored the use of growth factors to accelerate neutrophil engraftment, reduce the duration of neutropenia, decrease the use of antibiotics, and decrease the length of stay (Jagasia et al., 2005; Wannesson et al., 2011).

Therapeutic Interventions and Growth Factors

A Cochrane review of 13 randomized, controlled trials (N = 1,518) that compared the use of G-CSF and GM-CSF with antibiotics versus antibiotics alone for the treatment of established febrile neutropenia in children and adults with cancer revealed that the use of G-CSF and GM-CSF had no effect on mortality but reduced the length of hospital stay and neutrophil recovery period. Nine trials had data on infection-related mortality, and meta-analysis revealed a statistically significant result in favor of colony-stimulating factors. Results of data from eight trials analyzed for length of stay statistically favored colony-stimulating factor use, and five trials revealed that colony-stimulating factors decreased the time to engraftment (Clark, Lyman, Castro, Clark, & Djulbegovic, 2003). Since 2000, several relevant studies have supported the therapeutic use of colony-stimulating factors with antibiotics in patients with febrile neutropenia outside of the transplantation setting (Smith et al., 2006). The studies failed to show an advantage in terms of survival, and the use of colony-stimulating factors is not always economically feasible; as a result, the American Society of Clinical Oncology recommended against routine use of colony-stimulating factors as adjunctive treatment with antibiotic therapy in managing patients with febrile neutropenia (Smith et al., 2006).

Antibiotics in Febrile Neutropenia

Empiric use of antibiotics in febrile neutropenia is a universally accepted standard practice in oncology settings. However, choosing the type of antibiotic and the dosage and route of administration varies across institutions. A review of 95 randomized, controlled trials (N = 9,823) reported that antibiotic prophylaxis reduces all cause- and infection-related mortality in patients with neutropenia (Hart, 2006). A Cochrane review of 18 randomized, controlled trials conducted from 1989–2002 comparing the efficacy of empiric oral versus IV antibiotic therapy administration in patients with febrile neutropenia revealed no statistical difference in mortality and treatment failure; however, a trend toward more adverse events was observed in patients receiving oral antibiotics (Vidal et al., 2004). A study of systematic reviews

and meta-analyses found that endogenous flora suppression with oral antibiotics and antifungals were mediators of reduced mortality observed from environmental manipulation (i.e., the use of air filtration or contact precautions either independent of each other or combined) (Paul, Gafter-Gvili, Goldberg, & Yahav, 2011).

Of note, many of the studies were conducted outside of the transplantation setting, but the results often are extrapolated to this setting. In 2007, Slavin et al. discouraged the use of preemptive antibiotics in adult HSCT recipients when their study failed to translate findings into appreciable clinical benefit (e.g., length of stay, time to engraftment, use of additional antibiotics, 30-day mortality).

Neutropenic Patients With Infection and Granulocyte Transfusions

Reports from a Cochrane review of eight randomized, controlled trials (N = 310) conducted from 1977–1984 involving granulocyte transfusions to treat infections in patients with cancer with neutropenia revealed inconclusive evidence to support or refute the use of granulocyte transfusion therapy (Stanworth et al., 2005). Six of the trials had data on mortal-

ity that favored the treatment arm, and four studies that involved transfusion of higher granulocyte counts (greater than $1 \times 10^{10}/L$) showed significance in the effectiveness of granulocyte transfusions. The studies used different techniques in granulocyte collection and different processes in selecting donors, some of which did not consider leukocyte compatibility. In addition, the studies examined different outcomes that included survival, reversal of infection, duration of fever, and adverse events. The methodologic deficiencies and the observed clinical diversity between the studies make establishing whether granulocyte transfusion has a clinical benefit difficult.

In a within-group analysis of a case-control retrospective study (N = 491) of patients with *Candida* species bloodstream infection, patients who received a high-dose granulocyte transfusion therapy had a better than expected short-term survival when compared to a within-group analysis of patients who did not receive granulocyte transfusions and were expected to perform better. Only 29 of the 491 patients were treated with granulocyte transfusions and were found to have more predictors for increased mortality, including a higher incidence of underlying leukemia,

The following practices showed strong evidence for efficacy and clinical benefit and should always be used.

Room Ventilation

- High-efficiency particulate air filters with 99.97% efficiency for removing particles 0.3 μm in diameter or larger
- Prevent birds from nesting near hospital air-intake ducts.

Building Construction and Cleaning

- Consult recommendations regarding environmental controls during construction.
- Hematopoietic stem cell transplantation (HSCT) recipients should avoid construction areas, and staff should avoid transporting equipment and supplies used by HSCT recipients through those areas.
- Construction and renovation areas should have negative air-pressure-relative HSCT recipient care areas.
- Newly constructed or renovated areas should be cleaned and disinfected before patients are allowed to enter them.
- Clean, disinfect or sterilize, and maintain equipment and devices as directed by established guidelines.

Isolation and Barrier Precautions

- HSCT centers should follow published guidelines for hospital isolation practices, such as Centers for Disease Control and Prevention guidelines for preventing healthcare-associated infections (for more information, visit www.cdc.gov/hai).
- At a minimum, healthcare workers should follow standard isolation and barrier precautions, particularly hand hygiene, for all patient contacts.

Healthcare Personnel

- When indicated for coexisting conditions, place HSCT recipients on airborne, droplet, or contact precautions in addition to standard precautions.
- All healthcare workers should be immunized with all recommended vaccines.
- Restrict healthcare workers with transmissible infections from direct patient care.
- All visitors must be able to follow appropriate hand hygiene and isolation precautions.

Figure 1. Recommended Practices for Managing and Preventing Infection in Stem Cell Transplantation Recipients

Note. Based on information from Tomblyn et al., 2009.

persistent neutropenia, breakthrough invasive mycoses, intensive care admission, and history of HSCT. This study makes the case for the effectiveness of granulocyte transfusions for groups with more risk factors. A between-group analysis was not conducted because of the mismatch in the number of participants in the treatment versus nontreatment groups (Safdar et al., 2004). Significant concerns about the results are related to the methodologic quality of the study. A case-control retrospective study does not necessarily confer strong evidence supporting the use of the intervention, and the unequal allocation of participants for the treatment and nontreatment groups add to the lack of generalizability of the results.

A prospective, nonrandomized study (N = 52) investigating the benefit of granulocyte transfusion in controlling acute life-threatening infections and preventing

recurrence of severe fungal infections during intensive chemotherapy revealed a positive outcome, with 82% of acute life-threatening infections controlled by the intervention and no reactivation of previous control. In addition, no recurring infection was observed. Median survival was 170 days in the intervention group versus 185 days in the prophylactic group; most deaths correlated with an underlying progressive malignant disease (Mouset et al., 2005). The study compared the effectiveness of prophylactic versus therapeutic granulocyte transfusions in controlling and preventing infections. Adding a control group that will not receive granulocyte transfusions would add to the significance of this report, as previous studies have not found a significant clinical benefit for granulocyte transfusions.

Ofran et al. (2007) reported the results of a retrospective analysis of 47 patients

with neutropenia treated with granulocyte transfusions for life-threatening infections. This study reviewed the safety of granulocyte transfusions but did not establish the efficacy of the intervention. Ofran et al. (2007) concluded that granulocyte transfusions are safe and recommended prospective, randomized studies to determine clinical significance of the intervention. The Granulocyte Transfusion Task Force of the Japan Society of Transfusion Medicine and Cell Therapy published the most recent guidelines to date for the appropriateness and safe administration of granulocyte transfusion (Ohsaka et al., 2010).

Protective Isolation for Patients With Neutropenia

Research investigating the role of a therapeutic environment traditionally

The following practices showed moderate evidence for efficacy—or strong evidence for efficacy with limited clinical benefit—and should be used in general.

Room Ventilation

- Protective environment rooms with 12 or more air exchanges per hour
- Directed airflow
- Positive air pressure differential between the patient's room and the hallway of 2.5 pascals or higher
- Well-sealed rooms (i.e., filling the gaps between walls and windows)
- Continuous pressure monitoring to alert staff to possible engineering failure
- Self-closing doors
- Provisions for back-up emergency power and redundant air-handling and pressurization systems
- Develop protocols to protect hematopoietic stem cell transplantation (HSCT) recipients from mold spores when air-handling systems restart after routine shutdowns.
- Anterooms for HSCT center rooms are optional, except for HSCT recipients requiring airborne precautions for certain infections.
- Prioritize protective environment rooms for patients who are at highest risk for invasive mold infection.
- Portable, industrial-grade high-efficiency particulate air filters in nonprotective environment rooms for vulnerable patients

Hand Hygiene

- Encourage visitors to maintain hand hygiene before and after each patient visit.
- Educate HSCT recipients and candidates and their household contacts on the importance of maintaining hand hygiene during hospitalization and after hospital discharge.

Building Construction and Cleaning

- HSCT centers should direct pedestrian traffic occurring near construction areas away from patient care areas to limit the opening and closing of doors or other barriers that might contaminate air in patient areas.
- If fungal-contaminated materials cannot be removed, decontaminate with copper-8-quinolinolate after cleaning. Vacuum areas above dropped ceilings in rooms under or adjacent to construction areas.
- Clean HSCT centers at least daily with special attention to dust control. Perform wet dusting and avoid techniques that aerosolize dust.
- Upholstery in HSCT centers should be smooth, nonporous, and easily disinfected to minimize contamination.
- Floor surfaces and finishes in HSCT centers should be scrubbable, nonporous, and easily disinfected.
- Clean and repair water leaks within 72 hours to prevent mold proliferation in and around HSCT recipient care areas.

Healthcare Personnel

- HSCT centers should provide a written comprehensive policy regarding immunizations and vaccinations for employees that meets Centers for Disease Control and Prevention recommendations (for more information, visit www.cdc.gov/vaccines/hcp.htm).
- Healthcare workers with draining skin and soft tissue infections or other lesions that cannot be completely covered should be restricted from patient contact.

Isolation and Barrier Precautions

- Place HSCT recipients in single rooms, if possible.
- If availability is limited, prioritize single rooms for the most severely immunosuppressed patients.
- Allogeneic HSCT recipients are likely to benefit from protective isolation measures.
- For autologous HSCT recipients, individual circumstances should guide the prioritization of protective environment in settings with a limited number of rooms.
- Immunocompromised HSCT recipients and candidates undergoing conditioning therapy should minimize time in crowded areas to avoid exposure to community-acquired respiratory virus infections.

Visitors

- HSCT centers should have written policies regarding the screening of all visitors for communicable infections.
- Visitors with signs and symptoms of or recent known exposure to communicable infections should be excluded from direct contact with HSCT recipients or candidates undergoing conditioning therapy.
- Limit HSCT center visitors at any time to a number that permits nursing staff to perform appropriate infection screening and adequate instruction and supervision of hand hygiene and glove and mask use.
- Hospitals should share information on practices to prevent the spread of communicable infections with nearby family lodging facilities (e.g., Ronald McDonald houses).

Figure 2. Practices That Are Likely to Prevent or Manage Infection in Stem Cell Transplantation Recipients

Note. Based on information from Tomblyn et al., 2009.

has been reported in the nursing literature. Florence Nightingale instituted the practice of “fever nursing” when she separated patients with infectious diseases and stressed the importance of body substance isolation (Parker, 1999). Protective isolation has remained a practice standard since its initiation in the 1960s during the introduction of high-dose chemotherapy and HSCT (Mank & van der Lelie, 2003). The knowledge gap is remarkable considering that this ritualistic practice has been questioned as early as 1967 (Mank & van der Lelie, 2003).

A systematic literature review by Mank and van der Lelie (2003) looking at prospective, randomized trials on protective isolation reported inconclusive evidence of benefits. Most of the 160 publications were descriptive or included protective isolation as a prophylactic measure for patients with chemotherapy-induced neutropenia. Six randomized trials, most completed before the introduction of prophylactic antibiotics, showed that only two of the six studies revealed a decrease in infection rates in patients placed in isolation, with the rest of the studies revealing no difference between the treatment and control groups. Only one of the studies reported lower mortality in the experimental arm. Similarly, a review of nonrandomized studies revealed inconclusive reports in infection and mortality rates.

A systematic review by Dadd, Mc-Minn, and Monterosso (2003) addressing the use of protective isolation measures in the care of pediatric patients undergoing either autologous or allogeneic HSCT reported no difference in infection rates and overall morbidity and mortality among patients kept in isolation versus those who were not. The only consensus among the reports was that strict hand washing remains the most effective precaution for transplantation recipients. However, the risk of acquiring *Aspergillus* infection correlated with environmental measures in both reviews and, therefore, should be treated as an indication for protective isolation that includes a private room, high-efficiency particulate air filtration, and laminar air flow. The reviews also discussed the wide practice variations across institutions regarding the use of protective isolation. A review of the

contributions of systematic reviews and meta-analyses by Paul et al. (2011) confirmed the findings of many studies that beneficial effects of environmental manipulation are mediated mainly by suppressing the normal species of bacteria, viruses, fungi, and protozoa that are found within individuals through the use of antibiotic and antifungal prophylaxis.

The Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (1996) issued a set of guidelines for isolation control in hospitals (Siegel, Rhinehart, Jackson, & Chiarello, 2007). The guidelines cover a broad list of isolation practices including hand washing, use of personal protective equipment, patient placement, transportation of infected patients, patient equipment and articles, linen and laundry, routine and terminal cleaning, and isolation precautions. In addition, the guidelines include recommendations on staff education and monitoring of adherence to institutional policies. The guidelines are instituted in medical centers nationwide.

Manipulating the Immunologic Characteristics of Graft and Host

Advances in technology have allowed interventions to be done at the molecular level. In allogeneic HSCT, graft engineering has been investigated to improve clinical outcomes by altering the characteristics of donor stem cells and the immune attributes of the host (Noga & O'Donnell, 1998; Talmadge, 2003). Adverse clinical outcomes in HSCT including time to engraftment and the duration of graft-versus-host disease have been implicated in a prolonged state of neutropenia for the host (median recovery time = 5 days; SD = 2 days) (Lalami et al., 2006). Techniques for graft manipulation in allogeneic HSCT include T-cell depletion and purging, CD34+ stem cell selection, and the use of cytokines to modulate host immunity. The interventions have been shown to decrease the duration of graft-versus-host disease at the expense of durable remission. The field of graft engineering remains open for investigation by scientists and clinicians. In addition to molecular and genetic engineering, theoretic considerations highlight the

The following practices had moderate-to-strong evidence for adverse outcomes or lack of efficacy and should NOT be used.

- Laminar airflow for newly constructed rooms in hematopoietic stem cell transplantation (HSCT) centers
- Installing carpet in HSCT center hallways or inside patient rooms; contaminated carpeting may cause aspergillosis in HSCT recipients.
- Use of artificial fingernails or extenders in healthcare workers with direct patient contact
- Allowing plants and dried or fresh flowers in hospital rooms during conditioning or after HSCT
- Restricting patient contact for healthcare workers with blood-borne viral infections (e.g., HIV, hepatitis B or C viruses)

Figure 3. Infection Management in Stem Cell Transplantation: Not Recommended for Practice

Note. Based on information from Tomblyn et al., 2009.

potential role of environmental manipulation in improving donor and host immune characteristics.

Evidence-Based Nursing Interventions

The lack of data supporting the use of dietary modifications for patients with neutropenia has been reported consistently in the nursing literature (Larson & Nirenberg, 2004; Nirenberg et al., 2006b; Restau & Clark, 2008; West & Mitchell, 2004; Wilson, 2002; Zitella et al., 2006). The published reviews have reported that a large majority of institutions recommend the use of a neutropenic or low-microbial diet for patients with neutropenia, despite the lack of evidence linking the practice with a decrease in infection. The prescription for a low microbial diet varies widely across institutions, and research conducted to validate this practice is confounded by concurrent environmental manipulations. To date, recommendations include providing patient education on food hygiene and safe food handling in lieu of neutropenic dietary restrictions (Tarr & Allen, 2009).

Infection is the leading cause of non-relapse mortality in patients with cancer. In patients receiving myelosuppressive treatment, the risk for developing life-threatening infections is greatest during

the neutropenic phase of treatment and is relative to the degree and severity of neutropenia. Although strong evidence suggests the efficacy of interventions in the prophylactic and therapeutic setting for cancer-induced neutropenia, many gaps still exist and opportunities for knowledge development abound (see Figures 1, 2, and 3).

One example of the gap in the literature is the development of a validated tool to measure the quality of life of patients with neutropenia in the clinical setting (Ropka & Padilla, 2007). Many widely used instruments measuring quality-of-life research lack practicability for use in practice. Another gap in nursing research is the investigation of the psychological effects of protective isolation. What are the short- and long-term effects of implementing this intervention, which has not been proven to be effective in preventing infection in patients with neutropenia? What are the different costs associated with this intervention, and who must pay them?

Conclusion

Considerable gaps in evidence exist in the areas of clinical practice, research, and education related to the prevention and management of infection in HSCT recipients with chemotherapy-related neutropenia. The efficacy of pharmacologic interventions (e.g., growth factors and antibiotics) in the empiric or preemptive setting and the benefits from granulocyte transfusions all depend on appropriate identification of high-risk patients who have a more favorable benefit-risk ratio. Nurses have a holistic perspective, giving them a wider and more comprehensive view of the scope and breadth of the problem of infection in patients with neutropenia. Nurses should take advantage of their unique role to fill in the gaps that contribute to morbidity and mortality in this population.

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