Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update
Introduction

• Hematopoietic colony-stimulating factors (CSFs) have been shown to reduce the duration and severity of neutropenia and the risk of febrile neutropenia and enable delivery of more intensive or dose-dense chemotherapy when indicated.

• However, concerns with respect to adverse events and costs led the American Society of Clinical Oncology (ASCO) to develop clinical practice guidelines for the use of CSFs in 1994 and on four occasions since then.

• This guideline represents the first major update since 2006 and addresses the strengths and limitations of the use of the CSFs across a range of settings in clinical oncology practice on the basis of an exhaustive review of the medical literature.

• The purpose of these guidelines is to foster the appropriate use of these agents based on high-quality evidence from controlled clinical trials and a comprehensive understanding of the specific patient, disease, and treatment factors that are associated with the risk of neutropenic complications.

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ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee (CPGC) guideline process includes:

- a systematic literature review by ASCO guidelines staff
- critical review and evidence interpretation by an expert panel to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology supplement can be found at:
www.asco.org/guidelines/csf

Clinical Questions

1. Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians consider when selecting patients for primary prophylaxis of febrile neutropenia with a CSF?

2. Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians use to select patients for secondary prophylaxis of febrile neutropenia with a CSF?

3. Are there circumstances in which CSFs should be considered for the treatment of neutropenia among adults with cancer?

4. In what settings should CSFs be used in order to increase chemotherapy dose-density?

5. What is the role of CSFs as adjuncts to progenitor-cell transplantation?

6. What is the role of CSFs in the setting of acute leukemia or myelodysplastic syndromes?
Clinical Questions

7. Should CSFs be avoided in patients receiving concomitant chemotherapy and radiation therapy?

8. Are there CSF recommendations that apply specifically to older adults, and that differ from recommendations in younger adults?

9. How should CSFs be used in the pediatric population?

10. What are recommendations for the initiation, duration, dosing, and administration of CSFs?

11. Do CSFs differ in efficacy?

12. What is the role of CSFs in the treatment of radiation injury?
Target Population and Audience

Target Population
Adults or children with a solid tumor or lymphoma that is treated with chemotherapy.

Target Audience
Medical oncologists, hematologists, oncology nurses, other clinicians who care for people with cancer, and patients
Summary of Guideline Recommendations

1. Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on the basis of patient-, disease-, and treatment-related factors. Primary CSF prophylaxis should also be given in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available.

2. Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
Summary of Guideline Recommendations

3.1 CSFs should not be routinely used for patients with neutropenia who are afebrile.

3.2 CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 × 10⁹/L) neutropenia, age older than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Summary of Guideline Recommendations

4. Dose-dense regimens with CSF support should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data. Efficacy data support the use of CSFs with dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer, and with high dose–intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non-Hodgkin lymphoma (NHL), and it cannot routinely be recommended at this time.
Summary of Guideline Recommendations

5.1 CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells (PBPCs). Choice of mobilization strategy depends in part on type of cancer and type of transplantation.

5.2 CSFs should be administered after autologous SCT to reduce the duration of severe neutropenia.

5.3 CSFs may be administered after allogeneic SCT to reduce the duration of severe neutropenia.

6. The Update Committee did not provide recommendations regarding the use of CSFs in adults with acute myeloid leukemia or myelodysplastic syndromes.
Summary of Guideline Recommendations

7. CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.

8. Prophylactic CSF for patients with diffuse aggressive lymphoma age 65 years and older treated with curative chemotherapy (CHOP-R) should be considered, particularly in the presence of comorbidities.
9.1 The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a high likelihood of febrile neutropenia. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients.

9.2 For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing’s sarcoma, CSFs should be used to enable the administration of these regimens.

9.3 CSFs should not be used in pediatric patients with nonrelapsed acute lymphoblastic leukemia (ALL) or nonrelapsed acute myeloid leukemia (AML) who do not have an infection.
## Summary of Guideline Recommendations

### 10. Dosing and Administration of CSFs

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<tr>
<th>Agent</th>
<th>Dosing and Administration</th>
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<tr>
<td>Filgrastim</td>
<td>Filgrastim should be started 1 to 3 days after the administration of myelotoxic chemotherapy. In the setting of high-dose therapy and autologous stem-cell rescue, filgrastim can be started 1 to 5 days after administration of high-dose therapy. Filgrastim should be continued until reaching an absolute neutrophil count (ANC) of at least 2 to 3 × 10⁹/L. For PBPC mobilization, filgrastim should be started at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis.</td>
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<tr>
<td></td>
<td>In adults, the recommended filgrastim dose is 5 µg/kg per day for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, a dose of 10 µg/kg per day may be preferable. The preferred route of filgrastim administration is subcutaneous.</td>
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<tr>
<td>Filgrastim-sndz</td>
<td>Same as for filgrastim.</td>
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## Summary of Guideline Recommendations

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<tr>
<td>Tbo-filgrastim</td>
<td>Tbo-filgrastim should be started 1 to 3 days after the administration of myelotoxic chemotherapy. In adults, the recommended tbo-filgrastim dose is 5 µg/kg per day. The preferred route of tbo-filgrastim administration is subcutaneous.</td>
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<tr>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim 6 mg should be given once, 1 to 3 days after chemotherapy if at all possible. Because some patients will not be able to return for a dose of pegfilgrastim as a result of distance or immobility, for instance, alternatives to consider may include self-administered filgrastim or tbo-filgrastim, or same-day pegfilgrastim, recognizing that although same-day pegfilgrastim is not as effective as later pegfilgrastim, it is better than no pegfilgrastim. Pegfilgrastim is also available in a timed auto-inject device that delivers 6mg of pegfilgrastim subcutaneously, 27 hours after it is placed on the skin and activated. Pegfilgrastim is not currently indicated for stem-cell mobilization. The 6 mg formulation should not be used in infants, children, or small adolescents who weigh less than 45 kg.</td>
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<tr>
<td>Sargramostim</td>
<td>Because GM-CSF has been licensed specifically for use in mobilization and after transplantation of autologous PBPCs, after autologous or allogeneic bone marrow transplantation, and for AML, the manufacturer’s instructions for administration are limited to those clinical settings. GM-CSF should be initiated on the day of bone marrow infusion and not less than 24 hours after the last chemotherapy and 12 hours after the most recent radiotherapy. GM-CSF should be continued until an ANC greater than $1.5 \times 10^9$/L for 3 consecutive days is obtained. The drug should be discontinued early or the dose reduced by 50% if the ANC increases to greater than $20 \times 10^9$/L. The recommended dose for adults is 250 µg/m² per day.</td>
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11. Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars, as they become available) can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and the clinical situation. There have been no further data comparing G-CSF and GM-CSF since the 2006 update therefore there is no change in the recommendation regarding their therapeutic equivalency.

12. Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death as a result of injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.70-72
Health Disparities

• Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care.

• Analyses of SEER-Medicare data suggest that first-cycle CSF use among women with breast cancer is less common in nonwhites and women of low socioeconomic status, and varies substantially by geographic region.

• Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.
Multiple Chronic Conditions

• In the case of febrile neutropenia, observational studies have provided important information about the impact of comorbidity.

• A 2014 systematic review reported that the presence of comorbid conditions increased the risk of febrile neutropenia among patients with cancer treated with chemotherapy.\textsuperscript{87}

• Compared with patients with no comorbid conditions, patients with three or more comorbid conditions had an 81% increased risk of febrile neutropenia.

• The presence of renal, hepatic, and cardiovascular disease have each been associated with febrile neutropenia or febrile neutropenia–related hospitalization in patients with NHL treated with CHOP-based chemotherapy.\textsuperscript{89,90}
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/guidelines/csf

Patient information is available at www.cancer.net

Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.
# ASCO Guideline Panel Members

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<tr>
<th>Member</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Thomas J. Smith, MD, Co-Chair</td>
<td>Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD</td>
</tr>
<tr>
<td>James O. Armitage, MD, Co-Chair</td>
<td>University of Nebraska Medical Center, Omaha, NE</td>
</tr>
<tr>
<td>Gary H. Lyman, MD, MPH</td>
<td>Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA</td>
</tr>
<tr>
<td>Kenneth R. Carson, MD, PhD</td>
<td>Washington University, St Louis, MO</td>
</tr>
<tr>
<td>Jeffrey Crawford, MD</td>
<td>Duke Medicine, Durham, NC</td>
</tr>
<tr>
<td>Scott J. Cross, MD</td>
<td>Virginia Oncology Associates, Norfolk, VA</td>
</tr>
<tr>
<td>John M. Goldberg, MD</td>
<td>University of Miami Miller School of Medicine, Miami FL</td>
</tr>
<tr>
<td>Natasha B. Leighl, MD, MMSc</td>
<td>Princess Margaret Cancer Centre, Toronto, Ontario, Canada</td>
</tr>
<tr>
<td>James L. Khatcheressian, MD, PGIN Representative</td>
<td>Virginia Cancer Institute, Richmond, VA</td>
</tr>
<tr>
<td>Cheryl L. Perkins, MD, Patient Representative</td>
<td>Dallas, TX</td>
</tr>
<tr>
<td>George Somlo, MD</td>
<td>City of Hope National Medical Center, Duarte, CA</td>
</tr>
<tr>
<td>James L. Wade, MD</td>
<td>Cancer Care Specialists of Central Illinois, Decatur, IL</td>
</tr>
<tr>
<td>Antoinette J. Wozniak, MD</td>
<td>Karmanos Cancer Institute, Detroit, MI</td>
</tr>
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References


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