

ONCOLOGY NURSING SOCIETY WHITE PAPER

Neutropenia: State of the Knowledge Part I

Anita Nirenberg, RN, MS, AOCNP, Annette Parry Bush, RN, BSN, MBA, OCN®,
Arlene Davis, RN, MSN, AOCN®, Christopher R. Friese, RN, PhD, AOCN®,
Theresa Wicklin Gillespie, PhD, BA, BSN, MA, RN, and Robert David Rice, RN, NP-C, OCN®

Purpose/Objectives: To review neutrophil physiology, consequences of chemotherapy-induced neutropenia (CIN), CIN risk assessment models, national practice guidelines, the impact of febrile neutropenia and infection, and what is known and unknown about CIN.

Data Sources: Extensive review and summary of published neutropenia literature, guidelines, meta-analyses, currently funded National Institutes of Health and Oncology Nursing Society studies, and invited expert panel symposium presentations.

Data Synthesis: A comprehensive review of current literature regarding CIN risk assessment, practice guidelines, management, impact on dose-dense and dose-intense cancer treatment, complications, costs related to hospitalizations, and treatment strategies has been compiled.

Conclusions: CIN is the most common dose-limiting toxicity of cancer therapy. Medical practice guidelines and risk assessment models for appropriate use of myeloid growth factors and management of febrile neutropenia have been developed to assess patients for CIN complications prechemotherapy and during CIN episodes. CIN affects patients, families, practitioners, and the healthcare system. Although much is known about this common chemotherapy complication, a great deal remains to be learned.

Implications for Nursing: CIN is a serious and global problem in patients receiving cancer therapy. Oncology nurses need to critically analyze their own practices when assessing, managing, and educating patients and families about CIN.

Key Points . . .

- ▶ Chemotherapy-induced neutropenia (CIN) is the most common dose-limiting toxicity of cancer therapy.
- ▶ Clinical practice guidelines and validated risk assessment models are available for use in evaluating patients for complications related to CIN.
- ▶ Complications of CIN include infection, the need for hospitalization, and death.

The project team conducted an extensive review and summary of neutropenia literature, guidelines, and meta-analyses and reviewed current National Institutes of Health- and ONS-funded studies. The panel of experts was invited to participate in a two-day symposium held in January 2006 in Pittsburgh, PA, during which they presented their respective areas of expertise to the project team (see inset). The expert presentations were recorded and transcribed for use in the preparation of this article.

Neutropenia is the most common dose-limiting toxicity of cancer chemotherapy, and complications from chemotherapy-induced neutropenia (CIN) can cause significant morbidity and mortality. In fact, Given and Sherwood (2005) identified CIN as a nursing-sensitive patient outcome symptom. Expert nursing assessment, intervention, education, and evaluation facilitate patient management of CIN.

At the 2004 Oncology Nursing Society (ONS) Town Hall meeting, the Neutropenia Special Interest Group requested direction from ONS regarding CIN nursing care and management. The Society responded by appointing a project leader to develop the State of the Knowledge on Neutropenia Symposium. Project team members were chosen for their oncology nursing expertise in neutropenia. The team developed a roster of experts in neutropenia, including those knowledgeable in prevention and management in both inpatient and community settings, clinical outcomes, risk management, infection and infection control, translational research, nursing education, research, and health policy.

Anita Nirenberg, RN, MS, AOCNP, is an assistant professor of clinical nursing and director of the oncology masters program in the School of Nursing at Columbia University in New York, NY; Annette Parry Bush, RN, BSN, MBA, OCN®, is a nurse planner and project manager in the education team at the Oncology Nursing Society in Pittsburgh, PA; Arlene Davis, RN, MSN, AOCN®, is an oncology clinical nurse specialist at Malcom Randall VA Medical Center in Gainesville, FL; Christopher R. Friese, RN, PhD, AOCN®, is a postdoctoral fellow in the School of Public Health at Harvard University and in the Center for Outcomes and Policy Research at the Dana-Farber Cancer Center, both in Boston, MA; Theresa Wicklin Gillespie, PhD, BA, BSN, MA, RN, is an assistant professor in the Department of Surgery and Winship Cancer Institute at Emory University and the director of health services research and development at the Atlanta VA Medical Center, both in Atlanta, GA; and Robert David Rice, RN, NP-C, OCN®, is a research nurse practitioner at Memorial Sloan-Kettering Cancer Center in New York, NY. (Submitted June 2006. Accepted for publication June 30, 2006.)

Digital Object Identifier: 10.1188/06.ONF.1193-1201

**Invited Experts and Members of the Project Group
for the Oncology Nursing Society State of the Knowledge on Neutropenia Symposium**

Benjamin Djulbegovic, MD, PhD
Professor of Oncology and Medicine
Department of Interdisciplinary Oncology
H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida
Tampa, FL

Kenneth V.I. Rolston, MD
Professor
Department of Infectious Diseases
University of Texas M.D. Anderson Cancer Center
Houston, TX

Lee S. Schwartzberg, MD, FACP
Medical Director of the Myelosuppression Unit
Baptist Hospital
West Clinic
Memphis, TN

David C. Dale, MD
Professor of Medicine
School of Medicine
University of Washington
Seattle, WA

Christopher R. Friese, RN, PhD, AOCN®
Postdoctoral Fellow
Center for Outcomes and Policy Research
Dana-Farber Cancer Center
School of Public Health
Harvard University
Boston, MA

Ashley Morris Engemann, PharmD, BCOP
Codirector of Pharmaceutical Research
Duke Comprehensive Cancer Center
Durham, NC

Vivian Park, PharmD, BCOP
Clinical Coordinator
Department of Pharmacy
Memorial Sloan-Kettering Cancer Center
New York, NY

Joseph Lipscomb, PhD
Professor of Health Policy and Management
Georgia Cancer Coalition Distinguished Scholar
Department of Health Policy and Management
Rollins School of Public Health
Emory University
Atlanta, GA

Kathleen H. Mooney, RN, PhD, AOCN®, FAAN
Louis and Janet Peery Presidential Endowed
Chair in Nursing Research
College of Nursing
University of Utah
Salt Lake City, UT

June Eilers, PhD, APRN, BC, CS
Clinical Nurse Specialist and Clinical Nurse
Researcher
Nebraska Medical Center
Omaha, NE

Alison Gardner, RN, PhD
Advanced Practice Nurse
University of Texas M.D. Anderson Cancer Center
Houston, TX

Elaine Larson, RN, PhD, FAAN, CIC
Professor of Pharmaceutical and Therapeutic
Research
Associate Dean of Research
School of Nursing
Columbia University
New York, NY

Project Team Members

Anita Nirenberg, RN, MS, AOCNP
Project Team Leader
Assistant Professor of Clinical Nursing
Director, Oncology Masters Program
School of Nursing
Columbia University
New York, NY

Arlene Davis, RN, MSN, AOCN®
Oncology Clinical Nurse Specialist
Malcom Randall VA Medical Center
Gainesville, FL

Christopher R. Friese, RN, PhD, AOCN®
Postdoctoral Fellow
Center for Outcomes and Policy Research
Dana-Farber Cancer Center
School of Public Health
Harvard University
Boston, MA

Theresa Wicklin Gillespie, PhD, BA, BSN, MA, RN
Assistant Professor
Department of Surgery and Winship Cancer Institute
Emory University
Director of Health Services Research and Development
Atlanta VA Medical Center
Atlanta, GA

Robert David Rice, RN, NP-C, OCN®
Research Nurse Practitioner
Hematology Service
Memorial Sloan-Kettering Cancer Center
New York, NY

Scope of the Problem

Neutropenia is defined as a reduction in circulating neutrophils, and Table 1 lists the operational definitions of neutropenia and febrile neutropenia (FN). Serious patient outcomes of CIN include hospitalization; IV antibiotic use; effect on quality of life (QOL) for patients and caregivers; loss of productivity; economic costs to patients, families, and the healthcare system; and suboptimal delivery of potentially curative treatment regimens. However, the most significant outcome of CIN in patients with cancer is death as a result of infection and sepsis. The goal of this white paper is to address what is known about neutropenia and its management, what remains unknown, and how the care of patients at risk for CIN and its complications may be improved through evidence-

based nursing care and patient education, nursing education, and future research.

Neutrophil Physiology and Consequences of Neutropenia

A number of white blood cell subtypes with characteristic granules in their nuclei are referred to as granulocytes. The most prominent are neutrophils (also called polymorphonuclear segmented cells or segs or polys), accounting for about 60% of circulating white blood cells. Neutrophils are the body's first responders to infection by bacteria, viruses, and other pathogens.

Production of mature neutrophils in the bone marrow takes 10–14 days. However, once they are released from the bone

Table 1. National Cancer Institute Common Toxicity Criteria: Neutropenia and Febrile Neutropenia

Adverse Event	Grade				
	1	2	3	4	5
Neutropenia	< LLN–1,500/mm ³	< 1,500–1,000/mm ³	< 1,000–500/mm ³	< 500/mm ³	Death
Febrile neutropenia	–	–	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

LLN—lower limit of normal

Note. Febrile neutropenia can be defined as a single temperature of 38.3°C or more orally or 38.0°C or more over one hour and a total neutrophil count of less than 500 neutrophils/mcl or less than 1,000 neutrophils/mcl and a predicted decline to less than 500 mcl over the next 48 hours.

Note. Based on information from National Cancer Institute, 2003; National Comprehensive Cancer Network, 2005.

marrow into the blood circulation, they live for only four to eight hours. Neutrophils that move from the circulation to tissues may live for several days (Guyton, 1991). Neutrophils are drawn to pathogen invaders by random movement through the blood, as well as through chemotaxis. Chemotaxis is the process by which neutrophils are drawn toward pathogens in response to signals emitted from and products released by the microorganisms themselves. A neutrophil then can invaginate, encompassing the microorganism, and, through mechanisms such as lysosome production and production of hydrogen peroxide, destroy the pathogen (Dale, McCarter, Crawford, & Lyman, 2003).

A continuously replenishing supply of neutrophils moves from the marrow space through the blood and to sites of infection. Imagine the gastrointestinal track, where millions of bacteria reside and serve to create normal flora in the gut. Millions of neutrophils continuously travel to the gut to keep the local bacteria in check and prevent an overgrowth of bacteria that would result in uncontrolled infection.

Cyclic chemotherapy suppresses the normal production and subsequent availability of neutrophils to fight infection, which impairs the body's natural ability to fight infection. Usually, the white blood cell nadir from cyclic combination chemotherapies is 7–14 days from the chemotherapy administration. The effect on bone marrow's ability to maintain production of an adequate amount of neutrophils may result in severe neutropenia with or without fever. Bodey, Buckley, Sathe, and Freireich (1966) were the first to demonstrate that the severity, depth, and duration of neutropenia correspond with the risk of infection and death (see Figure 1).

The introduction of exogenous hematopoietic colony-stimulating factor (CSF) has been the single most useful pharmacologic intervention in reducing the overall adverse events associated with neutropenia. In a meta-analysis of 13 studies, Clark, Lyman, Castro, Clark, and Djulbegovic (2005) showed that the length of hospital stay was significantly reduced for FN and the time to neutrophil recovery improved when CSF was used. In addition, improvement in infection-related mortality with the use of CSF had been suggested (Clark et al.).

The appropriate use of prophylactic administration of CSF has been confusing but has been better elucidated in recent years. Because of the economic cost of CSF support and the questions regarding clinical benefit, an initial approach was to wait and see if a patient had a neutropenic event. However, the majority of neutropenic events in treatment of certain cancers,

including FN, occur in the first treatment cycle (Lyman, Dale, & Crawford, 2003; Vogel et al., 2005). The incidence of grade III and IV neutropenia historically has been underreported or poorly reported. In a systematic review of early-stage breast cancer and non-Hodgkin lymphoma chemotherapy trials conducted from 1990–2000, Dale et al. (2003) reported that 40% of trials did not include data on myelotoxicity.

The cost-to-benefit ratio to use prophylactic CSF originally was defined as combination chemotherapy that had an FN risk of 40% or greater (Ozer et al., 2000). However, Vogel et al. (2005) designed a placebo-controlled trial in which they hoped to achieve a 20% incidence of FN and evaluate the FN incidence with and without growth factor support. They chose a regimen of docetaxel 100 mg/m² given on an every-three-week schedule for four cycles. The placebo arm had a 17% incidence of FN and the treatment arm had a 1% incidence, which represents a dramatic decrease in the incidence of FN in a regimen whose risk of neutropenia could be considered moderate and that previously did not qualify for growth factor support. Secondary end points of the trial demonstrated a dramatic reduction in FN-related hospitalizations (from 14% to 1%) and FN-related IV anti-infective use (from 10% to 1%). The results of the trial have led to a revision in the recommendations of the National Comprehensive Cancer Network (NCCN) practice guidelines for the use of myeloid

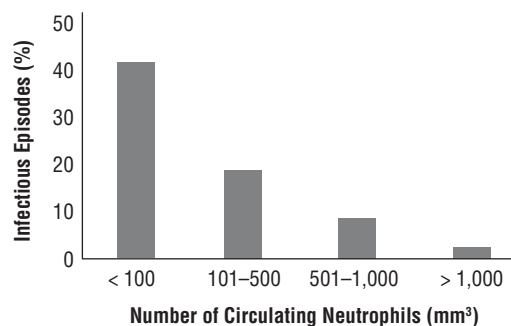


Figure 1. Severity of Neutropenia Corresponds With Risk of Infection

Note. From “Quantitative Relationships Between Circulating Leukocytes and Infection in Patients With Acute Leukemia,” by G.P. Bodey, M. Buckley, Y.S. Sathe, and E.J. Freireich, 1966, *Annals of Internal Medicine*, 64, p. 330. Copyright 1966 by the American College of Physicians. Reprinted with permission.

growth factors for the primary prophylaxis of FN and, more recently, to an update in the recommendations for the use of growth factors from the American Society of Clinical Oncology (Smith et al., 2006).

Treatment Intent and the Concept of Relative Dose Intensity

Combination chemotherapy regimens are designed to interfere with the growth cycle of the cancer cell at more than one time in the cell's life cycle. Protocols are developed to avoid overlapping toxicities with other drugs in the regimen. Maximally tolerated doses are based on the severity of side effects that are produced when drugs are given in combination (e.g., nausea, vomiting, diarrhea, bone marrow suppression). With many combination chemotherapies, myelosuppression is the major dose-limiting toxicity.

In recent years, the concepts of dose-dense and dose-intense chemotherapy have been applied to combination chemotherapy and have shown improved survival outcomes in patients with breast cancer and non-Hodgkin lymphoma. **Dose dense** indicates the ability to deliver combination chemotherapy more frequently than in the past (e.g., every two weeks as opposed to every three weeks). Prior to the use of CSF, chemotherapy was delivered approximately every 21–28 days to allow for recovery from bone marrow suppression. Currently, with the prophylactic use of CSF, recovery occurs more rapidly and allows chemotherapy to be given every 14 days, thereby exposing the cancer cells to cytotoxic therapy more frequently. **Dose intense** means giving the maximally tolerated doses of cytotoxic therapy to achieve the best survival benefit. An example of dose-dense and dose-intense combination chemotherapy is the accelerated R-CHOP protocol (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone given every two weeks, with the dose of cyclophosphamide intensified to 1 g/m²). To achieve dose density and dose intensity, CSF support must be administered.

Relative dose intensity reflects a percentage of the dose intensity that is delivered as a portion of the dose that is planned according to the protocol (Chu & DeVita, 2001). Bonadonna, Valagussa, Moliterni, Zambetti, and Brambilla (1995) first reported the importance of maintaining a relative dose intensity of more than 85% in women treated with adjuvant chemotherapy for breast cancer. That study, now updated with 30-year patient follow-up (Bonadonna et al., 2005), showed that patients being treated adjuvantly for breast cancer who received more than 85% dose intensity of cyclophosphamide, methotrexate, and 5-fluorouracil had a significantly improved survival benefit when compared with those who received less than 85% of the planned doses. In a large cohort of patients with breast cancer (N = 1,550) receiving adjuvant cyclophosphamide, doxorubicin, and 5-fluorouracil chemotherapy, Budman et al. (1998) showed improved disease-free and overall survival in patients who received full-dose intensity as compared with patients who received moderate- or low-dose intensity.

Kwak, Halpern, Olshen, and Horning (1990) demonstrated a significantly improved survival benefit in patients with non-Hodgkin lymphoma who were treated with doxorubicin-based regimens. Patients who received a relative dose intensity of greater than 75% had significantly improved survival. In a large sample of patients with non-Hodgkin lymphoma (N =

4,522), Lyman, Dale, Friedberg, Crawford, and Fisher (2004) showed that 53% received a relative dose intensity of less than 85%. Moreover, patients older than 60 years were more likely to receive less than 85% relative dose intensity (60%) than patients younger than 60 years (44%). Because the mean age of patients with non-Hodgkin lymphoma is the mid-60s, the data have significant clinical and practice implications.

The most common reasons for dose reductions and treatment delays in patients with breast cancer (Link et al., 2001) and those with non-Hodgkin lymphoma (Picozzi et al., 2001) are related to CIN and its complications. Lyman et al. (2004) demonstrated that patients who experienced a first-cycle neutropenic event were more likely to have dose reductions or delays in subsequent cycles. Additional patient-related reasons for dose reductions and treatment delays were age, race, socioeconomic status, comorbidities, compliance (Lyman, Lyman, & Agboola, 2005), and obesity (Lyman et al., 2003). Treatment intent (i.e., curative versus palliative) accounts for some treatment delays and dose reductions. In addition, practice-related differences, such as setting and location, may account for chemotherapy delays and dose reductions. Issues of access to care and lack of or poor insurance coverage for cancer treatment also may play roles in suboptimal cancer chemotherapy delivery.

Risk Assessment

The importance of risk models in determining patients who are at high or low risk of developing neutropenic complications was described first by Talcott, Finberg, Mayer, and Goldman (1988) and has been expanded in the current era of outpatient cancer therapy and the use of growth factor support. The creation of risk models to predict outcomes for patients who develop FN enables healthcare providers to identify patients who likely would have an uncomplicated recovery and those most likely to suffer major complications. The supportive care therapies of FN based on the predictions have allowed for some patients to be medically evaluated, and, if they have low-risk predictors, they may avoid hospitalization and be treated with an oral anti-infective regimen and close observation (Feld et al., 2002; Freifeld et al., 1999).

The Multinational Association of Supportive Care in Cancer (MASCC) developed a predictive model for patient evaluation at the time of presentation with FN in which the outcome measure was either uncomplicated recovery or development of serious complications (Klastersky et al., 2000). Seven independent risk factors were identified using a multiple regression model. Each of the seven factors was assigned a numeric weight, and each patient evaluated would score from 0–26, with a higher score (> 21) predictive of an uncomplicated outcome and a lower score (< 21) predictive of a complicated course of FN (see Table 2). Uys, Rapoport, and Anderson (2004) prospectively validated the MASCC risk assessment model. The validated model can be used to guide clinical decision making in the management of patients with cancer receiving myelosuppressive chemotherapy. Use of such a risk assessment may reduce inappropriate hospital admissions, thus saving that intervention for patients who need continuous monitoring by healthcare providers and immediate medical stabilization.

The Talcott et al. (1988) and MASCC models (Klastersky et al., 2000) attempt to predict high- and low-risk patients at the *time of presentation* with FN. However, a number of risk factors have been identified that are associated with increased risk for

Table 2. Multinational Association of Supportive Care in Cancer Risk Score Tool for Febrile Neutropenia

Dimension	Definition	Points Assigned
Burden of illness	Range from moribund to absence of signs and symptoms	0 = moribund to 5 = no signs or symptoms
Hypotension	Score if absent	5
Chronic obstructive pulmonary disease	Score if absent	4
Tumor type	Either solid tumor or hematologic malignancy without prior fungal infection	4
Dehydration	Score if absent	3
Patient location	Score if an outpatient	3
Age	Score if patient is younger than age 60	2

Note. Higher scores convey a lower risk of complications from febrile neutropenia. In the validation study (Uys et al., 2004), scores of 21 or more reflected lower risk of complications.

Note. Based on information from Klastersky et al., 2000.

FN development in patients receiving cancer chemotherapy. The risks may be classified as treatment related, patient related, or cancer related. Patients can be evaluated for the presence of one or more of the symptoms prior to initiating combination chemotherapy (see Figure 2).

In an effort to develop, test, and validate a prospective predictive model, Lyman et al. (2005) and the Awareness of Neutropenia in Chemotherapy Study Group began a nationwide study to determine factors that predispose patients to FN from cancer chemotherapy. Using a multivariate logistic regression model, seven variables were independently predictive of severe neutropenia or FN: (a) age, (b) hyperglycemia, (c) elevated alkaline phosphatase, (d) elevated bilirubin, (e) anthracycline-based chemotherapy, (f) body surface area less than 2 m², and (g) planned relative dose intensity greater than 85%. In the derivation sample (i.e., a statistical test used to validate a second sample), 58% of 296 patients experienced FN in the first cycle of chemotherapy. In the validation sample, no differences were noted in the predictive factors or in the distribution of neutropenic complications (Lyman et al., 2006). The model may provide clinicians with a readily available tool to predict which patients are most at risk for neutropenic complications, thereby allowing them to institute preventive measures.

The Awareness of Neutropenia in Chemotherapy model (Lyman et al., 2005) has important clinical implications because it attempts to predict patients at risk for neutropenic complications *before* treatment with chemotherapy begins. That information can have significant utility in community and inpatient practice settings.

National Practice Guidelines

Several national practice guidelines for the care and management of patients with cancer diagnosed with FN have been developed. The guidelines include those of the Infectious Diseases Society of America (Hughes et al., 2002),

which provide guidance for the use of IV antibiotic support, surveillance of patients with FN, and recommendations for the use of growth factors. The American Society of Clinical Oncology (Ozer et al., 2000) and NCCN (2005, 2006) have provided recommendations for the management of FN and the use of myeloid growth factors in patients receiving chemotherapy. The NCCN guidelines incorporate the MASCC risk assessment. Patients who score below 21 on the MASCC tool, for whom an absolute neutrophil count below 100 for seven or more days is anticipated, who appear clinically unstable, or who present with pneumonia, uncontrolled cancer, elevated creatinine, or liver function values are candidates for hospital admission and IV antibiotics. Patients who score 21 or higher on the MASCC, are outpatients, have an anticipated short duration of neutropenia, present with good performance status, have no active comorbidities, and have no signs of clinical instability are candidates for ambulatory management with oral antibiotics. Regardless of the oral or IV route, antibiotic therapy should be sufficient to cover gram-negative and gram-positive organisms. Furthermore, all patients should have a full physical assessment of common sites of infection and receive appropriate follow-up for progress (i.e., absence of fever and reduction in signs and symptoms). Choice of therapy and location of care should be reevaluated in nonresponders.

The American Cancer Society and NCCN (2006) developed fever and neutropenia treatment guidelines for patients with cancer. The practice guidelines are updated regularly to reflect new anti-infective agents, growth factor support, and diagnostic methods. Practice guidelines cannot be used universally because of differences in communities, institutional cultures, policies, and community organisms and resistance patterns. The common language in all of the guidelines reflects the need

Treatment related

- Previous history of severe neutropenia with similar chemotherapy
- Type of chemotherapy (anthracyclines and platinum-based regimens)
- Planned relative dose intensity greater than 80%
- Preexisting neutropenia or lymphocytopenia
- Extensive prior chemotherapy
- Concurrent or prior radiation therapy to marrow-containing bone

Patient related

- Older age
- Female gender
- Poor performance status
- Poor nutritional status (e.g., low albumin)
- Decreased immune function
- Open wounds or active tissue infection
- Comorbidities
 - Chronic obstructive pulmonary disease
 - Cardiovascular disease
 - Liver disease (elevated bilirubin, alkaline phosphatase)
 - Diabetes mellitus
 - Low baseline hemoglobin

Cancer related

- Bone marrow involvement with tumor
- Advanced cancer
- Elevated lactate dehydrogenase (lymphoma)

Figure 2. Risk Factors for Febrile Neutropenia

Note. Based on information from Dale, 2006; Djulbrgovic, 2006; Rolston, 2006; Schwartzberg, 2006.

for prompt initiation of anti-infective therapy as the gold standard for treating FN (Sipsas, Bodey, & Kontoyiannis, 2005).

The NCCN guidelines include algorithms based on the MASCC and Talcott et al. (1988) risk assessment models. Once a patient's risk of developing FN complications is determined, the sites of care and treatment options are outlined. Treatment options include hospitalization or ambulatory clinic treatment, IV or oral empiric antibiotic therapy, or home for "selected low-risk patients with adequate outpatient infrastructure established" (NCCN, 2005, p. FEV-3). All patients are required to have a prompt medical evaluation with appropriate review of laboratory results, administration of the first dose of antibiotics under observation, discharge planning, and patient education.

The American Cancer Society and NCCN (2006) patient treatment guidelines for patients with FN are comprehensive in describing neutropenia and risks for infection, defining fever, and recommending necessary laboratory tests and issues related to identifying infective organisms. Instructions to patients who have neutropenia with fever and other signs and symptoms of infection include the admonition to receive treatment without delay. The instructions continue to define antibiotics and state that physicians will examine patients closely to locate the infection. The patient document includes the treatment algorithm that is described in the NCCN practice guidelines with explanations for each of the possible decisions that will be made by healthcare providers evaluating patients for FN.

In the absence of fully validated models, the judicious application of national consensus practice guidelines represents a reasonable approach to neutropenia prophylaxis with growth factors and to the management of neutropenic complications. Based on the Vogel et al. (2005) trial in which growth factor prophylaxis for docetaxel as a single agent showed a significant reduction in neutropenic complications, NCCN (2005) suggested prophylaxis with regimens that present a risk of FN or are at high risk (i.e., > 20%) for neutropenic complications and recommended considering prophylaxis with chemotherapy regimens that are at moderate risk (i.e., 10%–20%) of causing neutropenia (see Figure 3). The goals of treatment also must be considered (e.g., curative, prolonged survival, symptom management, QOL).

Febrile Neutropenia and Infection

The principal adverse outcomes of concern for patients and clinicians are FN and infection. Although closely related, they remain distinct outcomes and both are worthy of study. A broad literature base has articulated poor outcomes for patients experiencing FN. Prevention of neutropenia is key to avoiding the graver outcomes related to FN and infection.

Since the 1950s, the principal management approach to FN was immediate hospitalization, administration of systemic anti-infectives, and diagnostic tests to ascertain a source of infection (Sipsas et al., 2005). The rationale for the strategy was based on the observation that patients with neutropenia and fever had extremely high death rates when broad-spectrum antibiotics were not administered promptly after the first fever. Although that approach often prevents rapid clinical deterioration, not all patients are spared complications, excess costs, and death.

From a database of acute care hospital discharges in seven states in 1999, researchers projected the number of patients hospitalized annually for FN as well as the projected length of stay, costs, and inpatient mortality (Caggiano, Weiss, Rickert, & Linde-Zwirble, 2005). The number of patients with cancer hospitalized annually for FN was estimated at 60,000, and roughly two-thirds had clinical infection. The average projected cost for hospitalization was \$13,272, with a range of \$8,100 for patients with solid tumors to \$20,400 for patients with hematologic malignancies. The average length of stay was 9.2 days, and the overall projected inpatient mortality rate for patients hospitalized for FN was 6.8%.

Hospitals are inherently dangerous places for vulnerable patient populations (Creditor, 1993). Unfamiliar environments, resistant nosocomial pathogens, and the potential for human errors place hospitalized patients at increased risk for adverse events (Institute of Medicine, 1999). Systemic anti-infectives and diagnostic procedures also convey risks to patients. A retrospective analysis of discharge data from 41,000 patients in 115 academic medical centers from 1995–2000 identified an average length of stay of 11.5 days for patients with FN (Kuderer, Dale, Crawford, Cosler, & Lyman, 2006). Although the average costs for inpatient care in a sample of 55,276 hospitalizations averaged \$19,110, the costs nearly doubled if patients experienced one complication (Kuderer, Cosler, Crawford, Dale, & Lyman, 2002). For the entire sample of patients studied, the cost of inpatient care was approximately \$1.6 billion. The inpatient mortality rate for the sample was 9.5%. Significant risk factors for inpatient mortality included the presence of comorbidities, age greater than 65 years, leukemia or lung cancer diagnoses (when compared with other tumor types), invasive bacterial or fungal infection, or circulatory collapse.

More recently, investigators have examined the effect of neutropenia and FN on QOL outcomes. Data from 34 patients who experienced grade IV neutropenia revealed significant deterioration in several components of QOL (Fortner, Tauer, Okon, Houts, & Schwartzberg, 2005). Patients experienced fatigue (91%); a decrease in social contacts with friends and family (59%); changes in daily activities, schedule, or routine (56%); sleep disturbances (41%); and muscle aches and pains (38%). Fifteen percent of the patients were admitted to the hospital for FN. Fortner et al. (2004) also surveyed 189 patients with cancer across 20 community oncology practices to identify the time spent on 13 specific treatment activities related to cancer treatment. Patients were instructed to document the time spent in the clinic, as well as travel time, and disruptions to work or social activities as a result of cancer treatment. Hospitalization for FN accounted for the largest amount of patient and family time. Approximately 8% of the patients in the survey were hospitalized, with an average time loss of 108 hours. That was followed by a physician visit with same-day chemotherapy (8 hours). Visits for physicians and nurse practitioners averaged 4 and 2.5 hours, respectively. In contrast, time loss to phlebotomy and administration of CSFs averaged three hours.

Once FN occurs, system factors may place patients at risk for poor outcomes. From an analysis of patients with FN that presented to an emergency department of a tertiary care medical center, the average waiting time was 90 minutes for evaluation, four hours to first IV antibiotic administration, and six hours to inpatient admission (Nirenberg, Mulhearn, Lin, & Larson, 2004).

Prophylaxis^e

Risk Level ^c	Treatment Intent		
	Curative/Adjuvant ^d	Prolong Survival/Quality of Life	Symptom Management/Quality of Life
High ^f (> 20%) →	CSF ^g	CSF ^g	CSF ^f
Intermediate (10%–20%) →	Consider CSF	Consider CSF ^f	Consider CSF ^f
Low (< 10%) →	No CSF ^h	No CSF	No CSF

^c There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen and patient risk factors.

^d See Risk Factors That May Compromise Ability to Deliver Full-Dose Chemotherapy (MGF-C)—go online to www.nccn.org.

^e This table applies to prophylaxis for the first and all subsequent cycles of chemotherapy for solid tumors and nonmyeloid malignancies.

^f One criterion that places a patient at high risk is a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity.

^g There is category 1 evidence for these endpoints: risk of febrile neutropenia, hospitalization, and intravenous antibiotics.

^h Only consider CSF if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

ⁱ The use of high-risk chemotherapy in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine this category, CSF is reasonable. Other alternatives, such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be considered.

CSF—colony-stimulating factor

Figure 3. National Comprehensive Cancer Network Algorithm for Prophylaxis With Growth Factors

Note. Reproduced with permission from the National Comprehensive Cancer Network (NCCN) Myeloid Growth Factors Guideline in the *Complete Library of NCCN Clinical Practice Guidelines in Oncology* [CD-ROM]. Jenkintown, PA: © National Comprehensive Cancer Network, June 2006. To view the most recent and complete version of the guideline, go online to www.nccn.org.

Note. These guidelines are a work in progress that will be refined as often as new significant data become available. The NCCN guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by the National Comprehensive Cancer Network. All rights reserved. These guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN.

A prospective study reported at the MASCC Symposium of 2005 collected weekly QOL data from 85 patients for three weeks following chemotherapy administration (Fortner, Houts, Johnson, & Schwartzberg, 2005). Grade III–IV neutropenia significantly predicted the presence of undesired symptoms on the Rotterdam Symptom Checklist and declines in physical and social function from the Short Form-36 questionnaire. Grade IV neutropenia was associated with a decrease in social functioning, depression, and social isolation. Although preliminary evidence suggests that QOL impairments are present for patients with neutropenia, to date, the research findings do not document a causal relationship. Further prospective studies with adequate statistical power to disentangle QOL impairments from other causes, such as pain and anemia, are warranted.

The question of antibiotic prophylaxis remains unclear. Evidence indicates that antibiotic prophylaxis (generally with a fluoroquinolone) decreases the frequency of febrile episodes, documented infections, and hospitalization, but no survival benefit exists (Bucaneve et al., 2005; Cullen et al., 2005). Several investigators have reported favorable outcomes among patients managed with oral antibiotics in the ambulatory setting. Oral moxifloxacin was administered to 54 patients categorized as low risk by the MASCC tool. No deaths occurred, and 91% of patients had a positive response (defined as resolution of fever or any sign of infection and avoidance of hospitalization). An absolute neutrophil count less than 100 significantly predicted poor response in the cohort (Chamilos et al., 2005).

Escalante et al. (2004) reported response rates for 257 patients with solid tumors and FN who were managed in the ambulatory setting. The standard protocol included a complete evaluation on day 1 of the FN episode. Patients were seen for follow-up on day 2 or 3. Days 4–6 consisted of telephone follow-up, and on day 7, patients returned for evaluation and a complete blood count. Twenty percent of the patients required hospitalization for poor response to initial antibiotic therapy. Significant predictors of hospitalization included presence of mucositis, age greater than 70 years, and an absolute neutrophil count less than 100.

Another study found no significant differences in clinical response between oral antibiotics and early discharge versus IV antibiotic therapy in a sample of low-risk patients with FN (Innes et al., 2003). Costs and length of stay were significantly reduced in the oral antibiotic arm. Nursing hours of care decreased from 21 hours in the IV arm to 11 in the oral arm. The one episode of clinical deterioration in the oral arm occurred within the two days of the inpatient period, reinforcing the need for providers to remain in close contact with patients should they choose ambulatory management.

From the trials and guidelines, clearly, a significant proportion of patients with FN can be managed successfully in the ambulatory setting with oral antibiotic therapy. That approach, however, does not negate the need for thorough physical assessment, close contact with patients, and frequent evaluation for satisfactory response. By using the evidence, the risk of adverse events related to hospitalization

will decrease and patients will enjoy more time with their families and friends.

Conclusions and Implications

CIN is a serious and global problem in patients receiving cancer therapy. Oncology nurses need to critically analyze their own practices when assessing, managing, and educating patients and families about CIN. Oncology nurses who work

in multiple practice settings are encouraged to approach the entire spectrum of the effect of CIN in the context of nursing-sensitive patient outcomes. Part II (see page 1202) discusses the ways in which evidence-based nursing care can support patients experiencing CIN.

Author Contact: Anita Nirenberg, RN, MS, AOCNP, can be reached at an207@columbia.edu, with copy to editor at ONFEditor@ons.org.

References

- American Cancer Society & National Comprehensive Cancer Network. (2006). *Fever and neutropenia: Treatment guidelines for patients with cancer (version VII)*. Retrieved June 7, 2006, from http://www.nccn.org/patients/patient_gls/_english/pdf/NCCN%20FN%20Guidelines.pdf
- Bodey, G.P., Buckley, M., Sathe, Y.S., & Freireich, E.J. (1966). Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Annals of Internal Medicine*, *64*, 328–340.
- Bonadonna, G., Moliterni, A., Zambetti, M., Daidone, M.G., Pilotti, S., Gianni, L., et al. (2005). 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: Cohort study. *BMJ*, *330*, 217.
- Bonadonna, G., Valagussa, P., Moliterni, A., Zambetti, M., & Brambilla, C. (1995). Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. *New England Journal of Medicine*, *332*, 901–906.
- Bucaneve, G., Micozzi, A., Menichetti, F., Martino, P., Dionisi, M.S., Martinelli, G., et al. (2005). Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *New England Journal of Medicine*, *353*, 977–987.
- Budman, D.R., Berry, D.A., Cirincione, C.T., Henderson, I.C., Wood, W.C., Weiss, R.B., et al. (1998). Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *Journal of the National Cancer Institute*, *90*, 1205–1211.
- Caggiano, V., Weiss, R.V., Rickert, T.S., & Linde-Zwirble, W.T. (2005). Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer*, *103*, 1916–1924.
- Chamilos, G., Bamias, A., Efstathiou, E., Zorzou, P.M., Kastiris, E., Kostis, E., et al. (2005). Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. *Cancer*, *103*, 2629–2635.
- Chu, E., & DeVita, V.T., Jr. (2001). Principles of cancer management: Chemotherapy. In V.T. DeVita Jr., S. Hellman, and S.A. Rosenberg (Eds.), *Cancer: Principles and practice of oncology* (6th ed., pp. 289–306). Philadelphia: Lippincott Williams and Wilkins.
- Clark, O.A., Lyman, G.H., Castro, A.A., Clark, L.G., & Djulbegovic, B. (2005). Colony-stimulating factors for chemotherapy-induced febrile neutropenia: A meta-analysis of randomized controlled trials. *Journal of Clinical Oncology*, *23*, 4198–4214.
- Creditor, M.C. (1993). Hazards of hospitalization of the elderly. *Annals of Internal Medicine*, *118*, 219–223.
- Cullen, M., Steven, N., Billingham, L., Gaunt, C., Hastings, M., Simmonds, P., et al. (2005). Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *New England Journal of Medicine*, *353*, 988–998.
- Dale, D. (2006, January). *Translational research: Putting research into clinical practice*. Presented at the Oncology Nursing Society State of the Knowledge on Neutropenia, Pittsburgh, PA.
- Dale, D.C., McCarter, G.C., Crawford, J., & Lyman, G.H. (2003). Myelotoxicity and dose intensity of chemotherapy: Reporting practices from randomized clinical trials. *Journal of the National Comprehensive Cancer Network*, *1*, 440–454.
- Djulbrgovic, B. (2006, January). *Febrile neutropenia: Clinical outcomes and clinical risk models*. Presented at the Oncology Nursing Society State of the Knowledge on Neutropenia, Pittsburgh, PA.
- Escalante, C.P., Weiser, M.A., Manzullo, E., Benjamin, R., Rivera, E., Lam, T., et al. (2004). Outcomes of treatment pathways in outpatient treatment of low risk febrile neutropenic cancer patients. *Supportive Care in Cancer*, *12*, 657–662.
- Feld, R., Paesmans, M., Freifeld, A.G., Klastersky, J., Pizzo, P.A., Rolston, K.V., et al. (2002). Methodology for clinical trials involving patients with cancer who have febrile neutropenia: Updated guidelines of the Immunocompromised Host Society/Multinational Association for Supportive Care in Cancer, with emphasis on outpatient studies. *Clinical Infectious Diseases*, *35*, 1463–1468.
- Fortner, B.V., Houts, A., Johnson, G., & Schwartzberg, L. (2005, June). *A prospective investigation of chemotherapy-induced neutropenia (CIN) and quality of life (QOL)*. Paper presented at the Multinational Association for Supportive Care in Cancer 17th International Symposium, Geneva, Switzerland.
- Fortner, B.V., Tauer, K.W., Okon, T., Houts, A.C., & Schwartzberg, L.S. (2005). Experiencing neutropenia: Quality of life interviews with adult cancer patients. *BMC Nursing*, *4*, 4.
- Fortner, B.V., Tauer, K.W., Zhu, L., Okon, T.A., Moore, K., Templeton, D., et al. (2004). Medical visits for chemotherapy and chemotherapy-induced neutropenia: A survey of the impact on patient time and activities. *BMC Cancer*, *4*(1), 22.
- Freifeld, A., Marchigiani, D., Walsh, T., Chanock, S., Lewis, L., Hiemenz, J., et al. (1999). A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *New England Journal of Medicine*, *341*, 305–311.
- Given, B.A., & Sherwood, P.R. (2005). Nursing-sensitive patient outcomes—A white paper. *Oncology Nursing Forum*, *32*, 773–784.
- Guyton, A.C. (1991). Resistance of the body to infection: I. Leukocytes, granulocytes, the monocyte-macrophage system, and inflammation. In *Textbook of medical physiology* (8th ed., pp. 365–373). Philadelphia: Saunders.
- Hughes, W.T., Armstrong, D., Bodey, G.P., Bow, E.J., Brown, A.E., Candalra, T., et al. (2002). 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clinical Infectious Diseases*, *34*, 730–751.
- Innes, H.E., Smith, D.B., O'Reilly, S.M., Clark, P.I., Kelly, V., & Marshall, E. (2003). Oral antibiotics with early hospital discharge compared with inpatient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: A prospective randomised controlled single centre study. *British Journal of Cancer*, *89*, 43–49.
- Institute of Medicine. (1999). *To err is human: Building a safer health system*. Washington, DC: National Academy Press.
- Klastersky, J., Paesmans, M., Rubenstein, E.B., Boyer, M., Elting, L., Feld, R., et al. (2000). The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *Journal of Clinical Oncology*, *18*, 3038–3051.
- Kuderer, N.M., Cosler, L.E., Crawford, J., Dale, D.C., & Lyman, G.H. (2002). *Cost and mortality associated with febrile neutropenia in adult cancer patients*. Retrieved June 5, 2006, from <http://www.asco.org/ascoposters/Abstract998/poster.htm>
- Kuderer, N.M., Dale, D.C., Crawford, J., Cosler, L.E., & Lyman, G.H. (2006). Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*, *106*, 2258–2266.
- Kwak, L.W., Halpern, J., Olshen, R.A., & Horning, S.J. (1990). Prognostic

- significance of actual dose intensity in diffuse large-cell lymphoma: Results of a tree-structured survival analysis. *Journal of Clinical Oncology*, 8, 963–977.
- Link, B.K., Budd, G.T., Scott, S., Dickman, E., Paul, D., Lawless, G., et al. (2001). Delivering adjuvant chemotherapy to women with early-stage breast carcinoma: Current patterns of care. *Cancer*, 92, 1354–1367.
- Lyman, G.H., Dale, D.C., & Crawford, J. (2003). Incidence and predictors of low dose-intensity adjuvant breast cancer chemotherapy: A nationwide study of community practices. *Journal of Clinical Oncology*, 21, 4524–4531.
- Lyman, G.H., Dale, D.C., Friedberg, J., Crawford, J., & Fisher, R.I. (2004). Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. *Journal of Clinical Oncology*, 22, 4302–4311.
- Lyman, G.H., Kuderer, N.M., Crawford, J., Wolff, D.A., Culakova, E., Poniwierski, M.S., et al. (2006). Prospective validation of a risk model for first cycle neutropenic complications in patients receiving cancer chemotherapy [Abstract 8561]. *Journal of Clinical Oncology*, 24(Suppl. 18), 4835.
- Lyman, G.H., Lyman, C.H., & Agboola, O. (2005). Risk models for predicting chemotherapy-induced neutropenia. *Oncologist*, 10, 427–437.
- National Cancer Institute. (2003). Common terminology for adverse events (CTCAE) 3.0. Retrieved June 1, 2006, from <http://ctep.cancer.gov/reporting/ctc.html>
- National Comprehensive Cancer Network. (2005). *Clinical practice guidelines in oncology: Fever and neutropenia*. Retrieved September 21, 2005, from http://www.nccn.org/professionals/physician_gls/PDF/fever.pdf
- National Comprehensive Cancer Network. (2006). *Clinical practice guidelines in oncology: Myeloid growth factors*. Retrieved June 20, 2006, from http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf
- Nirenberg, A., Mulhearn, L., Lin, S., & Larson, E. (2004). Emergency department waiting times for patients with cancer with febrile neutropenia: A pilot study. *Oncology Nursing Forum*, 31, 711–715.
- 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. American Society of Clinical Oncology Growth Factors Expert Panel. *Journal of Clinical Oncology*, 18, 3558–3585.
- Picozzi, V.J., Pohlman, B.L., Morrison, V.A., Lawless, G.D., Lee, M.W., Kerr, R.O., et al. (2001). Patterns of chemotherapy administration in patients with intermediate-grade non-Hodgkin's lymphoma. *Oncology*, 15, 1296–1306.
- Rolston, K.V. (2006, January). *Prevention and treatment of infection in patients with neutropenia*. Presented at the Oncology Nursing Society State of the Knowledge on Neutropenia, Pittsburgh, PA.
- Schwartzberg, L.S. (2006, January). *Dose intensity and management of neutropenia in the community setting*. Presented at the Oncology Nursing Society State of the Knowledge on Neutropenia, Pittsburgh, PA.
- Sipsas, N.V., Bodey, G.P., & Kontoyiannis, D.P. (2005). Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer*, 103, 1103–1113.
- Smith, T.J., Khatcheressian, J., Lyman, G.H., Ozer, H., Armitage, J.O., Balducci, L., et al. (2006). 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *Journal of Clinical Oncology*, 24, 3187–3205.
- Talcott, J.A., Finberg, R., Mayer, R.J., & Goldman, L. (1988). The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Archives of Internal Medicine*, 148, 2561–2568.
- Uys, A., Rapoport, B.L., & Anderson, R. (2004). Febrile neutropenia: A prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. *Supportive Care in Cancer*, 12, 555–560.
- Vogel, C.L., Wojtukiewicz, M.Z., Carroll, R.R., Tjulandin, S.A., Barajas-Figueroa, L.J., Wiens, B.L., et al. (2005). First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study. *Journal of Clinical Oncology*, 23, 1178–1184.