

CLINICAL APPROPRIATENESS GUIDELINES

MEDICAL ONCOLOGY

Appropriate Use Criteria: Febrile Neutropenia Risk

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Proprietary

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details. AIM Specialty Health disclaims any responsibility for the completeness or accuracy of the information contained herein.



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Description and Application of the Guidelines

The AIM Clinical Appropriateness Guidelines (hereinafter “the AIM Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by AIM, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The AIM guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. AIM reviews all of its Guidelines at least annually.

AIM makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the AIM Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, AIM considers the Guidelines to be important, proprietary information of AIM, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of AIM.

AIM applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The AIM Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, AIM will review requests based on health plan medical policy/guidelines in lieu of the AIM Guidelines.

The Guidelines may also be used by the health plan or by AIM for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Febrile Neutropenia Risk

Description and Scope

These guidelines address determination of the febrile neutropenia risk that guides the use of white blood cell growth factors for oncology drug treatment regimens for adults. For interpretation of the Guidelines, and where not otherwise noted, “adult” refers to persons age 19 and older. These drug treatments may include cytotoxic chemotherapy, biologic agents, and other targeted therapies used to treat cancer. Treatments may be given orally, by injection, or by infusion. A regimen may consist of a single agent or include two or more agents.

The purpose of these guidelines is to clarify the risk categorization of cancer treatment regimens (i.e., the combination of one or more anti-cancer drugs) and to specify which patient risk factors will be taken into account when assessing regimens that are considered intermediate risk. The Guidelines are intended to be coupled with health plan policies, specific to use of white blood cell growth factors, in order to bring greater transparency to the use of risk categorization in management of this category of drugs (when used prophylactically in the setting of cancer treatment). Although there are compendia that list examples of regimens in each risk category, these judgements can be difficult due to the lack of standardization in reporting febrile neutropenia in cancer research and the lack of consensus about how to weigh different types of evidence about febrile neutropenia risk.

Clinical Indications

Febrile neutropenia risk

Febrile neutropenia risk determination for use of white blood cell growth factors for primary prophylaxis

Primary prophylaxis with white blood cell growth factors is considered medically necessary in **EITHER** of the following scenarios:

- High risk of febrile neutropenia ($\geq 20\%$) based on chemotherapy regimen
- Intermediate risk of febrile neutropenia ($\geq 10\%$ but $< 20\%$) based on chemotherapy regimen, and **ANY** of the following additional risk factors* based on literature and consensus supported guidelines, including:
 - Age > 65 years
 - Poor performance status (ECOG 3 or 4)
 - Preexisting neutropenia, for example resulting from bone marrow damage or tumor infiltration (ANC $< 1500 \text{ mm}^3$)
 - Renal dysfunction with creatinine clearance $< 50 \text{ ml/min}$
 - Poor nutritional status (typically defined as a serum albumin $\leq 3.5 \text{ g/dL}$ or BMI < 20)
 - Active HIV infection

*Other risk factors and risk factor definition may depend on individual guidance from other sources, such as health plan clinical criteria.

The regimen-specific risk category will be based on published information in the medical literature with the highest weight given to rigorously conducted, prospective clinical trials that include patients enrolled in the U.S. Data from retrospective studies will also be considered and evaluated according to the scientific and methodological rigor of the work.

Commonly used outpatient regimens are shown in **Table 1. Febrile Neutropenia Risk**. Regimens considered high risk or intermediate risk for febrile neutropenia are summarized in **Appendix A. Guideline Notes**. Other selected regimens are risk-classified consistent with the NCCN as specified in the NCCN Guidelines for Hematopoietic Growth Factors.

Table 1. Febrile Neutropenia Risk

Tumor Type	Regimen	AIM FN Risk	Evidence Grade
Breast Cancer	Docetaxel (100-75 mg/m ²)	Intermediate	High
	Docetaxel (< 75 mg/m ²)	Low	Moderate
	TCHP	High	Moderate
	TC	Intermediate	Low
Cervical Cancer	Cisplatin and Paclitaxel +/- Bevacizumab	Low	Moderate
	Topotecan	Low	Low
Gastroesophageal Cancer	Cisplatin and Irinotecan	Low	Low
Head and Neck Squamous Cell Carcinoma	Cetuximab/Panitumumab plus platinum-based chemotherapy	Low	High
	Pembrolizumab plus platinum-based chemotherapy	Low	High
Non-Small Cell Lung Cancer	Carboplatin, Paclitaxel/nab-Paclitaxel, Pembrolizumab	Low	Moderate
	Carboplatin, Paclitaxel, Atezolizumab +/- Bevacizumab	Low	Moderate
	Carboplatin/Cisplatin, Pemetrexed, Pembrolizumab	Low	High
	Cisplatin and Vinorelbine	Intermediate	Moderate
	Cisplatin and Docetaxel	Low	Moderate to High
	Docetaxel	Low	High
	Docetaxel and Ramucirumab	Intermediate	Moderate
Small Cell Lung Cancer	Carboplatin, Etoposide, Atezolizumab	Low	High
Lymphoma	GDP +/- Rituximab	Intermediate	Low
Ovarian Cancer	Carboplatin and Docetaxel	Intermediate	Moderate
	Carboplatin and Paclitaxel	Low	High
	Topotecan	Intermediate	Moderate
Pancreatic Cancer	FOLFIRINOX	Low	High
Prostate Cancer	Cabazitaxel	Intermediate	Moderate to High
Sarcoma	Doxorubicin	Intermediate	High
Germ Cell Tumor	BEP	Intermediate	High
	EP	Intermediate	Moderate

Key: BEP = bleomycin plus etoposide and cisplatin; EP = etoposide and cisplatin; FN = febrile neutropenia; GDP = gemcitabine, dexamethasone, cisplatin; TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab; TC = docetaxel and cyclophosphamide

Rationale

A neutrophil is a type of white blood cell that helps protect against bacterial infections. Patients receiving treatment for cancer such as chemotherapy, targeted agents, and/or radiation therapy can experience a reduction in the number of neutrophils and this may cause serious infection and even death. The lower limit of normal for the neutrophil count is 1500 per microliter of blood. Neutropenia refers to lowering of the neutrophil count, and the risk of infection is significantly increased when the neutrophil count is below 1000, and further increased when it is below 500. In addition to the degree of neutropenia, the risk of having serious infection due to low neutrophil counts varies according to factors such as the underlying type of cancer, the timing and types of cancer treatment, and the burden of other types of illness that make some patients more vulnerable to infection.¹

Chemotherapy-induced neutropenia is a major risk factor for infection-related morbidity and mortality and also a significant dose-limiting toxicity in cancer treatment. This may impact the success of treatment, particularly when treatment intent is either curative or to prolong survival. White blood cell growth factors include drugs such as pegfilgrastim (Neulasta) and filgrastim (Neupogen) and also biosimilar agents for these products. These drugs have been shown to reduce the degree and duration of neutropenia. The use of these agents and the spending on this category of supportive care products has steadily increased over the past 18 years since these drugs were introduced. These drugs are very expensive, and they are frequently overused, particularly in the U.S. The U.S. accounts for over 75% of the world's purchases of white blood cell growth factors. Health plans and some provider organizations have specific policies related to the use of white blood cell growth factors in order to reduce underutilization or overutilization of these agents.^{1, 2}

Guidelines from the American Society of Clinical Oncology (ASCO) and other organizations consider the occurrence of fever and neutropenia (so-called "febrile neutropenia") to be the clinical scenario that requires action to protect patients who may be on the verge of serious infection. The safe care of patients with febrile neutropenia requires urgent assessment and rapid administration of antibiotics. Depending on the circumstances, such patients may require evaluation in the emergency room and sometimes require hospitalization. There is general agreement among guidelines on the definition of neutropenia and the definition of fever. In the context of cancer treatment, the ASCO and other guidelines that patients at high risk for febrile neutropenia (> 20%) should receive white blood cell growth factors prophylactically (i.e., after chemotherapy but before developing symptoms or signs of febrile neutropenia). There is also agreement that those with a < 10% risk of febrile neutropenia should not receive these growth factors. Patients whose risk of febrile neutropenia is between 10%-20% are considered intermediate risk, and for those patients the use of these growth factors depends on specific patient circumstances.^{3, 4} Unfortunately, there is significant overuse of white blood cell growth factors for primary prophylaxis, particularly for patients receiving palliative chemotherapy.^{5, 6}

Several studies demonstrate that a decision support-enabled utilization management tool can improve risk-appropriate, guideline-adherent use of white blood cell growth factors.^{7, 8} ASCO recommends primary prophylaxis with a white blood cell growth factor should also be administered in patients receiving dose dense chemotherapy. ASCO also recommends consideration to alternative, equally effective, and safe chemotherapy regimens not requiring white blood cell growth factors support when available. In patients receiving concomitant chemo-radiotherapy, use of white blood cell growth factors should be avoided, especially when radiation involves the mediastinum.^{2, 4}

Appendix A. Guideline Notes

Evidence grading system: GRADE methodology

Category	Interpretation	Criteria – reasons to downgrade or upgrade evidence quality	Examples
High	Very confident that future research will not change febrile neutropenia category assignment (low, moderate, high)	Internal validity / Risk of bias – methodological limitations in study design, such as incomplete randomization, high drop-out rates	Multiple consistent RCTs with methodological flaws but consistent results One or more well designed applicable RCTs
Moderate	Confident that future research is unlikely to change febrile neutropenia category assignment	Indirectness – applicability of the research to the population, intervention and outcomes of interest Imprecision – confidence intervals cross a decision-making threshold, inadequate sample size	RCTs with one or more reasons to downgrade evidence quality Well designed prospective studies with dramatic effect
Low	Less confident that future research will change febrile neutropenia category assignment	Inconsistency – unexplained heterogeneity in the data Publication bias – positive selection bias in published results	RCTs with two or more reasons to downgrade Well designed observational studies
Very low	Little confidence that future research will change febrile neutropenia category assignment	Effect size – dramatic effects may upgrade evidence quality	RCTs with three or more reasons to downgrade, poorly designed observational studies, case series

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; RCT = randomized controlled trial

Breast cancer

Febrile neutropenia risk in patients with advanced breast cancer treated with docetaxel (100 mg/m² given every 21 days; also weekly dosing or 75 mg/m² and lower dosing every 21 days): Intermediate

For docetaxel dosing at 100 mg/m² every 21 days, Intermediate risk* (versus NCCN intermediate risk) based on high-quality evidence. Estimated pooled risk of FN for all patients receiving docetaxel dosed at 100 mg/m² is 14% (range: 6%-21%) based on high-quality evidence. The addition of trastuzumab and/or pertuzumab appears to confer at least a FN risk of 10%-20%. The majority of the evidence provided addressed neutropenia and FN when docetaxel dosed at 100 mg/m² is used. Weekly and/or 75 mg/m² or lower dosing every 21 days is associated with a lower risk of FN and should be considered low risk (< 10%) (3%-10%) based on moderate-quality evidence.

*AIM Guidelines currently treat docetaxel as an intermediate-risk regimen when given sequential with doxorubicin and cyclophosphamide in the adjuvant and neoadjuvant setting and low risk in the metastatic setting.

Febrile neutropenia risk in a young adult with breast cancer on neoadjuvant TCHP: High

High risk based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving TCHP was 6%-17% (range: 1%-32%) based on moderate-quality evidence.^{1, 3, 4, 7, 8} Estimated pooled risk of FN in patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence.

Febrile neutropenia risk in an older adult with breast cancer on adjuvant TC: Intermediate

Intermediate based on low-quality evidence. Estimated pooled risk of FN for all patients receiving TC was 17%-23% (range: 1%-68%) based on low-quality evidence.^{9, 10} Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 20% based on low-quality evidence – downgrade evidence quality for applicability (and inconsistent definitions of FN), imprecision and unexplained heterogeneity.

Cervical cancer

Febrile neutropenia risk in patients with advanced cervical cancer treated with cisplatin and paclitaxel +/- bevacizumab: Low

Low risk* based on moderate-quality evidence. Estimated pooled risk of FN for all patients cisplatin and paclitaxel +/- bevacizumab is 10% (range: < 5%-16%) based on moderate-quality evidence. The estimation of FN is lower (< 10%) when not taking into account the Japanese trials (where neutropenia risk is generally higher based on Japanese ethnicity). Both GOG 240 and GOG 169 reported a low incidence of FN while GOG 204 reported an intermediate risk. *AIM Guidelines currently treat cisplatin and paclitaxel +/- bevacizumab for treatment of advanced cervical cancer a low-risk regimen.

Febrile neutropenia risk in patients with advanced cervical cancer treated with topotecan: Low

Low risk* based on low-quality evidence. Estimated pooled risk of FN for all patients topotecan is 5% (range: 0%-12%) based on low-quality evidence. The estimation of FN is difficult based on lack of large studies, multiple dosing regimens, and atypical reporting of febrile complications. *AIM Guidelines currently consider topotecan for treatment of advanced cervical cancer a low-risk regimen.

Gastroesophageal cancer

Febrile neutropenia risk in patients with gastroesophageal cancer treated with cisplatin and irinotecan: Low

Low risk based on low-quality evidence. Estimated pooled risk of FN for all patients receiving cisplatin and irinotecan is 9% (range: 0%-13%) based on low-quality evidence. The estimation of FN is problematic as multiple dosing schedules are used. Currently NCCN recommends irinotecan 65 mg/m² D 1, 8 and cisplatin 25-30 mg/m² D 1, 8 every 3 weeks. In total, patients studied under this specific regimen number approximately 120, and a definitive risk of FN is poorly estimated. Other schedules may have lower risk of FN. *AIM Guidelines currently treat cisplatin and irinotecan for treatment of gastroesophageal cancer as a low-risk regimen.

Head and neck cancer

Febrile neutropenia risk in patients with recurrent/metastatic head and neck cancer treated with EGFR-inhibitor (cetuximab or panitumumab) plus platinum-based chemotherapy: Low

Low risk based on high-quality evidence. Estimated pooled risk of FN for all patients receiving cetuximab plus platinum-based chemotherapy is < 10% based on high-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Febrile neutropenia risk in patients with recurrent/metastatic head and neck cancer treated with pembrolizumab plus platinum-based chemotherapy: Low

Low risk based on high-quality evidence. Estimated pooled risk of FN for all patients receiving pembrolizumab plus platinum-based chemotherapy is < 10% based on high-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Non-small cell lung cancer

Febrile neutropenia risk in patients with metastatic squamous non-small cell lung cancer treated with carboplatin, paclitaxel/nab-paclitaxel, and pembrolizumab: Low

Low risk based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving carboplatin, paclitaxel/nab-paclitaxel, and pembrolizumab is < 10% (range: < 10%-18%) based on moderate-quality evidence.^{11, 12} Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for imprecision.

Febrile neutropenia risk in patients with metastatic nonsquamous non-small cell lung cancer treated with carboplatin, paclitaxel, and atezolizumab +/- bevacizumab: Low

Low risk based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving carboplatin, paclitaxel, and atezolizumab +/- bevacizumab is 5%-9% (range: 5%-18%) based on intermediate-quality

evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for imprecision.

Febrile neutropenia risk in patients with metastatic non-small cell lung cancer treated with carboplatin/cisplatin, pemetrexed, and pembrolizumab: Low

Low risk based on high-quality evidence. Estimated pooled risk of FN for all patients receiving carboplatin/cisplatin, pemetrexed, and pembrolizumab is 2% (range: 2%- 5.7%) based on intermediate-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Febrile neutropenia risk in patients with non-small cell lung cancer treated with cisplatin and vinorelbine: Intermediate

Intermediate risk* based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving cisplatin and vinorelbine is 13% (range: 5%-26%) based on intermediate-quality evidence. The estimation of FN is highly dependent on dose and schedule. Currently NCCN recommends three different regimens that differ both in dosing and schedule. *AIM Guidelines currently consider cisplatin and vinorelbine for treatment of NSCLC as a low-risk regimen.

Febrile neutropenia risk in patients with advanced non-small cell lung cancer treated with cisplatin and docetaxel: Low

Low risk* based on intermediate-to-high quality evidence. Estimated pooled risk of FN for all patients receiving cisplatin and docetaxel for treatment advanced non-small cell lung is 8% (range: 0%-16%) based on intermediate-to-high quality evidence. Although there is a wide range, the low and high outliers are from Asian studies. The majority of the remaining studies report incidence of FN as low FN risk. *AIM Guidelines currently consider cisplatin and docetaxel for treatment advanced non-small cell lung cancer a low-risk regimen.

Febrile neutropenia risk in patients with advanced non-small cell lung cancer treated with docetaxel: Low

Low risk* based on high-quality evidence. Estimated pooled risk of FN for all patients receiving docetaxel is 7% (range: 0%-13%) based on high-quality evidence. The estimated pooled risk of FN for patients not receiving primary prophylaxis is less than 10% based on high-quality evidence. The risk of FN may be higher in patients receiving ramucirumab and docetaxel, docetaxel dosed at 100 mg/m², or an Asian population. Consideration should be given to ramucirumab and docetaxel as an intermediate-risk regimen based on the data from the original REVEL trial and subsequent updates. *AIM Guidelines currently treat docetaxel for treatment of advanced NSCLC as a low-risk regimen.

Small cell lung cancer

Febrile neutropenia risk in patients with extensive stage small cell lung cancer treated with carboplatin, etoposide, and atezolizumab: Low

Low risk based on high-quality evidence. Estimated pooled risk of FN for all patients receiving carboplatin, etoposide, and atezolizumab is 3% based on intermediate-quality evidence.¹⁵ Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Lymphoma

Febrile neutropenia risk in patients with lymphoma treated with gemcitabine, dexamethasone, and cisplatin +/- rituximab: Intermediate

Intermediate risk* based on low-quality evidence. Estimated pooled risk of FN for all patients receiving gemcitabine, dexamethasone, and cisplatin +/- rituximab is 15% (range: 3%-36%) based on low-quality evidence. The estimation of FN is challenging as most trials did not clearly detail myeloid growth factor use, relatively small study population with the exception of LY.12, and large number of studies not representative of an American population. *AIM Guidelines currently treat gemcitabine, dexamethasone, and cisplatin +/- rituximab for treatment of lymphoma as a low-risk regimen.

Ovarian cancer

Febrile neutropenia risk in patients with advanced ovarian cancer treated with carboplatin and docetaxel: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving carboplatin and docetaxel is 11% (range: 0%-23%).¹⁶ Estimated pooled risk of FN in patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence, downgrade for imprecision.

Febrile neutropenia risk in patients with advanced ovarian cancer treated with carboplatin and paclitaxel: Low

Low risk based on high-quality evidence. Estimated pooled risk of FN for all patients receiving carboplatin and paclitaxel is 2%-7% (range: 2%-7%) based on high-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence.

Febrile neutropenia risk in patients with advanced ovarian cancer treated with topotecan: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving topotecan is 3%-4% (range: 1%-18%) based on intermediate-quality evidence.²³⁻²⁷ Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for applicability (dosing regimen).

Pancreatic cancer

Febrile neutropenia risk in healthy middle aged adult with pancreatic cancer treated with FOLFIRINOX: Low

Low risk based on high-quality evidence. Estimated pooled risk of FN for all patients receiving FOLFIRINOX was 4%-10% (range: 2%-17%) based on moderate-quality evidence.²⁸⁻³² Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for imprecision and heterogeneity.

Prostate cancer

Febrile neutropenia risk in patients with castrate-resistant prostate cancer treated with cabazitaxel: Intermediate

Intermediate risk* based on moderate-to-high quality evidence (depending on dose). Estimated pooled risk of FN for all patients receiving cabazitaxel dosed at 25 mg/m² is < 10% (range: 8%-12%) based on moderate-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence; however, the risk of neutropenic complication should prompt categorization as intermediate risk. Estimated pooled risk of FN for all patients receiving cabazitaxel dosed at 20 mg/m² is < 10% based on high-quality evidence. *AIM Guidelines currently treat cabazitaxel for the treatment of castrate recurrent prostate cancer as a low-risk regimen.

Soft tissue sarcoma

Febrile neutropenia risk in patients with advanced soft tissue sarcoma treated with doxorubicin: Intermediate

Intermediate risk* based on high-quality evidence. Estimated pooled risk of FN for patients not receiving primary prophylaxis treated with single agent doxorubicin is 13% (9%-20%) based on high-quality evidence. *AIM Guidelines currently treat doxorubicin for the treatment of advanced soft tissue sarcoma as an intermediate-risk regimen.

Germ cell tumors

Febrile neutropenia risk in patients with advanced germ cell tumors treated with bleomycin, etoposide, and cisplatin: Intermediate

Intermediate risk* based on moderate-to-high quality evidence. Estimated pooled risk of FN for all patients receiving bleomycin, etoposide, and cisplatin is 15% (range: 5%-20%) based on moderate-quality evidence. The estimated pooled risk of FN for patients not receiving primary prophylaxis is 10%-20% based on moderate-quality

evidence. *AIM Guidelines currently treat bleomycin, etoposide, and cisplatin for treatment of advanced germ cell tumors as an intermediate-risk regimen.

Febrile neutropenia risk in patients with advanced germ cell tumors treated with etoposide and cisplatin: Intermediate

Intermediate risk* based on moderate-quality evidence. Estimated pooled risk of FN for all patients receiving etoposide and cisplatin is 15% (range: 3%-23%) based on moderate-quality evidence. The estimated pooled risk of FN for patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence. *AIM Guidelines currently treat etoposide and cisplatin for treatment of advanced germ cell tumors as an intermediate-risk regimen.

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Codes

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Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT

96377 Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]

HCPCS

J1442 Injection, filgrastim (G-CSF), excludes biosimilars, 1 microgram [Neupogen]

J1447 Injection, tbo-filgrastim, 1 microgram [Granix]

J2505 Injection, pegfilgrastim, 6 mg [Neulasta]

J2820 Injection, sargramostim (GM-CSF), 50 mcg [Leukine, Prokine]

Q5101 Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram

Q5108 Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg

Q5110 Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram

Q5111 Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg

Q5120 Injection, pegfilgrastim-bmez, biosimilar, (ziextenzo), 0.5 mg

Q5122 Injection, pegfilgrastim-apgf, biosimilar, (nyvepria), 0.5 mg

ICD-10 Diagnosis

All diagnoses

History

Status	Review Date	Effective Date	Action
Created	02/03/2020	07/01/2021	Independent Multispecialty Physician Panel review. Original effective date.