Ontario Health
Cancer Care Ontario

Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients

Clinical Practice Guideline – Summary of Recommendations

Crespo A, Forbes L, Vu K, Gallo-Hershberg D, Enright K, Abdallah M, Febbraro M, Gowanlock T, Kennedy K, Lim C, Liu S, Mackenzie T, Newton J, Spadafora S, Zeppieri J

November, 2021; updated January, 2022

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 ≥ 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 ≥ 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[18]

For regimens that are < every 14 days:

Filgrastim* 300 mcg (if < 90 kg) or 480 mcg (if ≥ 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

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.

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.

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.

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.

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.

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 ≤ 1 x 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.*

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 3rd generation cephalosporin.

***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** (≥ 20mg prednisone daily** for ≥ 4 weeks), and **temozolomide with concurrent radiotherapy**.***

  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.
** or equivalent dose of corticosteroid (e.g. ≥ 3mg dexamethasone daily for ≥ 4 weeks)
***Prophylaxis should continue for duration of anticipated neutropenia and depends on disease, regimen, and patient factors.

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.

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.

Acyclovir 400 mg PO twice daily

OR

Valacyclovir 500 mg PO twice daily

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).

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,

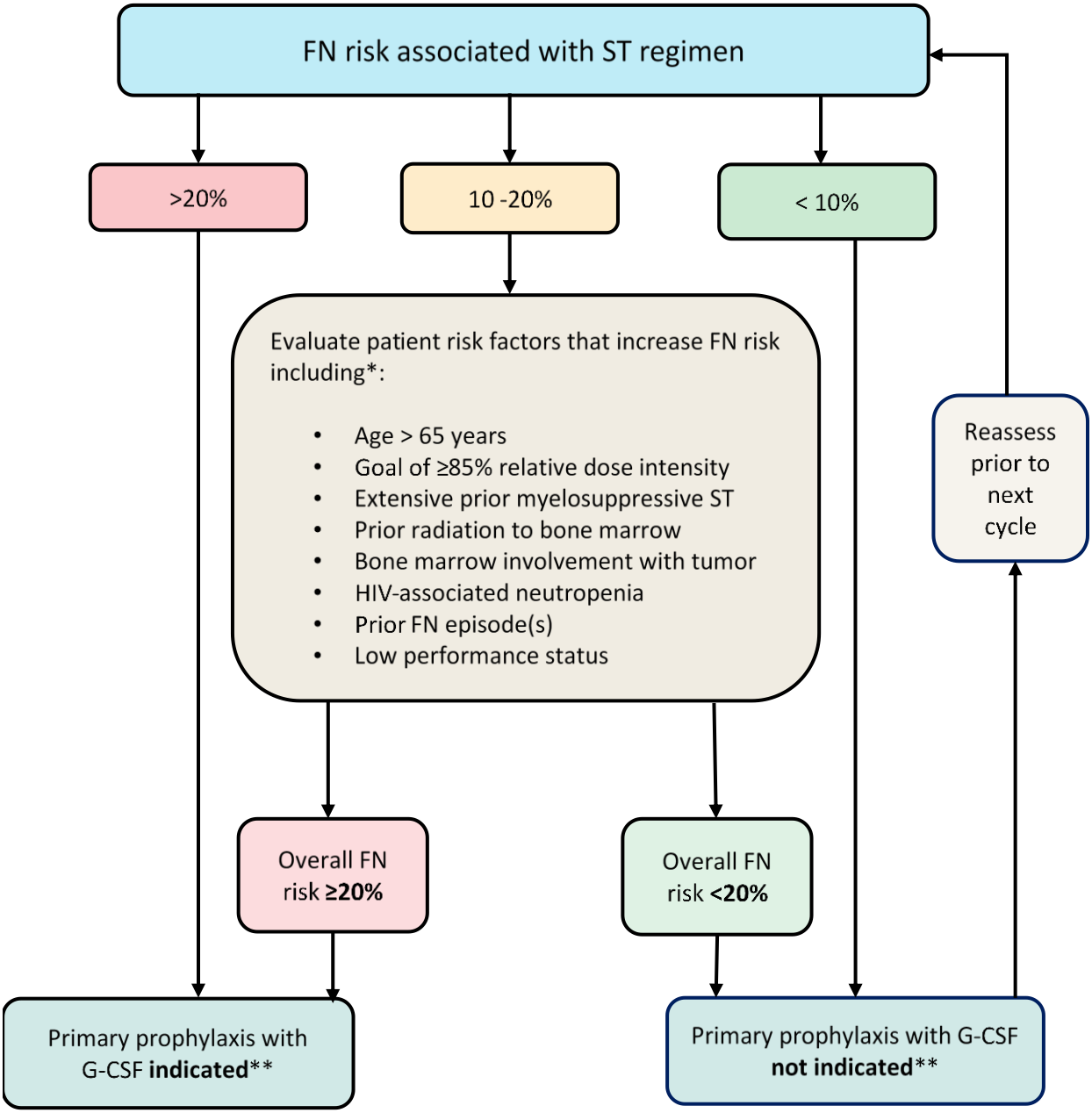
and comorbidities. The risk factors with the highest level of evidence are outlined in Figure 1. Refer to appendix 1 for a more extensive list of risk factors.

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.

Figure 1 : Evaluating febrile neutropenia (FN) risk based on systemic treatment (ST) regimen and patient factors



*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.

Clinical Question 6:

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

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.

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.

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).

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.

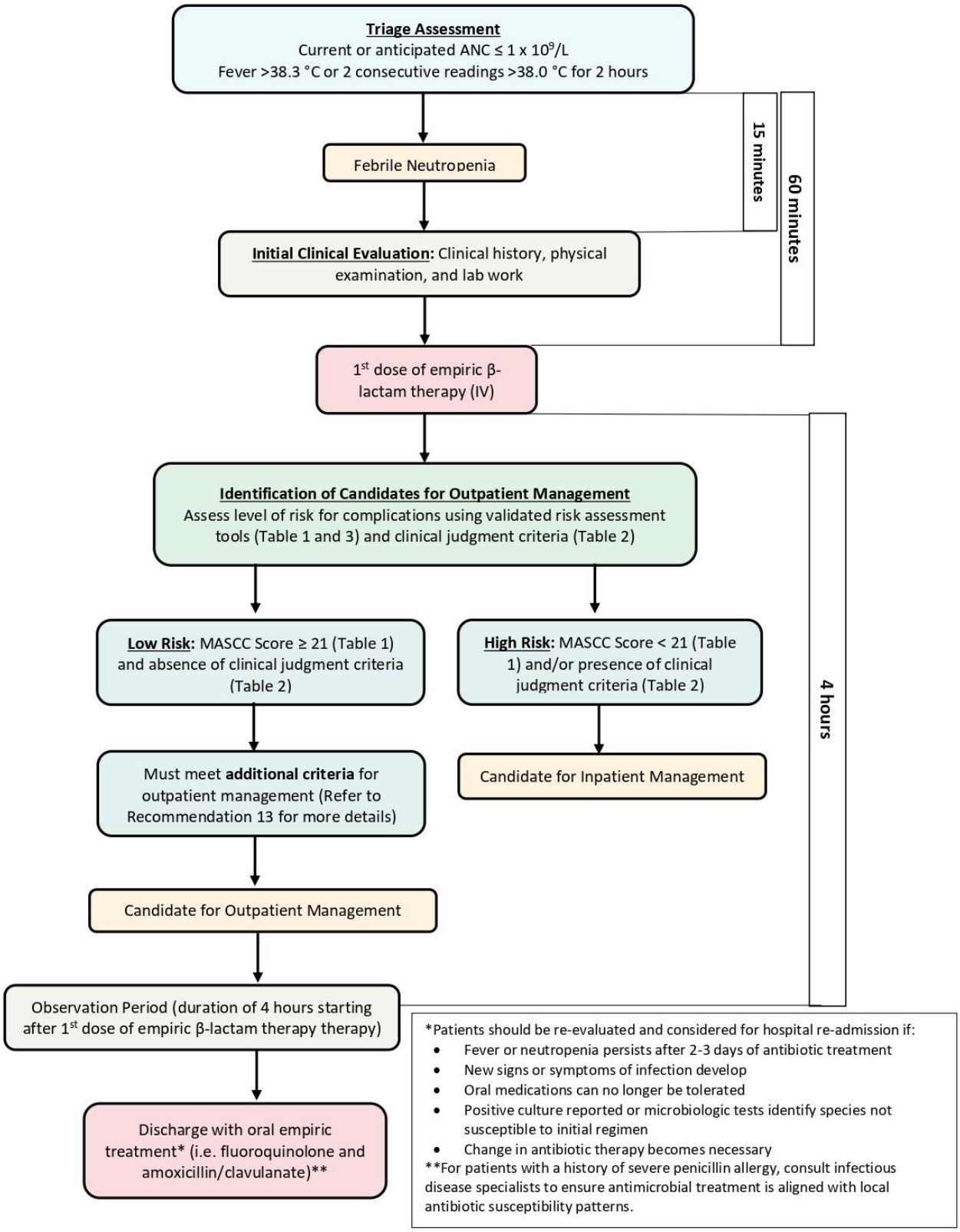
Clinical Question 10:

Is there a role for G-CSF in the setting of neutropenia in patients receiving immune checkpoint inhibitors (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.

Figure 2: Overview of Outpatient Management of FN



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.

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:

β-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.

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 ≥ 21.
- Refer to Table 2 below for a list of risk factors for complications that contraindicate initial outpatient management (even if MASCC score is ≥ 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

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 ≥ 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*

High Risk (Outpatient management contraindicated if patient meets ANY of the below criteria)
• Inpatient status at time of fever development • MASCC Score < 21 • Significant medical comorbidity or clinically unstable • Anticipated prolonged severe neutropenia (ANC ≤ 1 x 10^9/L for ≥ 7 days) or profound neutropenia (ANC < 0.1 x10^9) • Hepatic insufficiency (aminotransferase levels > 5X ULN) • Renal insufficiency (CrCl < 30 mL/min) • Uncontrolled/progressive cancer • Pneumonia or other complex infection(s) • Severe mucositis (Grade 3 or higher) • CISNE score ≥ 3 (see below; for patients with solid tumours)

*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)

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 10^9/L	1

Low risk=0
Intermediate risk= 1 to 2
High risk= 3 to 8

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:

- 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

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:

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.

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*:
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.

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 > $0.5x10^9$/L for ≥ 2 days

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

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

For a complete list of references and a detailed summary of the evidence and discussion, refer to the full report: Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients Clinical Practice Guideline

Need this information in an accessible format? 1-877-280-8538, TTY 1-800-855-0511 info@ontariohealth.ca.