Overview

Neutropenia (< 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 hours) and resulting febrile neutropenia (≥ 38.3°C orally or ≥ 38.0°C over 1 hour) can be induced by myelosuppressive chemotherapy. Febrile neutropenia (FN) in turn is a major dose-limiting toxicity of chemotherapy, often requiring prolonged hospitalization and broad-spectrum antibiotic use.\(^1\) These can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome. Studies have shown that prophylactic use of colony-stimulating factors (CSFs) can reduce the risk, severity, and duration of FN, but its cost has prevented its routine use for all patients undergoing myelosuppressive chemotherapy.

Please Note

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chemotherapy. Selective use of CSFs in patients at increased risk for neutropenic complications may, however, enhance the cost-effectiveness.

The risk of FN is usually based on the treatment regimen and delivered dose intensity. A survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin’s lymphoma (NHL) has shown, however, that the rates of myelosuppression and delivered dose intensity are underreported. When reported, the rates of myelosuppression with the same and similar regimens varied greatly, making the actual risk for neutropenic complications associated with common chemotherapy regimens difficult to determine.

Differences in the reported rates of neutropenic complications may relate to differences in study patient populations and the delivered dose intensity. Treatment dose intensity was reported with even less consistency, making differences in reported rates of toxicity or treatment efficacy very difficult to interpret.

A review by Dale showed that 25% to 40% of treatment-naive patients develop FN with common chemotherapy regimens. Occurrence of FN may delay subsequent chemotherapy courses or result in dose reduction that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. In addition, correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.

Filgrastim and pegfilgrastim, both granulocyte-colony stimulating factors (G-CSFs), are currently FDA approved for use in preventing chemotherapy-related FN. These agents have been shown to decrease the duration of neutropenia and the incidence of infection, allowing patients to continue chemotherapy at full dose levels.

NCCN Myeloid Growth Factors Panel Members

*Jeffrey Crawford, MD/Chair†‡
  Duke Cancer Institute
Jeffrey Allen, MD†
  St. Jude Children’s Research Hospital/University of Tennessee Cancer Institute
James Armitage, MDP
  UNMC Eppley Cancer Center at The Nebraska Medical Center
Douglas W. Blayney, MD†
  University of Michigan Comprehensive Cancer Center
Spero R. Cataland, MD†
  The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
Mark L. Heaney, MD, PhD†‡
  Memorial Sloan-Kettering Cancer Center
Sally Htoy, PharmDΣ
  City of Hope Comprehensive Cancer Center
Susan Hudock, PharmD, BCOPΣ
  The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Dwight D. Kloth, PharmD, BCOPΣ
  Fox Chase Cancer Center
David J. Kuter, MD, DPhil†‡
  Massachusetts General Hospital Cancer Center
Gary H. Lyman, MD, MPH†‡
  Duke Cancer Institute
Brandon McMahon, MD†
  Robert H. Lurie Comprehensive Cancer Center of Northwestern University
David P. Steensma, MD†
  Dana-Farber/Brigham and Women’s Cancer Center
Saroj Vadhan-Raj, MD
  The University of Texas MD Anderson Cancer Center
Peter Westervelt, MD, PhD†
  Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
Michael Westmoreland, PharmDΣ
  The University of Texas MD Anderson Cancer Center
NCCN Staff: Mary Dwyer, MS, and Maria Ho, PhD

KEY:

*Writing Committee Member

Specialties: †Medical Oncology; ‡Hematology/Hematology Oncology; ÌInternal Medicine; ΣPharmacology
### CHEMOTHERAPY

**malignancies**

**with solid tumors**

**EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE**

<table>
<thead>
<tr>
<th>Evaluation of risk for febrile neutropenia after chemotherapy in adult patients with solid tumors and nonmyeloid malignancies</th>
</tr>
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</table>
| 1. Disease  
2. Chemotherapy regimen  
   - High-dose therapy  
   - Dose-dense therapy  
3. Standard-dose therapy  
4. Patient risk factors  
5. Treatment intent  
   - (curative vs. palliative) |

<table>
<thead>
<tr>
<th>Chemotherapy Treatment Intent</th>
<th>Curative/Adjuvant</th>
<th>Prolong Survival/Quality of Life</th>
<th>Symptom Management/Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF (category 1 for G-CSF)</td>
<td>Consider CSF</td>
<td>Consider CSFk</td>
<td>Consider CSFk</td>
</tr>
<tr>
<td>CSF (category 1 for G-CSF)</td>
<td>Consider CSFk</td>
<td>Consider CSFk</td>
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<tr>
<td>No CSF</td>
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</tbody>
</table>

**PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA**

**CHEMOTHERAPY CYCLE**

- **Curative**
  - No CSF
- **Adjuvant**
  - No CSF
- **Prolong Survival**
  - No CSF
- **Symptom Management**
  - No CSF

**Risk Assessment For Febrile Neutropenia**

- **High** (> 20%)
- **Intermediate** (10%-20%)
- **Low** (< 10%)

**CSF** = colony stimulating factors

---

**Evaluation of Risk Factors:**

- **Disease**
- **Chemotherapy regimen**
  - High-dose therapy
  - Dose-dense therapy
- **Standard-dose therapy**
- **Patient risk factors**
- **Treatment intent** (curative vs. palliative)

**Clinical trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

Evaluate patient before second and subsequent chemotherapy cycles

Prior use of CSF

- Febrile neutropenia or dose-limiting neutropenic event
- No prior use of CSF

Consider dose reduction or change in treatment regimen

Consider CSF (See Risk Assessment For Febrile Neutropenia on previous page)

Repeat assessment after each subsequent cycle

SECONDARY PROPHYLAXIS

| Febrile neutropenia is defined as single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).
| A dose-limiting neutropenic event could be a nadir count or day-of-treatment count that may otherwise impact planned dose of chemotherapy. |
THERAPEUTIC USE OF CSF FOR FEBRILE NEUTROPENIA

PRESENTATION
Patients receiving prophylactic CSF (filgrastim or sargramostim)

Patients who have received prophylactic pegfilgrastim

Patients who did not receive prophylactic CSF

CSF USE DURING CURRENT CHEMOTHERAPY CYCLE
Continue CSF
No additional CSF
No CSF
Consider CSF

MANAGEMENT OF PATIENTS WITH FEBRILE NEUTROPENIA

Risk factors not present for an infection-associated complication
Risk factors present for an infection-associated complication

Notes:

Febrile neutropenia is defined as single temperature: ≥ 38.3°C orally or ≥ 38.0°C over 1 h; neutropenia: < 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to < 500/mcL over the next 48 h. See the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

For antibiotic therapy recommendations for fever and neutropenia, see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

The decision to use CSF in the therapeutic setting is controversial. See discussion for further detail.

See Patient Risk Factors for Poor Clinical Outcomes or for Developing Infection-Associated Complications (page 924).

No studies have addressed therapeutic use of filgrastim for febrile neutropenia in patients who have already received prophylactic pegfilgrastim. However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggest that additional CSF will not be beneficial.

See discussion for further detail. No data are available on pegfilgrastim in the therapeutic setting. Either filgrastim or sargramostim should be used with initial dosing, as outlined in Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (page 923) and discontinued at time of neutrophil recovery.
Examples of Disease Settings and Chemotherapy Regimens with a High Risk of Febrile Neutropenia (> 20%)

- This list is not comprehensive: other agents/regimens have a high risk for development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment-naive vs. heavily pretreated patients; see page 916).
- The type of chemotherapy regimen is only one component of the risk assessment (See Patient Risk Factors for Developing Febrile Neutropenia, page 923)
- Pegfilgrastim has not been documented to have benefit in regimens given for < 2 weeks.
- Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic) 1

Breast Cancer
- Docetaxel + trastuzumab (metastatic or relapsed) 2
- Dose dense AC + T (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant) 3
- AT (doxorubicin, paclitaxel) (metastatic or relapsed) 4
- AT (doxorubicin, docetaxel) (metastatic or relapsed) 5
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant) 6

Esophageal and Gastric Cancer
- Docetaxel/cisplatin/fluorouracil 7

Hodgkin Lymphoma
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) 8

Kidney Cancer
- Doxorubicin/gemcitabine 9

Non-Hodgkin's Lymphomas
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory) 10,11
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, second-line, salvage) 12
- RICE* (rituximab, ifosfamide, carboplatin, etoposide) 13
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) 14
- MINE (mesna, ifosfamide, novantrone, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, second-line, salvage) 15
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphoma, diffuse large B-cell lymphoma, second-line, refractory) 16
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, second-line, recurrent) 17
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab) 18,19

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent) 20
- Dacarbazine-based combination with IL-2, interferon-alpha (dacarbazine, cisplatin, vinblastine, IL-2, interferon-alpha) (advanced, metastatic, or recurrent) 20

Multiple Myeloma
- Modified HyperCVAD 21

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine 22

Decitabine 23

Ovarian Cancer
- Topotecan 24
- Paclitaxel 25
- Docetaxel 26

Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine) 27
- Doxorubicin 28

Small Cell Lung Cancer
- Topotecan 29

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin) 30
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin) 31

*In general, dose-dense regimens require growth factor support for chemotherapy administration.

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (page 920)

See Chemotherapy Regimen References (pages 921 and 922)
**Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (10%-20%)**

- **This list is not comprehensive;** there are other agents/regimens that have an intermediate risk for development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment naive vs. heavily pretreated patients; see page 916).
- The type of chemotherapy regimen is only one component of the risk assessment.

(See Patient Risk Factors for Developing Febrile Neutropenia, page 923)

- Pegfilgrastim has not been documented to have benefit in regimens given for <2 weeks.
- Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

### Occult Primary-Adenocarcinoma
- Gemcitabine, docetaxel
- Docetaxel every 21 days
- Epirubicin (adjuvant)
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)
- AC + sequential docetaxel + trastuzumab (adjuvant)
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel
- Paclitaxel every 21 days (metastatic or relapsed)
- Vinblastine (metastatic or relapsed)

### Breast Cancer
- Cisplatin + topotecan (recurrent or metastatic)
- Topotecan (recurrent or metastatic)
- Irinotecan (RECIST or metastatic)

### Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)

### Esophageal and Gastric Cancer
- Irinotecan/cisplatin
- Epirubicin/cisplatin/5-fluorouracil
- Epirubicin/cisplatin/capecitabine

### Hodgkin Lymphoma
- ABVD* (doxorubicin, bleomycin, vinblastine, dacarbazine)
- Stanford V* (methotrexate, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)

### Non-Hodgkin’s Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt’s lymphoma, recurrent)
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, diffuse large B-cell lymphoma, recurrent)
- ACOD (modified CHOP, doxorubicin, cyclophosphamide, vincristine, prednisone)
- GDP (gemcitabine, dexamethasone, cisplatin) (peripheral T-cell lymphoma, diffuse large B-cell lymphoma, second-line)
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (diffuse large B-cell lymphoma, second-line)
- FM (fludarabine, mitoxantrone)
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) including regimens with pegylated liposomal doxorubicin or mitoxantrone substituted for doxorubicin

### Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel (adjuvant, advanced/metastatic)
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)
- Cisplatin/irinotecan (advanced/metastatic)
- Cisplatin/etoposide (adjuvant, advanced/metastatic)
- Carboplatin/paclitaxel (adjuvant, advanced/metastatic)
- Docetaxel (advanced/metastatic)

### Ovarian Cancer
- Carboplatin/docetaxel
- Carboplatin/paclitaxel
- Etoposide/carboplatin
- Etoposide/cisplatin
- Oxaliplatin

### Small Cell Lung Cancer
- Etoposide/carboplatin

### Testicular Cancer
- Etoposide/cisplatin

### Uterine Cancer
- Docetaxel (uterine sarcoma, advanced or metastatic)

---

*One retrospective review suggests pulmonary toxicity may be increased using G-CSF in bleomycin-containing regimens. (See discussion for further detail.)*

1 The published results for cabazitaxel have an 8% rate of febrile neutropenia and neutropenic deaths were reported. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features.

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See Disease Settings and Chemotherapy Regimens with a High Risk of Febrile Neutropenia (page 919)

See Chemotherapy Regimen References (pages 921 and 922)
† The published results for cabazitaxel have an 8% rate of febrile neutropenia and neutropenic deaths were reported. Primary prophylaxis

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Myeloid Growth Factors Version 1:2011

CHEMOTHERAPY REGIMEN REFERENCES


PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

Chemosensitivity, in particular, and host factors may be major determinants of outcomes in patients with cancer. Myeloid growth factors (G-CSF and GM-CSF) have been shown to significantly reduce the incidence and severity of febrile neutropenia. These factors are now an integral part of standard care for most chemotherapy regimens in various cancer types. The NCCN guidelines reflect the current evidence on the use of prophylactic myeloid growth factors, with recommendations for the prevention and treatment of cancer-related infections.

**CHEMOTHERAPY REGIMEN REFERENCES**


Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

In addition to the risk of the chemotherapy regimen and the specific malignancy being treated, these factors need to be considered when evaluating a patient’s overall risk for febrile neutropenia:

- Older patient, notably patients aged 65 and older (see NCCN Guidelines for Senior Adult Oncology; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org)
- Previous chemotherapy or radiation therapy
- Preexisting neutropenia or bone marrow involvement with tumor
- Preexisting conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

MYELOID GROWTH FACTORS FOR PROPHYLAXIS AND TREATMENT OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until postnadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start 24–72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.
- Pegfilgrastim (category 1) (For prophylactic use only)
  - One dose of 6 mg per cycle of treatment.
  - Start 24–72 h after completion of chemotherapy. Administration of growth factor on same day as chemotherapy is not recommended.\(^1\)
  - Evidence supports use for chemotherapy regimens given every 3 weeks (category 1).
  - Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 weeks.
  - Data are insufficient to support dose and schedule of weekly regimens or chemotherapy schedules less than 2 weeks, and therefore these cannot be recommended.
- Sargramostim (category 2B)
  - Used in clinical trials at a dose of 250 mcg/m\(^2\)/d (rounding to the nearest vial size by institution-defined weight limits).
  - Start 24–72 h after completion of chemotherapy and treat through postnadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.
- Prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.
- Subcutaneous route is preferred for all 3 agents.
- No data support alternative dosing schedules in intermediate- and high-risk patients.
- The safety data appear to be similar between filgrastim and pegfilgrastim.
- Prophylactic antibiotics are not routinely recommended for standard-dose chemotherapy, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

\(^1\)Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after chemotherapy have shown an increase in febrile neutropenia and/or other adverse events. See discussion for details.

\(^2\)There is category 1 evidence to support filgrastim or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence for a category 1 recommendation for sargramostim in this setting. Sargramostim is indicated for use after induction chemotherapy in older adult patients with AML. Studies are ongoing in other areas.
TOXICITY RISKS WITH GROWTH FACTORS

Filgrastim

- **Warnings**
  - Allergic reactions
  - Skin: rash, urticaria, facial edema
  - Respiratory: wheezing, dyspnea
  - Cardiovascular: hypotension, tachycardia
  - Spleenic rupture
  - Adult respiratory distress syndrome
  - Precipitate sickle cell disease crisis
  - MDS and AML (see discussion for details)
- **Adverse reactions**
  - Medullary bone pain (> 10%)
  - Precautions
  - Cutaneous vasculitis

Pegfilgrastim

- **Warnings**
  - Spleenic rupture
  - Adult respiratory distress syndrome
  - Allergic reactions
  - Skin: rash, urticaria
  - Respiratory: anaphylaxis
  - Precipitate sickle cell disease crisis
  - Adverse reactions
  - Bone pain

Sargramostim

- **Warnings**
  - Fluid retention: edema, capillary leak syndrome, pleural and/or pericardial effusion
  - Respiratory symptoms: sequestration of granulocytes in pulmonary circulation dyspnea
  - Cardiovascular symptoms: occasional transient supraventricular arrhythmia. Use with caution in patients with preexisting cardiac disease
  - Renal and hepatic dysfunction: elevation of serum creatinine or bilirubin and hepatic enzymes. Monitor patients who display renal or hepatic dysfunction before initiation of treatment
  - Adverse reactions with autologous bone marrow transplant or peripheral blood progenitor cell transplant
  - Asthenia, diarrhea, rash
  - Adverse reactions with allogeneic bone marrow transplant or peripheral blood progenitor cell transplant
  - Abdominal pain, chest pain, diarrhea, nausea, vomiting, gastrointestinal hemorrhage, pruritus, bone pain, eye hemorrhage, hyperglycemia, hypomagnesemia, pharyngitis, insomnia, anxiety, high BUN, high cholesterol

1 View filgrastim prescribing information.
2 View pegfilgrastim prescribing information.
3 View sargramostim prescribing information.
4 Toxicity data are based primarily on studies from leukemia and transplant patients.

PATIENT RISK FACTORS FOR POOR CLINICAL OUTCOMES OR FOR DEVELOPING INFECTION-ASSOCIATED COMPLICATIONS

Patient risk factors include:
- Sepsis syndrome
- Age > 65 years
- Severe neutropenia (absolute neutrophil count < 100/mcL)
- Neutropenia expected to last more than 10 days
- Pneumonia
- Invasive fungal infection
- Other clinically documented infections
- Hospitalization at the time of fever
- Prior episode of febrile neutropenia

1 The decision to use or not use CSFs in the treatment of febrile neutropenia is controversial. See discussion for further detail.
induced neutropenia. In contrast, the labeled indication for sargramostim, a granulocyte-macrophage CSF (GM-CSFs), is limited to use after induction therapy for acute myeloid leukemia (AML) and in various stem cell transplantation settings. Recommendations are based on evidence derived mainly from studies on G-CSFs; head-to-head comparative studies are lacking on the clinical benefits of G-CSFs and GM-CSFs.

These NCCN Guidelines focus on the use of CSFs in the cancer setting, specifically in adult patients with solid tumors and nonmyeloid malignancies. Growth factors in the treatment of myeloid malignancies are discussed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myelodysplastic Syndromes (in this issue; also available at www.NCCN.org) and the NCCN Guidelines for Acute Myeloid Leukemia (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Benefits and Risks of CSFs

The prophylactic use of G-CSFs has been shown to reduce the incidence, length, and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, and NHL.5–16 G-CSFs also improved delivery of full dose intensity of chemotherapy at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival.5,7,9,12–15,17,18 However, in node-positive breast cancer19 and aggressive lymphoma,20 dose-dense regimens supported by G-CSFs improved disease-free and/or overall survival compared with conventional chemotherapy.

Meta-analyses have confirmed the efficacy of prophylactic CSFs in decreasing rates of infection21,22 and risk of neutropenia.21,22 In a meta-analysis of 17 randomized trials of prophylactic G-CSFs, including 3493 adult patients with solid tumors and lymphoma,23 G-CSF as primary prophylaxis reduced the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; \( P < .001 \)) and improved relative dose intensity of the chemotherapy delivered (average difference between study arms, 8.4%; \( P = .001 \)). For the first time, this analysis also reported a substantial reduction in risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; \( P = .018 \)) and all early deaths during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; \( P = .002 \)). The survival advantage is confirmed in a recent systematic review by Lyman et al.24 of 25 randomized controlled trials involving more than 12,000 patients undergoing chemotherapy with or without G-CSF support. With an average follow-up of 5 years, G-CSF was associated with 0.897% and 3.40% reductions in relative and absolute risks for all-cause mortality, respectively, although this is associated with an increased risk for AML and myelodysplastic syndromes (MDS; see later discussion). The degree of benefit correlated with chemotherapy dose intensity.

Over the past decade, the costs of inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.25 Economic analyses of CSFs have yielded mixed results, depending on the context of use.26–30 However, the policy of the panel is to primarily examine issues of therapeutic efficacy and clinical benefit, rather than cost. The indication for prophylactic CSF use depends on the risk of FN or other neutropenic events that can potentially compromise treatment.

To date, the main consistently observed toxicity associated with G-CSF therapy was mild to moderate bone pain.31,32 This is usually effectively controlled by nonnarcotic analgesics. The meta-analysis by Kuderer et al.23 confirmed a heightened risk of musculoskeletal pain associated with CSFs (RR, 4.03; 95% CI, 2.15–7.52; \( P < .001 \)). In a retrospective review, a heightened rate of bleomycin pulmonary toxicity has been linked to G-CSF use in patients with Hodgkin lymphoma undergoing bleomycin-containing therapy.33 This has not been seen with G-CSF use in bleomycin-containing testicular cancer chemotherapy regimens.38

Rare cases of splenic rupture with G-CSF use have also been reported, some of which were fatal.31,32 These cases occurred in patients and healthy donors in the stem cell transplantation setting. Some patients develop allergic reactions in the skin, respiratory system, or cardiovascular system (filgrastim only).

Although some epidemiologic studies have suggested a potentially increased risk of AML/MDS with G-CSF administration, this was not observed in individual randomized trials.34 The recent analysis by Lyman et al.24 reported an increase in relative and absolute risk of AML/MDS of 1.92% and 0.41%, respectively, related to G-CSF. Whether the risk of AML/MDS is secondary to G-CSFs or related to the
higher total doses of chemotherapy cannot be determined from this meta-analysis. Overall mortality was nevertheless decreased.

**Prophylactic Use of CSFs**

**Risk Assessment**
The NCCN Guidelines begin with an evaluation of risk for chemotherapy-induced FN before the first cycle. The risk assessment involves varied components, including the disease type, chemotherapeutic regimen (high-dose, dose-dense, or standard-dose therapy), patient risk factors, and treatment intent. Three categories based on the intent of chemotherapy have been designated by the panel, including curative/adjuvant therapy, treatment directed toward prolongation of survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to a high-risk group (> 20% risk of FN), an intermediate-risk group (10%–20% risk), and low-risk group (< 10% risk). No consensus nomogram exists for risk assessment. Although the panel outlines criteria to aid in assessment, independent clinical judgment should be exercised based on the patient's situation. When determining the appropriate use of CSFs, in addition to assessing patient and treatment-related risk, consideration should be given to the intent of cancer treatment. For example, one criterion that identifies a high-risk patient is a previous neutropenic complication in the immediate previous cycle with no plan to reduce the dose intensity.

**Patients at High Risk for FN**
Panel discussions have focused on defining a risk level of FN that would warrant routine use of prophylactic growth factors. The NCCN Guidelines recommended prophylactic CSFs if the risk of FN was 20% or greater. The most recent update of the ASCO and EORTC guidelines both adopted the 20% threshold for considering routine prophylactic treatment. These consistent recommendations are based on the results of several large randomized trials that have documented that the risk of FN can be significantly reduced by primary prophylaxis when the risk of FN without prophylaxis is 20%. For example, Vogel et al. reported on the results of a double-blind, randomized, placebo-controlled multicenter study to show whether first and subsequent cycle prophylactic CSF support with pegfilgrastim would significantly reduce FN in a regimen that had previously been associated with an expected FN incidence of 20%. This is the largest randomized study of prophylactic growth factor support performed to date. Among women with breast cancer who received docetaxel at 100 mg/m² every 3 weeks, 465 received a placebo injection and 463 pegfilgrastim, each administered 24 hours after chemotherapy in a double-blind study designed with FN as the primary end point. The overall incidence of FN was 17% in the placebo group, compared with 1% in the pegfilgrastim group. The incidence of hospitalization was reduced from 4% to 1%, and the use of intravenous anti-infectives was reduced from 10% to 2%, with all of these differences statistically significant (P < .001). In cycle 1, the rate of FN in the first cycle was 11% in the placebo group versus less than 1% in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN compared with less than 1% in the pegfilgrastim group.

A second trial reported the results of 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF. In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with 9 patients (10%) in the antibiotics plus FN group (P = .01). In cycles 2 to 5, the incidences of FN were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis is effective in reducing FN and infections in patients with small cell lung cancer with the first cycle of chemotherapy. Furthermore, this strategy could be considered for other patients with cancer who have a similar risk for developing FN.

The NCCN, ASCO, and EORTC guidelines all recognize a variety of special circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens may nonetheless be at high risk of FN because of bone marrow compromise or comorbidity.

Prophylactic CSF is recommended for any patient considered at high risk, regardless of whether the treatment is intended to be curative, prolong survival, or manage symptoms.

**Patients at Intermediate Risk for FN**
The panel defines intermediate risk as a 10% to 20% probability of developing FN or a neutropenic event that would compromise treatment. In all 3 categories
of treatment intent, the panel recommends CSFs be considered on an individualized basis after discussion between the physician and patient regarding the risk/benefit ratio of the likelihood of developing FN, the potential consequences of a neutropenic event, and the implications of reduced chemotherapy dose delivery. When the intent of chemotherapy is to prolong survival or manage symptoms, the use of CSF is a difficult decision and requires careful discussion between the physician and patient. If patient risk factors determine the risk, CSF is reasonable. If the risk is from the chemotherapy regimen, other alternatives, such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

**Patients at Low Risk for FN**

For low-risk patients, defined as those with a less than 10% risk, routine use of CSFs is not considered cost-effective, and alternative treatment options are appropriate. However, CSFs may be considered if the patient is undergoing curative or adjuvant treatment and is at significant risk for serious medical consequences of FN, including death.

**Evaluation of Subsequent Chemotherapy Cycles**

After the first cycle, patient evaluation should be performed before each subsequent cycle to determine the risk categorization and treatment intent. Patients who experience a previous episode of FN or a dose-limiting neutropenic event (a nadir or a day-of-treatment count impacting the planned dose of chemotherapy) during the previous cycle of treatment with the same dose and schedule planned for the current cycle are now considered high-risk.

If the patient experiences an episode such as this despite receiving CSF, the panel recommends a chemotherapy dose reduction or change in treatment regimen unless it has an impact on patient survival. If the patient does not develop FN or a dose-limiting neutropenic event and is thought to be benefiting from chemotherapy, the previous assessment should be repeated after each subsequent cycle.

**Chemotherapy Regimens and Risk for FN**

The development of FN is a common dose-limiting toxicity of many single agents and combination chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy regimens that have an incidence of FN greater than 20% in clinical trials in chemotherapy-naïve patients are considered high risk by the panel, and CSF prophylaxis is recommended. Notably, some regimens, such as RICE and CHOP-14 for NHL, have only been tested with growth factor support. Benefits of pegfilgrastim have not been shown in regimens given for fewer than 2 weeks. Pegfilgrastim should be avoided in patients undergoing weekly chemotherapy.

Controversy has surrounded the use of G-CSFs for patients with Hodgkin lymphoma undergoing bleomycin-containing chemotherapy. A retrospective study of 141 patients reported an increased risk of bleomycin-related pulmonary toxicity associated with G-CSF use in patients with Hodgkin lymphoma. A systematic review of case reports by Azoulay et al. identified 70 cases of G-CSF–related pulmonary toxicity in patients with cancer and neutropenia. Of these patients, 36 received bleomycin, but most had NHL and had also received drugs known to induce pulmonary toxicity (cyclophosphamide and/ or methotrexate). Notably, this possible risk of increased pulmonary toxicity was not seen with bleomycin-containing testicular cancer chemotherapy.

Evens et al. showed that standard chemotherapy for Hodgkin lymphoma (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]) can be safely administered at full dose without G-CSF support. However, this requires treatment with ABVD in some patients at the time of neutropenia. Until further evidence from larger prospective studies becomes available, prophylactic G-CSF use with ABVD can be considered after discussion of risks and benefits with the patient.

**Patient Risk Factors for Developing FN**

As previously mentioned, patient risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk. Patient factors may elevate the overall risk to a high-risk category, where prophylactic CSFs are more routinely recommended. For example, many regimens for breast and lung cancer are associated with an intermediate risk of neutropenic complications, and identifying which of these patients would be considered at high risk is important. Even a low-risk regimen does not necessarily preclude the use of CSFs in a patient with high-risk factors.

Higher age, notably over 65 years, is the most important risk factor for developing severe neutropenia.
(see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Senior Adult Oncology; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).32-47 Other risk factors include previous chemotherapy or radiotherapy; preexisting neutropenia or tumor involvement in the bone marrow; poor performance status; comorbidities, including renal or liver dysfunction; and preexisting conditions, such as neutropenia and infection.

Therapeutic Use of CSFs

Compared with prophylactic use, less evidence supports therapeutic use of CSFs for FN as an adjunct to antibiotics. In a Cochrane meta-analysis involving 1518 patients from 13 trials, Clark et al.48 reported a shorter length of hospitalization (hazard ratio [HR], 0.63; 95% CI, 0.49–0.82; P = .0006) and shorter time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; P < .00001), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al.49 again found no difference in mortality, but they were unable to assess other clinical benefits. Notably, this analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF or placebo.50 The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days; P = .0004), antibiotic therapy (median 5 vs. 6 days; P = .013), and hospital stay (median 5 vs. 7 days; P = .015).

Patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, because pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional CSFs.51 Also, because of the current lack of evidence for therapeutic use of pegfilgrastim, only filgrastim or sargramostim should be administered in the therapeutic setting. For patients who have not received prophylactic CSFs, the panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome, including old age (> 65 years), sepsis syndrome, severe (absolute neutrophil count [ANC] < 100/mcL) or anticipated prolonged (> 10 days) neutropenia, pneumonia, invasive fungal infection or other clinically documented infections, hospitalization, and prior episode of FN. If risk factors are present, CSFs should be considered.

Dosing and Administration

Currently used myeloid growth factors for the prophylaxis of FN and maintenance of scheduled dose delivery include filgrastim, pegfilgrastim, and sargramostim. Although data from randomized studies support the use of filgrastim and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on their use after induction therapy for AML and in various stem cell transplantation settings. Therefore, when choosing among myeloid growth factors, filgrastim and pegfilgrastim are considered category 1 recommendations, whereas sargramostim is considered a category 2B recommendation.

Initial doses of filgrastim are initiated beginning within 1 to 3 days after completion of chemotherapy in a daily dose of 5 mcg/kg until postnadir ANC recovery is to normal or near-normal ANC levels according to laboratory standards. The dose may be rounded to the nearest vial size according to institution-defined weight limits. Evidence also supports the use of pegfilgrastim 24 hours after completion of chemotherapy given every 3 weeks in 1 dose of 6 mg per cycle of treatment.6,52 Data are insufficient to support dose and schedule of weekly regimens or schedules less than 2 weeks, and these cannot be recommended. Same day administration of filgrastim or pegfilgrastim (within 24 hours of chemotherapy) is not recommended. Phase II studies of pegfilgrastim administration the same day as chemotherapy versus the day after chemotherapy have shown increased incidence of FN and/or adverse events in breast cancer and lymphoma.53-55 Same day administration of pegfilgrastim showed comparable benefit in one study of a regimen with low risk for neutropenia, but in this setting pegfilgrastim would not be routinely indicated.56

Evidence from randomized trials is insufficient to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. Sargramostim is indicated for use after induction chemotherapy in older adult patients with AML.57 Again, administration of sargramostim on the same day as chemotherapy is not recommended. The subcutaneous route is preferred for all 3 agents. No data are available to
support alternative dosing schedules in intermediate- and high-risk patients. The panel members do not routinely recommend use of prophylactic antibiotics in these settings. In addition, prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.

Severe Chronic Neutropenia

These NCCN Guidelines focus on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia that requires G-CSF therapy is briefly discussed in this section. G-CSF is established as an effective treatment for cyclic, congenital, and idiopathic neutropenia (types of severe chronic neutropenia) based a randomized controlled trial involving 123 patients. In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers, and infections. Subsequent observation studies show that patients with idiopathic and cyclic neutropenia generally respond to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF (1–3 mcg/kg/d). Patients with congenital neutropenia generally require somewhat higher doses (3–10 mcg/kg/d). All patients should have doses adjusted to maintain a blood neutrophil level in the normal or low-normal range. Acute adverse effects include bone pain, arthralgias, and myalgias, which usually diminish in the first few weeks of treatment.

The greatest concern is that patients diagnosed with severe congenital neutropenia, but not all patients with chronic neutropenia, are at risk of having their condition evolve to myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, which are those requiring higher doses of G-CSF, seem to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following up with these patients carefully. Currently, the only alternative therapy is hematopoietic stem cell transplantation. For further reading on chronic neutropenia, refer to the Web site developed by The Severe Chronic Neutropenia International Registry (http://depts.washington.edu/registry/index.html).

References

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## Individual Disclosures of the NCCN Myeloid Growth Factors Panel Members

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<tr>
<td>Jeffrey Allen, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>6/11/10</td>
</tr>
<tr>
<td>James Armitage, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>12/16/09</td>
</tr>
<tr>
<td>Douglas W. Blayney, MD</td>
<td>None</td>
<td>Amgen Inc.; and Bristol-Myers Squibb Company</td>
<td>None</td>
<td>American Society of Clinical Oncology</td>
<td>8/10/10</td>
</tr>
<tr>
<td>Spero R. Cataland, MD</td>
<td>None</td>
<td>Amgen Inc.</td>
<td>None</td>
<td>None</td>
<td>12/10/09</td>
</tr>
<tr>
<td>Jeffrey Crawford, MD</td>
<td>Celgene Corporation; Facet Biotech; and Hoffman LaRoche</td>
<td>Amgen Inc.; GlaxoSmithKline; Johnson &amp; Johnson; Medtronic, Inc.; Aggenix AG; Chugai Pharmaceuticals; and Ono Pharmaceuticals</td>
<td>None</td>
<td>None</td>
<td>2/21/11</td>
</tr>
<tr>
<td>Mark L. Heaney, MD, PhD</td>
<td>None</td>
<td>Genzyme Corporation</td>
<td>None</td>
<td>None</td>
<td>12/4/09</td>
</tr>
<tr>
<td>Sally Htoy, PharmD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1/6/10</td>
</tr>
<tr>
<td>Susan Hudock, PharmD, BCOP</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/11/10</td>
</tr>
<tr>
<td>Dwight D. Kloth, PharmD, BCOP</td>
<td>None</td>
<td>Amgen Inc.; and Eisai Inc.</td>
<td>None</td>
<td>None</td>
<td>5/9/11</td>
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<tr>
<td>David J. Kuter, MD, DPhil</td>
<td>None</td>
<td>Amgen, Inc; and Caremark</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
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<tr>
<td>Gary H. Lyman, MD, MPH</td>
<td>Amgen Inc.</td>
<td>None</td>
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<tr>
<td>Brandon McMahon, MD</td>
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<tr>
<td>David P. Steensma, MD</td>
<td>None</td>
<td>Amgen Inc.; and Ortho Biotech Products, L.P.</td>
<td>None</td>
<td>None</td>
<td>8/12/10</td>
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<tr>
<td>Saroj Vadhan-Raj, MD</td>
<td>Amgen Inc.</td>
<td>Amgen Inc.</td>
<td>None</td>
<td>None</td>
<td>12/16/09</td>
</tr>
<tr>
<td>Peter Westervelt, MD, PhD</td>
<td>None</td>
<td>Celgene Corporation; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
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<td>10/6/09</td>
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<tr>
<td>Michael Westmoreland, PharmD</td>
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<td>Merck &amp; Co., Inc.</td>
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