FOX CHASE CANCER CENTER
FEBRILE NEUTROPENIA EMPIRIC TREATMENT GUIDELINE

This document is designed to serve as a guideline and is not meant to be a strict procedure. Deviations from the treatment decisions established by this guideline or protocol are allowed, as deemed medically appropriate by the treating providers, in order to optimize care for an individual patient.

References:

1. Freifeld AG, Bow EJ, Sepkowitz KA. et. al: Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56-93. doi: 10.1093/cid/cir073.
2. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.;2024. Accessed March 29, 2024.
3. National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections (Version 2.2023 – December 5, 2023). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed March 25, 2024.
4. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-655. PMID: 7165009.
5. Taplitz RA, Kennedy EB, Bow EJ. et. al: Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018 May 10;36(14):1443-1453. doi: 10.1200/JCO.2017.77.6211. Epub 2018 Feb 20.

The purpose of this guideline is to improve and standardize the empiric treatment of febrile neutropenia in adult patients at Fox Chase Cancer Center in the Direct Referral Unit (DRU) and inpatient units. This guideline is based on the best available evidence and practices, as determined by the National Comprehensive Cancer Network, the Infectious Diseases Society of America, and the American Society of Clinical Oncology.

DEFINITIONS

CISN: Clinical Index of Stable Febrile Neutropenia
CrCl: Creatinine clearance
ECOG: Eastern Cooperative Oncology Group
Hb: Hemoglobin
Hct: Hematocrit
HCT: Hematopoietic cell transplantation
ID: Infectious Diseases
IV: Intravenous
MASCC: Multinational Association of Supportive Care in Cancer
MRSA: Methicillin-resistant *Staphylococcus aureus*
PO: Oral
ULN: Upper limit normal
VRE: Vancomycin-Resistant Enterococci

GUIDELINE

1. Initial Evaluation of fever and neutropenia

Fever:

- Single temperature equivalent to ≥38.3°C (101°F) orally
- Equivalent to ≥38.0°C (100.4°F) orally over 1-hour period

Neutropenia:

- ≤500 neutrophils/mcL
- ≤1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 hours

2. Empiric treatment recommendations for patients with low risk

Risk Level	Criteria	Treatment Options
Low	**None of the high-risk factors and most of the following:** • Outpatient status at time of development of fever • No associated acute comorbid illness, independently indicating inpatient treatment or close observation • Anticipated short duration of severe neutropenia (≤100 cells/mcL for <7 days) • Good performance status (ECOG* 0–1) • No hepatic insufficiency • No renal insufficiency • MASCC* Risk-Index Score of ≥21 or CISNE* score of <3 • Solid tumors who have undergone chemotherapy and appear to be clinically stable	**Outpatient PO antibiotic therapy:** • Ciprofloxacin plus amoxicillin/clavulanate (PCN allergy: ciprofloxacin plus clindamycin) • Levofloxacin Oral antibiotic regimen <u>not</u> recommended if patient received prior quinolone prophylaxis **Specific reasons to return to clinic:** • Any positive culture from blood or other sterile source • New signs/symptoms reported by the patient • Persistent or recurrent fever at 3–5 days • Inability to continue prescribed antibiotic regimen (i.e., oral intolerance)
*see appendix		

2-A. Dosing Recommendations for PO antibiotics

PO antibiotic	Creatinine Clearance (ml/min)			
	≥50	30-49	10-29	<10 or HD*
Amoxicillin/clavulanate	875/125 mg q12h	875/125 mg q12h	500/125 mg q12h	500/125 mg q24h
Ciprofloxacin	750 mg q12h	750 mg q12h	750 mg q24h	750 mg q24h
Clindamycin	300 mg q6h			
Levofloxacin	750 mg regimen			
	750 mg q24h	CrCl 20-49 ml/min: 750 mg q48h CrCl <20 ml/min or HD*: 750 mg x1, then 500 mg q48h or 250 mg q24h		
	500 mg regimen			
	500 mg q24h	CrCl 20-49 ml/min: 500 mg x1, then 250 mg q24h CrCl <20 ml/min or HD*: 500 mg x1, then 250 mg q48h		
*give dose after hemodialysis (HD)				

3. Empiric treatment recommendations for patients with high risk

- The first dose of empirical therapy should be administered within 1 hour after triage from initial presentation
- Patients colonized or suspected to have MRSA, VRE, or *Stenotrophomonas* infection should be considered for inpatient management

Risk Level	Criteria	Treatment Options
High	**Any of the following:** • MASCC* Risk-Index Score of <21 or CISNE score of ≥3 • Inpatient status at time of development of fever • Significant medical comorbidity or clinically unstable • Allogeneic HCT • Anticipated prolonged severe neutropenia: ≤100 cells/mcL and ≥7 days • Hepatic insufficiency (5x ULN for aminotransferases) • Renal insufficiency (CrCl <30 mL/min) • Severe thrombocytopenia (<10,000 platelets/mcL)	**Inpatient IV antibiotic therapy:** • Cefepime (consider adding metronidazole for suspected gingivitis, neutropenic enterocolitis, or peri-rectal cellulitis) • Piperacillin/tazobactam • Meropenem • For severe beta-lactam allergy: vancomycin plus aztreonam, consider ID consultation (consider adding metronidazole for suspected gingivitis, neutropenic enterocolitis, or peri-rectal cellulitis) **Empiric Addition of Vancomycin:** Routine addition of vancomycin to initial therapy is <u>not</u> recommended. Vancomycin should be discontinued, if already initiated, within 48-72 hours if neither MRSA nor Enterococcus are identified.

	• Anemia (Hb <7 g/dL or Hct <21%) • Has received alemtuzumab • Uncontrolled/progressive cancer (e.g. any patients with leukemia not in complete remission, or patients with other cancers and evidence of disease progression after more than 2 courses of chemotherapy) • Pneumonia or other complex infections at clinical presentation • Mucositis grade 3–4	Vancomycin should be considered only in patients at high risk for serious gram-positive infection in the following situations: • Clinically apparent, serious IV catheter-related infection (to cover coagulase-negative staphylococcal isolates, which are usually beta-lactam antibiotic-resistant and MRSA) • Blood cultures positive for gram-positive bacteria before final identification and susceptibility testing • Known colonization with penicillin/cephalosporin–resistant pneumococci or MRSA • Clinical instability (e.g., hypotension or shock), pending the results of cultures • Soft tissue infection (particularly in regions where MRSA infection is common) • Severe cases of pneumonia with hypoxia or extensive infiltrates or if MRSA is suspected (sputum culture and MRSA nares swabs are recommended)
*see appendix		

3-A. Dosing Recommendations for IV antibiotics

IV antibiotic	Creatinine Clearance (ml/min)				
	≥50	30-49	10-29	<10 or HD*	CVVHDF
Aztreonam	2 g q8h	2 g q8h	2 g q12h	2 g q24h	2 g q12h
Cefepime	2 g q8h	2 g q12h	2 g q24h	1 g q24h	2 g q12h
Meropenem	2 g q8h	2 g q12h	1 g q12h	1 g q24h	2 g q12h
Metronidazole	500 mg q12h				
Piperacillin/tazobactam	CrCl ≥20 ml/min: Loading dose 4.5 g over 30 minutes once, followed by 3.375 g over 4 hours q8h CrCl <20 ml/min or HD: 4.5 g over 30 minutes q12h				4.5 g over 30 minutes q8h
Vancomycin	Please utilize Pharmacy-To-Dose consultation service				
*give dose after hemodialysis (HD)					

4. Duration of therapy

<table>
<tr><th>Clinical Stability</th><th>Source of Fever</th><th>Therapy Duration</th></tr>
<tr><td rowspan="3">Clinically stable or improving and fever resolved</td><td>known</td><td>Complete a standard course of antimicrobial therapy for that source or until neutrophils ≥500 cells/mcL, whichever is longer</td></tr>
<tr><td rowspan="2">unknown</td><td>Neutrophils ≥500 cells/mcL: discontinue antimicrobial therapy</td></tr>
<tr><td>Neutrophils <500 cells/mcL: In patients who defervesce for at least 48 hours, consider de-escalating to prophylaxis until neutropenia resolves
Levofloxacin 500-750 mg q24h</td></tr>
<tr><td>Clinically worsening
OR
Fever ≥ 4 days of empiric antibiotic therapy</td><td colspan="2">ID consultation to discuss changing therapy:
Broadening coverage
Addition of anti-fungal therapy</td></tr>
</table>

APPENDIX

Table 2. 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 (ie, systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease†	4
Solid tumor 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.[7]

Abbreviations: FN, febrile neutropenia; MASCC, Multinational Association for Supportive Care in Cancer.

*Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score, 5), moderate symptoms (score, 3), and severe symptoms or moribund (score, 0). Scores of 3 and 5 are not cumulative.

†Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, or need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

‡Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

Taplitz RA, et. al. *J Clin Oncol*. 2018 May 10;36(14):1443-1453.

Table 4. The Clinical Index of Stable Febrile Neutropenia

Explanatory Variable*	No. of Points
Eastern Cooperative Oncology Group performance status ≥ 2	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2	1
Monocytes < 200/μL	1
Stress-induced hyperglycemia	2

*The six variables are integrated into a score ranging from 0 to 8, which classifies patients into three prognostic classes: low risk (0 points), intermediate risk (1 to 2 points), and high risk (≥ 3 points).

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GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken MM, et. al. *Am J Clin Oncol.* 1982 Dec;5(6):649-655.

Revision history

12/2018	1. Approved by the FCCC AMS Committee and the P&T Committee
05/2019	1. Updated from 2018
05/2024	Following updates made: 1. Risk criteria for low and high modified 2. CISNE added 3. Low risk outpatient antibiotic therapy recommendation updated 4. High risk inpatient antibiotic therapy recommendation updated 5. Vancomycin addition criteria updated 6. Medication dosing table included 7. Duration (neutrophil count cut-off) updated