

Review article

Management of febrile neutropenia in adult cancer patients: a practical step-by-step guide for emergency and clinical practice

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ABSTRACT

Febrile neutropenia is a life-threatening oncological emergency requiring immediate evaluation and treatment. Rapid recognition, risk stratification, and empiric antimicrobial administration within the first hour (the golden hour) are essential to lower mortality. This practical guide presents a streamlined framework for managing adult cancer patients with febrile neutropenia. We discuss diagnostic work-up, risk assessment via MASCC and CISNE scores, empiric antibiotic selection, criteria for outpatient care, and therapeutic use of granulocyte colony-stimulating factors.

Key words: febrile neutropenia, oncological emergencies, empiric antimicrobial therapy, MASCC score, CISNE score

INTRODUCTION AND CLINICAL DEFINITIONS

Febrile neutropenia (FN) is a major dose-limiting toxicity of cytotoxic chemotherapy that places patients at high risk for overwhelming sepsis and rapid clinical deterioration [1, 2]. Mortality rates range from 5% in low-risk solid tumor populations to over 15% in high-risk hematological malignancies or severe septic shock [2, 3].

Accurate management begins with strict diagnostic criteria [1, 4]:

- **Fever:** a single oral temperature measurement of $\geq 38.3^{\circ}\text{C}$ (101.0°F) or a sustained temperature of 38.0°C (100.4°F) for more than one hour.
- **Neutropenia:** an absolute neutrophil count (ANC) of $<500/\mu\text{L}$, or an ANC predicted to decline to $<500/\mu\text{L}$ within the subsequent 48 h.

$$\text{ANC} = \text{WBC} \times (\% \text{neutrophils} + \% \text{bands}) / 100$$

The primary determinant of infection severity is the duration and depth of neutropenia [1]. Patients with prolonged neutropenia (>7 days) and severe nadirs ($\text{ANC} < 100/\mu\text{L}$) face the highest incidence of documented bacteremia and invasive fungal infections [1, 5]. Emergency management mandates initiating empiric systemic antibacterial therapy within 60 min of triage [2, 6].

TRIAGE AND RISK STRATIFICATION

Not all patients with FN require prolonged inpatient admission or intravenous broad-spectrum coverage [4, 7]. Risk stratification must occur immediately upon triage to distinguish high-risk candidates requiring inpatient hospitalization from low-risk candidates suitable for outpatient oral therapy [1, 7].

HIGH-RISK FEATURES

Patients exhibiting any of the following parameters are classified as high risk [1, 4]:

- Anticipated duration of severe neutropenia ($\text{ANC} < 100/\mu\text{L}$) exceeding 7 days.
- Significant medical comorbidities (e.g., hemodynamic instability, altered mental status, severe chronic obstructive pulmonary disease, acute renal or hepatic impairment).
- Inpatient status at the onset of fever.
- Severe local infection signs (e.g., pneumonia, complex soft-tissue infection, central line catheter-site infection, or severe mucositis).

VALIDATED RISK SCORING SYSTEMS

Two primary scoring tools guide clinical decision-making:

1. **Multinational Association for Supportive Care in Cancer (MASCC) Risk Index:** evaluates general clinical status, burden of illness, presence of hypotension, chronic lung disease, tumor type, dehydration, and age [8]. A MASCC score ≥ 21 denotes low risk for severe complications [8].
2. **Clinical Index of Stable Febrile Neutropenia (CISNE):** Specifically validated for outpatients with solid tumors presenting with apparently stable FN [9]. A CISNE score of 0 classifies the patient as low risk, whereas scores of 1–2 indicate intermediate risk and ≥ 3 represent high risk [9].

INITIAL DIAGNOSTIC WORKUP

The diagnostic workup must be thorough but must **never delay** the initial administration of empiric antimicrobial agents [1, 6].

Table 1. Risk stratification systems for patients presenting with febrile neutropenia. Comparison of MASCC and CISNE scoring systems.

Scoring system	Evaluated parameters	Scoring/cut off thresholds	Clinical management strategy
MASCC Risk Index (Multinational Association for Supportive Care in Cancer)	• burden of illness (no/mild = 5, moderate = 3, severe = 0) • absence of hypotension ($\text{SBP} > 90 \text{ mmHg}$) = 5 • absence of COPD = 4 • solid tumor OR hematological malignancy without prior fungal infection = 4 • no dehydration requiring i.v. fluids = 3 • outpatient status at onset = 3 • age < 60 years = 2	Score: ≥ 21 – low risk (risk of severe complications $< 5\%$; mortality $< 1\%$) < 21 – high risk	Low risk: eligible for early discharge or outpatient oral antibiotic therapy. High risk: mandatory inpatient admission with i.v. broad-spectrum antibiotics.
CISNE Score (Clinical Index of Stable Febrile Neutropenia – for solid tumors)	• ECOG performance status ≥ 2 = 2 • stress hyperglycemia ($> 121 \text{ mg/dL}$) = 2 • COPD = 1 • chronic cardiovascular disease = 1 • mucositis $\geq$ grade 2 (CTCAE) = 1 • monocytes $< 200/\mu\text{L}$ = 1	Score: 0 – low risk (1.1% complication rate) 1–2 – intermediate risk (6.2% complication rate) ≥ 3 – high risk (24% complication rate)	Score 0: high safety profile for outpatient management. Score 1–2: close outpatient monitoring or short observation. Score ≥ 3: inpatient admission required.

CISNE – Clinical Index of Stable Febrile Neutropenia; COPD – chronic obstructive pulmonary disease; CTCAE – Common Terminology Criteria for Adverse Events; ECOG – Eastern Cooperative Oncology Group; i.v. – intravenous; MASCC – Multinational Association for Supportive Care in Cancer; SBP – systolic blood pressure.

1. Microbiological cultures:

- **Blood cultures** – draw at least 2 sets of blood cultures simultaneously before antimicrobial infusion [1, 4]. If a central venous catheter (CVC) or port is present, draw one set from each lumen and one set from a peripheral vein [1]. If no peripheral access is obtainable, draw two sets from different central lumens [1].
- **Site-specific cultures** – obtain urine, sputum, stool, or cutaneous lesion cultures only when clinical signs or symptoms localize to those specific anatomical sites [1, 4]. Routine swab collection of asymptomatic sites is discouraged [1].

2. Laboratory evaluation:

- Complete blood count (CBC) with differential [1].
- Comprehensive metabolic panel, including serum creatinine, blood urea nitrogen, total bilirubin, and transaminases [1].
- Inflammatory biomarkers: serum C-reactive protein (CRP) and procalcitonin (PCT) aid in monitoring treatment response, though decisions regarding immediate antibiotic initiation should not await these results [2, 10].

3. Diagnostic imaging:

- Chest radiography is indicated for patients with respiratory symptoms or hypoxia [1, 4]. Low-dose computed tomography (CT) of the chest should be prioritized over plain radiographs in high-risk patients with unexplained fever or localized chest symptoms, given its higher sensitivity for early invasive fungal disease or atypical pneumonia [1, 5].

EMPIRIC ANTIMICROBIAL THERAPY FRAMEWORK

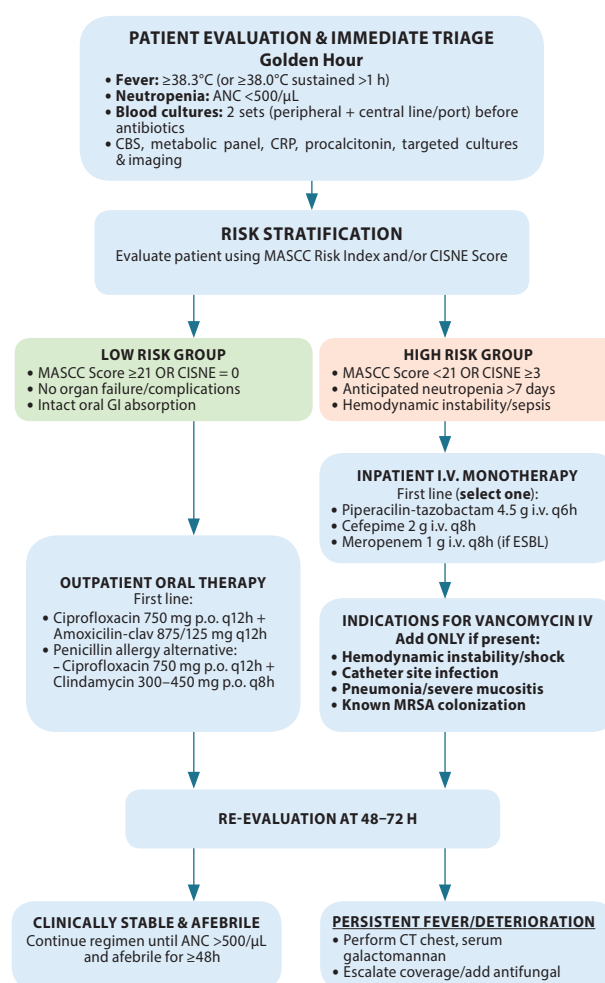
Antimicrobial selection depends on patient risk status, localized epidemiological patterns, previous colonization, e.g., methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum β -lactamase (ESBL), and organ function (fig. 1) [1, 2].

HIGH-RISK INPATIENT MANAGEMENT

High-risk patients require immediate intravenous monotherapy with an antipseudomonal β -lactam agent [1, 4]:

- **piperacillin-tazobactam** (4.5 g i.v. every 6 h) [1]
- **cefepime** (2 g i.v. every 8 h) [1]
- **meropenem** (1 g i.v. every 8 h; preferred if ESBL colonization or history is documented) [1, 2].

Figure 1. Clinical decision algorithm for the emergency evaluation, risk stratification, and initial management of adult cancer patients presenting with febrile neutropenia.



ANC – absolute neutrophil count; CBC – complete blood count; CISNE – Clinical Index of Stable Febrile Neutropenia; CRP – C-reactive protein; CVC – central venous catheter; ESBL – extended-spectrum β -lactamase; GI – gastrointestinal; i.v. – intravenous; MASCC – Multinational Association for Supportive Care in Cancer; MRSA – methicillin-resistant *Staphylococcus aureus*; PCT – procalcitonin; p.o. – per os (orally); q6h – every 6 hours; q8h – every 8 hours; q12h – every 12 hours.

INDICATIONS FOR ADDING GRAM-POSITIVE COVERAGE (E.G., VANCOMYCIN)

Routine empiric inclusion of vancomycin or alternative Gram-positive agents (teicoplanin, linezolid) is **not recommended** due to the risk of selecting resistant strains [1, 11]. Empiric Gram-positive coverage should be reserved for specific clinical triggers [1, 4]:

- Hemodynamic instability or septic shock.
- Suspected catheter-related bloodstream infection (e.g., erythema or purulence at the exit site).
- Radiologically confirmed pneumonia.
- Known colonization with MRSA or penicillin-resistant *Streptococcus pneumoniae*.
- Severe mucositis treated with fluoroquinolone prophylaxis.

LOW-RISK OUTPATIENT MANAGEMENT

Low-risk patients (MASCC ≥ 21 or CISNE 0) who have intact oral absorption, stable vital signs, reliable home support, and rapid access to a medical center can be managed in the outpatient setting [1, 7].

- **First-line oral regimen:** ciprofloxacin (750 mg p.o. every 12 h) plus amoxicillin-clavulanate (875/125 mg p.o. every 12 h) [1, 4].
- **Penicillin-allergic patients:** substitute amoxicillin-clavulanate with clindamycin (300–450 mg p.o. every 8 h) combined with ciprofloxacin [1].
- **Fluoroquinolone prophylaxis caution:** patients who developed FN while receiving prophylactic fluoroquinolones must **not** be treated with oral fluoroquinolones; they require i.v. inpatient management [1, 4].

RE-EVALUATION AT 48–72 H

- **Clinically stable and afebrile:** continue current empiric coverage until ANC recovers to $>500/\mu\text{L}$ and the patient remains afebrile for ≥ 48 h [1, 4].
- **Persistent fever with clinical stability:** antimicrobial adjustment is generally unnecessary within the first 48–72 h if blood cultures are negative and vital signs remain stable [1, 2].
- **Clinical deterioration or persistent fever (>4 –7 days):** expand coverage to address resistant Gram-negative organisms, add empiric Gram-positive therapy if not already initiated, and consider fungal diagnostics (serum galactomannan, CT imaging) with initiation of empiric antifungal therapy (e.g., liposomal amphotericin B, caspofungin, or voriconazole) [1, 5].

ROLE OF GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSFS)

Primary and secondary prophylaxis

- **Primary prophylaxis:** recommended when the overall risk of FN for a given chemotherapy regimen is $\geq 20\%$ [12, 13]. Filgrastim, lenograstim, or pegfilgrastim should be administered 24–48 h after completion of chemotherapy [12].
- **Secondary prophylaxis:** indicated for patients who experienced a prior episode of FN during a previous chemotherapy cycle where primary prophylaxis was omitted, and for whom dose reduction would compromise overall survival [12, 13].

Therapeutic usage

Routine therapeutic administration of G-CSF in patients with established FN is **not recommended** [12, 14]. Therapeutic G-CSF should be restricted to high-risk patients with clear factors predictive of adverse outcomes, such as [12, 14]:

- profound neutropenia (ANC $<100/\mu\text{L}$) expected to be prolonged
- septic shock or severe sepsis
- systemic fungal infections
- pneumonia or progressive multiorgan dysfunction.

PRACTICAL CLINICAL TAKEAWAYS

1. **Enforce the golden hour:** administer the first dose of empiric i.v. antipseudomonal β -lactam within 60 min of presentation.
2. **Stratify early:** use MASCC or CISNE scores to identify candidates safe for outpatient oral management.
3. **Culture correctly:** always obtain blood cultures from both peripheral sites and central lumens prior to antibiotic infusion.

Table 2. Recommended empiric antimicrobial regimens and dosing considerations in adult febrile neutropenia.

Setting/risk group	First-line antibiotic regimen	Standard dosing (adults)	Dose adjustments & clinical notes
High risk (inpatient/i.v.)	piperacillin–tazobactam (monotherapy)	4.5 g i.v. q6h	adjust for CrCl <50 mL/min extended infusion (3.5 h) improves PK/PD efficacy.
	cefepime (monotherapy)	2 g i.v. q8h	adjust for <50 mL/min caution in severe renal impairment (neurotoxicity risk)
	meropenem (monotherapy)	1 g i.v. q8h	preferred if ESBL-producing organism colonization or previous infection is known
Gram-positive addition (specific triggers only)	vancomycin	15–20 mg/kg i.v. q8–12h	target trough level 15–20 $\mu\text{g/mL}$: indicated ONLY for shock, catheter infection, pneumonia, or MRSA
Low risk (outpatient/oral)	ciprofloxacin + amoxicillin-clavulanate	750 mg p.o. q12h + 875/125 mg p.o. q12h	standard first-line oral regimen for low-risk patients with intact oral absorption
Low Risk (penicillin allergy)	ciprofloxacin + clindamycin	750 mg p.o. q12h + 300–450 mg p.o. q8h	substitute clindamycin for amoxicillin-clavulanate in patients with severe β -lactam allergy

CrCl – creatinine clearance; ESBL – extended-spectrum β -lactamase; i.v. – intravenous; MRSA – methicillin-resistant *Staphylococcus aureus*; PD – pharmacodynamics; PK – pharmacokinetics; p.o. – *per os* (orally); q6h – every 6 hours; q8h – every 8 hours; q12h – every 12 hours.

4. **Avoid unnecessary vancomycin:** reserve Gram-positive coverage for specific indications such as hemodynamic instability, catheter infections, or soft-tissue breakdown.
5. **Target G-CSF support:** limit therapeutic G-CSF use to cases complicated by severe sepsis, lung infection, or prolonged severe neutropenia.

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