

NATIONAL QUALITY FORUM—Evidence (subcriterion 1a)

Measure Number (if previously endorsed): [Assigned by NQF](#)

Measure Title: [Febrile Neutropenia Risk Assessment Prior to Chemotherapy](#)

IF the measure is a component in a composite performance measure, provide the title of the

Composite Measure here: [Click here to enter composite measure #/ title](#)

Date of Submission: [3/11/2016](#)

Instructions

- For composite performance measures:
 - A separate evidence form is required for each component measure unless several components were studied together.
 - If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.
- Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of supplemental materials may be submitted, but there is no guarantee it will be reviewed.
- If you are unable to check a box, please highlight or shade the box for your response.
- Maximum of 10 pages (includes questions/instructions; minimum font size 11 pt; do not change margins).
Contact NQF staff if more pages are needed.
- Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](#).

Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF's evaluation criteria.

1a. Evidence to Support the Measure Focus

The measure focus is evidence-based, demonstrated as follows:

- **Health outcome:** ³ a rationale supports the relationship of the health outcome to processes or structures of care. Applies to patient-reported outcomes (PRO), including health-related quality of life/functional status, symptom/symptom burden, experience with care, health-related behavior.
- **Intermediate clinical outcome:** a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence ⁴ that the measured intermediate clinical outcome leads to a desired health outcome.
- **Process:** ⁵ a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence ⁴ that the measured process leads to a desired health outcome.
- **Structure:** a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence ⁴ that the measured structure leads to a desired health outcome.
- **Efficiency:** ⁶ evidence not required for the resource use component.

Notes

3. Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.

4. The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](#) and [methods](#), or Grading of Recommendations, Assessment, Development and Evaluation ([GRADE](#)) [guidelines](#).

5. Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.

6. Measures of efficiency combine the concepts of resource use and quality (see NQF's [Measurement Framework: Evaluating Efficiency Across Episodes of Care](#); [AQA Principles of Efficiency Measures](#)).

1a.1. This is a measure of: *(should be consistent with type of measure entered in De.1)*

Outcome

- ☐ Health outcome: Click here to name the health outcome
- ☐ Patient-reported outcome (PRO): Click here to name the PRO
PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors
- ☐ Intermediate clinical outcome (e.g., lab value): Click here to name the intermediate outcome
- ☒ Process: **Febrile Neutropenia Risk Assessment Prior to Chemotherapy**
- ☐ Structure: Click here to name the structure
- ☐ Other: Click here to name what is being measured

HEALTH OUTCOME/PRO PERFORMANCE MEASURE *If not a health outcome or PRO, skip to 1a.3*

1a.2. Briefly state or diagram the path between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.

Not applicable; the measure does not relate to a health outcome.

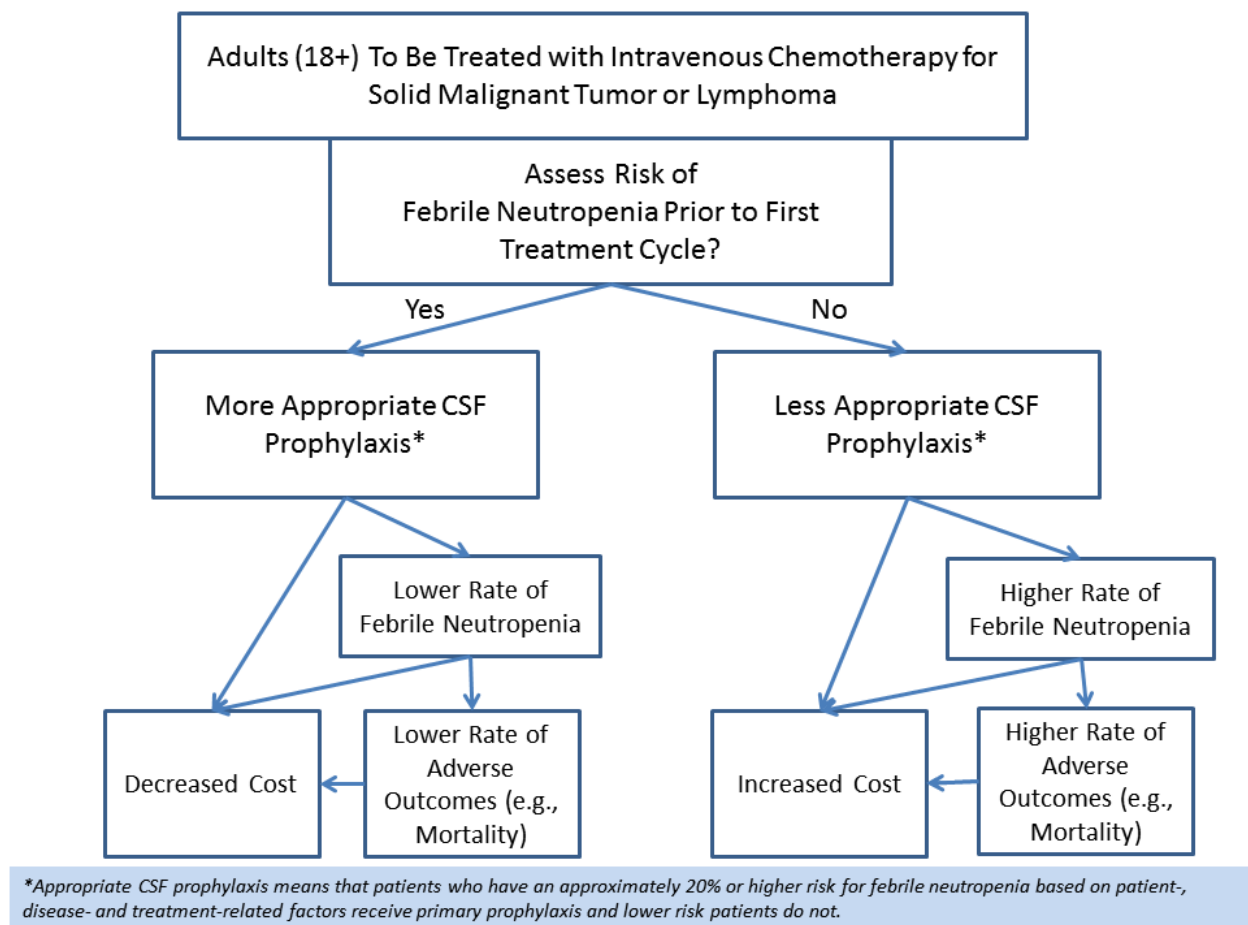
1a.2.1. State the rationale supporting the relationship between the health outcome (or PRO) to at least one healthcare structure, process, intervention, or service (*i.e., influence on outcome/PRO*).

Not applicable; the measure does not relate to a health outcome.

Note: For health outcome/PRO performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.

INTERMEDIATE OUTCOME, PROCESS, OR STRUCTURE PERFORMANCE MEASURE

1a.3. Briefly state or diagram the path between structure, process, intermediate outcome, and health outcomes. Include all the steps between the measure focus and the health outcome.



1a.3.1. What is the source of the systematic review of the body of evidence that supports the performance measure?

- ☒ Clinical Practice Guideline recommendation – **complete sections 1a.4, and 1a.7**
- ☐ US Preventive Services Task Force Recommendation – **complete sections 1a.5 and 1a.7**
- ☐ Other systematic review and grading of the body of evidence (e.g., Cochrane Collaboration, AHRQ Evidence Practice Center) – **complete sections 1a.6 and 1a.7**
- ☒ Other – **complete section 1a.8**

Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (including date) and URL for guideline (if available online):

Two clinical practice guidelines contain recommendations that support risk assessment for chemotherapy-induced febrile neutropenia (FN):

- 2015 American Society of Clinical Oncology (ASCO) Recommendations for the Use of WBC Growth Factors, and
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

The citation and URL are provided below for each of these guidelines:

2015 ASCO Clinical Practice Guideline Update:

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leigh NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 October 1; 33(28): 3199–3212. Available December 2, 2015, at <http://jco.ascopubs.org/content/33/28/3199.full.pdf+html>

URL:

<http://jco.ascopubs.org/content/33/28/3199.full.pdf+html>

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Crawford, J., Becker, P. S., Armitage, J. O. et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Myeloid Growth Factors, Version 1.2015. Available December 2, 2015, at http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf

URL:

http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf

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1a.4.2. Identify guideline recommendation number and/or page number and quote verbatim, the specific guideline recommendation.

The two guideline recommendations listed below provide strong support for conducting an FN risk assessment prior to the first cycle of chemotherapy to determine which patients with solid tumors should receive primary prophylaxis with a CSF. Bold italics were added in each recommendation to emphasize the text related to conducting an FN risk assessment.

Recommendation 1 (page 3203 in 2015 ASCO Clinical Practice Guideline Update; see complete citation in Section 1a.4.1 above):

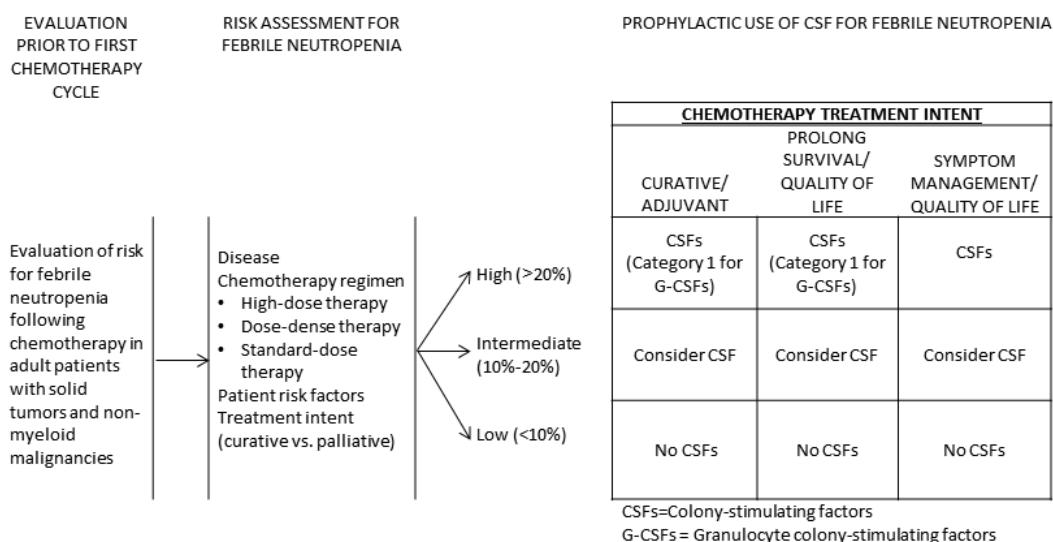
“Recommendation 1: Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in ***patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors***. Primary CSF prophylaxis should also be administered 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.” (Emphasis added.)

Recommendation on Risk Assessment for Prophylactic Use of CSFs (page MS-9 in NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines®]; see complete citation in Section 1a.4.1 above):

“The guidelines begin with ***an evaluation of risk for chemotherapy-induced FN prior to the first cycle of chemotherapy***. The risk assessment includes 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 NCCN Panel. These include 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 either an overall high-risk group (>20% risk of FN), intermediate risk group (10%-20% risk), or low-risk group (<10% risk). Of note, there is currently no consensus nomogram for risk assessment. While the NCCN Panel outlines criteria to aid in the assessment of FN risk, independent clinical judgment should be exercised based on the patient’s situation (see Patient Risk Factors for Developing Febrile Neutropenia in the algorithm). In addition to assessing patient- and treatment-related risk, consideration should be given to the intent of cancer treatment when determining the appropriate use of CSFs. For example, a patient with a previous neutropenic complication in the immediately prior cycle of chemotherapy, with no plan to reduce the dose intensity should be considered high risk.” (Emphasis added.)

Diagram related to Recommendation on Risk Assessment for Prophylactic Use of CSFs (page MGF-1 in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®); see complete citation in Section 1a.4.1 above):

The NCCN Algorithm shown on page MGF-1 of the 2015 NCCN Clinical Practice Guidelines on Myeloid Growth Factors (NCCN Guidelines®) and reproduced below illustrates the factors leading to the decision about prophylactic use of CSF for febrile neutropenia that is described in the paragraph above:



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Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:

ASCO Recommendation 1:

Grades assigned to Recommendation 1 (page 3203 of 2015 ASCO Clinical Practice Guideline Update; see complete citation in Section 1a.4.1 above):

Type: **Evidence-based**, benefits outweigh harms.

Strength of recommendation: **Strong**.

Definitions:

Definition of “Evidence-based” Rating for Type of Recommendation (page 7 of 2015 ASCO Guideline Methodology Supplement; see complete citation in Section 1a.4.5 below):

Evidence-based=“There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.”

Definition of “Strong” Rating for Strength of Recommendation (page 8 of 2015 ASCO Guideline Methodology Supplement; see complete citation in Section 1a.4.5 below):

Strong= “There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists’ agreement. Other compelling considerations (discussed in the guideline’s literature review and analyses) may also warrant a strong recommendation.”

NCCN Recommendation on Risk Assessment for Prophylactic Use of CSFs from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®):

Grade assigned to the quoted recommendation (pages MGF-1 and MS-9 from 2015 NCCN Clinical Practice Guidelines on Myeloid Growth Factors; see complete citation in Section 1a.4.1 above):

Category 2A (page MGF-1)

Definition of Category 2A (page MS-1 from 2015 NCCN Clinical Practice Guidelines on Myeloid Growth Factors [NCCN Guidelines®]; see complete citation in Section 1a.4.1 above):

Category 2A= “Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.”

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (Note: If separate grades for the strength of the evidence, report them in section 1a.7.)

2015 ASCO Clinical Practice Guideline Update:

Definitions of Other Types of Recommendation (page 7 of 2015 ASCO Guideline Methodology Supplement; see complete citation in Section 1a.4.5 below):

“Formal consensus: The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., “strong,” “moderate,” or “weak”). The

results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.”

“Informal consensus: The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., “strong,” “moderate,” or “weak”).”

“No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.”

Definitions of Other Ratings for Strength of Recommendation (page 8 of 2015 ASCO Guideline Methodology Supplement; see complete citation in Section 1a.4.5 below):

“Moderate: There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists’ agreement. Other compelling considerations (discussed in the guideline’s literature review and analyses) may also warrant a moderate recommendation.”

“Weak: There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists’ agreement. Other considerations (discussed in the guideline’s literature review and analyses) may also warrant a weak recommendation.”

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®):

Other NCCN Categories of Evidence and Consensus (page MS-12015 of 2015 NCCN Clinical Practice Guidelines on Myeloid Growth Factors [NCCN Guidelines®]; see complete citation in Section 1a.4.1 above):

“Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.”

“Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.”

“Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.”

1a.4.5. Citation and URL for methodology for grading recommendations (if different from 1a.4.1):

Complete Citation for ASCO definitions in Sections 1a.4.3 and 1a.4.4:

ASCO Guideline Methodology Supplement. Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Available December 2, 2015, at

<http://www.instituteofquality.org/sites/instituteofquality.org/files/METHODOLOGY%20SUPPLEMENT%20WBCGF.pdf>

URL:

<http://www.instituteofquality.org/sites/instituteofquality.org/files/METHODOLOGY%20SUPPLEMENT%20WBCGF.pdf>

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

☒ Yes → **complete section 1a.7**

☐ No → **report on another systematic review of the evidence in sections 1a.6 and 1a.7; if another review does not exist, provide what is known from the guideline review of evidence in 1a.7**

1a.5. UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

1a.5.1. Recommendation citation (including date) and URL for recommendation (if available online):

Not applicable

1a.5.2. Identify recommendation number and/or page number and quote verbatim, the specific recommendation.

Not applicable

1a.5.3. Grade assigned to the quoted recommendation with definition of the grade:

Not applicable

1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system. (Note: the grading system for the evidence should be reported in section 1a.7.)

Not applicable

1a.5.5. Citation and URL for methodology for grading recommendations (if different from 1a.5.1):

Not applicable

Complete section 1a.7

1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE

1a.6.1. Citation (including date) and URL (if available online):

Citation:

ASCO Guidelines Data Supplement. 2015. Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Available December 2, 2015, at <http://www.instituteofquality.org/sites/instituteofquality.org/files/DATA%20SUPPLEMENT%20WBCGF.pdf>

URL:

<http://www.instituteofquality.org/sites/instituteofquality.org/files/DATA%20SUPPLEMENT%20WBCGF.pdf>

1a.6.2. Citation and URL for methodology for evidence review and grading (if different from 1a.6.1):

Citation:

ASCO Guidelines Methodology Supplement. 2015. Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Available December 2, 2015, at <http://www.instituteforquality.org/sites/instituteforquality.org/files/METHODOLOGY%20SUPPLEMENT%20WBCGF.pdf>

URL:

<http://www.instituteforquality.org/sites/instituteforquality.org/files/METHODOLOGY%20SUPPLEMENT%20WBCGF.pdf>

Complete section 1a.7

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE

If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?

2015 ASCO Clinical Practice Guideline Update: To evaluate the effect of colony-stimulating factors (CSFs) on clinical outcomes (e.g., febrile neutropenia, all-cause and infection-related mortality) in adults or children with a solid tumor or lymphoma treated with chemotherapy

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade:

Grade assigned to the evidence:

Evidence quality: high (page 3203 of 2015 ASCO Clinical Practice Guideline Update; see complete citation in Section 1a.4.1 above)

Definition of Rating for Strength of Evidence (page 9 of 2015 ASCO Guideline Methodology Supplement; see complete citation in Section 1a.4.5 above):

“High= High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.”

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.

Definition of All Other Ratings for Strength of Evidence (page 9 of 2015 ASCO Guideline Methodology Supplement; see complete citation in Section 1a.4.5 above):

“Intermediate: Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.”

“Low: Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.”

“Insufficient: Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.”

1a.7.4. What is the time period covered by the body of evidence? (provide the date range, e.g., 1990-2010). Date range: 1992-2010

QUANTITY AND QUALITY OF BODY OF EVIDENCE

1a.7.5. How many and what type of study designs are included in the body of evidence? (e.g., 3 randomized controlled trials and 1 observational study)

Seven meta-analyses, two RCTs, and one systematic review are included in the body of evidence cited as support for Recommendation 1 in the 2015 Recommendations in the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update (see Section 1a.4.1 in this form for complete citation of this Guideline). One meta-analysis, three clinical practice guidelines, one RCT, and one systematic review which were cited by the ASCO Guidelines were excluded from this Measure Submission Form because they do not provide specific evidence to support the measure topic.

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population)

For information related to the “overall quality of evidence across studies”, see “Appendix Table 2. Quality of Methods Used in Studies Cited in Support of Recommendation 1 by ASCO Guidelines on the Use of WBC Growth Factors (Smith et al., 2015)” in the Appendix below.

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE

1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (e.g., ranges of percentages or odds ratios for improvement/decline across studies, results of meta-analysis, and statistical significance)

Excerpt from page 3203 of the 2015 ASCO Clinical Practice Guideline Update (see complete citation in Section 1a.4.1 above):

“Of the 16 publications that addressed primary prophylaxis (eight meta-analyses, three clinical practice guidelines, three RCTs, and two systematic reviews), none prompted a change in the level of febrile neutropenia risk warranting primary prophylaxis with a CSF. ... ***The 20% cutoff for febrile neutropenia risk has been maintained from the 2005 guideline based on the evidence from randomized trials, especially the trial of CSFs in patients with breast cancer*** (Vogel et al., 2005), in which the baseline risk for febrile neutropenia was 17%. Independent systematic reviews of eight trials with 2,156 patients with breast cancer confirmed that CSFs reduce the risk of febrile neutropenia, with possible reductions in the

need for hospitalization and all-cause mortality, but with no effect on infection-related mortality (Renner et al., 2012). Subsequent studies have shown that CSFs can reduce the risk of hospitalization for febrile neutropenia in elderly patients (age > 65 years) with solid tumors from 9% in all cycles to 5% (Balducci et al., 2007), but ***no other differences, such as in mortality, have been reported to justify treating a large number of patients who would not benefit and would experience potential toxicities and costs.***” (Emphasis added.)

“However, recent publications have provided additional information about the likely benefits of primary prophylaxis. Meta-analyses of RCTs conducted in varying patient populations have confirmed that primary prophylaxis with a CSF reduces the risk of febrile neutropenia during chemotherapy for a solid tumor or lymphoma (Bohlius, Herbst, Reiser, Schwarzer, & Engert, 2008; Cooper, Madan, Whyte, Stevenson, & Akehurst, 2011; Kuderer, 2011; Kuderer, Dale, Crawford, & Lyman, 2007; Renner et al., 2012; Sung, Nathan, Alibhai, Tomlinson, & Beyene, 2007). Primary prophylaxis may also reduce the risk of hospitalization (Renner et al., 2012) and infection (Bohlius et al., 2008; Sung et al., 2007). Results for all-cause or infection-related mortality are less consistent. A meta-analysis of 59 RCTs among patients with solid tumors or lymphoma reported that primary prophylaxis with a G-CSF was associated with a modest reduction in all-cause mortality compared with no primary prophylaxis (risk ratio [RR], 0.93; 95%CI, 0.90 to 0.96; absolute risk difference, -3.2%; 95% CI, -2.1% to -4.2%) (Lyman et al., 2013). The greatest benefit was observed among patients who received dose-dense chemotherapy. In studies that evaluated the same dose and schedule of chemotherapy in different treatment arms, primary prophylaxis did not have a statistically significant effect on mortality. (Lyman et al., 2013). Another large meta-analysis considered 148 RCTs of primary prophylaxis in children or adults who were receiving cancer chemotherapy or undergoing stem-cell transplantation (SCT) (Sung et al., 2007). Only RCTs in which all study arms received the same chemotherapy or SCT conditioning regimen were included. On the basis of the 80 trials with all-cause mortality results, short-term all-cause mortality was 7.6% with primary prophylaxis and 8.0% without primary prophylaxis (RR, 0.95; 95% CI, 0.84 to 1.08). Results for infection-related mortality were also null (RR, 0.82; 95% CI, 0.66 to 1.02) (Sung et al., 2007). In contrast, the addition of a G-CSF was associated with a statistically significant reduction in infection-related mortality in a 2011 meta-analysis of 12 RCTs in adults with a solid tumor or lymphoma; risk was 1.5% among patients who received primary prophylaxis with a CSF, compared with 2.8% among patients who did not receive primary prophylaxis (RR, 0.55; 95% CI, 0.34 to 0.90) (Kuderer, 2011).”

Here we list studies published from 2006-2012 that were cited in the 2015 ASCO Clinical Practice Guideline Update and reported on the effects of CSF on outcomes for adults with solid tumors:

- Febrile neutropenia (Renner et al., 2012; Balducci et al., 2007; Kuderer et al., 2007; Sung et al., 2007)
- All-cause mortality (Lyman et al., 2013; Lyman et al., 2010; Bohlius et al., 2008; Sung et al., 2007)
- Infection-related mortality (Renner et al., 2012; Bohlius et al., 2008; Kuderer et al., 2007; Sung et al., 2007)
- Early mortality (Renner et al., 2012; Kuderer et al., 2007)
- Planned chemotherapy doses at scheduled times and doses (Renner et al., 2012; (Wildiers & Reiser, 2011); Balducci et al., 2007; (Papaldo et al., 2006)
- Acute myeloid leukemia/ myelodysplastic syndrome (AML/MDS) (Lyman et al., 2010)
- Infections (Bohlius et al., 2008; Sung et al., 2007)

For more detail about the results from these studies, see “Appendix Table 1. Summary of Studies Cited in Support of Recommendation 1 by ASCO Guidelines on the Use of WBC Growth Factors (Smith et al., 2015)” in the Appendix below under the column heading “Benefit of Prophylaxis with CSF.”

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)?

Excerpt from page 3203 of the 2015 ASCO Clinical Practice Guideline Update (see complete citation in Section 1a.4.1 above):

“Adverse effects of CSFs include bone pain, but a randomized trial of naproxen versus placebo suggested that nonsteroidal anti-inflammatory drugs may reduce the incidence, duration, and severity of bone pain among CSF-treated patients. (Kirshner et al., 2012). Naproxen was administered at a dose of 500 mg twice per day starting on the day of pegfilgrastim administration and continuing for 5 to 8 days.”

Other “harms” of prophylaxis with CSF were reported in studies cited by the 2015 ASCO Clinical Practice Guideline Update, including injection-site reactions, arthralgia, and anemia. For more detail on bone pain and the other conditions, see “Appendix Table 1. Summary of Studies Cited in Support of Recommendation 1 by ASCO Guidelines on the Use of WBC Growth Factors (Smith et al., 2015)” in the Appendix below under the column heading “Adverse Events Associated with CSF Prophylaxis.”

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE

1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.

Not applicable.

1a.8 OTHER SOURCE OF EVIDENCE

If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.

1a.8.1 What process was used to identify the evidence?

The study by O’Brien et al. (2014) was identified by an oncologist on the research team. The other articles were identified by a citation search on the O’Brien et al. (2014) article and by a manual search of cited references in various articles.

1a.8.2. Provide the citation and summary for each piece of evidence.

Seven articles published from 2006 to 2016 provide insights into the benefits of FN risk assessment:

- Donohue (2006): Among patients receiving chemotherapy, the rates CSF prophylaxis were higher in those who were managed with a Risk Assessment Tool, than those in a “control group” that received care without use of the tool in an earlier time period (72% versus 28%, respectively, $p < 0.001$). Conversely, the rates of adverse outcomes were higher in the control group than in the Risk Assessment Tool Group, but not statistically significant: febrile neutropenia (14% versus 11%, respectively), treatment with IV antibiotics (28% versus 14%), hospitalizations secondary to febrile neutropenia (16% versus 11%), and chemotherapy dose reductions (10% versus 3%).

- Doyle (2006): In a pre-post intervention study of patients initiating chemotherapy or a new regimen, use of tool for assessing patient risk of FN lowered the rate of FN-related hospitalization by 78%, from 9.7% among 155 patients in FY04 to 2.1% among 189 patients in FY05 (P = 0.003).
- Miller (2006): In a study of an intervention with a computer-based risk assessment tool (CBRAT), the rate of documenting performance of an FN risk assessment was 13% before use of the CBRAT and 100% after its introduction (p<0.001).
- O'Brien et al. (2014): An intervention study in a hospital-based oncology unit used an FN risk assessment tool to decide which patients receiving chemotherapy to treat with CSF. Comparing the time periods before (N=233 patients) and after (N=226 patients) the tool was used, the incidence of FN was reduced by 52% (p=0.02).
- Krzemieniecki et al. (2014): A total of 1,347 patients with solid tumors were eligible for the study based on being scheduled for "myelotoxic" chemotherapy and having an "investigator-assessed FN risk" of $\geq 20\%$. The study found 45-80% of these patients, depending on the tumor site, did not receive G-CSF that was indicated by results of the FN risk assessment by the investigator and guideline recommendations.
- Freyer et al. (2015): In a study of 165 physicians and 944 patients, each physician rated FN risk for their own patients using factors they selected. Only 82% of patients with an FN risk at or above 20% based on the physician-assessed FN risk were scheduled to receive CSF indicating almost one of five patients would not receive G-CSF PP even though the patient's risk was rated higher than the threshold of 20%.
- Mäenpää et al. (2016): In a study of 690 breast cancer patients (stages I-III) receiving chemotherapy, a higher proportion of those with a high-risk regimen were given G-CSF primary prophylaxis than those with a lower-risk regimen (48% versus 22%). However, these results indicate that less than half of patients on a high-risk regimen received appropriate treatment with G-CSF.

The full abstracts for these articles are provided below:

Citation: Donohue RB. (2006). Development and Implementation of a Risk Assessment Tool for Chemotherapy-Induced Neutropenia ONCOLOGY NURSING FORUM –33(2), 347-352.

"Purpose/Objectives: To evaluate a tool developed and implemented to help practitioners assess the risk of chemotherapy-induced neutropenia (CIN) and its complications in patients with nonleukemia cancer types."

"Design: Retrospective survey of chart records."

"Setting: Community-based oncology practice."

"Sample: The medical records of 85 adult patients treated with new courses of chemotherapy, regardless of the cancer type or stage; 50 charts belonged to patients treated before the implementation of the tool and 35 to patients evaluated with the tool."

"Methods: A risk assessment tool for CIN that was developed using risk factors from published studies and national guidelines was implemented. Patients who were found to be at increased risk for CIN were given colony-stimulating factor (CSF) support starting with the first chemotherapy cycle. The

effectiveness of the tool was evaluated by comparing clinical outcomes before and after the implementation of the risk assessment tool.”

“Main Research Variables: Febrile neutropenia, IV antibiotic use, hospitalization for neutropenia, and chemotherapy dose reductions and delays.”

“Findings: Chemotherapy dose delays, febrile neutropenia, treatment with IV antibiotics, and hospitalization for neutropenia occurred less frequently in patients assessed with the tool and managed with the algorithm for CSF use than in those who were not assessed.”

“Conclusions: The Risk Assessment for Neutropenic Complications Tool is effective in helping practitioners determine which patients are at high risk for CIN and its complications.

Implications for Nursing: By using the tool to identify patients treated with chemotherapy who need growth factor support, nurses can help to reduce the incidence of neutropenia and its complications.”

Citation: Doyle AM. (2006). Prechemotherapy Assessment of Neutropenic Risk. ONCOLOGY Nurse Edition 20(10), 32-39.

“ABSTRACT: Chemotherapy-induced febrile neutropenia (FN) predisposes patients to life-threatening infections and typically requires hospitalization. The goal was to investigate whether a risk assessment tool aligned with national guidelines could help identify patients at risk of FN and reduce FN-related hospitalizations. Beginning in October 2004, oncology nurses applied the new risk assessment tool to all patients initiating chemotherapy or a new regimen. Patients at risk for FN received prophylactic colony stimulating factor. Charts for 189 patients receiving chemotherapy in fiscal year 2005 (FY05) were compared with charts of 155 patients receiving chemotherapy in FY04, before the tool was implemented. The incidence of FN-related hospitalization declined by 78%, from 9.7% in FY04 to 2.1% in FY05 ($P = .003$). Total hospital days decreased from 117 to 24. Routine systematic evaluation by oncology nurses improves recognition of patients at risk of FN and substantially reduces FN-related hospitalization.”

Citation: Miller K. (2010). Using a Computer-Based Risk Assessment Tool to Identify Risk for Chemotherapy-Induced Febrile Neutropenia. Clinical Journal of Oncology Nursing 14(1), 87-91.

“This article evaluates the feasibility of developing and implementing a computer-based risk assessment tool (CBRAT) for febrile neutropenia and determines whether it could improve documentation of risk assessment in patients starting myelosuppressive chemotherapy regimens. The CBRAT was designed using a template creator in a commercial electronic medical records system. The effectiveness of the CBRAT was evaluated by comparing medical records data of patients with one or more risk factor for febrile neutropenia who were given prophylactic granulocyte–colony-stimulating factor before and after implementation. CBRAT usage significantly increased the likelihood of documented febrile neutropenia risk assessment from 13% before implementation to 100% after implementation ($p < 0.001$). No significant changes occurred in febrile neutropenia incidence rates, dose reductions, or dose delays. In addition, healthcare providers quickly learned how to operate the CBRAT and used it routinely, significantly improving the number of patients with documented febrile neutropenia risk assessment. Implementation of a computer-based tool can help nurses follow evidence-based guidelines that recommend routine febrile neutropenia risk assessment for patients initiating myelosuppressive chemotherapy.”

Citation: O'Brien C, Dempsey O, Kennedy MJ. Febrile neutropenia risk assessment tool: Improving clinical outcomes for oncology patients. Eur J Oncol Nurs. 18 (2014) 167-174

"Purpose: To develop, implement and evaluate the effectiveness of a nurse-led risk assessment tool to reduce the incidence of febrile neutropenia (FN) and evaluate the nurse's role in FN risk assessment in a hospital-based oncology unit."

"Methods and sample: **A FN risk assessment tool was developed, implemented and evaluated.** A comparative prospective observational chart review was undertaken to evaluate the tool. Clinical data were collected from 459 patients' records from August 2008 through July 2009. Patients had no intervention during the first six months (n = 233). Patients in the following six months (n = 226) had the FN risk assessment completed and appropriate granulocyte-colony stimulating factor prescribed. A self-questionnaire was utilised to evaluate the nurses' role in FN risk assessment."

"Key results: **The incidence of FN was reduced by 52% (p=0.02). Hospital days, dose reductions and treatment delays were reduced.** Nurses felt they were the most appropriate person to carry out the assessment."

"Conclusions: Through consistent risk assessment, nurses could determine which patients were at high risk of developing FN leading to significant reduction in life-threatening infections, hospitalisations, dose reductions and delays. Nurses can be confident and competent in decision-making to reduce life threatening infections through the use of an FN risk assessment tool."
(Emphasis added.)

Citation: Krzemieniecki K, Sevela P, Erdkamp F, Smakal M, Schwenkglenks M, Puertas J, et al. (2014). Neutropenia management and granulocyte colony-stimulating factor use in patients with solid tumours receiving myelotoxic chemotherapy - findings from clinical practice. Support Care Cancer 22, 667e77.

"Purpose: Clinical practice adherence to current guidelines that recommend primary prophylaxis (PP) with granulocyte colony stimulating factors (G-CSFs) for patients at high ($\geq 20\%$) overall risk of febrile neutropenia (FN) was evaluated."

"Methods: Adult patients with breast cancer, non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), or ovarian cancer were enrolled if myelotoxic chemotherapy was planned, and they had an investigator-assessed overall FN risk $\geq 20\%$. The primary outcome was FN incidence."

"Results: In total, 1,347 patients were analyzed (breast cancer, n = 829; NSCLC, n = 224; SCLC, n = 137; ovarian cancer, n = 157). **Patients with breast cancer exhibited fewer individual FN risk factors than patients with other cancers and were far more likely to have received a high-FN-risk chemotherapy regimen. However, a substantial proportion of all patients (45–80 % across tumour types) did not receive G-CSF PP in alignment with investigator risk assessment and guideline recommendations.** FN occurred in 127 patients overall (9%, 95% confidence interval (CI) 8–11%), and incidence was higher in SCLC (15%) than other tumor types (8% in ovarian and NSCLC, 9% in breast cancer). A post hoc analysis of G-CSF use indicated that G-CSF prophylaxis was not given within the recommended timeframe after chemotherapy (within 1–3 days) or was not continued across all cycles in 39% of patients."

"Conclusions: **FN risk assessment was predominantly based on clinical judgement and individual risk factors, and guidelines regarding G-CSF PP for patients at high FN risk were not consistently followed. Improved education of physicians may enable more fully informed neutropenia management in patients with solid tumours.**"

(Emphasis added.)

Citation: Freyer G, Kalinka-Warzocha E, Syrigos K et al. (2015). Attitudes of physicians toward assessing risk and using granulocyte colony-stimulating factor as primary prophylaxis in patients receiving chemotherapy associated with an intermediate risk of febrile neutropenia. Med Oncol 32, 236.

Abstract

“Febrile neutropenia (FN) is a potentially fatal complication of chemotherapy. This prospective, observational study describes physicians’ approaches toward assessing FN risk in patients receiving chemotherapy regimens with an intermediate (10–20 %) FN risk. In the baseline investigator assessment, physicians selected factors considered important when assessing overall FN risk and deciding on granulocyte colony-stimulating factor (G-CSF) primary prophylaxis (PP). Physicians then completed patient assessments using the same lists of factors. The final FN risk scores and whether G-CSF PP was planned were reported. The final analysis included 165 physicians and 944 patients. The most frequently considered factor in both assessments was chemotherapy agents in the backbone (88 % of investigator and 93% of patient assessments). History of FN (83%), baseline laboratory values (76%) and age (73%) were commonly selected at baseline, whereas tumor type (72%), guidelines (62%) and tumor stage (43 %) were selected most during patient assessments. Median investigator-reported FN risk threshold for G-CSF PP was 20% (range 10–85%). ***G-CSF PP was planned in 82% of patients with an FN risk at or above this threshold; therefore, almost one-fifth of qualifying patients would not receive G-CSF PP.*** Physicians generally follow guidelines, but also consider individual patient characteristics when assessing FN risk and deciding on G-CSF PP. ***A standardized FN risk assessment may optimize the use of G-CSF PP, which may minimize the incidence of FN in patients undergoing chemotherapy with an intermediate FN risk.***”

(Emphasis added.)

Citation: Mäenpää J, Varthalitis I, Erdkamp F, Trojan A, Krzemieniecki K, Lindman H, et al. (2016). The use of granulocyte colony stimulating factor (G-CSF) and management of chemotherapy delivery during adjuvant treatment for early-stage breast cancer. Further observations from the IMPACT solid study. The Breast 25, 27e33

“Objective: To investigate the use and impact of granulocyte colony-stimulating factors (G-CSF) on chemotherapy delivery and neutropenia management in breast cancer in a clinical practice setting.”

“Methods: IMPACT Solid was an international, prospective observational study in patients with a physician-assessed febrile neutropenia (FN) risk of $\geq 20\%$. This analysis focused on stages I-III breast cancer patients who received a standard chemotherapy regimen for which the FN risk was published. Chemotherapy delivery and neutropenia-related outcomes were reported according to the FN risk of the regimen and intent of G-CSF use.”

“Results: 690 patients received a standard chemotherapy regimen; 483 received the textbook dose/schedule with a majority of these regimens (84%) having a FN risk $\geq 10\%$. Patients receiving a regimen with a FN risk $\geq 10\%$ were younger with better performance status than those receiving a regimen with a FN risk $<10\%$. ***Patients who received higher-risk regimens were more likely to receive G-CSF primary prophylaxis (48% vs 22%), complete their planned chemotherapy (97% vs 88%) and achieve relative dose intensity $\geq 85\%$ (93% vs 86%) than those receiving lower-risk regimens.*** Most first FN events (56%) occurred in cycles not supported with G-CSF primary prophylaxis.”

“Conclusion: Physicians generally recommend standard adjuvant chemotherapy regimens and were more likely to follow G-CSF guidelines for younger, good performance status patients in the curative setting, and often modify standard regimens in more compromised patients. However, ***G-CSF support is***

not optimal, indicated by G-CSF primary prophylaxis use in <50% of high-risk patients and observation of FN without G-CSF support.”
(Emphasis added.)

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Appendix

Summary of Additional Evidence in Support of Proposed Measure on Febrile Neutropenia Risk Assessment Prior to Chemotherapy

Appendix Tables 1 and 2 below summarize information about the studies cited by the ASCO Guidelines on the Use of WBC Growth Factors (Smith et al., 2015) in support of Recommendation 1. The set of studies cited by these ASCO guidelines included adult or pediatric patients and patients with solid tumors or lymphoma. To the extent possible, we dropped entire studies or subsets of results that were focused on pediatric patients to more accurately reflect the focus of the measure, which is on adult patients with a solid tumor or lymphoma. However, for a few studies, dropping the subset of results on children was not feasible, and we present results that include this subgroup (as noted in the last column of Table 1).

Appendix Table 1. Summary of Studies Cited in Support of Recommendation 1 by ASCO Guidelines on the Use of WBC Growth Factors (Smith et al., 2015)

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
Lyman 2013 (1)	Meta-analysis of data from 61 randomized comparisons; outcome=all-cause mortality.	From Table 1: Patients with solid tumors Relative risk (RR) for G-CSF vs. no G-CSF for all-cause mortality Breast (N=20) RR=0.954 (CI 0.898, 1.013) Genitourinary (N=7) RR=0.946 (CI 0.884, 1.013) Lung (N=16) RR=0.930 (CI 0.882, 0.980) Lymphoma (N=16) RR=0.895 (CI 0.841, 0.952) Other (N=2) RR=0.867 (CI 0.630, 1.193)	Adverse events were reported in all 58 of 59 RCTs (98%) and were systematically reported in 51 of 59 RCTs. However, specific information about adverse events was not included in the Lyman 2013 article.	
Renner 2012	Meta-analysis (Number of Main Comparison studies: 6 Febrile Neutropenia (FN), 8 Early Mortality, 8 Infection-related mortality; Number of Secondary Outcome studies:	From “Summary of Findings for the Main Comparison” table (Page 4): Patients with breast cancer in randomized control trials receiving primary prophylactic G-CSF/GM-CSF vs. no primary G-CSF/GM-CSF: Febrile Neutropenia (N=2073) Risk Ratio (RR)=0.27 (CI 0.11,0.70) Early Mortality (N=2143) RR=0.32 (CI 0.13,0.77) Infection-related mortality (N=2143) RR=0.14 (CI 0.02,1.29) From “Additional Summary of Findings” table	Patients with breast cancer in randomized control trials receiving primary prophylactic G-CSF/GM-CSF vs. no primary G-CSF/GM-CSF: Bone pain (N=388) RR=5.88 (CI 2.54,13.6) Injection-site Reaction (N=262) RR=3.59 (CI 2.33,5.53)	Patients with breast cancer

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
	4 Severe Neutropenia, 3 Infections, 4 Hospitalizations, 4 IV antibiotics, 4 Chemotherapy, 3 Bone Pain, 2 Injection-site Reaction)	(Page 21): Severe Neutropenia (Grade IV) (N=712) RR=0.44 (CI 0.17,1.18) Infections (N=210) RR=0.86 (CI 0.72,1.02) Hospitalization (N=1149) RR=0.14 (CI 0.06,0.3) IV Antibiotics (N=1568) RR=0.35 (CI 0.22,0.55) Rate of patients who received the planned chemotherapy doses at scheduled times and doses (N=1588) RR=1.05 (CI 0.97,1.13)		
Cooper 2011	Meta-analysis 13 studies (5 Pegfilgrastim, 10 Filgrastim, 5 Lenograstim); outcome=FN incidence.	From Figure 2: Risk ratios for FN incidence (From Section 4.1.1) Patients with solid tumors or lymphoma for Pegfilgrastim vs. none in five studies: 0.08 (CI 0.03, 0.18) - 0.77 (CI 0.23, 2.60) Overall for Pegfilgrastim (N=2060): 0.30 (CI 0.14, 0.65) (From Section 4.1.2) Patients with solid tumors or lymphoma for Filgrastim vs. none in ten studies: 0.25 (CI 0.09, 0.72) - 0.82 (CI 0.64, 1.04) Overall for Filgrastim (N=2183): 0.57 (CI 0.48, 0.69) (From Section 4.1.3) Patients with solid tumors or lymphoma for Lenograstim vs. none in five studies: 0.34 (CI 0.15, 0.77) - 0.83 (CI 0.64, 1.08) Overall for Lenograstim (N=467): 0.62 (CI 0.44, 0.88) Overall for all treatments (N=4710): 0.51 (CI 0.41, 0.62)	None listed in Cooper 2011 article (one study includes patients below 18 years old)	
Kuderer 2011	Meta-analysis (same results were reported in Kuderer 2007)	See Kuderer 2007 below for results.	See Kuderer 2007 below for adverse events.	Results from same meta-analysis were reported in an earlier article (see Kuderer 2007 below).
Wildiers 2011	Systematic review 7 studies of breast cancer and 11	Impact of G-CSF on RDI in patients with breast cancer From Table 7:	None listed in article	

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
	studies of lymphoma; outcome=relative dose intensity (RDI)	<p>Four studies showed statistically significantly higher rates of achieving target rates of RDI with G-CSF treatment (compared to no G-CSF or no primary G-CSF), three studies do not show a difference.</p> <p>Primary G-CSF prophylaxis led to a statistically significant reduction in chance of receiving RDI <85% OR=0.733 (CI 0.61,0.88) p=0.001</p> <p>Impact of G-CSF on RDI in patients with lymphoma</p> <p>From Table 8:</p> <p>Seven studies showed statistically significantly higher rates of achieving target rates of RDI with G-CSF treatment (compared to no G-CSF or no primary G-CSF), three studies do not show a difference.</p> <p>Primary G-CSF prophylaxis led to a statistically significant reduction in chance of receiving RDI <85% OR=0.70 (CI 0.55,0.89)</p>		
Lyman 2010	Meta-analysis outcomes= acute myeloid leukemia/ myelodysplastic syndrome (AML/MDS) and all-cause mortality; 23 studies for AML/MDS and 25 studies for all-cause mortality;	<p>From Table 2:</p> <p>Risk ratio for AML/MDS among patients treated with G-CSF vs. no CSF</p> <p>Breast (7 studies): 1.811 (CI 0.897, 3.656)</p> <p>Endometrial (2 studies): 2.916 (CI 0.305, 27.872)</p> <p>Germ Cells (1 study): 0.336 (CI 0.014, 8.170)</p> <p>Hodgkin's Lymphoma (1 study): 2.013 (CI 0.820, 4.942)</p> <p>Non-Hodgkin's Lymphoma (8 studies): 2.732 (CI 0.804, 9.280)</p> <p>Lung (3 studies):0.956 (CI 0.101, 9.072)</p> <p>Urothelial (1 study): 0.963 (CI 0.061, 15.229)</p> <p>Risk ratio for all-cause mortality among patients treated with G-CSF vs. no CSF</p> <p>Breast (7 studies): 0.902 (CI 0.815, 0.998)</p> <p>Endometrial (2 studies): 0.945 (CI 0.874, 1.021)</p> <p>Germ Cells (1 study): 0.849 (CI 0.568, 1.269)</p> <p>Hodgkin's Lymphoma (1 study): 0.660 (CI 0.452,</p>	None listed in article	

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
		0.963) Non-Hodgkin's Lymphoma (10 studies): 0.895 (CI 0.832, 0.963) Lung (3 studies): 0.945 (CI 0.875, 1.021) Urothelial (1 study) : 0.868 (CI 0.772, 0.977)		
Bohlius 2008	Meta-analysis; 13 RCTs (11 survival rate, 6 FFTF, 8 neutropenia, 5 febrile neutropenia ANC<1000, 3 febrile neutropenia ANC<500, 11 infection, 4 parental antibiotics treatment, 11 mortality during chemotherapy, 12 infection related mortality, 13 complete response) Adverse events (9 bone pain, 5 thrombosis and related complications, 2 skin rash, 2 infection site reaction, 2 myalgia, 4 mucositis, 2 headache)	From Figure 1: Patients treated with G-CSF and GM-CSF compared to no prophylaxis survival rate in 11 studies: OR=0.33 (CI 0.03, 3.27) – 2.04 (CI 0.55, 7.59) Overall survival rate OR=0.97 (CI 0.87 to 1.09) From Figure 10: Patients treated with G-CSF and GM-CSF compared to no prophylaxis freedom from treatment failure (FFTF) in six studies: OR=0.96 (CI 0.28, 3.31) – 1.41 (CI 0.45, 4.41) Overall FFTF OR=1.11 (CI 0.91, 1.35) From Figure 11: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from neutropenia in eight studies: RR=0.42 (CI 0.27, 0.66) – 1.48 (CI 0.57, 3.82) Overall neutropenia RR=0.67 (CI 0.60, 0.73) From Figure 22: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from febrile neutropenia (ANC <1000) in five studies: RR=0.23 (CI 0.03, 1.75) – 1.09 (CI 0.48, 2.48) Overall febrile neutropenia (ANC<1000) RR=0.74 (CI 0.62, 0.89) From Figure 29: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from febrile neutropenia (ANC <500) in three studies: RR=0.42 (CI 0.27, 0.66) – 0.67 (CI 0.48, 0.94) Overall febrile neutropenia (ANC<500) RR=0.59 (CI 0.48, 0.72) From Figure 30: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from infection in 11 studies: RR=0.25 (CI 0.09, 0.72) – 1.33 (CI 0.46, 3.85)	From Figure 52: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for bone pain in nine studies: RR=1.30 (CI 0.47, 3.60) – 14.29 (CI 0.84, 242.02) Overall bone pain RR=3.57 (2.09, 6.12) From Figure 59: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for thrombosis and related complications in five studies: RR= 0.34 (CI 0.01, 8.14) – 4.76 (CI 0.24, 96.16) Overall thrombosis and related complications RR=1.29 (CI 0.56, 3.01) From Figure 60: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for skin rash in two studies: RR=4.33 (CI 1.04, 18.01) – 11.24 (CI 2.73, 46.25) Overall skin rash RR=7.69 (CI 2.84, 20.82) From Figure 61: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for injection site reaction in two studies: RR=6.52 (CI 2.91, 14.58) – 6.91 (CI 0.36, 131.75) Overall injection site reaction RR=6.55 (3.01, 14.25)	Adults with lymphoma

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
		<p>Overall infection RR=0.74 (CI 0.64 to 0.85)</p> <p>From Figure 40: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from parental antibiotic treatment in four studies: RR=0.09 (CI 0.00, 1.51) – 1.21 (CI 0.80, 1.83)</p> <p>Parental antibiotic treatment RR=0.82 (CI 0.57, 1.18)</p> <p>From Figure 41: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from mortality during chemotherapy in 11 studies: RR=0.31 (CI 0.01, 6.94) – 3.07 (CI 0.66, 14.37)</p> <p>Overall mortality during chemotherapy RR=0.93 (CI 0.60, 1.43)</p> <p>From Figure 42: Patients treated with G-CSF and GM-CSF compared to no prophylaxis from infection-related mortality during chemotherapy in 12 studies: RR=0.21 (CI 0.02, 1.76) – 6.14 (CI 0.77, 48.87)</p> <p>Overall infection-related mortality RR=0.93 (CI 0.51, 1.71)</p> <p>From Figure 43: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for complete response in 13 studies: RR=0.88 (CI 0.66, 1.17) – 3.50 (CI 0.40, 30.77)</p> <p>Overall complete tumor response RR=1.03 (CI 0.95, 1.10)</p>	<p>From Figure 62: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for myalgia in two studies: RR=0.87 (CI 0.56, 1.37) – 2.60 (CI 0.29, 23.50)</p> <p>Overall myalgia RR=0.94 (CI 0.60, 1.45)</p> <p>From Figure 63: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for mucositis in four studies: RR=0.81 (CI 0.43, 1.54) – 1.33 (0.30, 5.84) Overall mucositis RR=0.95 (CI 0.64, 1.41)</p> <p>From Figure 64: Patients treated with G-CSF and GM-CSF compared to no prophylaxis for headache in two studies: RR=1.14 (CI 0.40, 3.26) – 2.19 (CI 1.38 – 3.49)</p>	
Balducci 2007	RCT; treatment= outcomes= febrile neutropenia, grade 3 or 4 neutropenia, grade 4 neutropenia, chemotherapy delays, chemotherapy dose reductions,	<p>Physician Discretion vs. Pegfilgrastim on all cycles in elderly patients with solid tumors (N=701):</p> <p>From Figure 2, Lower incidence of Febrile Neutropenia 10.0% vs. 4.0% (p=0.001)</p> <p>From Figure 4A, Lower incidence of Grade 3 or 4 Neutropenia 80% vs. 30% (Significant)</p> <p>From text: Lower incidence of Grade 4 Neutropenia 58% vs. 22% (Significant)</p> <p>From Figure 4A, Lower rates of antibiotic use associated with neutropenia-related events 10%</p>	<p>Greater than or equal to 5% of patients experienced pancytopenia, pneumonia, pyrexia, dehydration, and syncope in studies of solid tumors and lymphomas.</p> <p>Pegfilgrastim treatment was associated with arthralgia in studies of solid tumors and lymphomas (no point estimates listed).</p>	Patients ≥65 yo with lymphoma, lung, breast, or ovarian cancer

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
	antibiotic use associated with neutropenia-related events	<p>vs. 28% (Significant)</p> <p>From Figure 4A, Lower rates of hospitalization for febrile neutropenia and neutropenia 9% vs. 5% (Not significant, NS)</p> <p>From Figure 4A, Fewer chemotherapy delays 28% vs. 16% (Significant)</p> <p>From Figure 4A, Fewer chemotherapy dose reductions 14% vs. 7% (NS)</p> <p>Physician Discretion vs. Pegfilgrastim on cycle 1 on elderly patients with solid tumors:</p> <p>From Figure 2, Lower incidence of Febrile Neutropenia 7% vs. 3% (NS)</p> <p>From text: Lower incidence of Grade 3 or 4 Neutropenia 68% vs. 26% (Significant)</p> <p>Physician Discretion vs. Pegfilgrastim on all cycles in elderly patients with NHL (N=151):</p> <p>From Figure 2, Lower incidence of Febrile Neutropenia 37.0% vs. 15.0% (p=0.004)</p> <p>From Figure 4B, Lower incidence of Grade 3 or 4 Neutropenia 90% vs. 82% (Not Significant, NS)</p> <p>From text: Lower incidence of Grade 4 Neutropenia 86% vs. 75% (NS)</p> <p>From Figure 4B, Higher rates of antibiotic use associated with neutropenia-related events 53% vs. 55% (NS)</p> <p>From Figure 4B, Lower rates of hospitalization for febrile neutropenia and neutropenia 37% vs. 17% (NS)</p> <p>From Figure 4B, More chemotherapy delays 23% vs. 29% (NS)</p> <p>From Figure 4B, More chemotherapy dose reductions 8% vs. 16% (NS)</p> <p>From text: Lower incidence of grade 4 neutropenia 86% vs. 75% (NS)</p> <p>Physician Discretion vs. Pegfilgrastim on cycle 1 on elderly patients with NHL:</p>	<p>Pegfilgrastim treatment vs. Physician Discretion in patients with solid tumors:</p> <p>Higher incidence of bone pain 12% vs. 5%</p> <p>Pegfilgrastim treatment vs. Physician Discretion in patients with NHL:</p> <p>Higher incidence of bone pain 9% vs. 4%</p>	

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
		<p>From Figure 2, Lower incidence of Febrile Neutropenia 25% vs. 7% (NS)</p> <p>From text: Lower incidence of Grade 3 or 4 Neutropenia 88% vs. 69% (NS)</p>		
Kuderer 2007 (results of the same meta-analysis also reported in Kuderer 2011)	Meta-analysis 12-15 studies (7-9 Filgrastim, 4-5 Lenograstim, 1 Pegfilgrastim) 14 studies for bone or musculoskeletal pain; outcomes=infection-related mortality, early mortality, and febrile neutropenia	<p>From Figure 2: Infection-Related Mortality Range of relative risks for patients with solid tumor or lymphoma for Filgrastim vs. none in seven studies: 0.328 (CI 0.035, 3.073) – 1.095 (CI 0.226, 5.293) Overall for Filgrastim: 0.529 (CI 0.304, 0.921) Range of relative risks for patients with solid tumor or lymphoma for Lenograstim vs. none in four studies: 0.650 (CI 0.112, 3.790) – 1.174 (CI 0.024, 56.861) Overall for Lenograstim: 0.829 (CI 0.257, 2.680) Relative risk for patients with solid tumor or lymphoma for Pegfilgrastim vs. none in one study: 0.201 (CI 0.010, 4.172) Overall for all treatments: 0.552 (CI 0.338, 0.902)</p> <p>From Figure 3: Early Mortality Range of relative risks for patients with solid tumor or lymphoma for Filgrastim vs. none in eight studies: 0.206 (CI 0.024, 1.732) – 1.427 (CI 0.435, 4.675) Overall for Filgrastim: 0.603 (CI 0.410, 0.887) Range of relative risks for patients with solid tumor or lymphoma for Lenograstim vs. none in four studies: 0.767 (CI 0.294, 2.002) – 1.174 (CI 0.024, 56.861) Overall for Lenograstim: 0.837 (CI 0.383, 1.833) Range of relative risks for patients with solid tumor or lymphoma for Pegfilgrastim vs. none in one study: 0.359 (CI 0.130, 0.988) Overall for all treatments: 0.599 (CI 0.433, 0.830)</p> <p>From Figure 4: Febrile Neutropenia Range of relative risks for patients with solid</p>	<p>Risk ratio for patients treated with G-CSF with bone or musculoskeletal pain (N=3029) RR=4.023 (CI 2.156,7.52). These results may include patients under 18 years of age.</p>	Three studies include patients below 18 years old.

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
		<p>tumor or lymphoma for Filgrastim vs. none in nine studies: 0.249 (CI 0.087, 0.716) – 0.816 (CI 0.641, 1.039)</p> <p>Overall for Filgrastim: 0.614 (CI 0.525, 0.718)</p> <p>Range of relative risks for patients with solid tumor or lymphoma for Lenograstim vs. none in five studies: 0.338 (CI 0.148, 0.770) – 0.829 (CI 0.636, 1.080)</p> <p>Overall for Lenograstim: 0.623 (CI 0.442, 0.879)</p> <p>Range of relative risks for patients with solid tumor or lymphoma for Pegfilgrastim vs. none in one study: 0.077 (CI 0.034, 0.175)</p> <p>Overall for all treatments: 0.538 (0.430, 0.673)</p> <p>From Table 2:</p> <p>Summary risk ratios for patients with solid tumors treated with G-CSF vs. none: Febrile Neutropenia 0.44 (CI 0.30, 0.65), Early Mortality 0.55 (CI 0.37, 0.84), Infection-Related Mortality 0.53 (CI 0.28, 1.02).</p> <p>Summary risk ratios for patients with lymphomas treated with G-CSF vs. none: Febrile Neutropenia 0.71 (CI 0.59, 0.85), Early Mortality 0.69 (CI 0.40, 1.17), Infection-Related Mortality 0.58 (CI 0.28, 1.23).</p> <p>Bold = statistically significant differences.</p>		
Sung 2007	<p>Meta-analysis</p> <p>In Appendix Figure 3: 26 lymphoma/solid tumor studies</p> <p>In Appendix Figure 6: 30 lymphoma/solid tumor studies</p> <p>In Appendix Table 3: Number of G-CSF</p>	<p>From Appendix Figure 3:</p> <p>All-cause mortality associated with CSF for lymphoma/solid tumor patients (n=4359) Risk ratio (RR)=0.91 (CI 0.64,1.28)</p> <p>From Appendix Figure 6:</p> <p>Infection-related mortality associated with CSF for lymphoma/solid tumor patients (N=4777) RR=0.70 (CI 0.47,1.05)</p> <p>From Appendix Table 3:</p> <p>For patients treated with G-CSF:</p> <p>All-cause mortality RR=0.98 (0.83, 1.15)</p>	None listed in article	<p>Adults and children with cancer</p> <p>Limitations: these data are not limited to adults 18+.</p>

Author Year	Type of Study	Benefit of Prophylaxis with CSF	Adverse Events Associated with CSF Prophylaxis	Notes
	studies: 45 all-cause mortality, 42 infection-related mortality, 41 documented infections, 29 microbiologically documented infection, 33 febrile neutropenia. Number of GM-CSF studies: 34 all-cause mortality, 24 infection-related mortality, 17 documented infections, 12 microbiologically documented infection, 15 febrile neutropenia.	Infection-related mortality RR=0.84 (CI 0.66, 1.06) Documented infections RR=0.83 (CI 0.76, 0.91) Microbiologically documented infection RR=0.85 (CI 0.76, 0.96) Febrile neutropenia RR=0.72 (CI 0.64, 0.81) From Appendix Table 3: For patients treated with GM-CSF All-cause mortality RR=0.95 (0.84, 1.08) Infection-related mortality RR=0.82 (CI 0.49, 1.38) Documented infections RR=0.92 (CI 0.78, 1.07) Microbiologically documented infection RR=0.90 (CI 0.68, 1.19) Febrile neutropenia RR=0.88 (CI 0.75, 1.03)		
Papaldo 2006	RCT; outcomes=delayed cycles; dose reduction, dose intensity	Impact of G-CSF on all cycles on patients with early breast cancer (N=506): Decreased rate of delayed cycles for patients with G-CSF (10.0% vs. 3.6% p=0.00001) Decreased frequency of dose reduction for patients with G-CSF (3.6% vs. 1.4% p=0.002) No difference in dose intensity of adjuvant therapy between the G-CSF and control (98.1% vs. 95.5% in G-CSF and non-G-CSF, respectively; p=0.17).	Impact of G-CSF on all cycles on anemia rate in patients with early breast cancer (N=506): Mean hemoglobin value from cycle 3 onwards was lower for each cycle for patients with G-CSF (p<0.0001). Increased rate of Grade 2 or worse anemia in patients with G-CSF (38.8% vs. 26.2% p=0.005).	Female breast cancer patients

Appendix Table 2. Quality of Methods Used in Studies Cited in Support of Recommendation 1 by ASCO Guidelines on the Use of WBC Growth Factors (Smith et al., 2015)

Information about Quality of Study Methods
Lyman et al., 2013: Meta-analysis; 61 separate randomized comparisons of chemotherapy with (N= 11,337 patients) or without (N= 13,456 patients) the initial use of G-CSFs. Methodologic flaws of the meta-analysis may include: may have missed relevant studies; subject to the weaknesses of ecologic studies; control patients may have received CSFs later in the study; little or no data on dose and length of G-CSF treatment; survival of patients based on original study data; minimum follow-up of two years to be eligible for meta-analysis; biased selection of patient sample to include those without comorbidities and “poor performance”; possible publication bias.
Renner et al., 2012: Meta-analysis; methodologic flaws of the meta-analysis may include small number of studies (N=8) and number of patients (N= 2156); heterogeneous disease stages and chemotherapy treatments; outcome definitions varied across studies; some studies were conducted before current recommendations for CSF were in place.
Cooper et al., 2011: Meta-analysis; 20 studies compared primary G-CSF prophylaxis with no primary G-CSF prophylaxis; number of patients in analyses by type of G-CSF ranged from 467 to 4710. Methodologic flaws of the meta-analysis may include heterogeneity across studies in patient groups (age, cancer type), chemotherapy regimen, and number and length of cycles.
Wildiers et al., 2011: Systematic review with only one reviewer evaluating the studies; seven studies ranged in size from 41 patients with G-CSF and 403 without, to a study of 5253 patients with G-CSF and 14645 patients without.
Lyman et al., 2010: Meta-analysis; 25 studies were included in the meta-analysis, for a total of 12,804 patients (6,058 patients randomly assigned to G-CSF and 6,746 controls). Methodologic flaws of the meta-analysis may include not identifying some relevant studies; control patients may have received CSFs later in the study; little or no data on dose and length of G-CSF treatment making an analysis of a dose-response relationship impossible; possible publication bias.
Bohlius et al., 2008: Meta-analysis; 13 randomized controlled trials were included with 2607 randomized patients; the method of allocation concealment was unknown for three studies, but concealment of allocation was adequate in the other studies; five studies were placebo-controlled; seven studies and one substudy were based on an intention-to-treat analysis; the rest were “based on full set analysis and excluded patients who did not meet the eligibility criteria, had major protocol violation or did not receive any study medication.”
Kuderer et al., 2007: Meta-analysis; Infection-related mortality was reported as an outcome in 12 trials with 1,454 control patients and 1,463 patients receiving G-CSF; early mortality was an outcome in 13 trials with 3,122 patients; FN was an outcome in 15 trials with 3,182 patients. Methodologic flaws of the meta-analysis may include lack of inclusion of dose-intensification trials; based on aggregate data not on individual patient data; small sample sizes limit ability to analyze data on secondary outcomes such as infection-related mortality, early mortality, and RDI; insufficient statistical power to detect effects; possible under-reporting of FN, FN-related mortality, and cost.
Balducci et al., 2007: Randomized controlled trial (RCT) of 701 patients with solid tumors; the quality of this randomized controlled trial (RCT) was evaluated by

Information about Quality of Study Methods
<p>Smith et al. (2015) as having an overall risk of bias of “intermediate” based on the following: The RCT had adequate randomization, sufficient sample size, similar groups, validated and reliable measures, and adequate follow-up. However, the RCT was not blinded, did not perform intent-to-treat analyses, and had significant conflicts of interest.</p>
<p>Sung et al., 2007: Meta-analysis; 4,359 patients (2,204 treated, 2,155 control) in mortality analysis; 4,777 patients (2,413 treated, 2,364 control) in analysis of infection-related mortality. A total of 148 studies were rated on the Jadad scale for study quality which assesses whether randomization was adequate, double-blinding was performed, and withdrawals and dropouts were described. The median Jadad score was 2 (range, 0 [lowest quality] to 5 [highest quality]), with substantial interrater agreement (weighted 0.73 [CI, 0.66 to 0.80]). Patients in all included studies were randomized to either CSF, or to placebo or no treatment, but patient and study characteristics were heterogeneous. All-cause mortality, the primary outcome, was defined without heterogeneity, as were most secondary outcomes, but not all outcomes were reported for every study, which may mean there was “selective reporting” and possible bias.</p>
<p>Papaldo et al., 2006: RCT; 506 patients randomly assigned to treatment with G-CSF or no G-CSF; the quality of this RCT was evaluated by Smith et al. (2015) as having an overall risk of bias of “high” based on the following: It was unclear whether the RCT had adequate randomization, sufficient sample size, similar groups, or blinding, and intent-to-treat analyses were not performed. However, the RCT did have validated and reliable measures, and adequate follow-up. In addition, the study may have had significant conflicts of interest.</p>

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