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 as promptly as possible (ideally 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*, Enterobacterales (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***	

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** 750 mg PO BID ***AND*** **Amoxicillin-clavulanate** 875/125 mg PO BID
	If severe hypersensitivity reaction to penicillin: Ciprofloxacin 750 mg PO BID *AND* Clindamycin 450 mg PO QID
High risk **In-patient management**	*Patient on **NO** methotrexate or on low-dose (dose lower than 500mg/m^2) IV or Intrathecal methotrexate* **Piperacillin-tazobactam** 4.5 g IV q6h (extended infusion over 3h) *Patient on **high-dose** methotrexate (dose greater than 500mg/m^2)* **Meropenem** 1g IV q8h until methotrexate levels less than 0.05mmol/L then switch to **Piperacillin-tazobactam** 4.5g IVq6h (extended infusion over 3h) *Add vancomycin **ONLY** if known colonization with MRSA, if clinical signs of central line infection, or if in septic shock* *Consult Pharmacy for Vancomycin dosing* *Reassess vancomycin at 72 hours if no β-lactam resistant gram (+) organisms identified*
	If severe hypersensitivity reaction to penicillin: *Meropenem* ***1g IV q8h*** ***If severe hypersensitivity reaction to all beta-lactams:*** *Consult ID*

*Fluoroquinolones have several FDA black box safety warnings (ex: tendinitis, tears of aorta blood vessels and neurotoxicity)

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

REFERENCES

- Taplitz RA, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and IDSA Clinical Practice Guideline Update. J Clin Oncol. 2018;36(14):1443-53.
- Freifeld AG, 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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