Myelosuppressive chemotherapy for cancer represents a major advance in effecting remission and cure, but it is not free from risk. One of the serious adverse effects of chemotherapy is the development of neutropenia, which greatly increases the risk of infection when it is severe. The absolute neutrophil count (ANC) is the total white blood cell count multiplied by the combined percentage of segmented (mature) neutrophils and band cells. A normal ANC is greater than or equal to 2–7 x 10^9/liters. Neutropenia has an...
ANC of less than $2 \times 10^9$/liters and is graded as slight (grade 1 < $2 \times 10^9$/liters), minimal (grade 2 < $1.5 \times 10^9$/liters), moderate (grade 3 < $1 \times 10^9$/liters), or severe (grade 4 < $0.5 \times 10^9$/liters) (National Cancer Institute, 1999; National Cancer Institute Cancer Therapy Evaluation Team, 1999). The healthcare-associated (nosocomial) infection rate among hospitalized patients with severe neutropenia has been reported to be at least 40% (Carlisle, Gucalp, & Wiernik, 1993; Oren, Haddad, Finkelstein, & Rowe, 2001; Velasco, Thuler, Martins, Dias, & Goncalves, 1997; Viscoli et al., 1999). Further, if an infection develops, it tends to be more severe when neutropenia is present. For example, sepsis is lethal in 47% of infected patients with neutrophil counts less than $0.1 \times 10^9$/liters as compared with 14% when counts are more than $1 \times 10^9$/liters (Giamarellou & Antoniadou, 2001).

Regardless of whether neutropenic patients are hospitalized or in the community, the patients’ own microbial floras pose a major risk because of severe immunosuppression. Therefore, the role of the nurse in the acute care setting is supportive, focused on reducing risk to patients from their own floras and the hospital environment. The primary approaches to preventing healthcare-associated infections in neutropenic patients include outpatient treatment (i.e., keeping patients away from the hospital environment); antimicrobial prophylaxis and colony-stimulating factor; environmental protective controls in hospitals such as laminar airflow with high-efficiency particulate air (HEPA) filtration, gowns, and private rooms; personal hygiene and skin decontamination; aseptic management of invasive devices such as central vascular catheters; and clean food and water (Bodey, 1997; Fenelon, 1998; Kenny & Lawson, 2000; Schimpff, 1997; Thio et al., 2000). The purpose of this article is to review studies that have assessed the effectiveness of selected nursing interventions (i.e., low microbial diets, protective clothing and environments, and personal hygiene and oral care) used in hospitals to prevent healthcare-associated infections in neutropenic patients with cancer.

### Conceptual Underpinnings

Oncology nurses devote considerable effort to educating patients and caregivers about the potential complications of cancer therapy in an effort to reduce the impact of symptoms on health outcomes (Ropka & Spencer-Cisek, 2001). To this end, the Oncology Nursing Society (ONS, 2002) developed the position titled “Quality Cancer Care,” affirming that symptom management for patients with cancer is an important component of quality cancer care. To develop education programs, research, healthcare services, and health policy, the Priority Symptom Management (PRISM) project was initiated by the ONS Foundation Center for Leadership, Information, and Research. The goals of this initiative include addressing cancer and cancer-related symptoms through assessment of current knowledge, education programs for oncology nurses and the public, and research grants to enhance symptom management and cancer-related symptoms. In addition, the project seeks to demonstrate the impact of oncology nurse management of cancer-related symptoms in diverse populations (Ropka & Spencer-Cisek). This systematic literature review is designed to contribute to the PRISM project by assessing the current knowledge regarding environmental controls to prevent healthcare-associated infections in severely neutropenic patients with cancer. To assess the quality of the evidence, the PRISM levels of evidence (see Table 1) were used to categorize the clinical practices reviewed in the literature.

### Infections in Neutropenic Patients With Cancer

Neutropenic patients with cancer constitute a heterogeneous population with a variable risk for developing serious complications (Paesmans, 2000). When the neutrophil count decreases to less than 1,000 cells/mm$^3$, increased susceptibility to infection is expected, with the frequency and severity inversely proportional to neutrophil count (Hughes et al., 2002). Approximately 70%–75% of the deaths from acute leukemia and 50% of deaths in patients with solid tumors are related to infection secondary to neutropenia (Barber, 2001). At least half of neutropenic patients who become febrile have an established or occult infection, and at least one-fifth of the patients with neutrophil counts greater than 100 cells/mm$^3$ have bacteremia (Hughes et al.).

Significant advances in supportive care for neutropenic patients have been made since the mid-1990s (Elting & Cantor, 2000).

### Table 1. Evidence Base for Various Clinical Practices to Reduce the Risk of Infection in Neutropenic Patients With Cancer

<table>
<thead>
<tr>
<th>Level$^a$</th>
<th>Source of Evidence</th>
<th>Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Integrative reviews, meta-analysis of multiple, well-designed, randomized, controlled trials of adequate quality</td>
<td>Ice chips to prevent mucositis</td>
</tr>
<tr>
<td>2</td>
<td>At least one properly designed, randomized clinical trial of appropriate size</td>
<td>None found</td>
</tr>
<tr>
<td>3</td>
<td>Well-conducted trial without randomization</td>
<td>Influenza immunization for staff</td>
</tr>
<tr>
<td>4</td>
<td>Well-conducted qualitative systematic review of nonexperimental design studies</td>
<td>Low microbial diets (no evidence of benefit)</td>
</tr>
<tr>
<td>5</td>
<td>Well-conducted case-control study</td>
<td>None found</td>
</tr>
<tr>
<td>6</td>
<td>Poorly controlled study or uncontrolled studies</td>
<td>Patients wear high-efficiency masks outside of the room, have private room isolation, and are treated with oral care regimens (e.g., chlorhexidine, honey, calcium phosphate) to prevent mucositis.</td>
</tr>
<tr>
<td>7</td>
<td>Conflicting evidence with weight of evidence supporting the recommendation or meta-analysis showing a trend, National Institutes of Health Consensus Reports, and published practice guidelines</td>
<td>Patients are under protective isolation, do not wear cover gowns, and have antiseptic bathing. Visitors and pets are restricted and screened. Plants and flowers are restricted.</td>
</tr>
<tr>
<td>8</td>
<td>Qualitative designs, case studies, and opinions from experts</td>
<td>None found</td>
</tr>
</tbody>
</table>

$^a$ Levels of evidence as designated by Ropka and Spencer-Cisek (2001). The lower the number is, the stronger the evidence.
2002); however, despite these achievements, infection continues to be the major cause of morbidity and mortality in this population. These advances have resulted in response rates to initial antimicrobial therapies that exceed 70%, and fewer than 10% of patients with febrile neutropenia die as a result of their infections (Elting & Cantor). Patients with hematologic malignancies are at greater risk of developing complications because of prolonged periods of neutropenia and delayed hematologic recovery (Garcia-Carbonero et al., 2001).

Many clinically stable patients with cancer who develop neutropenia now are treated as outpatients, but a substantial proportion of infections in this population (up to 50%) continues to be associated with a hospital stay (Schimpff, 1997). Surprisingly, very few studies have systematically monitored infection rates in neutropenic patients undergoing chemotherapy for cancer. Although studies often have focused on a specific pathogen such as the Aspergillus species or Clostridium difficile, particularly in outbreak situations (Gorschulter et al., 2001; Thio et al., 2000), the usual gram-negative and gram-positive bacteria seen in other healthcare-associated infections continue to predominate as causes of infection among neutropenic patients with cancer (Hamzeh, Kanj, & Uwaydah, 2000; Healey & Selva-Nayagam, 2001; Snydman, 2001; Viscoli et al., 1999).

Carlisle et al. (1993) recommended that because neutropenia is such a major risk factor for infections, programs for surveillance, control, and management of infections in this population should be modified. Additionally, in a collaborative study conducted in eight nations, neutropenia was associated with high levels of resource consumption, meaning that this is a costly problem (Harbarth, Beeler, Viot, & Szucs, 1999). Routine, ongoing surveillance of infections in neutropenic patients is uncommon and generally not part of hospitals’ infection control programs. For that reason, what is known about infection rates in this group of patients comes from a minimal number of published studies. According to these studies, infection rates have reduced very little since the 1990s with rates of 40%–60% increasing to nearly 100% for those whose severe neutropenia continues for more than a week (Carlisle et al.; Crokaert, 2000; Giamarellou & Antoniadou, 2001; Schimpff, 1997; Velasco et al., 1997).

Efforts to Prevent Healthcare-Associated Infection

The major emphasis in medical prevention or treatment of infections associated with neutropenia has been on the development and testing of various regimens of antimicrobial agents, growth factors, and other cytokines and biologic agents. Nevertheless, the cure rate, even with effective treatment, is considerably lower among patients who are severely neutropenic when compared with patients who have adequate neutrophil counts (Bodey, 1997). Such pharmacologic and biologic advances are vital to improving the prognosis for neutropenic patients but do not provide guidance regarding ongoing, day-to-day clinical management and care.

In addition to antimicrobial prophylaxis, Fenelon (1998) summarized five other specific strategies to prevent infections among patients with short-duration (i.e., ≤ 14 days) neutropenia: protective environment, clean food and sterile water, protective clothing, management of intravascular devices, and hand hygiene. Management of intravascular devices and hand hygiene are not specific to neutropenic patients, and much has been published recently about the effectiveness of these interventions (e.g., national evidence-based guidelines for the prevention of intravascular infections) (Boyce & Pittet, 2002; O’Grady et al., 2002). A review of the maintenance of venous access devices in patients with neutropenia also was published by Moran and Camp Sorrell (2002). Readers should refer to these publications for reviews of research related to the management of intravascular devices and hand hygiene.

Literature Review

The English-language literature in PubMed; the Cumulative Index of Nursing and Allied Health Literature; the National Guideline Clearinghouse, 1980–June 2003; and the Cochrane Database of Systematic Reviews was reviewed for descriptive or intervention studies related to three specific clinical practices influenced by nurses: clean food and water, protective environment and clothing, and skin care and oral hygiene. Studies related specifically to autologous and allogeneic bone marrow transplantation were not included in this review because transplants are not used for most common cancers (e.g., lung, breast, colon, prostate) and because guidelines have been published regarding this population (Centers for Disease Control and Prevention, Infectious Disease Society of America, & American Society of Blood and Marrow Transplantation, 2000; Dykewicz, 2001).

Low Microbial Diets

Smith and Besser (2000) conducted a survey of current practices in 156 institutions and found that the majority placed neutropenic patients on dietary restrictions. Somerville (1986) discussed the issue of special diets for neutropenic patients, but the review is outdated and did not present any original data. Moody, Charlson, and Finlay (2002) published a comprehensive review of evidence from clinical trials regarding the effectiveness of such diets and concluded that the majority of these studies were confounded by other concurrent manipulations (e.g., a total protected environment). Despite the fact that many hospitals continue to use low microbial diets (French, Levy-Milne, & Zibrik, 2001), no recent studies were found that linked dietary restrictions with lower risk for infection.

Bottled water was found to be a source of multiresistant gram-negative bacteria among neutropenic patients in a British study (Wilkinson & Kerr, 1998), and one report was published about a disseminated mycobacterial infection in a patient with leukemia that was associated with a contaminated showerhead (Kauppinen, Nousiainen, Jantunen, Mattila, & Katila, 1999). In an evidence-based practice project in which current guidelines and publications were reviewed and analyzed, Wilson (2002) concluded that the scientific basis for food restrictions is lacking, policies related to low microbial diets vary widely, and compliance with restricted diets is inconsistent. In addition, this lack of consistent practice was not related to incidence of infection.

Protective Clothing and Environments

Numerous studies have assessed the effect of laminar airflow or HEPA filtration (Ohira, Shibata, & Ise, 1983; Oren et al., 2001; Pizzo, 1981; Talbot & Pizzo, 1980; Ueda et al., 1983). Some of these studies, however, tested several interventions
simultaneously (e.g., chemoprophylaxis, protective clothing, and sterile food), making it difficult to determine whether independent effects of individual interventions were present. Although most published studies have demonstrated some protective effect of laminar airflow and HEPA filtration against infections, particularly aspergillosis (Akiyama, Mori, Tanikawa, Sakamaki, & Onozawa, 1994; Loo et al., 1996; Withington et al., 1998), no measurable effect has been found on rates of remission or mortality (Fenelon, 1995).

More recently, a new type of clean room was compared to standard laminar airflow for preventing infections in neutropenic patients. Significantly lower rates of pneumonia were documented in patients housed in the new room, but, at present, this technology is not available in the United States (Shinjo et al., 2002). Generally, costs and other practical issues have limited the use of laminar airflow or HEPA filtration primarily to bone marrow transplantation units (Fenelon, 1995).

In several studies of pediatric populations (i.e., neonates, children after organ transplantation, or those in critical care units), cover gowns or other protective clothing have not been shown to reduce the risk of infections (Donowitz, 1986; Duquette-Petersen, Francis, Dohnalek, Skinner, & Dudas, 1999; Slota, Green, Farley, Janosky, & Carlcio, 2001; Tan, Lim, & Malathi, 1995). In their pilot study, Kenny and Lawson (2000) examined the efficacy of cotton cover gowns in reducing infection rates in neutropenic patients. Based on their findings and a systematic literature review, they concluded that no benefit could be achieved in wearing gowns. However, in their study, the sample size was only 11 patients: Five were randomly assigned to the gowned group and six to the ungowned group, which yields a power of only 0.18 to detect a 50% change in infection rates.

This failure to attain a sufficient sample size, unfortunately, is common in studies of such clinical practices. A second example of an insufficient sample size is a study of 50 neutropenic patients randomly assigned to IV tubing changes every 24 or 48 hours. Again, no difference in infection rates was detected (deMoissac & Jensen, 1998), but a false negative result cannot be ruled out. Another example is a study that often is cited as evidence that no benefits exist to placing neutropenic patients in single rooms. Published in 1981, the study included only 43 patients, 20 randomized to private room isolation and 23 randomized to standard care (Nauseef & Maki, 1981).

Two studies demonstrated a significant positive association between the use of protective environments and reduced incidence of healthcare-associated infections. Klein, Perloff, and Maki (1989) reported that nonimmunosuppressed children in a pediatric intensive care unit who were randomly assigned to wear gloves and a gown in private rooms had significantly lower healthcare-associated infection rates. Raad et al. (2002) reported a decrease in nosocomial aspergillosis infections during hospital construction from 0.73 to 0.24 per 1,000 patient days when neutropenic patients with hematologic malignancies wore high-efficiency masks when they left their rooms.

Ueda et al. (1983) divided patients with leukemia into three treatment groups. In one group (n = 106), patients were placed in laminar airflow rooms under strictly “clean nursing” (i.e., nurses wore gowns, gloves, and masks when touching patients). In a second group (n = 99), patients were in laminar airflow rooms without special nursing precautions, and patients in a third group (n = 188) were on conventional wards.

The researchers reported a marked and stepwise reduction in the incidence of infection among these three groups, suggesting that the benefit was incremental to various levels of intervention.

In addition to the problem of small sample sizes, many studies were conducted in the 1970s and 1980s and not necessarily among patients with febrile neutropenia; therefore, their current relevance may be limited. The ONS publication Chemotherapy and Biotherapy: Guidelines and Recommendations for Practice (Brown et al., 2001) recommended neither protective isolation nor precautions for fresh foods as part of the care for neutropenic patients.

Restrictions on plants and flowers, as well as visitors, are common for hospitalized neutropenic patients. Flowers, plants, soil, and flower water harbor large numbers of antibiotic-resistant microorganisms (Kates, McGinley, Larson, & Leyden, 1991). For this reason, they often have been prohibited from oncology units (Johnson, Gilmore, Newman, & Stephens, 2000), although no evidence has revealed that infection actually results from flowers.

Visitors to oncology units are often restricted or screened. Screening of visitors for respiratory symptoms and immunizing staff for influenza clearly are important and have been associated with a reduction in certain respiratory infections in patients undergoing bone marrow transplant (Garcia et al., 1997; Raad, Abbas, & Whimbey, 1997). Although no specific research is available among other neutropenic patients, policies regarding visitor screening and immunizations are important for hospitalized neutropenic patients as well. Given an appropriate institutional screening program, pets and service animals most likely pose no more risk than human visitors (Duncan, 2000). Nevertheless, some institutions find it prudent to restrict pets because of difficulties and costs of surveillance and monitoring.

**Personal Hygiene and Oral Care**

Because a large proportion of infections in patients with neutropenia is associated with their own microbial flora (Carter, 1994), personal hygiene may be one important preventive strategy. Aside from studies of hand hygiene, however, the evidence of an association between antiseptic bathing and reduced risk of infection is contradictory (Larson, 2001). No studies of antiseptic bathing were found that are specific to the neutropenic population. Nevertheless, antiseptics have been shown in other populations to reduce microbial counts on the skin (Byrne, Napier, & Cuschieri, 1990; Byrne, Napier, Phillips, & Cuschieri, 1991) and their use most likely is prudent for neutropenic patients. Products containing chlorhexidine gluconate generally are used because of their sustained activity.

Mucositis, ulcerative lesions, and other mouth problems are a frequent cause of morbidity among many patients with neutropenia and those undergoing radiotherapy and pose challenging nursing management problems (Alvarado, Bellm, & Giles, 2002; Garden, 2003; Vissink, Burlage, Spijkervet, Jansma, & Coppes, 2003). Several recent single-intervention studies using 0.2% chlorhexidine mouth rinse (Cheng, Molassiotis, & Chang, 2002), a calcium phosphate mouth rinse (Papas et al., 2003), or topical application of honey (Biswal, Zakaria, & Ahmad, 2003) have reported positive results, but the most comprehensive data available regarding the prevention and treatment of oral mucositis and candidiasis are from five Cochrane Database systematic reviews (Clarkson,
Implications for Nursing

Practice

A major focus of nursing care for hospitalized neutropenic patients is the prevention of complications and the maintenance of optimal functioning to bring patients through such episodes safely. Nurses generally are responsible for maintaining the physical and psychosocial inpatient environment in which care is provided. Unfortunately, however, many aspects of the management of hospitalized neutropenic patients are determined by tradition, habit, prudence, theoretical considerations, or expediency rather than evidence, and the appropriate and effective environmental management for these patients is not always clear. Table 1 summarizes the levels of evidence for the clinical practices reviewed. Clearly, major gaps exist in the literature regarding which interventions within the purview of nursing practice might be helpful in preventing or controlling healthcare-associated infections in neutropenic patients.

Hospitals vary in their practices regarding food and drink restrictions or protective clothing and environments, perhaps because of the scant evidence for the effectiveness of these interventions. In the absence of evidence for effectiveness, continuing to use scarce resources for unproven practices seems inappropriate. Current guidelines exist for the use of antimicrobial agents in neutropenic patients with cancer (Hughes et al., 2002), and ONS published guidelines for the nursing care of these patients (Brown et al., 2001). These guidelines should serve to direct practice until further evidence is available.

References


Research

Because of the generally low levels of evidence available for the nursing management of neutropenic patients, studies are sorely needed to provide the underpinnings for evidence-based nursing practices to prevent infections in hospitalized neutropenic patients. Empirical evidence is lacking regarding the role of the care environment in the potential risk of infection for hospitalized neutropenic patients.

Designing appropriate studies poses tremendous challenges to researchers, however, because of problems with randomization of extremely ill patients, the need for large sample sizes and risk stratification, and difficulties in standardizing other practices that affect the risk of healthcare-associated infections. When experimental designs are not feasible, carefully conducted observational studies, systematic reviews, and meta-analyses can provide valid evidence on which to base practice (Lorenz & Paneth, 2003; Ropka & Spencer-Cisek, 2001). In a recent comparison, results from randomized and nonrandomized trials have been shown to be highly correlated (Ioannidis et al., 2001), as have comparisons of observational studies and randomized, controlled trials (Benson & Hartz, 2000). Guidelines for the conduct of meta-analyses have been published that can be helpful to nurse researchers in conducting well-designed reviews (Stroup et al., 2000). Unfortunately, too little research has been conducted about most interventions to conduct a meta-analysis. Fruitful areas for research include examining the association among low microbial diets, patient room assignment, skin and mouth hygiene regimens, and risk of healthcare-associated infections.

Infections continue to be prevalent and serious in neutropenic patients with cancer. Nursing care practices to prevent or control such infections are not often supported by high levels of evidence. Clearly, more collaboration is needed among clinicians and researchers to identify and systematically evaluate nursing interventions to improve care for these patients.

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➤ Hardin Library’s Evidence-Based Nursing Filters
www.lib.uiowa.edu/hardin/ebmfilt_nursing.html

➤ National Breast Cancer Centre Evidence-Based Information
www.nbcc.org.au

➤ ONS Evidence-Based Practice Resource Area
http://onsopcontent.ons.org/toolkits/ebp/index.htm

Links can be found at www.ons.org.