Febrile neutropenia (FN)

Neutrophils are critical in providing host defense against infection. If not rapidly and appropriately managed, neutropenic fever syndromes (FN) can lead to major complications in 25-30% of cases, with mortality in up to 11%. In the setting of septic shock, mortality can be as high as 50%. Patients with fever seeking emergency care within 6 weeks of receiving chemotherapy should be rapidly triaged and receive empiric antibiotics within: 1 hour of presentation *if clinically unstable* (tachycardia, hypotensive, tachypnea > 30, altered mental status), or within 2h if clinically stable.
The focus of this guideline is on the appropriate empiric antibiotic management of FN. It does not include the full clinical management of FN or recommendations for prophylaxis.

DEFINITION OF NEUTROPENIA: Absolute neutrophil count (ANC) equal to or below 0.5 following chemotherapy or ANC expected to decrease below 0.5 within 48 hours

DEFINITION OF FEVER: Oral temperature of > 38°C for a period of 1 hour or peak ≥ 38.3°C

MOST COMMON BACTERIAL ORGANISMS

Empiric therapy is directed at *S. aureus*, Enterobacteriacea (e.g. *E. coli, Klebsiella sp*), other gram-negative bacilli (e.g. *Pseudomonas sp)*, *Streptococcus sp*

CATEGORIZATION

Low risk (all of the criteria)	• Expected duration of neutropenia < 7 days • **CISNE* score < 2** • No or minimal comorbidities • Clinically and hemodynamically stable • Adequate renal (CrCl > 30 mL/min) and hepatic function (ALT < 5x normal value, INR normal)
High risk (≥ 1 of the criteria)	• Profound neutropenia (ANC ≤ 0.1) expected to last > 7 days • **CISNE* score ≥ 3** • Allogenic stem cell transplant recipient • Acute myeloid leukemia (AML) • High risk myelodysplastic syndrome (MDS) • Clinically unstable (e.g. hypotension requiring vasopressors, altered mental status) • New pulmonary infiltrate or underlying COPD • Unable to tolerate PO intake (mucositis) • Renal failure (CrCl < 30 mL/min) • Hepatic failure (ALT ≥ 5x normal value)

***CISNE**
(Clinical Index of Stable FN)

Variable	*Points*
ECOG status ≥ 2	2
COPD	1
Chronic cardiovascular disease	1
Mucositis grade ≥ 2	1
Monocytes < 200/μL	1
Stress-induced hyperglycemia	2
*0 points = **Low risk***	
*1-2 points = **Intermediate risk***	
*≥3 points = **High risk***	

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INITIAL DIAGNOSTIC TESTS

- 2 sets of blood cultures (ideally both from peripheral access, and *before* antibiotics)
- CBC, creatinine, LFTs
- Urine culture
- Culture other sites according to clinical symptoms
- Chest X-ray

EMPIRIC TREATMENT

Low risk **Consider outpatient management**	First choice: **Ciprofloxacin** 500 mg PO BID ***AND*** **Amoxicillin-clavulanate** 875/125 mg PO BID
	If type 1 β-lactam allergy: Ciprofloxacin 500 mg PO BID *AND* Clindamycin 450 mg PO QID
High risk **In-patient management**	First choice: **Piperacillin-tazobactam** 4.5 g IV q6h *Add vancomycin ONLY if known colonization with MRSA, if clinical signs of central line infection, or if in septic shock* *Reassess vancomycin at 72 hours if no β-lactam resistant gram (+) organisms identified*
	***If type 1 β-lactam allergy**: Consult ID*

DURATION OF EMPIRIC TREATMENT

- Until clinically recovered and afebrile for ≥ 72 h off antipyretics, or ANC > 500 (whichever occurs first)
- If source of infection identified, base decision of duration on specific source
- If persistent fever for more than 4 days without obvious cause or recrudescent fever: consider adding antifungals after appropriate work-up in consultation with ID

ADDITIONAL COMMENTS

Fluoroquinolones: FDA black box safety warnings have been issued regarding:

- Increased risk of ruptures or tears in the aorta blood vessel (2018)
- Significant decreases in blood sugar and certain mental health side effects (2018)
- Disabling side effects of the tendons, muscles, joints, nerves, central nervous system (2016)
- Peripheral neuropathy (2013)
- Tendinitis and tendon rupture (2008)

REFERENCES

- Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, 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;36(14):1443-53.
- Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, 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;52(4):e56-93.

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