# The Relevance of Febrile Neutropenia in Oncology

## Introduction

Febrile neutropenia (FN) is among the most serious clinical complications in patients with cancer who are undergoing chemotherapy. Patients with neutropenia, or low neutrophil counts, are predisposed to serious and life-threatening infections because of their immune system's impaired ability to mount inflammatory responses to bacteria, fungi, and yeast.[1,2] Because fever is often the only sign of infection in these patients, the presence of both fever and neutropenia must be treated as a medical emergency.[2,3] Despite advances in treatment and prevention, mortality rates in patients with cancer and FN can range from 5% to 20%. Higher mortality rates are associated with patients who have higher occurrences of infectious complications and more comorbidities.[3]

Although there are slightly varying definitions of FN, most clinical guidelines follow the definitions set forth by the Infectious Diseases Society of America (IDSA).[4,5] The IDSA defines fever as a single oral temperature ≥38.3°C (101°F) or a temperature ≥38.0°C (100.4°F) lasting more than 1 hour, and defines neutropenia as an absolute neutrophil count (ANC) <500 cells/mm$^3$.[6]

Treatment guidelines for FN have been released by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the IDSA. These guidelines detail proper risk stratification, empirical therapy regimens, antimicrobial prophylaxis, and follow-up procedures.[4,6] The risk of mortality associated with FN may be reduced if healthcare providers and clinicians follow these guidelines to detect and treat febrile neutropenia appropriately. This article will discuss the general guidelines, management, and role of granulocyte-colony stimulating factors (G-CSFs) in the treatment of FN.

## Treatment Guidelines and Management

### *Initial Assessment*

The ASCO, IDSA, and NCCN guidelines all recommend taking a minimum of 2 sets of blood cultures from 1 peripheral and 1 central site. These guidelines also indicate that clinicians should review patient characteristics such as complete blood counts, liver enzymes, prior antimicrobial therapy, and potential sites of infection.[5]

### *Risk Stratification*

It is essential to perform proper risk stratification because the patient's level of risk determines the type of empirical therapy they will receive.[4,6,7] Risk stratification is conducted by using a risk index called the Multinational Association of Supportive Care in Cancer (MASCC) score, a validated scale in all 3 guidelines.[5] The MASCC score has several criteria such as »

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

PUBLISHING STAFF

**Senior Vice President, Managed Markets**
Jeff Prescott, PharmD

**Sr. Director and Head, Clinical Communications**
Naomi Musaji, PharmD

**Associate Editorial Director**
Surabhi Dangi-Garimella, PhD

**Managing Editor**
Mary K. Caffrey

**Project Manager**
Jessica Toye

**Copy Chief**
Jennifer Potash

**Copy Editor**
Maggie Shaw

**Senior Designer**
Gwendolyn Salas

SALES & MARKETING

**Director of Sales**
Gilbert Hernandez

**National Accounts Associate**
James Pastena

OPERATIONS & FINANCE

**Circulation Director**
Jon Severn

**Vice President of Finance**
Leah Babitz, CPA

**Accountant**
Katherine Wyckoff

CORPORATE OFFICERS

**Chairman and CEO**
Mike Hennessy, Sr

**Vice Chairman**
Jack Lepping

**President**
Mike Hennessy, Jr

**Chief Financial Officer**
Neil Glasser, CPA/CFE

**Chief Marketing Officer**
Warren Dardine

**Chief Digital Strategy Officer**
Steve Ennen

**Vice President of Editorial Services and Production**
Kerrie Keegan

**Vice President of Digital Media**
Jung Kim

**Vice President Live Events**
Tom Tolve

**Chief Creative Officer**
Jeff Brown

**Director of Human Resources**
Shari Lundenberg

Michael J. Hennessy Associates, Inc.

2 Clarke Drive Suite 100
Cranbury, NJ 08512 • (609) 716-7777



*The American Journal of Managed Care*® ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512.

**TABLE 1.** General Guidelines for Follow-Up Outpatient Management of Low-Risk Patients With Febrile Neutropenia[4,6,7]

| |
|---|
| Frequent evaluations for at least 3 days through clinic visits or at home |
| Daily phone calls to assess fever status, symptom severity or resolution, treatment adherence, and signs of toxicity |
| Monitoring of ANC and platelet counts to ensure adequate myeloid count recovery |
| Readmission if there is occurrence of PNF, new symptoms of infections, change in empirical therapy, or addition of new antimicrobial agents, or if cultures identify species with resistance to empirical therapy |
| Outpatients should live within 1 hour of a local medical clinic in the event that readmission is necessary |

ANC indicates absolute neutrophil count; PNF, persistent neutropenic fever.

age, symptom severity, and comorbidities, all of which are given a weighted numerical value. Patients who score ≥21 or <21 are classified as low risk and high risk, respectively.[3] Risk stratification helps determine the route (oral vs intravenous [IV]) and duration of empirical therapy, and location of treatment (inpatient vs outpatient).[6]

## *Initiation of Therapy*

The 3 guidelines in FN management have slightly different recommendations regarding the timing of initial empirical therapy. The ASCO guidelines recommend starting empirical therapy within 1 hour of admission, while the IDSA guidelines recommend starting within 2 hours of admission. The NCCN guidelines do not provide a time frame for empirical therapy initiation.[5]

## *Low-Risk Patients*

If clinically indicated, patients who are classified as low risk through their MASCC score may receive IV antibiotic therapy with agents such as meropenem, piperacillin/tazobactam, or extended-spectrum antipseudomonal cephalosporins. Outpatient treatment may be considered for low-risk patients with favorable factors such as hemodynamic stability, lack of comorbid conditions, good performance status, no renal or hepatic insufficiency, and absence of organ dysfunction. For these low-risk outpatient individuals, empirical treatment of oral fluoroquinolones (ciprofloxacin or levofloxacin) with the addition of amoxicillin/clavulanate or clindamycin is generally recommended.[4,6,7] If the patient had received prior fluoroquinolone-based prophylaxis or if local antibiograms indicate fluoroquinolone resistance to be ≥20%, then fluoroquinolone monotherapy is not recommended.[5]

Follow-up procedures for outpatient management include frequent evaluation for at least 3 days, daily telephone evaluations, and frequent monitoring of absolute neutrophil count and platelets for myeloid count recovery (see **Table 1**[4,6,7] for additional information).[4,7]

## *High-Risk Patients*

Patients who have MASCC scores below 21 or unfavorable prognostic factors are classified as high risk. These high-risk patients are recommended to be hospitalized and treated as inpatients with IV empirical therapy. The guidelines recommend monotherapy with piperacillin-tazobactam, a carbapenem (imipenem/cilastatin or meropenem), or an empirical IV antipseudomonal beta-lactam agent, such as cefepime.[4,6] Depending on blood cultures and local antibiotic resistance patterns, the administration of additional agents such as vancomycin for suspected methicillin-resistant *Staphylococcus aureus* infection may be warranted.[6] However, unless otherwise indicated by blood cultures or microbiology tests, combination therapy is not recommended because of the risk of breakthrough infections and increasing resistance.[4]

## *Persistent Neutropenic Fever Syndrome*

Persistent neutropenic fever (PNF) syndrome occurs when patients remain continuously febrile and neutropenic after initiation of empirical broad-spectrum therapy. Patients with PNF should be closely monitored for proper follow-up treatment.[7] Treatment guidelines recommend hospitalizing patients and initiating empirical antifungal therapy for patients who show no response to broad-spectrum antibiotics after 4 to 7 days, and who are expected to remain neutropenic for more than 7 days. Empirical antifungal agents should provide better coverage against fluconazole-resistant *Candida* infections and molds such as *Aspergillosis,* the most common invasive mold infection. Additional agents may be added if indicated through blood culture lab tests.[6] Amphotericin B products are commonly used as empirical therapy when the etiology of PNF is unknown (see **Table 2**[4,6,7] for additional information).[4]

## *Antibacterial and Antifungal Prophylaxis Guidelines*

Antibacterial and antifungal prophylaxis may be considered as a preventative measure in patients at high risk for FN. The ASCO, NCCN, and IDSA guidelines share similar recommendations and suggest using antibacterial and antifungal prophylaxis in patients whose neutrophil

**TABLE 2.** General Guidelines for Management of Persistent Neutropenic Fever[4,6,7]

| |
|---|
| Patients who are clinically stable, have rising ANC levels, and expect imminent myeloid recovery should be observed and no actions are required unless new symptoms of infection manifest |
| Patients who were receiving fluconazole for anti-yeast prophylaxis should receive empirical antifungal therapy with anti-mold coverage (voriconazole, echinocandin, or an amphotericin B product) that can better protect against fluconazole-resistant *Candida* infections and *Aspergillus* molds |
| While not a practice standard, certain patients with persistent neutropenic fever who are clinically stable, have negative CT scans, and have negative serologic assays may use preemptive antifungal management as an alternative to empirical antifungal therapy. If patients display symptoms of an invasive fungal infection, then antifungal therapy should be initiated |
| Patients who were receiving anti mold prophylaxis should switch to a different class of anti mold agents |
| Patients with a documented infection who do not improve should be reevaluated with additional tests and add on broad-spectrum antimicrobial therapy. An infectious disease consult may also be considered |

ANC indicates absolute neutrophil count.

counts are expected to be below 100 cells/µL for more than 7 days. Additionally, the guidelines do not support the use of antibiotic prophylaxis in low-risk patients who are expected to remain neutropenic for fewer than 7 days. Generally, if there are no documented resistance patterns, then a fluoroquinolone agent is recommended for antibacterial prophylaxis. The ASCO guidelines recommend using an oral triazole as an agent of choice for antifungal prophylaxis.[4,6,7]

## Role of G-CSFs in Treatment of FN

Granulocyte colony stimulating factors (G-CSFs) are used to increase production of granulocytes and neutrophils for myeloid count recovery, and they have been shown to reduce the risk and duration of FN.[8,9] Currently, G-CSFs are indicated for decreasing the incidence of FN in patients with nonmyeloid cancers who are undergoing myelosuppressive chemotherapy.[9] Current guidelines recommend the use of G-CSFs as primary prophylaxis (defined as the use of G-CSFs during the first cycle of myelosuppressive chemotherapy to prevent the occurrence of neutropenic fever) when the risk of FN exceeds ≥20% and it is clinically indicated by patient-, treatment-, and medication-specific factors.[6,8,10,11]

G-CSFs are not recommended when the risk of developing FN is less than 10%, the patient is afebrile, or as adjunctive treatment with antibiotic therapy in patients with established FN.[6,8,10] However, guideline recommendations note that patients at high risk for infection-related complications or patients who have poor prognostic factors, such as sepsis and elderly age, may benefit from G-CSFs to improve clinical outcomes.[8,10]

When the risk of FN is intermediate (between 10% and 20%), the NCCN guidelines recommend assessing patient-specific risk factors and prior chemotherapy regimens. G-CSF use may be considered if a patient demonstrates at least 1 risk factor, such as impaired liver or kidney function.[8]

In certain circumstances, G-CSFs may be used as secondary prophylaxis for FN recurrence. Patients who have experienced episodes of FN in prior chemotherapy cycles have a 50% to 60% chance of FN reoccurrence in subsequent cycles. To reduce this risk, dose reduction or treatment delay of future cycles may be recommended.[11] However, if dose reduction or treatment delay would compromise the patient's overall survival or treatment outcomes, then it is recommended to use G-CSFs as secondary prophylaxis to reduce the risk of FN recurrence.[10] Interestingly, while the European Society for Medical Oncology (ESMO) guidelines describe similar recommendations to North American guidelines for G-CSF primary and secondary prophylaxis in FN,[12] one notable difference is that the ESMO guidelines do not mention recommendations in patients who have less than a 20% risk of FN. However, similar to the North American guidelines, the ESMO guidelines suggest considering G-CSF if chemotherapeutic dose reduction or treatment delay would negatively impact patient outcomes.[12]

## Conclusion

Although FN is a medical emergency that can cause serious adverse complications and must be treated promptly, guidelines and recommendations may help facilitate appropriate decision making. The ASCO, NCCN, and IDSA guidelines all stress the importance of proper risk stratification and patient assessment to determine the correct course of broad-spectrum empirical therapy. Clinicians must also be aware of the benefits and limitations »

of G-CSFs in oncologic therapy and their role in the prophylaxis and treatment of FN. By adhering to evidence-based clinical guidelines, healthcare providers have the potential to provide optimized treatment regimens and lower the risk of FN for their patients.


**REFERENCES**

1. Neutropenia. American Society of Clinical Oncology website. www.cancer.net/navigating-cancer-care/side-effects/neutropenia. Published October 2016. Accessed August 2017.
2. Wingard JR. Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults. UpToDate website. www.uptodate.com/contents/prophylaxis-of-infection-during-chemotherapy-induced-neutropenia-in-high-risk-adults. Updated September 13, 2016. Accessed August 2017.
3. Lyman GH, Rolston KV. How we treat febrile neutropenia in patients receiving cancer chemotherapy. *J Oncol Pract.* 2010;6(3):149-152. doi: 10.1200/JOP.091092.
4. Prevention and treatment of cancer-related infections. National Comprehensive Cancer Network website. www.nccn.org/professionals/physician_gls/PDF/infections.pdf. Published February 2017. Accessed August 2017.
5. Pherwani N, Ghayad JM, Holle LM, Karpiuk EL. Outpatient management of febrile neutropenia associated with cancer chemotherapy: risk stratification and treatment review. *Am J Health Syst Pharm.* 2015;72(8):619-631. doi: 10.2146/ajhp140194.
6. Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52(4):e56-e93. doi: 10.1093/cid/cir073.
7. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013;31(6):794-810. doi: 10.1200/JCO.2012.45.8661.
8. Myeloid growth factors. National Comprehensive Cancer Network website. www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Published April 2017. Accessed August 2017.
9. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in neutropenia. *J Immunol.* 2015;195(4):1341-1349. doi: 10.4049/jimmunol.1500861.
10. Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2015;33(28):3199-3212. doi: 10.1200/JCO.2015.62.3488.
11. Larson RA. Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. UpToDate website. www.uptodate.com/contents/use-of-granulocyte-colony-stimulating-factors-in-adult-patients-with-chemotherapy-induced-neutropenia-and-conditions-other-than-acute-leukemia-myelodysplastic-syndrome-and-hematopoietic-cell-transplantation. Updated August 17, 2017. Accessed August 2017.
12. Crawford J, Caserta C, Roila F; ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. *Ann Oncol.* 2010;21(suppl 5):v248-v251. doi: 10.1093/annonc/mdq195.


# The Value of Granulocyte Colony-Stimulating Factors in Managing Febrile Neutropenia

## Cost Burdens of Cancer and Febrile Neutropenia

In 1987, the total medical cost of cancer in the United States, adjusted to 2007 US dollars, was $24.7 billion. From 1987 to the period between 2001 and 2005, costs nearly doubled, to approximately $48.1 billion.[1] However, despite significantly increased spending on oncologic treatment, survival rates have not improved proportionally. As much as an estimated 30% of healthcare expenditures provide minimal value in changing patient outcomes. Despite the United States investing more healthcare dollars than other countries, the life expectancies of men and women in the United States are shorter than those in comparable industrialized nations.[2]

In 2013, the estimated cost of febrile neutropenia (FN) in the United States ranged from $16,054 to $34,756 per patient, the highest in the world (followed by Singapore, Europe, Australia, Canada, and Spain); the per-patient cost outside the United States ranged from $5819 to $13,823.[3] To contain and manage rising costs associated with febrile neutropenia (FN), it is important to make value-based assessments before administering treatment.