



**Ontario Health**  
Cancer Care Ontario



# Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients

## Clinical Practice Guideline

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## Objective

Provincial guidance and standardization of outpatient febrile neutropenia (FN) management has been identified as a quality and safety gap in Ontario. Optimal prevention and safe management of FN in the outpatient setting, when clinically appropriate, can help to keep vulnerable patients from experiencing severe complications requiring hospitalization. The objective of this guideline is to provide clinicians with updated recommendations for prevention of FN and new guidelines for the outpatient management of FN in adult cancer patients receiving systemic treatment in Ontario.

## Background

Febrile neutropenia (FN) is a common complication with myelosuppressive systemic treatment. FN is defined as a fever that occurs during a period of significant neutropenia. Fever is defined as a single oral temperature of  $\geq 38.3$  °C or 38.0 °C or higher for at least one hour.<sup>1-4</sup> Neutropenia is defined as an absolute neutrophil count (ANC)  $\leq 1 \times 10^9/L$ , especially if counts are not likely to recover within 48 hours.<sup>1-3,5-7</sup> Moderate neutropenia is defined as an ANC  $0.5 \times 10^9/L - 1 \times 10^9/L$ , whereas severe neutropenia is defined as an ANC  $\leq 0.5 \times 10^9/L$ .<sup>6</sup> Clinical guidelines support the initiation of outpatient management for FN when ANC levels are expected to fall below  $\leq 0.5 \times 10^9/L$ .<sup>3,7</sup> To facilitate timely patient care and clinical decision-making in emergency practice settings, an ANC  $\leq 1 \times 10^9/L$  is recommended as the cut-off for outpatient FN management in this clinical practice guideline.

There are many clinical implications of FN including, but not limited to: decreased total treatment dose, delayed treatment schedule, broad-spectrum antimicrobial exposure, hospitalization/prolonged hospitalization and, rarely, death.<sup>8,9</sup>

The likelihood of developing FN is stratified according to high (>20%), moderate (10-20%) and low (<10%) risk. Each patient's overall risk for developing FN is determined based on patient-specific factors, systemic treatment (ST) regimen administered, and cancer-related characteristics. Treatment with granulocyte colony-stimulating factor (G-CSF) is an important supportive measure to help prevent FN in patients who are at an overall high risk.<sup>1,3,5,7,9</sup>

In 2016, Cancer Care Ontario (CCO) guidelines on the use of G-CSF to help prevent FN were published. Since then, biosimilar G-CSF products have become available in Ontario and are considered to be clinically comparable to the brand name (reference) products. The introduction of biosimilars has resulted in improved affordability and cost-effectiveness of G-CSF products.<sup>10-14</sup> Updates to the 2016 prevention of FN recommendations focus on whether the clinical guidance around G-CSF should be revised based on the increased availability of G-CSF products and any new literature published since 2016. Other FN prevention measures were also evaluated as part of this work (e.g. the use of antibiotics).

In addition to FN prevention, outpatient management recommendations have been added to this guideline. Optimal outpatient management of FN for eligible patients can help to optimize the use of health system resources and provide patients with a more comfortable treatment-setting.

## Methods

This clinical practice guideline was developed by a multidisciplinary Working Group (WG) consisting of physicians (oncologists, hematologists, and a general practitioner in oncology), pharmacists, nurses, and administrators who are knowledgeable in the areas of prevention and management of FN in adult cancer patients. The WG reviewed current relevant guidelines and available literature on primary and secondary FN prophylaxis and FN management, with an emphasis on the optimal use of G-CSF and appropriate FN management in the outpatient setting.<sup>1–3,5–7,15–17</sup> The 2016 CCO recommendations on the use of G-CSF were used as the foundation for the prevention of FN recommendations in this guideline. Existing outpatient FN management guidelines, including the European Society for Medical Oncology (ESMO) guideline from 2016, American Society of Clinical Oncology (ASCO) and Infectious Diseases Society of America (IDSA) guideline from 2018 and the National Comprehensive Cancer Network (NCCN) guideline from 2021, were reviewed in detail. New literature published since the publication of these two guidelines were the focus of the literature search. Key clinical questions were identified by the WG and literature related to these specific questions were additional area of focus. All content was approached with an Ontario-specific lens. An iterative consensus-building process was used to develop a comprehensive practical guideline. Final guideline content was validated by external experts.

### Literature Search Strategy

A limited literature search was conducted using the following bibliographic databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 11, 2020> and Embase <1996 to 2020 Week 32>, with the date limits of March 1, 2016-December 31, 2021. A subsequent search was also conducted using Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 17, 2020>, and Ovid Embase <1996 to 2020 Week 46>. No methodological filters were applied to limit retrieval by publication type. Duplicates were manually removed in EndNote, version 8.

Grey literature was located through a targeted Internet search, as well as utilizing previously identified Canadian and international organizations and sources. The grey literature search was run on September 18, 2020 and was limited to English-language documents published between March 1, 2016, and December 31, 2021. Please refer to the appendix for detailed search strategies.

After preliminary review of the search results, additional searches were performed using PubMed, GoogleScholar, articles referenced within other studies, CCO (Ontario Health) Drug Formulary documents, manufacturer published product monographs and organization-specific febrile neutropenia management algorithms. Publications that were new since the CCO 2016 G-CSF guideline and the 2018 ASCO Febrile Neutropenia guideline were the primary focus of the searches.

# Prevention of Febrile Neutropenia in Adult Cancer Patients

The severity of neutropenia (which directly influences the incidence of FN) is related to the intensity of myelosuppressive systemic treatment. Regimens are categorized as producing a high risk (>20%), a moderate risk (10%–20%) or a low risk (<10%) of FN. <sup>1–3,5–7,15–17</sup>

## High Risk (> 20%)

Clinical practice guidelines consistently recommend routine prophylactic use of G-CSF for patients that have an overall high risk for FN. <sup>1–3,5–7,15–17</sup> High risk is defined as a > 20% risk of FN, based on the systemic treatment regimen, or an overall > 20% risk of FN, based on a moderate risk treatment regimen together with patient risk factors. <sup>1–3,5–7,15–17</sup> Refer to Appendix 1 for a list of patient risk factors with level of evidence. Refer to appendix 2 for examples of treatment regimens that are considered to have a moderate risk for FN.

### Clinical Question 1:

**What is the optimal G-CSF primary prophylaxis in adult patients at high risk (> 20%) of FN receiving myelosuppressive systemic treatment with curative intent?**

### Recommendation 1:

For regimens that are  $\geq$  every 14 days\*:

Pegfilgrastim\*\* 6 mg Subcut as a single dose given 24 to 72 hours after all cycles  
OR  
Filgrastim\*\* 300 mcg (if < 90 kg) or 480 mcg (if  $\geq$  90 kg or < 90 kg if poor response to 300 mcg) Subcut daily, starting 24–72 hours post treatment for at least 7 days\*\*\*, after all cycles

\*Should be at least 12 days from pegfilgrastim to next dose of myelosuppressive systemic treatment; however, there may be exceptions depending on the treatment regimen and clinical trial protocol

\*\*Reference product or biosimilar

\*\*\*May consider 5 days for early breast cancer patients<sup>18</sup>

For regimens that are < every 14 days:

Filgrastim\* 300 mcg (if < 90 kg) or 480 mcg (if  $\geq$  90 kg or < 90 kg if poor response to 300 mcg) Subcut daily, starting at least 24 hours post treatment until ANC recovery (or anticipated ANC recovery)\*\*, after all cycles

\* Reference product or biosimilar

\*\*Filgrastim to stop at least 24hrs prior to next dose of myelosuppressive systemic treatment

## SUMMARY OF EVIDENCE & DISCUSSION:

Existing guidelines recommend primary prophylaxis with G-CSF in the high risk setting for all adult patients treated with curative intent.<sup>1-3,5-7,15-17</sup> There is some variability in the dose, timing, and duration of G-CSF administration. In addition, guidance regarding the use of short- vs long-acting G-CSF (filgrastim or pegfilgrastim) is unclear.<sup>1,3,5,9</sup>

### **Clinical Question 1.1: Is there a preference between pegfilgrastim or filgrastim?**

#### Recommendation 1.1:

Both a single dose of pegfilgrastim or at least 7 days of filgrastim are appropriate primary prophylaxis G-CSF options for patients that are at high risk for FN and are receiving systemic treatment regimens that are administered every 14 days or greater (see Clinical Question 1.2). Pegfilgrastim may be preferred in certain scenarios, such as when adherence to a 7- day treatment is unlikely or for patient convenience. Filgrastim may be preferred for patients who experience toxicity (such as severe musculoskeletal pain) with pegfilgrastim or when a lower-cost alternative is needed.

## SUMMARY OF EVIDENCE & DISCUSSION:

Aapro *et al* developed consensus guidelines to better define the appropriate use of pegfilgrastim for the prevention of febrile neutropenia.<sup>19</sup> They concluded that:

- pegfilgrastim and 11 days of filgrastim have similar efficacy and safety
- pegfilgrastim is preferred to < 11 days of filgrastim (and may be preferred to ≥ 11 days of filgrastim based on adherence and convenience)
- pegfilgrastim is not appropriate in weekly chemotherapy
- pegfilgrastim is recommended for regimens that are every 14 days or greater

A systematic review and meta-analysis of 12 randomized controlled trials (RCTs) and 24 non-RCTS demonstrated that there is little difference in efficacy between short and long-acting G-CSF if dosed according to guidelines (filgrastim ≥ 7 days).<sup>20</sup> There was some evidence for improved efficacy with long-acting G-CSF in non-RCTS with respect to the incidence of FN (overall relative risk (ORR) = 0.67, p = 0.023), hospitalizations (ORR = 0.68, p = 0.05), and chemotherapy dose delays (ORR = 0.68, p = 0.020); however, these results may be related to underdosing of filgrastim.<sup>4,20</sup>

A systematic review and Bayesian meta-analysis of 70 RCTs from 1991 to 2018 included pairwise and network meta-analysis. Both found that pegfilgrastim significantly reduced the incidence of FN, when compared with filgrastim (OR [95% CI]: 1.63 [1.07, 2.46]).<sup>21</sup> They also concluded that biosimilar filgrastim products all performed similarly. The duration of filgrastim administration was not defined.<sup>21</sup>

A recent multicentre, randomized trial (n=466) compared 5-, 7-, and 10-day schedules of filgrastim administration for the primary prophylaxis of chemotherapy-induced FN in patients with early-stage breast cancer.<sup>18</sup> The primary analysis showed that the difference in risk of either FN or treatment-related hospitalization per cycle was -1.52% (95% CI: -3.22% - 0.19%), indicating that 5 days of filgrastim was non-inferior to 7/10 days.<sup>18</sup> Based on the recognized



toxicity and cost of filgrastim, they recommend making the 5-day duration the standard of care for breast cancer patients receiving commonly used adjuvant chemotherapy regimens.<sup>18</sup>

A recent systematic review and meta-analysis of pegfilgrastim vs filgrastim in breast cancer patients concluded that (with the premise of sufficient G-CSF dose according to guidelines) there was no significant difference in: incidence/duration of  $\geq$  grade 3 neutropenia, duration of grade 4 neutropenia, incidence of FN, time to ANC recovery, grade 4 adverse events, and skeletal and/or muscle pain.<sup>22</sup>

There are two non-inferiority RCTs of pegfilgrastim vs filgrastim in lymphoma and breast cancer patients receiving high risk regimens.<sup>23,24</sup> Both demonstrated non-inferiority and similar safety results for pegfilgrastim and filgrastim. The breast cancer study reported similar duration of severe neutropenia (mean duration of grade 4 neutropenia in cycle 1 was 2.08 +/- 0.85 days for the filgrastim group and 2.28 +/- 1.14 days for pegfilgrastim; the difference between groups was 0.2 +/- 1.10 days (95 % confidence interval (CI) = 0.26, 0.66)) and no statistically significant differences in nadir ANC or time to ANC recovery.<sup>24</sup>

Additionally, a recent narrative review concluded that pegfilgrastim has been shown to be superior to filgrastim at reducing chemotherapy-related neutropenia and at achieving target dose intensity, primarily because filgrastim is often under-dosed in clinical practice.<sup>4</sup> They also state that biosimilar pegfilgrastim offers an opportunity to rethink neutropenia management and the value of G-CSF, based on the significant potential for both clinical and economic benefits.<sup>4</sup>

### **Clinical Question 1.2: Can pegfilgrastim be administered for dose dense regimens?**

#### **Recommendation 1.2:**

Pegfilgrastim can be given with regimens that are administered every 14 days or more. There must be an interval of at least 12 days from the time of pegfilgrastim to the next dose of myelosuppressive systemic treatment.

#### **SUMMARY OF EVIDENCE & DISCUSSION:**

The CCO 2016 G-CSF recommendations state that pegfilgrastim is not to be given at less than 14- day intervals, which was based on the information available at that time. Since then, use of pegfilgrastim with dose dense regimens has been evaluated and appears to be safe and efficacious.

A prospective study of 240 breast cancer patients evaluated the use of pegfilgrastim primary prophylaxis on day 2 of each cycle of dose dense (every 14 day) chemotherapy with epirubicin and cyclophosphamide.<sup>25</sup> 12 patients (5.0%, 95% CI 2.2-7.8%) developed a total of 13 episodes of FN. Of the 221 patients that completed 4 chemo cycles with pegfilgrastim support, 209 patients (94.6%, 95% CI 91.6-97.6%) had a 100% relative dose intensity (RDI).<sup>25</sup> A RDI  $\geq$  85% was achieved in 217 of 221 patients (98.2%, 95% CI 96.5-99.9%).<sup>25</sup>



In the consensus guideline from Aapro *et al*, it was noted that pegfilgrastim has been used effectively in dose dense (every 14 day) R-CHOP chemotherapy.<sup>19</sup> They recommend that pegfilgrastim administration occur 24 hours after the last chemotherapy dose and 14 days before the next dose.<sup>19</sup>

The 2020 NCCN guidelines recommend G-CSF for dose-dense regimens and state that pegfilgrastim may be given after each treatment if chemotherapy is administered on days 1 and 15, and that there are phase II data to support the use in this setting.<sup>3</sup> The guideline also states that there should be at least 12 days between the dose of pegfilgrastim and the next chemotherapy dose, which is supported by a handful of small studies, predominantly in the setting of gastrointestinal cancer treatment.<sup>3,26–28</sup>

A recent systemic literature review compared pegfilgrastim to other G-CSFs or no prophylactic G-CSF in patients with non-myeloid malignancies receiving biweekly chemotherapy who were at moderate or high risk of FN.<sup>29</sup> Most studies showed that prophylactic pegfilgrastim reduced the incidence of FN in patients receiving biweekly regimens across a wide variety of non-myeloid malignancies.<sup>29</sup> Pegfilgrastim, filgrastim, and placebo had comparable safety profiles.<sup>29</sup> The data supports current guidelines on the use of prophylactic pegfilgrastim to prevent FN in moderate- or high-risk patients receiving biweekly chemotherapy.<sup>29</sup>

### **Clinical Question 1.3: Can G-CSF be discontinued after 1-2 cycles?**

#### **Recommendation 1.3:**

When G-CSF is being used as primary prophylaxis in the high-risk setting, it should be administered after every cycle of myelosuppressive systemic treatment.

#### **SUMMARY OF EVIDENCE & DISCUSSION:**

Literature that has been published since the 2016 CCO guideline continues to support the use of G-CSF for every cycle of myelosuppressive systemic treatment in the high FN risk setting.

Real world evaluation of non-metastatic cancer patients at high risk of FN who received primary prophylaxis in the 1st cycle and then stopped was compared to a matched cohort of patients who continued for all cycles.<sup>30,31</sup> Of 47254 “younger” patients with a mean age of approximately 54 years, 9% did not continue and the risk of FN in cycle 2 was significantly higher (OR = 1.7, 95% CI = 1.2-2.3,  $p < 0.001$ ) than in those who did continue.<sup>30</sup> Of 77616 “elderly” patients with a mean age of approximately 73 years, 5.3% did not continue and the risk of FN in cycle 2 was significantly higher (OR = 1.9, 95% CI = 1.6-2.3,  $p < 0.001$ ) than those who did.<sup>31</sup>

A phase III study of breast cancer patients at high risk of FN (n=167) randomized patients to G-CSF prophylaxis for all 6 cycles or G-CSF for the first 2 cycles.<sup>32</sup> Nadir blood cell counts were studied in the 47 patients who remained after patients who developed FN, received secondary G-CSF prophylaxis or chemotherapy dose reductions were excluded.<sup>32</sup> There was no protective effect of prior G-CSF or prior chemotherapy on nadir blood counts in subsequent cycles.<sup>32</sup> The median nadir white blood cell count (WBC) and ANC slowly decreased while continuing on G-CSF prophylaxis, and the median ANC nadir remained steadily low in cycles 3-6 in those who did

not continue with G-CSF.<sup>32</sup> Discontinuation of G-CSF prophylaxis after the first 2 chemotherapy cycles resulted in a rebound high FN incidence in the next chemotherapy cycles.<sup>32</sup>

**Clinical Question 1.4: Can G-CSF be administered < 24 hours after myelosuppressive systemic treatment administration?**

**Recommendation 1.4:**

When G-CSF is being used as prophylaxis, it should be administered at least 24 hours after the administration of myelosuppressive systemic treatment.

**SUMMARY OF EVIDENCE & DISCUSSION:**

Literature that has been published since the 2016 CCO guideline continues to support the administration of G-CSF at least 24 hours after the administration of myelosuppressive systemic treatment.

Same day vs 24-72 hr post chemotherapy dosing was evaluated in a retrospective review of 65001 Medicare patients (> 65 yrs.) who received primary prophylaxis with pegfilgrastim in 261184 cycles.<sup>33</sup> They identified that 5% of cycles had pegfilgrastim administered on the same day of chemotherapy administration.<sup>33</sup> FN incidence was significantly higher with 11.4% FN in cycle 1 for Day 0 versus 8.4% for Days 1-3 (adjusted OR = 1.4, 95% CI = 1.3-1.6 (p < .001)).<sup>33</sup> FN for all cycles was 7.7% for Day 0 vs 6.0% for Days 1-3 (adjusted OR = 1.3, 95% 1.2-1.4(p < .001)).<sup>33</sup>

A systematic review of 11 publications evaluated same day vs next day dosing of G-CSF.<sup>34</sup> Of the 11 publications included in the analysis, 6 reported higher rates and longer duration of neutropenia/FN for same day administration (2 RCTs, 4 retrospective studies).<sup>34</sup> Five of the 11 reported lower or comparable rates and duration of neutropenia/FN; however, these were smaller retrospective studies.<sup>34</sup> The authors concluded that administration of pegfilgrastim at least 24 h after chemotherapy resulted in improved outcomes for patients across a variety of tumor types.<sup>34</sup> The NCCN 2020 guidelines also support the administration of G-CSF at least one day after myelosuppressive systemic therapy.<sup>3</sup>

**Clinical Question 1.5: For regimens containing 5-FU continuous infusion (such as mFOLFOX6, FOLFIRI, FOLFIRINOX), can G-CSF be administered at the same time the infusion pump is disconnected?**

**Recommendation 1.5:**

There is insufficient information to make a recommendation at this time. Based on the limited data available, administration of pegfilgrastim at the time of 5-FU pump disconnect does not appear to worsen neutropenia.

**SUMMARY OF EVIDENCE & DISCUSSION:**

A retrospective analysis of patients receiving FOLFOX or FOLFIRI compared patients who had pegfilgrastim administered at the time of 5-FU disconnect (n=105) with a historical control group of patients who had next day pegfilgrastim or placebo.<sup>26</sup> The FN incidence was 3.7% (95% CI, 1.1–9.4%) in the same day group vs. 3.2% (95% CI, 1.0–8.3%) and 9.4% (CI, 5.1–16.4%) in the control cohort (next day pegfilgrastim and placebo, respectively).<sup>26</sup> A total of 11.9% grade 3/4

neutropenia (95% CI, 7.0–19.5%) was reported in the same day group compared to 22.2% in the next day (95% CI, 15.5–30.1%) and 87.9% in the placebo group (95% CI, 81.0–92.9%).<sup>26</sup> There was a 10.1% incidence of dose reductions due to neutropenia or FN in the same day group (95% CI, 5.6–17.3%) vs. 4.1% (95% CI 1.5–9.4%) and 22.1% (95% CI 15.5–30.4%) in the control group (next day peg and placebo, respectively).<sup>26</sup> Data limitations include the study's retrospective design, and the fact that it included both adjuvant and metastatic patients, and many patients were receiving G-CSF as secondary prophylaxis.<sup>26</sup> The authors concluded that study results demonstrate that same-day pegfilgrastim administration may be a safe and effective alternative to 24-h post-chemotherapy administration in patients with esophageal, gastric, appendiceal, or colorectal cancer undergoing treatment with FOLFOX or FOLFIRI and that the effects may be consistent whether using pegfilgrastim as primary or secondary prophylaxis.<sup>26</sup> They also indicated that the results warrant further investigation.<sup>26</sup>

A small phase 2 single-arm trial (n=23) evaluated patients with squamous cell carcinoma of the esophagus receiving neoadjuvant/adjuvant chemotherapy with docetaxel, cisplatin, and 5FU continuous infusion (DCF) and pegfilgrastim administration on day 3.<sup>27</sup> The incidence of grade 4 neutropenia in cycle 1 was 8.7% (2/23, 95% CI: 1.1–28.0%).<sup>27</sup> There were no incidences of FN or serious ADRs associated with pegfilgrastim.<sup>27</sup> The authors concluded that this prospective study demonstrated an efficacious dosing schedule of pegfilgrastim for preventing hematological toxicity during DCF therapy and that the results might be generalized to other similar regimens where continuous infusions of 5-FU are used.<sup>27</sup>

A retrospective cohort study of colorectal and pancreatic patients with chemotherapy regimens containing 5-FU continuous infusion (mFOLFIRINOX, FOLFOX, and FOLFOX + Beva) evaluated the safety of administering pegfilgrastim on the last day of infusion. Of the 300 patients included, 39% had prior neutropenic events or FN and 61% were using pegfilgrastim as primary prophylaxis.<sup>28</sup> The most common cancers were colorectal (25%) and pancreatic (60%), with 77% of patients having late-stage disease.<sup>28</sup> The risk of a patient developing neutropenia was 1.0% (95% CI 0.2–2.9%) and 0.7% (95% CI 1–2.4%) for Grades 3 and 4, respectively.<sup>28</sup> The risk for FN was 0.7% (95% CI 0.1–2.4%) and the risk for treatment delay and dose reduction was 1.3% (95% CI 0.4–3.4%) and 1.0% (95% CI 0.2–2.9%), respectively.<sup>28</sup> Despite pegfilgrastim administration on the same day as 5-FU, grade 3 and 4 neutropenia, as well as FN rates were very low.<sup>28</sup>

## Clinical Question 2:

**What is the optimal use of antibiotic prophylaxis in adult patients at high risk (>20%) of FN receiving myelosuppressive systemic treatment?**

### Recommendation 2:

An antibiotic **should** be prescribed when G-CSF use is not possible. Consider prophylaxis for patients who are at moderate or high risk for FN and are expected to have a duration of neutropenia ( $ANC \leq 1 \times 10^9/L$ ) for more than 7 days (i.e. most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens).

Fluoroquinolones (FQ) are preferred in most situations.\*<sup>1,2,9,15</sup>

**Levofloxacin 500 mg PO daily**

**OR**

**Ciprofloxacin 500 mg PO q12 hours**

\*Antibiotic prophylaxis should continue for duration of anticipated neutropenia and depends on disease, regimen, and patient factors. Patients who are intolerant to FQ may consider TMP/SMX or an oral 3<sup>rd</sup> generation cephalosporin.<sup>2</sup>

### ***Pneumocystis jirovecii* pneumonia (PJP) prophylaxis:**

- **Sulfamethoxazole-trimethoprim (SMX-TMP)** is preferred for PJP prophylaxis and **should** be given for patients being treated with **fludarabine-based** and **alemtuzumab-based** regimens, as well as **acute lymphoblastic leukemia (ALL)** patients receiving active systemic treatment\*.
- **Consider** PJP prophylaxis for patients being treated with **PI3K inhibitors (e.g. idelalsilib)**, **prolonged courses of corticosteroids** ( $\geq 20\text{mg}$  prednisone daily\*\* for  $\geq 4$  weeks), and **temozolomide with concurrent radiotherapy**.\*\*\*<sup>2,35-39</sup>

**One double-strength SMX-TMP (160 mg/800 mg) tablet PO daily three times per week**

**OR**

**One single-strength SMX-TMP (80 mg/400 mg) tablet PO daily (for normal renal function)**

\*SMX-TMP desensitization or atovaquone, dapsone, or pentamidine (aerosolized or IV) can be considered for patients who are SMX-TMP intolerant.<sup>2</sup>

\*\* or equivalent dose of corticosteroid (e.g.  $\geq 3\text{mg}$  dexamethasone daily for  $\geq 4$  weeks)

\*\*\*Prophylaxis should continue for duration of anticipated neutropenia and depends on disease, regimen, and patient factors.

### SUMMARY OF EVIDENCE & DISCUSSION:

Current guidelines recommend fluoroquinolone prophylaxis for patients who are at moderate or high risk for FN and are expected to have a duration of neutropenia ( $ANC \leq 1 \times 10^9/L$ ) for more than 7 days (i.e. most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens).<sup>2,15</sup> There are no chemotherapy regimens for solid tumours that are

routinely expected to produce profound neutropenia for  $\geq 7$  days; therefore, routine fluoroquinolone prophylaxis is not recommended for patients with solid tumours undergoing conventional chemotherapy with or without biologics such as trastuzumab, bevacizumab, or cetuximab.<sup>40</sup> However, it may be recommended for some patients with solid tumours or lymphoma who are expected to experience profound neutropenia for at least 7 days and for whom G-CSF is not being prescribed.<sup>15</sup>

A literature review of RCTs and observational studies demonstrated that fluoroquinolone prophylaxis did not have a significant effect on mortality (pooled OR 1.01, 95% CI = 0.73-1.41), but was associated with a reduced rate of bloodstream infections (pooled OR 0.57, 95% CI = 0.43-0.74) and episodes of fever during neutropenia (pooled OR 0.32, 95% CI = 0.20-0.50).<sup>41</sup> There was no observed effect of the background rate of fluoroquinolone resistance on its efficacy as prophylaxis; however, a few studies showed that fluoroquinolone prophylaxis led to increased colonisation or infection with multi-drug resistant strains.<sup>41</sup> Therefore, the benefits for blood stream infections should be weighed against the risks in terms of toxicity and resistance when considering usage of routine fluoroquinolone prophylaxis.<sup>41</sup>

Guidelines consistently recommend the use of fluoroquinolones as the preferred antibiotics for FN prophylaxis.<sup>9</sup> No new primary literature was found to suggest that changes to this recommendation are needed. A few studies evaluated the use of moxifloxacin as a fluoroquinolone option in this setting. A retrospective chart review of acute myeloid leukemia patients receiving induction chemotherapy (n=170) looked at moxifloxacin vs. levofloxacin or ciprofloxacin.<sup>42</sup> They found that there were similar rates of FN (76% vs. 81% for moxifloxacin vs. levofloxacin or ciprofloxacin, respectively; p=0.42).<sup>42</sup> Hospital readmission for an infectious issue within 30 days of hospital discharge (9 vs. 5%, p = 0.39) was also similar between groups as was the incidence of *Clostridium difficile* (9 vs. 9%, p = 0.96).<sup>42</sup> Infection with *C. difficile* was not shown to correlate more with a specific agent, but it does correlate with treatment duration.<sup>42</sup>

A retrospective quasi-experimental analysis (n=85) of patients with acute leukemia undergoing induction or consolidation chemotherapy found that there were similar FN rates with moxifloxacin vs levofloxacin (55% vs. 67%, respectively; p=0.190).<sup>43</sup> They determined that duration of neutropenia was a greater predictor of FN development rather than choice of fluoroquinolone.<sup>43</sup> These small retrospective studies suggest that moxifloxacin may be an option for FN prophylaxis; however, there is more robust data for the use of ciprofloxacin and levofloxacin. There is also evidence that moxifloxacin carries a greater risk of *C. difficile* infection compared to ciprofloxacin and levofloxacin.<sup>44</sup> There was consensus to keep the fluoroquinolone recommendation the same as what was outlined in the 2016 CCO recommendations.

In the 2016 CCO report, PJP prophylaxis was recommended for patients receiving fludarabine-based regimens. Since then, other guidelines (i.e., NCCN) suggest additional indications. Based on product monographs and disease site expert consensus, PJP prophylaxis should routinely be used for Acute Lymphoblastic Leukemia (ALL) patients throughout the duration of active systemic treatment and for all patients being treated with alemtuzumab.<sup>2,35,45</sup> Patients treated with alemtuzumab should receive PJP prophylaxis for at least 2 months.<sup>2</sup> With that said,

alemtuzumab and other chemotherapy regimens that are associated with high rates of late-onset PJP (i.e. fludabarine, cyclophosphamide, and rituximab) may require an extended period of PJP prophylaxis of up to 12 months, particularly in pre-treated patients.<sup>46</sup> Additionally, consideration should be given to patients who are being treated with PI3K inhibitors, prolonged courses of corticosteroids ( $\geq 20$ mg prednisone or  $\geq 3$ mg dexamethasone daily for  $\geq 4$  weeks), and temozolomide with concurrent radiotherapy.<sup>2,37-39,47</sup> Patients receiving corticosteroids should continue prophylaxis during the tapering period and/or for a period of 6 weeks after cessation. PJP prophylaxis is recommended for allogeneic HCT recipients for at least 6 months and autologous HCT recipients until 3-6 months post-transplant.<sup>2</sup>

For patients who are intolerant to SMX-TMP, desensitization should ideally be performed as SMX-TMP is the most effective regimen.<sup>2,48</sup> Alternative prophylactic therapies include atovaquone, dapson, or pentamidine; however, there is limited data to support the use of these regimens in patients with malignancies.<sup>2,48</sup> If dapson is required, patients should consider assessing G6PD levels due to risk of hemolysis.<sup>2,48</sup>

### Clinical Question 3:

**What is the optimal use of antifungal prophylaxis in adult patients at high risk (> 20%) of FN receiving myelosuppressive systemic treatment?**

### Recommendation 3:

The addition of an antifungal should be considered for high-risk hematologic patients. Antifungal treatment should be continued for the duration of anticipated neutropenia. Duration may vary depending on indication.

**Fluconazole 400 mg PO once daily**

**OR**

**Posaconazole loading dose 300 mg PO (delayed- release tablets) BID on Day 1, then 300 mg once a day thereafter\***

**OR**

**Posaconazole suspension 200 mg PO three times a day\***

Posaconazole is recommended for patients with a higher risk of developing invasive aspergillosis, such as patients with AML and MDS during active induction and consolidation treatment.

\*Posaconazole delayed-release tablets and suspension are not funded by the Ontario Drug Formulary.



#### SUMMARY OF EVIDENCE & DISCUSSION:

Guidelines consistently recommend the use of azoles as the preferred antifungal agents for FN prophylaxis.<sup>2,15</sup> No new primary literature was found to suggest that changes to this recommendation are needed. A 2017 review of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO) concluded that there is some evidence to suggest that prophylaxis with oral posaconazole during remission induction chemotherapy for AML and MDS is preferred.<sup>49,50</sup>

A small prospective study compared posaconazole with fluconazole for prophylaxis in 37 AML patients during induction and consolidation chemotherapy. Invasive fungal infection (IFI) rates did not differ significantly (10 and 7 cases), but posaconazole drug costs exceeded fluconazole considerably; however, posaconazole was demonstrated to have a survival benefit in prospective randomised controlled clinical trials when given for fungal prophylaxis treatment and decreased indirect and overall costs.<sup>49</sup>

No significant differences in invasive fungal infection were noted when posaconazole was compared to voriconazole in patients with high-risk hematologic malignancies (majority (67%) AML) in a retrospective study (n=200).<sup>51</sup> Patients receiving voriconazole had more clinically significant adverse events compared with those receiving posaconazole.<sup>50,51</sup>

In general, antifungal prophylaxis with voriconazole has demonstrated comparable efficacy to fluconazole and posaconazole in studies of high-risk patients; however, it is not as well-tolerated compared to the other antifungals and is associated with toxicities such as neurologic, ophthalmic, renal and cutaneous adverse effects.<sup>2</sup>

#### Clinical Question 4:

**What is the optimal use of antiviral prophylaxis in adult patients at high risk (> 20%) of FN receiving myelosuppressive systemic treatment?**

#### Recommendation 4:

Consider antiviral prophylaxis for patients who are at risk of varicella-zoster virus (VZV) or herpes-simplex virus (HSV) infection or reactivation, such as those who are receiving treatment regimens containing proteasome inhibitors (e.g., CYBORD) or fludarabine (e.g., FLAG+IDA), for the duration of anticipated neutropenia.<sup>2,9,15,52</sup>

**Acyclovir 400 mg PO twice daily**

OR

**Valacyclovir 500 mg PO twice daily**

#### SUMMARY OF EVIDENCE & DISCUSSION:

The CCO 2016 recommendations list acyclovir as the only antiviral option; however, valacyclovir is also used in practice.<sup>9</sup> Both the NCCN 2021 and the ASCO 2018 guidelines recommend antiviral prophylaxis with a nucleoside analogue, and neither specify a preferred agent.<sup>2,15</sup> The



2016 CCO guideline recommended acyclovir specifically since it was the most economical option and was publicly funded.<sup>9</sup> Valacyclovir costs have decreased since then, and it is now also publicly funded in Ontario. A single-blinded study comparing valacyclovir to acyclovir in patients with hematologic malignancies undergoing chemotherapy or stem cell transplant (n=151) found that valacyclovir is an effective and safe alternative to acyclovir.<sup>53</sup> A prospective trial with historical control (n=120) compared valacyclovir to acyclovir in patients who had prior HSV-1 infection in the transplant setting.<sup>54</sup> They concluded that acyclovir and valacyclovir are comparably effective and safe at preventing reactivation of HSV in this setting.<sup>54</sup> Additionally, a 2015 guideline on antiviral prophylaxis from the German Society for Hematology and Medical Oncology concluded that superiority of one of the two drugs could not yet be demonstrated.<sup>52</sup> Since evidence to suggest a strong preference between acyclovir or valacyclovir is lacking, either option may be considered for use as antiviral prophylaxis for patients who are at risk of VZV or HSV infection or reactivation.

Current guidelines recommend antiviral prophylaxis against HSV during period of neutropenia in HSV-seropositive patients who are receiving chemotherapy for acute leukemia, and during neutropenia and potentially longer in allogeneic and autologous HCT recipients based on the degree of immunosuppression.<sup>2,55</sup> Allogeneic HCT recipients with graft versus host disease (GVHD) or with frequent HSV reactivations should have a longer period of prophylaxis.<sup>56</sup> Since HSV and herpes zoster infections are common in patients with CLL treated with alemtuzumab, antiviral prophylaxis is recommended until at least 2 months after completion of alemtuzumab therapy.<sup>2</sup>

VZV prophylaxis is recommended for at least 1 year after allogeneic HCT in patients who are seropositive for VZV pre-transplant.<sup>2</sup> An extended duration of prophylaxis is recommended in patients who continue to receive systemic immunosuppressive therapy.<sup>2</sup> Since the risk of VZV reactivation extends through the first year, prophylaxis is recommended for at least 6-12 months post-transplant in autologous HCT recipients.<sup>2,57</sup>

## Moderate Risk (10 to 20%)

Moderate risk is defined as a 10 to < 20% risk of FN, based on the systemic treatment regimen and patient risk factors. Refer to Appendix 2 for examples of treatment regimens that are considered to have a moderate or high risk for FN.

### Clinical Question 5:

**What is the optimal approach for adult patients at moderate risk (10 to < 20%) of FN receiving myelosuppressive systemic treatment with curative intent?**

### Recommendation 5:

For patients who are receiving systemic treatment regimens that carry an FN risk of 10 to < 20%:

The use of G-CSF and/or antibiotic primary prophylaxis should be determined at the discretion of the prescriber based on a patient risk assessment (see Figure 1).\*

- If, after risk assessment, the patient is still deemed to be at an overall moderate risk for FN, no primary prophylaxis is recommended.
- If, after risk assessment, the patient is deemed to be at an overall high risk of FN, follow the guidance for high-risk patients.
- Use of antifungal prophylaxis may be considered during the period of neutropenia.
- Consider antiviral prophylaxis for patients who are at risk of VZV or HSV infection or reactivation.

\* Modifications may be considered at the discretion of the prescriber based on patient risk assessment and environmental factors/exceptional circumstances (e.g. a pandemic).

### SUMMARY OF EVIDENCE & DISCUSSION:

Guidelines consistently recommend a patient risk assessment to determine if patients receiving moderately myelosuppressive systemic therapy should receive primary prophylaxis for FN prevention.<sup>1-3,5-7,15-17</sup> No new evidence was found to suggest a need to update this recommendation. COVID-19 related guidance was discussed. There was consensus to add the qualifying statement above (\*) to indicate that there may be rare circumstances (such as during a pandemic) in which primary prophylaxis may be warranted in the setting of overall moderate risk.

### **Clinical Question 5.1: What are the risk factors for development of FN?**

#### Recommendation 5.1:

There are many risk factors that increase the chance of a patient developing FN and include considerations such as optimal treatment intensity, previous treatment history, cancer type, and comorbidities. The risk factors with the highest level of evidence are outlined in Figure 1. Refer to appendix 1 for a more extensive list of risk factors.

#### SUMMARY OF EVIDENCE & DISCUSSION:

Risk factors are consistent across guidelines with few exceptions.<sup>1-3,5-7,15-17</sup> Risk factors that were outlined in some guidelines but are not included in the CCO 2016 recommendations include: recent surgery, renal dysfunction, neutropenia in the context of human immunodeficiency virus (HIV), and lab parameters (lymphocytopenia, hyperalbuminuria, hyperbilirubinemia).<sup>1,2,4,19</sup> There is little evidence that has been published in this area since 2016. A patient risk model has been described by Lyman *et al* and includes HIV and poor renal function as FN risk factors.<sup>58</sup> There was consensus to add the above risk factors from other guidelines, as they are clinically appropriate.

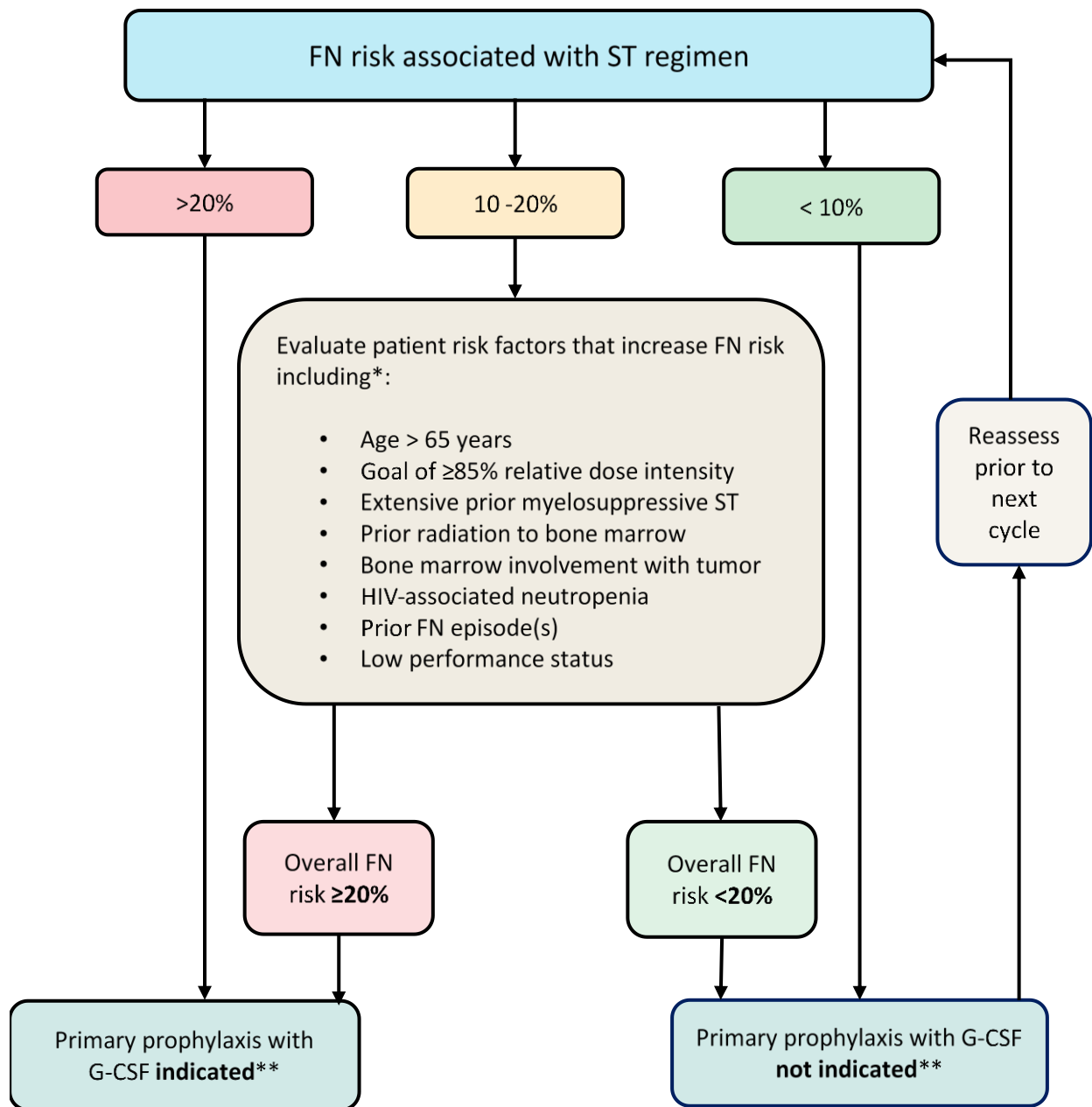
#### **Clinical Question 5.2: Are there validated online tools to assess FN risk?**

**Recommendation 5.2:** There is insufficient evidence at this time to suggest an online tool is preferred over individual clinical assessment by the oncology team. The FENCE tool may be considered as an additional tool in FN risk assessment; however, it should not be used as a replacement for individual clinical assessment.

#### SUMMARY OF EVIDENCE & DISCUSSION:

Aagaard *et al* conducted a cohort study of patients with treatment-naïve patients with solid tumours or diffuse large B-cell lymphoma (n=9457).<sup>59</sup> They developed and validated a risk score for FN in the first cycle of chemotherapy (FENCE) that is available as an online tool.<sup>59</sup> The tool requires the user to answer 16 questions about the patient and uses the results to calculate FN risk.<sup>59</sup> The tool does provide a quick and simple estimate for risk of FN in patients who are treated with regimens that are moderate risk for FN and is internally validated.<sup>59</sup> It is, however, missing multiple established risk factors for FN, has not been externally validated, and relied on blood cultures (rather than temperature readings) for FN diagnosis.<sup>59</sup> There was consensus that risk assessment by experienced oncology professionals is preferred to assessment using the FENCE tool.

Figure 1 : Evaluating febrile neutropenia (FN) risk based on systemic treatment (ST) regimen and patient factors<sup>1,3-5</sup>



\*for an extensive list of risk factors with level of evidence, refer to appendix 1

\*\*refer to Recommendations 2 to 5 for information on antibiotic, antifungal, and antiviral prophylaxis.

## Low Risk (< 10%)

Low risk is defined as < 10% overall risk of FN.

### Clinical Question 6:

**What is the optimal approach for adult patients at low risk (< 10 %) of FN receiving myelosuppressive systemic treatment with curative intent?**

### Recommendation 6:

For patients who have an overall FN risk of < 10 %:

The use of G-CSF and/or antibiotics as primary prophylaxis is not recommended.

- Use of antifungal prophylaxis may be considered for hematologic patients at high risk of infection for the duration of neutropenia.
- Use of antiviral prophylaxis should be based on patient-specific history of HSV infections.

### SUMMARY OF EVIDENCE & DISCUSSION:

Guidelines consistently state that primary prophylaxis with G-CSF or antibiotics is not necessary for patients who are at a low risk of developing FN.<sup>1-3,5-7,15-17</sup> There is no evidence to suggest a change to this recommendation is warranted.

## Secondary Prophylaxis

Secondary prophylaxis refers to FN prophylaxis in patients who have had FN in a previous cycle of their current systemic treatment.

### Clinical Question 7:

**What is the optimal approach for secondary prophylaxis of FN?**

#### Recommendation 7:

For patients who have experienced FN and no G-CSF was used for primary prophylaxis:

**Secondary prophylaxis with G-CSF** should be considered if:

- further infections in the next treatment cycle are considered life-threatening
  - a dose reduction would bring the dose below the studied/effective threshold
- AND/OR
- a lack of protocol adherence compromises the cure rates or disease free or overall survival.

**A dose reduction** may be a reasonable alternative to using G-CSF if:

- the threshold for efficacy is not reached
- the patient is being treated with palliative intent

AND/OR

- the patient is being treated with a low FN risk systemic treatment.

For patients who have experienced FN despite receiving primary FN prophylaxis with G-CSF\*, it is recommended to:

- change to a less myelosuppressive treatment regimen, if clinically appropriate
- OR
- continue G-CSF\*\* use and consider a dose reduction for future cycles

\*Assuming that patient received optimal dose and duration of primary FN prophylaxis.

\*\*Consider extending the duration of filgrastim.

#### SUMMARY OF EVIDENCE & DISCUSSION:

The primary reason that G-CSF is used as secondary prophylaxis is the need to maintain relative dose intensity (RDI) to optimize clinical outcomes.<sup>60</sup> RDI is the ratio of the delivered dose intensity of chemotherapy to the standard dose intensity and is an important determinant of efficacy of cytotoxic chemotherapy.<sup>61</sup> With that said, there is a significant amount of data showing a dose-response relationship for chemotherapy in cancer patients for both early and advanced stages of disease.<sup>62</sup> Reductions in dose intensity are associated with poorer outcomes in early-stage cancers, as shown by clinical data from retrospective studies and prospective clinical trials.<sup>62</sup> The use of G-CSF as secondary prophylaxis is associated with an approximate 50% reduction in episodes of FN and, theoretically, provides a survival benefit by enabling

administration of dose-dense regimens and minimizing dose intensity reductions.<sup>63</sup> However, to our knowledge, there is a lack of data demonstrating improved survival outcomes associated with the use of secondary prophylaxis with maintained RDI in any setting. Secondary prophylaxis with G-CSFs should be limited to patients who experience a neutropenic complication (i.e., fever or treatment delay) from a prior chemotherapy cycle (for which primary prophylaxis was not received) if reduced dose intensity might impact the treatment outcome.<sup>1,5</sup>

## G-CSF in the Palliative Setting

The introduction of biosimilars has resulted in reduced G-CSF prices. Public funding for filgrastim and pegfilgrastim is no longer restricted to specific clinical scenarios in Ontario. As a result, these medications can be prescribed more broadly now than when the CCO 2016 recommendations were developed. We looked at whether there is a need to update the previous recommendation (which states to limit G-CSF prophylaxis to the curative setting) to now include prophylaxis use in the palliative setting.

### Clinical Question 8:

**Is there a role for G-CSF prophylaxis in the palliative setting?**

### Recommendation 8:

G-CSF is not recommended for routine use in the palliative setting. Use of G-CSF may be considered in certain clinical scenarios (e.g. when relative dose intensity significantly impacts outcomes and/or for specific regimens/patient populations).

### SUMMARY OF EVIDENCE & DISCUSSION:

There is variation in guidelines around the use of G-CSF in the palliative setting. It is either not mentioned, limited to use as secondary prophylaxis, added to the risk assessment criteria, or recommended for use only after consideration of delays, dose reductions or change in treatment.<sup>1,3,5,16,19</sup>

The use of G-CSF has been shown to reduce the risk of FN; however, its impact on survival outcomes is not well-defined. A RCT was conducted to compare chemotherapy + primary prophylaxis with G-CSF (3 consecutive days starting 24 hrs post chemo) with chemotherapy + saline placebo in metastatic colorectal cancer patients (n=100).<sup>64</sup> In the G-CSF arm, there were no cases of FN vs 6% in the placebo arm (p<0.05).<sup>64</sup> Grade 3 or higher neutropenia was reported in 2% of G-CSF patients vs 18% in the placebo arm (p<0.05).<sup>64</sup> The data did not include information around progression free survival (PFS) or OS and the chemotherapy regimens were not specified.<sup>64</sup>

There are a number of small studies that evaluated specific regimens/patient populations that may benefit from use of G-CSF in the palliative setting. A retrospective analysis of patients with



advanced non-small cell lung cancer (NSCLC) (n=171) found that 26% of patients developed FN, which is higher than previously reported.<sup>65</sup> Age  $\geq$  65 years and previous FN were identified as independent risk factors ( $p < 0.5$ ).<sup>65</sup> The authors concluded that it may be beneficial to give G-CSF primary prophylaxis to elderly NSCLC patients treated with docetaxel.<sup>65</sup>

Another group looked at castrate-resistant prostate cancer (CRPC) patients treated with docetaxel (n=30) and compared those who received primary prophylaxis (n=12) with those who did not (n=18).<sup>66</sup> FN incidence was 8.3% vs 44.4% ( $p=0.049$ ) and there were no differences in relative dose intensity.<sup>66</sup> The average medical costs per course were lower in the G-CSF arm.<sup>66</sup> The authors concluded that primary prophylaxis is useful in this setting and does not increase overall medical costs.<sup>66</sup>

A small prospective study (n=21) evaluated heavily pretreated metastatic CRPC patients treated with cabazitaxel who received primary prophylaxis with pegfilgrastim.<sup>67</sup> Full dose cabazitaxel (25 mg/m<sup>2</sup>) was administered for a median of 7 cycles, for a relative dose intensity of 67.4%.<sup>67</sup> They reported a 9.5% incidence of FN, which is significantly lower than the 43% reported in the phase 1 trial with no primary prophylaxis.<sup>67</sup> The time to PSA progression was similar to historical data.<sup>67</sup> The authors concluded that pegfilgrastim is safe and effective for mCRPC patients.<sup>67</sup>

A prospective single arm trial (n=32) analysed locally advanced pancreatic cancer patients with good performance status who had 5 days of filgrastim primary prophylaxis with mFOLFIRINOX treatment.<sup>68</sup> An average of 7 cycles were administered.<sup>68</sup> They reported 28.1% grade 3 or higher neutropenia and only 1 case of FN (3%).<sup>68</sup> 34% of patients required further dose reduction and 19% discontinued due to toxicity (mostly N/V, fatigue, neuropathy, diarrhea).<sup>68</sup> Progressive disease at 6 and 9 months was 53.3% and 76.7%, respectively.<sup>68</sup> The 1-year overall survival (OS) probability was 71.5%.<sup>68</sup> The authors concluded that primary prophylaxis with G-CSF was effective at preventing FN and maintaining doses that resulted in a high level of disease control and survival.<sup>68</sup>

A retrospective analysis (n=45) of advanced pancreatic cancer patients treated with mFOLFIRINOX identified that 28 (62%) had grade 3 or higher neutropenia and 11 (39%) of those received pegfilgrastim support for all further cycles.<sup>69</sup> Patients who had less than 3 cycles were excluded from the analysis.<sup>69</sup> There were no dose reductions or delays in the pegfilgrastim group vs 61.5% in the non-pegfilgrastim group.<sup>69</sup> Median PFS was 7 vs 3.1 months ( $p=0.02$ ). After a 1-year observation period, 7 (64%) were alive in the pegfilgrastim group compared to 1 (6%) in the non-pegfilgrastim group.<sup>69</sup> Overall survival improvement was not statistically significant.<sup>69</sup>

A pooled safety analysis of metastatic colorectal cancer patients (n=1187) treated with first line FOLFOX/FOLFIRI/FOLFOXIRI+beva within the TRIBE and TRIBE2 studies was conducted.<sup>70</sup> It was found that 16% of elderly patients on FOLFOXIRI+beva developed FN (vs 6% in  $<70$  yrs;  $p<0.01$ ; 8% with FOLFIRI+beva and 2% with FOLFOX+beva ).<sup>70</sup> The authors concluded that patients over 70 should receive primary prophylaxis with G-CSF when treatment with FOLFOXIRI+beva is the preferred option.<sup>70</sup>

A prospective study of previously untreated indolent non-Hodgkin lymphoma patients (n=122) compared filgrastim as secondary prophylaxis to pegfilgrastim primary prophylaxis.<sup>71</sup> FN-related chemo disruptions, defined as at least 1 week delay or a bendamustine dose reduction, were 11.4% vs 1.6% in the primary prophylaxis group (p=0.04).<sup>71</sup> The median number of days of hospitalization due to FN were 18 vs 6 (p=0.04).<sup>71</sup> There were no differences in terms of G-CSF-related side effects. PFS and OS data were not reported.<sup>71</sup>

A retrospective review of 169 metastatic breast cancer patients who received chemotherapy as first to third line treatment was conducted.<sup>72</sup> Risk of FN for the chemotherapy regimens given is < 10%, while overall risk of grade 3–4 neutropenia varied widely (14 to 70%).<sup>72</sup> Of the patients included in this study, 32.5% received at least one dose of G-CSF and were compared to a similar cohort of patients that did not.<sup>72</sup> Analysis determined that the use of G-CSF to maintain chemotherapy dose intensity did not improve time to progression, PFS, and OS nor did it result in improved performance status compared with lack of G-CSF.<sup>72</sup> The authors concluded that there is no evidence to support the use of G-CSF over dose delays.<sup>72</sup>

In a phase 3, double-blind trial, 845 patients with advanced colorectal cancer receiving bevacizumab plus first-line chemotherapy (FOLFOX or FOLFIRI) were randomized to pegfilgrastim versus placebo.<sup>73</sup> Pegfilgrastim significantly reduced grade 3 or higher FN (2.4% vs 5.7% (p=0.014)) and grade 3 or higher neutropenia (3.6% vs 17% (p<0.001)).<sup>73</sup> Relative dose intensity was high in both arms (>90%), and bone pain was reported by 16% vs 10.9% of patients.<sup>73</sup> The authors stated that the FN reduction was less than the targeted reduction of 66.7%, in part because of the lower-than-expected incidence of grade 3/4 FN overall.<sup>73</sup> There were no statistically significant differences in tumour response rates, survival outcomes, or non-hematological toxicities.<sup>73</sup>

Based on the limited amount of high-quality data, the WG was unable to make a strong recommendation around the use of G-CSF in the palliative setting. For most patients, using a reduced dose, delaying treatment, or changing to a different treatment is the most appropriate approach. The group did, however, agree that there may be certain scenarios where G-CSF use may be clinically appropriate and this decision should be made on a case-by-case basis.

## Neutropenia Related to Targeted Therapies

### Clinical Question 9:

Is there a role for G-CSF in the setting of neutropenia related to targeted therapies?

### Recommendation 9:

Routine use of G-CSF for neutropenia with targeted therapies is not recommended.

#### SUMMARY OF EVIDENCE & DISCUSSION:

Neutropenia is a documented side effect of many classes of targeted therapies.<sup>74–80</sup> Neutropenia due to PARP and CDK4/6 inhibitors is of particular interest since use of these medications in the curative setting is increasing.

A meta-analysis of 12 RCTs (n=2479) described the risk of severe hematologic toxicities in cancer patients treated with PARP inhibitors.<sup>81</sup> Neutropenia occurred in 32.9% of patients.<sup>81</sup> An increased incidence of neutropenia was observed when PARP inhibitors were added to standard chemotherapy.<sup>81</sup> This was most notable with single agent chemotherapy (RR 3.52 p=0.004) vs the combination of carboplatin/paclitaxel (RR 1.05, p=0.626).<sup>81</sup> The authors concluded that the finding was likely due to higher incidences of neutropenia with combinations overall and that monitoring of neutropenia for all patients treated with PARP inhibitors is warranted.<sup>81</sup>

LaFargue *et al* characterized and compared toxicities associated with PARP inhibitors, with a particular focus on potential management strategies to help mitigate toxic effects.<sup>82</sup> PARP inhibitors can cause neutropenia at rates of 18 to 30% (all grades).<sup>82</sup> Grade 3 and 4 neutropenia was highest with niraparib (20%) vs rucaparib (7%) and olaparib (5%).<sup>82</sup> For grade 2 or higher neutropenia, the authors recommend withholding the PARP inhibitor for up to 28 days and to monitor blood counts weekly until neutrophil counts recover, then resume the PARP inhibitor at a reduced dose.<sup>82</sup> The PARP inhibitor should be discontinued if neutrophils have not returned to acceptable concentrations after 28 days.<sup>82</sup>

A recent ASCO guideline on the use of PARP inhibitors in gynecologic cancers included clinical questions around management of toxicities.<sup>83</sup> It states that neutropenia has not reached levels defined as requiring primary prophylaxis with G-CSF and that primary prophylaxis with G-CSF is not feasible due to continuous dosing.<sup>83</sup> For neutropenia (grade four lasting more than 5-7 days), the authors recommend holding the PARP inhibitor until infection resolution and neutrophil recovery.<sup>83</sup> They suggest that G-CSF support (e.g. 3 days of filgrastim) may be used to support patient safety during the drug hold.<sup>83</sup>

A review article summarized CDK4/6 toxicity information from landmark trials. The incidence of neutropenia (all grade) is 42-92% and the incidence of grade 3 or higher neutropenia is 21-66%.<sup>84</sup> Abemaciclib has a 50% lower neutropenia rate compared to the others.<sup>84</sup> Neutropenia associated with CDK4/6 inhibitors is different from the chemotherapy-induced type.<sup>84</sup> It is

associated with a low infection rate, is rapidly reversible (usually resolves within 7 days of holding the drug), and incidence decreases cycle by cycle.<sup>84</sup> The authors concluded that there is no need for G-CSF support and management should include dose delays and reductions, as per product monographs.<sup>84</sup>

In general, for continuous dosing schedules, G-CSF prophylaxis is not feasible. Product monographs of targeted therapies that can cause neutropenia were reviewed and the majority recommend dose delays and reductions to manage neutropenia. Consideration of G-CSF as secondary prophylaxis is mentioned for a handful of hematologic medications (e.g., lenalidomide, pomalidomide, venetoclax) which are predominantly used in the palliative setting.<sup>78–80</sup>

## Neutropenia and Immune Checkpoint Inhibitors (ICI)

### Clinical Question 10:

**Is there a role for G-CSF in the setting of neutropenia in patients receiving ICI?**

### Recommendation 10:

G-CSF appears to be a safe and acceptable treatment approach for neutropenia in patients receiving ICI (either alone or in combination with other ST). If an ICI is combined with myelosuppressive ST and the patient is at high-risk of developing FN, it is reasonable to follow the high-risk primary prophylaxis recommendations with close monitoring.

### SUMMARY OF EVIDENCE & DISCUSSION:

The use of immune-checkpoint inhibitors (ICI) in cancer patients is associated with neutropenia on rare occasions; however, the incidence of severe hematological toxicities may rise over the next few years as more cancer patients become eligible for ICI therapy.<sup>85</sup>

Based on limited evidence, G-CSFs appear to be safe, and it is reasonable for them to be used similarly to manage both immune and non-immune-related FN. A recent meta-analysis (n=34) of rare immune-related adverse side effects from ICI demonstrated that the median onset of neutropenia was 10.5 weeks after the first ICI administration, with a normalization of the neutrophil count after a median duration of neutropenia of 13 days; 68% of the sample (n=15) presented with fever > 38°C.<sup>85</sup> The study presented the combination of intravenous corticosteroids and G-CSF treatment as an acceptable clinical treatment approach in these patients, even in inconclusive cases with concurrent therapies that may be causing neutropenia.<sup>85</sup> Broad-spectrum antibiotic therapy was recommended for all cases of FN. Since neutropenia relapsed during dose reduction of corticosteroids, they recommended a slow tapering of steroids during follow-up.<sup>85</sup> Initial antifungal therapy did not seem to be needed due to the absence of prolonged ICI-induced neutropenia in most cases.<sup>85</sup>

There is a lack of literature focusing on the use of G-CSF in the management of FN associated with the combination of myelosuppressive ST and ICI. G-CSF was included in the study protocol for a phase 3 RCT that evaluated pembrolizumab compared to placebo in combination with myelosuppressive neoadjuvant therapy for early triple-negative breast cancer.<sup>86</sup> There are ongoing studies in neoadjuvant breast cancer that are allowing the use of G-CSF. Further data in patients receiving ICI with or without myelosuppressive ST is required to support a more detailed treatment approach.

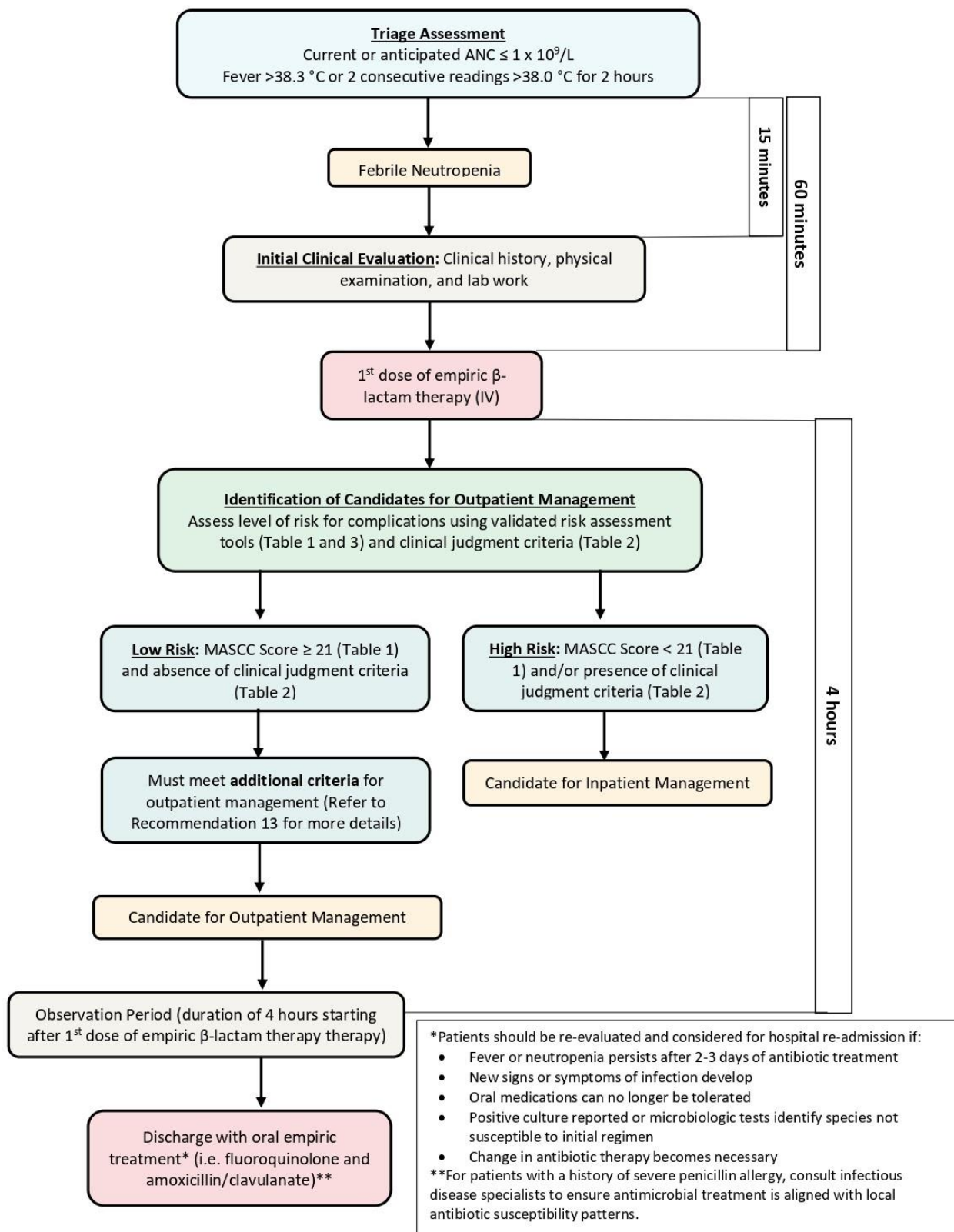
## Outpatient Management of Febrile Neutropenia in Adult Cancer Patients

Febrile neutropenia is a common complication of treatment with myelosuppressive systemic treatment. **FN** is defined as a fever that occurs during a period of significant neutropenia.

- **Neutropenia** is defined as  $ANC \leq 1 \times 10^9/L$ , especially if counts are not likely to recover within 48 hours.
- **Fever** is defined as a single oral temperature of  $\geq 38.3^\circ C$  or  $38.0^\circ C$  or higher for at least one hour. Fever can be an important indicator and is often the only sign or symptom of infection.<sup>1,2,6,7</sup>

Appropriate management of FN is important because the rate of major complications (e.g., hypotension, acute renal, respiratory, heart failure) in the context of FN is approximately 25% to 30%, and the mortality rate ranges up to 12% in high-risk groups.<sup>6,7</sup> Inpatient treatment of FN requires significant resources (costs and health human resources).<sup>1</sup> Recommendations for identifying patients with FN who may be treated in the outpatient setting can help to optimize the use of health system resources and provide patients with a more comfortable treatment-setting.

Figure 2: Overview of Outpatient Management of FN<sup>6,7,69</sup>



## Initial Evaluation and Risk Assessment

Clinical practice guidelines consistently state that patients who have recently received myelosuppressive systemic treatment and develop fever should be considered to have neutropenic fever.<sup>2,6</sup>

### Clinical Question 11:

**What are the recommendations for the initial evaluation of fever and neutropenia in cancer patients?**

### Recommendation 11:

Any neutropenic fever should be considered an infection. The initial diagnostic approach should focus on establishing a clinical and microbiologic diagnosis that may affect antibacterial choice and prognosis.

The initial clinical evaluation should take place within 15 minutes after triage and should include:

- clinical history,
- physical examination\*(including initial vital signs),
- bloodwork (CBC, electrolytes, SCr, LFTs; consider serum lactate)
- cultures and swabs, as clinically indicated (prior to starting antimicrobial therapy)

And chest x-ray or CT, as clinically appropriate

\*Rectal examinations are not recommended due to risk of bacteremia.

### SUMMARY OF EVIDENCE & DISCUSSION:

Guidelines are consistent in the approach to the initial evaluation of fever in neutropenic patients.<sup>1,2,6,7</sup> The Spanish Medical Oncology Society (SEOM) and ASCO recommend that two sets of blood cultures and microbiological specimens (as clinically appropriate) should be obtained prior to initiating empirical antibiotic therapy.<sup>6,7</sup> SEOM also state that the initial evaluation may include procalcitonin levels for the diagnosis of presumed bacterial infection and prognostic stratification and suggest that a more comprehensive microbiological study in patients with clinical suspicion or history of specific infections, or with severe immunosuppression should be considered.<sup>7</sup> NCCN 2021 recommends that one peripheral and one catheter blood culture be obtained.<sup>2</sup> They suggest a urine culture for symptoms or an abnormal urinalysis, and site-specific diagnostics for specific symptoms (such as diarrhea, skin lesions, or respiratory symptoms). The various guideline recommendations are largely consensus-based; however, the WG agrees that the approach is clinically appropriate.



## Initial Empirical Treatment

### Clinical Question 12:

**What is the optimal first dose of empirical therapy for patients presenting with FN?**

### Recommendation 12:

The first dose of empirical therapy should be administered **intravenously** within **1 hour** after triage:

**$\beta$ -lactam with broad spectrum coverage and antipseudomonal activity\***  
(e.g. piperacillin-tazobactam, a carbapenem\*\*)

\* Selection of antibiotic should be based on guidance from infectious disease specialists according to local resistance patterns. If infection with an antibiotic-resistant bacteria is suspected, consult with an infectious disease specialist. Clarify allergy history and modify antibiotic choice accordingly.

\*\*Meropenem or imipenem-cilastatin are preferred; ertapenem is not recommended due to lack of antipseudomonal activity.<sup>2</sup>

### SUMMARY OF EVIDENCE & DISCUSSION:

The WG agree that choice of standard empiric antibiotic treatment for patients presenting with FN should be made in consultation with infectious disease specialists and based on local resistance patterns. Initial empirical treatment should be selected based on the type and severity of the infection, and the probability of antibiotic-resistant microorganisms being involved in its etiology.<sup>7</sup> Guidelines consistently recommend a “door-to-needle time” of 1 hour and an initial dose of monotherapy with antipseudomonal beta-lactam.<sup>1,2,6,7,16</sup> ASCO recommends that if infection with an antibiotic-resistant organism (i.e. MRSA, VRE, ESBL, CPE is suspected or proven, aminoglycoside, fluoroquinolones, or vancomycin should be added, as clinically appropriate, especially if the patient’s condition is unstable.<sup>6</sup> Empiric vancomycin should only be used for specific clinical indications (e.g. suspected catheter-related, skin, or soft tissue infection, pneumonia, hemodynamic instability).<sup>6</sup>

SEOM recommends that modifications to the first dose should be made depending on the patient’s prognosis and characteristics (such as a catheter-related infection, enterocolitis, and past antibiotic-resistant infection).<sup>7</sup> The University Health Network/Mount Sinai Hospital antimicrobial stewardship group in Ontario has an online Solid Tumour or Lymphoma Febrile Neutropenia Protocol that recommends an initial dose of IV cefazolin + tobramycin.<sup>88</sup> If there is penicillin hypersensitivity, meropenem should be given.<sup>88</sup> The addition of oral vancomycin is recommended if *C. difficile* is suspected, azithromycin if pneumonia is suspected, vancomycin if cellulitis or IV site infection suspected, and acyclovir for mucocutaneous HSV infection.<sup>88</sup>

## Risk Assessment

### Clinical Question 13:

Which patients presenting with FN are eligible for treatment in the outpatient setting?

### Recommendation 13:

Patients with neutropenic fever who are at low risk of complications may be treated in the outpatient setting. To determine risk level:

- The MASCC tool is preferred. Patients at low risk have a MASCC score of  $\geq 21$ .
- Refer to Table 2 below for a list of risk factors for complications that contraindicate initial outpatient management (even if MASCC score is  $\geq 21$ ).
- The CISNE may be used as an additional tool to determine the risk in patients with solid tumours who have received mild- to moderate-intensity chemotherapy and who appear to be clinically stable.

**Table 1: MASCC Scoring System to Identify Patients With Cancer and FN at Low Risk of Medical Complications<sup>1,6,89</sup>**

Characteristic	Score
Burden of FN with no or mild symptoms*	5
No hypotension (i.e. Systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease (COPD)	4
Solid tumour or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of FN with moderate symptoms*	3
Outpatient status	3
Age < 60 years	2

Note: Maximum score is 26. Scores  $\geq 21$  indicate a low risk for medical complications.

\*Burden of FN refers to the general clinical status of the patients as influenced by the FN episode. It should be evaluated on the following scale: no or mild symptoms (5), moderate symptoms (3), severe symptoms (0). Scores are not cumulative.

**Table 2: Risk Factors for Complications That Contraindicate Initial Outpatient Management of FN\*<sup>2,6,7,90</sup>**

High Risk (Outpatient management contraindicated if patient meets ANY of the below criteria)
<ul style="list-style-type: none"> <li>• Inpatient status at time of fever development</li> <li>• MASCC Score &lt; 21</li> <li>• Significant medical comorbidity or clinically unstable</li> <li>• Anticipated prolonged severe neutropenia (ANC ≤ 1 x 10<sup>9</sup>/L for ≥ 7 days) or profound neutropenia (ANC &lt; 0.1 x10<sup>9</sup>)</li> <li>• Hepatic insufficiency (aminotransferase levels &gt; 5X ULN)</li> <li>• Renal insufficiency (CrCl &lt; 30 mL/min)</li> <li>• Uncontrolled/progressive cancer</li> <li>• Pneumonia or other complex infection(s)</li> <li>• Severe mucositis (Grade 3 or higher)</li> <li>• CISNE score ≥ 3 (see below; for patients with solid tumours)</li> </ul>

\*This is not an exhaustive list. **Refer to appendix 3 for a more detailed description.** Independent professional clinical judgement must be employed when considering eligibility for outpatient FN management.

**Table 3: Clinical Index of Stable Febrile Neutropenia (CISNE)<sup>6,7</sup>**

Characteristic	Points
ECOG-Performance Status ≥ 2	2
Stress-induced hyperglycemia	2
Chronic obstructive pulmonary disease (COPD)	1
Chronic cardiovascular disease	1
Mucositis Grade ≥ 2	1
Monocytes < 0.2 x 10 <sup>9</sup> /L	1

**Low risk=0**

**Intermediate risk= 1 to 2**

**High risk= 3 to 8**

## SUMMARY OF EVIDENCE & DISCUSSION:

The Multinational Association for Supportive Care in Cancer (MASCC) scoring system for identifying patients with cancer and FN who are at low risk for medical complications is a validated tool that is endorsed by many guidelines.<sup>1,2,6,9</sup> More recently, the clinical index of stable FN (CISNE) has been recommended as an additional tool to determine the risk in patients with solid tumours who have received mild- to moderate-intensity chemotherapy and who appear to be clinically stable.<sup>2,6</sup> One FN guideline lists the CISNE as the preferred risk assessment tool.<sup>7</sup> All guidelines also include a list of additional clinical criteria that excludes patients from eligibility for outpatient FN management, as the presence of any of the clinical factors shifts the patient to the high risk for medical complications risk category.<sup>1,2,6,7</sup>

Pooled analysis of 571 patients who presented with FN in 3 large cancer emergency centres in USA, UK, and South Korea concluded that overall, the MASCC score had a greater discriminatory power in the detection of low-risk patients than the CISNE score (AUC 0.772, 95% CI 0.726-0.819 vs. 0.681, 95% CI 0.626-0.737,  $p = 0.0024$ ), but had lower specificity.<sup>91</sup> A prospective single centre study of 129 patients with chemo-induced FN concluded that both CISNE and MASCC have fair discriminatory power in identifying low risk febrile neutropenia cases.<sup>89</sup> A systematic review and meta-analysis of 26 studies ( $n=6617$ ) concluded that the CISNE score had higher sensitivity and may be more useful than the MASCC score in the acute setting (since fewer false negatives).<sup>92</sup> They noted that risk scores should always be used in conjunction with clinical judgment.<sup>92</sup>

A prospective analysis from a UK cancer centre ( $n=100$ ) provides real world evidence around the use of the MASCC tool for identifying low-risk FN patients.<sup>93</sup> Patients were considered for outpatient FN management if they presented with a fever  $\geq 38^{\circ}\text{C}$ , ANC  $<1.0 \times 10^9/\text{L}$ , MASCC score  $\geq 21$  and psychosocial stability, as per the NICE guideline.<sup>17,93</sup> No patients in the study developed serious complications.<sup>93</sup> Sixteen (16%) had a CISNE score  $>1$  (moderate risk); 1 patient had a CISNE score of 3 (high risk).<sup>93</sup> Eight (8% [95% confidence interval {CI} 4.1–15.0%]) patients had a 7-day readmission (3 due to ongoing symptomatic fever) and no one required critical care admission.<sup>93</sup> The authors concluded that outpatient FN management of low-risk patients identified by MASCC is safe.<sup>93</sup>

An older FN risk classification tool, called Talcott's rules, was recommended by ASCO as a tool to help identify patients that may be candidates for outpatient management.<sup>6</sup> The WG discussed this tool and determined that it is not used regularly in Ontario practice, and that it does not offer much value above and beyond the MASCC tool. Additionally, this classification tool is not mentioned in the 2021 NCCN or SEOM guidelines. There was consensus to exclude Talcott's Rules from our recommendations.

A meta-analysis of 10 RCTs comparing inpatient empirical antimicrobial therapy versus outpatient management for patients with low-risk FN was conducted by the Cochrane group in 2019. Low risk definitions were described to be similar across studies but were not standardized. Risk evaluation tools included Talcott's and MASCC but not CISNE. There was no evidence of differences between outpatient and inpatient treatment of low-risk FN in terms of treatment failure and mortality. Resolution of fever, duration of neutropenia, and adverse drug

reactions were similar between the groups; however, for these outcome measures there was low-certainty of evidence. There was low to moderately-certain evidence to support the conclusion that outpatient treatment is as effective as inpatient treatment for people with low-risk FN.<sup>94</sup>

The WG concluded that it is safe to recommend outpatient management for patients who are considered low risk, as per MASCC, and do not have any additional clinical factors that would shift them to the high-risk category. Consensus was reached to recommend that the CISNE tool be considered as an additional tool, but that the MASCC tool is preferred for most patients.

## Clinical Question 14:

**What additional requirements must be met for patients to be eligible for outpatient FN management?**

### Recommendation 14:

For patients with FN to be treated at home safely, all the following criteria **must** also be met:<sup>2,6,7</sup>

- Patient consents to outpatient treatment
- Reside within 1 hour or less from a hospital
- Have the approval of their referring oncologist/clinician or on-call oncology service
- Availability of caregiver/family support 24 hours/day
- Have a means of transportation available
- Have access to a telephone
- Demonstrated adherence to previous treatment protocols
- Able to tolerate oral medications
- Not on prior fluoroquinolone prophylaxis
- Able to access oral antimicrobial in a timely manner

For patients with FN to be treated at home safely, it is **recommended** that the following criteria also be met:

- Frequent evaluation for at least 3 days (in clinic or at home)
- Daily or frequent telephone contact to verify that fever resolves (oral temperature measured with a digital thermometer)
- Monitoring of ANC and platelet count
- Frequent return visits to clinic

#### SUMMARY OF EVIDENCE & DISCUSSION:

Psychosocial and logistical requirements needed for safe outpatient FN management were consistent across guidelines.<sup>2,6,7</sup> The recommendations are largely consensus-based with a focus on patient safety. The ability for frequent assessment and a prompt return to the hospital, if needed, are paramount. The WG evaluated recommendations from various guidelines, and those deemed most relevant are outlined above.

## Outpatient Treatment

### Clinical Question 15:

**When should patients with FN who are appropriate candidates for outpatient management be discharged to home?**

### Recommendation 15:

For patients with FN who are eligible for outpatient treatment:<sup>2,6,7</sup>

After initiating empirical antibiotic therapy and prior to discharge, patients must remain in observation for at least **4 hours** to verify their clinical stability and tolerance to treatment.

#### SUMMARY OF EVIDENCE & DISCUSSION:

It is important to ensure that patients are stable and can tolerate empiric antibiotic treatment. The most common recommendation is for patients to be observed for at least 4 hours after the first dose of antibiotics is administered.<sup>6,7</sup> NCCN recommends that low risk patients be discharged with a prescription for antibiotic treatment to start at home or that patients are observed for 2-12 hours so they can receive the first dose of antibiotics, ensure they are stable, organize discharge plans, and provide patient education.<sup>2</sup> The WG agrees that at least 4 hours of observation after the first dose of antibiotic therapy is a safe and reasonable approach.

## Clinical Question 16:

**What is the optimal antimicrobial therapy for the outpatient treatment of FN in low-risk patients?**

### Recommendation 16:

For patients with FN who are at low risk for infection by resistant microorganisms or complications:

Oral empirical treatment with a **fluoroquinolone** and **amoxicillin/clavulanate** is recommended\*.<sup>2,6,7,88,90</sup>

**Ciprofloxacin 750 mg PO bid**

OR

**Levofloxacin 750 mg PO daily**

AND

**Amoxicillin/clavulanate 875/125 mg PO bid**

\*For patients with a history of severe penicillin allergy, consult infectious disease specialists to ensure antimicrobial treatment is aligned with local antibiotic susceptibility patterns. Some examples of alternative options include: Sulfamethoxazole-trimethoprim or clindamycin in place of amoxicillin-clavulanic acid, levofloxacin or moxifloxacin monotherapy, or if a cephalosporin is deemed to be safe, cefixime.<sup>2,6,7,88,90</sup>

### SUMMARY OF EVIDENCE & DISCUSSION:

Fluoroquinolone plus amoxicillin-clavulanate is the preferred treatment because it has the largest body of evidence to support its use in this setting.<sup>2,6</sup> Use of fluoroquinolone monotherapy is not the preferred approach due to varying local resistance patterns; however, it may be considered in certain low-risk scenarios.<sup>2,6,7</sup> In the setting of high prevalence of resistant microorganisms, such as MRSA, VRE, invasive fungal infection, and ESBL-producing gram-negative bacilli, consult with infectious disease experts to determine the most appropriate antimicrobial therapy and hospital admission should be strongly considered.<sup>2,6,7</sup> Antimicrobial treatment should be adapted to the isolates and patterns of resistance.<sup>7</sup> The WG acknowledges that antibiotic susceptibility patterns vary across regions; thus, the preference is to defer to the local experts for treatment selection.



## Outpatient Treatment Follow-Up

### Clinical Question 17:

**When should empiric antibiotic treatment be discontinued?**

#### Recommendation 17:

For patients who are being treated in the outpatient setting with empirical antibiotics, discontinuation of treatment may be considered if the patient is:

- Clinically stable/improving
- Afebrile  
AND
- ANC has recovered to  $> 0.5 \times 10^9/L$  for  $\geq 2$  days<sup>2,6,7,88,90</sup>

#### SUMMARY OF EVIDENCE & DISCUSSION:

Empirical antibiotic treatment should continue until the patient is no longer deemed to be at risk of infection. Signs that indicate a patient is no longer at risk include absence of fever, improvement of infection-related symptoms, and ANC recovery. The exact duration will depend on infection severity and patient factors. SEOM recommends that empirical antibiotic treatment should last for a minimum of 7 days in low-risk FN without an identified clinical or microbiological focal site.

### Clinical Question 18:

**When should patients with FN who are being treated in the outpatient setting be considered for hospital admission?**

#### Recommendation 18:

For patients with FN who are being treated in the outpatient setting, re-evaluation\* and consideration for hospital admission must occur when:

- Fever or neutropenia persists after 2–3 days of treatment with empirical antibiotic therapy
- New or worsening signs or symptoms of infection or deterioration of existing comorbidities
- Oral medications can no longer be tolerated
- Any positive culture is reported, or microbiologic tests identify species not susceptible to the initial regimen  
OR
- Change in antibiotic therapy becomes necessary<sup>2,6,7,88,90</sup>

\* Re-evaluation should be conducted in-person by the oncology health care team

## SUMMARY OF EVIDENCE & DISCUSSION:

Consensus-based guidelines are consistent in recommending re-evaluation and consideration of hospitalization for the above scenarios that indicate a patient's clinical status is potentially unstable. In-person evaluation by the oncology health care team should be standard, as per WG consensus.

## Additional Considerations

### Patient Education

It is important to properly inform the patients who are at risk of developing FN or are treated for FN in the outpatient setting about the detection of warning signs and symptoms, as well as how to contact the health care team 24 hours/day. Refer to the [Neutropenia](#) handout for patient-friendly information about FN prevention and management that can be shared with patients and caregivers.

### Vaccinations

Patients receiving myelosuppressive systemic treatment should be vaccinated against the flu every year in accordance with Canadian immunization guidelines for immunosuppressed patients.<sup>95</sup> Other vaccinations may be advisable depending on the systemic treatment regimen, the patient's clinical status, or a specific indication.<sup>7</sup>

### Guideline Adherence

Underuse and overuse of G-CSF as primary prophylaxis is well documented.<sup>96–98</sup> Optimizing the use of G-CSF can reduce the incidence of FN and the resulting sequelae of care and issues that may follow. Optimizing G-CSF use can also prevent patients from receiving unnecessary therapy (if overuse is an issue). Adhering to guideline recommendations can result in improved patient care, as well as cost and human resource savings for the health care system. To improve adherence, the WG recommends including G-CSF in the Computerized Prescriber Order Entry (CPOE) treatment protocol for all high-risk regimens.

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## Appendix

See below for additional information that may be useful.

### Appendix 1: Risk Factors for the Development of FN with Level of Evidence

Level of Evidence	Risk Factors
High level of supporting evidence	<ul style="list-style-type: none"><li>• <math>\geq 85\%</math> relative dose intensity</li><li>• Extensive prior chemotherapy</li><li>• Prior radiation to bone marrow</li><li>• Age greater than 65 years</li><li>• Bone marrow involvement with tumor</li><li>• HIV-associated neutropenia</li></ul>
Intermediate level of supporting evidence	<ul style="list-style-type: none"><li>• Poor performance status</li><li>• Low albumin/high LDH</li><li>• Pulmonary disease</li><li>• Cardiovascular disease</li><li>• Renal dysfunction</li><li>• Liver disease</li><li>• Diabetes mellitus</li></ul>
Low level of supporting evidence	<ul style="list-style-type: none"><li>• Open wounds or active infection</li><li>• Poor nutritional status</li><li>• Hgb &lt; 120 g/L</li><li>• Female sex (smaller BSA)</li><li>• Recent surgery</li><li>• Bloodwork – lymphocytopenia, hyperalbuminuria, hyperbilirubinemia</li></ul>

NOTE: This is not a comprehensive list and does not replace the need for independent clinical judgment

## Appendix 2: Examples of Treatment Regimens With a Moderate or High Risk of FN<sup>3,9</sup>

Disease Site	Moderate Risk Regimens (10-20%)	High Risk Regimens (> 20%)
Breast	<ul style="list-style-type: none"> <li>• DOCE</li> <li>• PACL</li> </ul>	<ul style="list-style-type: none"> <li>• AC-PACL(DD)</li> <li>• FEC-D</li> <li>• CYCLDOCE</li> </ul>
Gastrointestinal	<ul style="list-style-type: none"> <li>• ECF</li> <li>• ECX</li> <li>• FOLFOX</li> <li>• mFOLFIRINOX*</li> </ul>	<ul style="list-style-type: none"> <li>• FOLFOXIRI</li> </ul>
Genitourinary	<ul style="list-style-type: none"> <li>• CISPFU</li> <li>• CISPGEMC</li> </ul>	<ul style="list-style-type: none"> <li>• BEP(3D), BEP(5D)</li> <li>• MVAC(HD)</li> <li>• TIP</li> </ul>
Gynecologic	<ul style="list-style-type: none"> <li>• CRBPPACL</li> <li>• CISPDOXCRBPDOXO</li> </ul>	<ul style="list-style-type: none"> <li>• EMA-CO</li> </ul>
Head and Neck	<ul style="list-style-type: none"> <li>• CISPFU(RT)</li> </ul>	<ul style="list-style-type: none"> <li>• CISPDOCEFU</li> </ul>
Hematologic	<ul style="list-style-type: none"> <li>• CHOP+/-R*</li> <li>• GDP+/-RITU</li> <li>• CHP+BREN</li> <li>• ABVD</li> </ul>	<ul style="list-style-type: none"> <li>• DHAP+/-RITU</li> <li>• ICE+/-RITU</li> <li>• ESHAP</li> <li>• EPOCH+/-RITU</li> <li>• MINIBEAM</li> <li>• HYPERCVAD</li> <li>• MATRIX</li> <li>• CODOXM+/-RITU</li> </ul>
Lung	<ul style="list-style-type: none"> <li>• DOCE</li> <li>• CISPETOP(3D)</li> <li>• CRBPETOP(3D)</li> </ul>	<ul style="list-style-type: none"> <li>• CISPETOP(RT)</li> <li>• CISPETOP(PO)</li> <li>• TOPO</li> </ul>
Sarcoma	<ul style="list-style-type: none"> <li>• CISPDOXO</li> <li>• ETOPIFOS</li> </ul>	<ul style="list-style-type: none"> <li>• DOXOIFOS</li> <li>• EPIRIFOS</li> </ul>

NOTE: This is not a comprehensive list and does not replace the need for independent clinical judgment. Refer to the [OH-CCO Drug Formulary](#) for details around other regimens and for more information on the regimens listed above.

\*Patient factors often increase the risk associated with this regimen

## Appendix 3: Risk Factors for Complications That Contraindicate Initial Outpatient Management of FN\*

Organ or System	Risk Factor
Cardiovascular	Presyncope/syncope, new or worsening hypotension, hypertensive crisis, arrhythmias, heart failure, clinically relevant bleeding, angina pectoris, pericardial effusion
Hematological	Other clinically relevant cytopenias, thromboembolic disease, allogeneic HCT, anticipated prolonged severe neutropenia (ANC $\leq 1 \times 10^9/L$ for $\geq 7$ days) or profound neutropenia (ANC $< 0.1 \times 10^9$ )
Gastrointestinal	Oral intolerance, vomiting, new onset or clinically worsening diarrhea, abdominal pain, jaundice, alteration of liver function tests (impaired hepatic function), melena, hematochezia (hemorrhoid unrelated), or hematemesis, ascites
Infectious	Complex infections at clinical presentation (pneumonia, extensive cellulitis, bacteremia, catheter, pyelonephritis, meningitis, cholecystitis, and other surgical infections), sepsis, antibiotics for $\leq 72$ hours before presentation, allergies to antimicrobials used for outpatient treatment
Neurological	Presence of focal neurological symptoms, suspicion of meningitis, altered mental status, seizures
Pulmonary	Tachypnea, hypopnea, abscesses, pneumothorax, pleural effusion, acute respiratory failure, pulmonary infiltrates, or cavitary nodules
Others	Acute kidney failure, dehydration, electrolyte alterations, other alterations of vital signs, other complications considered severe, pregnant/nursing, fractures, uncontrolled progressive cancer, alemtuzumab treatment, inpatient status at time of fever development, physically or medically frail (as determined by the treating physician), need for IV control, the need for urgent radiation therapy

\*adapted from existing guidelines<sup>2,6,7,17,19</sup>

NOTE: This is not a comprehensive list and does not replace the need for independent clinical judgment.



## Appendix 4: Detailed Literature Search Strategy

Date: November 18, 2020

Subject: Cancer Care Ontario GCSF Recommendations Update

Date range: March 2016- Current

Language: English

Database(s): Medline and Embase

((Set 1 OR Set 2) AND Set 3)

Medline

Set 1 GCSF

Exp "Granulocyte Colony-Stimulating Factor"/ or exp "Granulocyte-Macrophage Colony-Stimulating Factor"/ or exp "Biosimilar Pharmaceuticals"/

or

(Granulocyte Colony-Stimulating Factor or Granulocyte Colony-Stimulating Factors or Granulocyte-Macrophage Colony-Stimulating Factor or G-MCSF or GMCSF or GCSF or G-CSF).tw,kw

or

(Biosimilar\$).tw,kw

or

((Biologic\$) and (Follow-on or subsequent entry)).tw,kw

Set 2 Primary prophylactic management

Exp Antibiotic Prophylaxis/ or exp Infection Control/

or

((Antibiotic\* or Anti-fungal\* or antifungal\* or antiviral\* or anti-viral or anti-microb\* or antimicrob\* or primary)

adj2 (prophyla\* or Premedicat\*)).tw,kw

or

(infection control).tw,kw

Set 3 Febrile neutropenia prevention

Exp Antineoplastic Combined Chemotherapy Protocols/ or exp Neoplasms/dt [drug therapy]

or

(chemotherap\* or chemotreat\* or chemo-treat\* or neoadjuvant chemotherapy treatment\* or adjuvant chemotherapy treatment\*).tw,kw

and

Exp Fever/pc [Prevention and control] or exp Neutropenia/pc [Prevention and control]

or

(febrile neutropenia or FN prophyla\* or drug fever\*).tw,kw

Embase

Set 1 GCSF

Exp "Granulocyte colony stimulating factor"/ or exp "granulocyte macrophage colony stimulating factor"/ or exp "Biosimilar Agent"/

or

(Granulocyte Colony-Stimulating Factor or Granulocyte Colony-Stimulating Factors or Granulocyte-Macrophage Colony-Stimulating Factor or G-MCSF or GMCSF or GCSF or G-CSF).tw,kw

or

(Biosimilar\$).tw,kw

or

((Biologic\$) and (Follow-on or subsequent entry)).tw,kw

Set 2 Primary prophylactic management

Exp Antibiotic Prophylaxis/ or exp Infection Control/

or

((Antibiotic\* or Anti-fungal\* or antifungal\* or antiviral\* or anti-viral or anti-microb\* or antimicrob\* or primary)

adj2 (prophyla\* or Premedicat\*)).tw,kw

or

(infection control).tw,kw

Set 3 Febrile neutropenia prevention

Exp Antineoplastic agent/ or exp Neoplasm/dt [drug therapy]

(chemotherap\* or chemotreat\* or chemo-treat\* or neoadjuvant chemotherapy treatment\* or adjuvant chemotherapy treatment\*).tw,kw  
and

Exp drug fever/pc [Prevention and control] or exp Febrile Neutropenia/pc [Prevention and control]  
or

(febrile neutropenia or FN prophyla\* or drug fever\*).tw,kw

Search history

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 17, 2020> November 18, 2020

#	Searches	Results
1	exp "Granulocyte Colony-Stimulating Factor"/ or exp "Granulocyte-Macrophage Colony-Stimulating Factor"/ or exp "Biosimilar Pharmaceuticals"/	31011
2	(Granulocyte Colony-Stimulating Factor or Granulocyte Colony-Stimulating Factors or Granulocyte-Macrophage Colony-Stimulating Factor or G-MCSF or GMCSF or GCSF or G-CSF).tw,kw.	34012
3	Biosimilar\$.tw,kw.	3715
4	(Biologic\$ and (Follow-on or subsequent entry)).tw,kw.	244
5	1 or 2 or 3 or 4	46644
6	exp Antibiotic Prophylaxis/ or exp Infection Control/	80495
7	((Antibiotic* or Anti-fungal* or antifungal* or antiviral* or anti-viral or anti-microb* or antimicrob* or primary) adj2 (prophyla* or Premedicat*)).tw,kw.	22682
8	infection control.tw,kw.	21613
9	6 or 7 or 8	110535
10	exp Antineoplastic Combined Chemotherapy Protocols/ or exp Neoplasms/dt	537394
11	(chemotherap* or chemotreat* or chemo-treat* or neoadjuvant chemotherapy treatment* or adjuvant chemotherapy treatment*).tw,kw.	419273
12	10 or 11	771154
13	exp Fever/pc or exp Neutropenia/pc	2326
14	(febrile neutropenia or FN prophyla* or drug fever*).tw,kw.	7199
15	13 or 14	9033
16	12 and 15	5999
17	9 and 16	510
18	5 and 16	1581
19	17 or 18	1782
20		
21	limit 19 to ed=20160301-20211231	
Limit 20 to english language		394
357		

Embase <1996 to 2020 Week 46>

#	Searches	Results
1	exp "Granulocyte colony stimulating factor"/ or exp "granulocyte macrophage colony stimulating factor"/ or exp "Biosimilar Agent"/	72468
2	(Granulocyte Colony-Stimulating Factor or Granulocyte Colony-Stimulating Factors or Granulocyte-Macrophage Colony-Stimulating Factor or G-MCSF or GMCSF or GCSF or G-CSF).tw,kw.	41473
3	Biosimilar\$.tw,kw.	7657
4	(Biologic\$ and (Follow-on or subsequent entry)).tw,kw.	417
5	1 or 2 or 3 or 4	87970
6	exp Antibiotic Prophylaxis/ or exp Infection Control/	123434
7	((Antibiotic* or Anti-fungal* or antifungal* or antiviral* or anti-viral or anti-microb* or antimicrob* or primary) adj2 (prophyla* or Premedicat*)).tw,kw.	29337
8	infection control.tw,kw.	27389
9	6 or 7 or 8	149397
10	exp Antineoplastic agent/ or exp Neoplasm/dt	2033553
11	(chemotherap* or chemotreat* or chemo-treat* or neoadjuvant chemotherapy treatment* or adjuvant chemotherapy treatment*).tw,kw.	581329
12	10 or 11	2234778

13 exp drug fever/pc or exp Febrile Neutropenia/pc 1141  
 14 (febrile neutropenia or FN prophyla\* or drug fever\*).tw,kw. 15217  
 15 13 or 14 15773  
 16 12 and 15 13403  
 17 9 and 16 1124  
 18 5 and 16 3088  
 19 17 or 18 3544  
 20 (conference abstract or "Case Reports" or editorial or comment or letter or newspaper article).pt.  
 5356100  
 21 19 not 20 2117  
 22 limit 21 to em=201610-202152 569  
 23 limit 22 to english language 539  
 24 remove duplicates from 23 531

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