Guidelines for

MANAGEMENT OF NEUTROPENIC FEVER

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GUIDELINES FOR MANAGEMENT OF NEUTROPENIC FEVER

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1 INTRODUCTION

Most infections in neutropenic patients have minimal clinical signs and symptoms. These infections can progress rapidly resulting in a life-threatening events. Prompt management of the patient is therefore critical.

2 PURPOSE

This guideline has been written in order to standardize treatment of neutropenic fever in patients admitted at AFBMTC

3 DUTIES

All healthcare practitioners (doctors, nurses and pharmacists) involved in the process of managing neutropenic patients should be familiar with and adhere to these guidelines.

4 DEFINITIONS

a. Neutropenic fever

A temperature measurement of ≥38.3 °C (101 F) once or ≥ 38.0 °C (100.4 F) lasting for at least 1 hour or being measured twice within 12 hour in a patient with absolute neutrophil count <500/ul or expected to be less than 500/ul within next 48 hours.

b. Profound neutropenia (High risk for febrile neutropenic episode)

neutrophils <100/µL (equivalent to $0.1x10^9$/L).

period of neutropenia lasts for > 7 days.

Risk stratification of neutropenic fever:

1. Multinational Association of Supportive Care in Cancer (MASCC) criteria

In addition to risk stratification based on duration of neutropenia, there are individual risk factors which places patient at high risk for complicated neutropenic fever. These individual factors can be identified by the use of the Multinational Association of Supportive Care in Cancer (MASCC) criteria (table 1). Low-risk patients with a MASCC score of ≥ 21 constitute a group of patients with a high likelihood of a uncomplicated clinical course of infection.

		Yes	No	Score
Does the patient have a solid tumour or lymphoma (except Burkitts)?		4	0	
Is the patient dehydrated or requiring IV fluids?		0	3	
Is the systolic BP <90 mmHg?		0	5	
How sick is the patient now? (select one)	No or mild symptoms (events barely noticeable, not interfering with performance or functioning)	5	0	
	Moderate symptoms (patient uncomfortable or events influence performance of daily activities)	3	0	
	Severe symptoms (severe discomfort and/or performance of daily activities limited)	0	0	
Is the patient <60 years old		2	0	
Does the patient have COPD?		0	4	
Did the patient develop febrile neutropenia while an inpatient?		0	3	
Total MASCC score:				

Score ≥ 21 = low risk: assess whether patient can be managed as outpatient with oral abx
Score < 21 = high risk: treat as inpatient with iv antibiotics

Identification of early sepsis (qSOFA)

It is important to recognize that patients with neutropenia may not spike fever despite ongoing sepsis or fever may be masked due to use of corticosteroids or antipyretics.
The quick sepsis related organ failure assessment score (qSOFA) is easy to calculate since it only has three components, each of which are readily identifiable at the bedside and are allocated one point:

i. Respiratory rate ≥22/minute
ii. Altered mentation (GCS<15)
iii. Systolic blood pressure ≤100 mmHg

A “positive" qSOFA Score (≥2) suggests high risk of poor outcome in patients with suspected infection. These patients should be more thoroughly assessed for sepsis and for evidence of organ dysfunction

Epidemiology

Commonly documented infections

Common infectious organisms in neutropenic patients include Staphylococcus aureus, Streptococcus spp., enterococci, coagulase-negative staphylococci, Klebsiella pneumonia, gram-negative enterobacteria, and Pseudomonas aeruginosa. Among fungal pathogens,

Candida spp. and Aspergillus spp. are predominant, the latter typically being associated with a prolonged duration of neutropenia in high-risk patients

Baseline screening of newly or re-admitted patients for multidrug-resistant pathogens, i.e., MRSA, VRE, CRE and ESBL, and Fungal scoring should be considered.

Local epidemiological data, previous infections during admission and results of institutional antibiotic sensitivity patterns needs to be considered before selecting empirical antibiotics.

Diagnosis

1. Signs of Infection in Neutropenic Patients

Any one of following:

a. Fever or other signs of fever (chills, shivering, constant or intermittent sweating, body aches, flushed complexion or hot skin)
b. Sore throat, cough, urinary symptoms, skin lesions, diarrhea

Please note that focal signs of infection may be absent

c. Unexplained abdominal pain
d. Unexplained hypotension
e. Unexplained tachycardia

2. Assessment

a. Patients must be seen immediately and assessed (history and examination)
b. Assess the patient's risk of septic complications using MASCC score and qSOFA.
c. Any patient at risk of neutropenia should be considered to be severely neutropenic until blood count is known. Antibiotic treatment should be started as soon as possible, aiming for a **door-to- needle/ fever to needle time of less than 1 hour**.

3. Ongoing Clinical examination

Initial and ongoing clinical assessment should include

a. Temperature
b. Pulse,
c. Blood pressure
d. Respiratory rate
e. Oxygen saturation
f. Fluid balance (input and output charting)
g. Clinical examination should be performed with special attention paid to skin, mucosa, puncture, and vascular catheter exit sites, paranasal sinuses, lungs, and the perianal region

Thorough clinical exam must be repeated daily

4. Base-line investigations for all neutropenic patients

a. Complete blood counts
b. Liver enzymes (Bilirubin, ALT, ALP)
c. Urea, creatinine
d. Serum Sodium, Potassium, magnesium
e. C-reactive protein
f. Serum LDH
g. PT/APTT/INR
h. Urinalysis
i. Chest X-ray
j. USG abdomen (if clinically indicated)

5. Investigations at onset of fever in neutropenia

They must not delay the start of appropriate antibiotic therapy.

a. Samples for Cultures and sensitivity:

i. A minimum of two separate pairs of **blood cultures** must be taken prior to initiation of antibiotic therapy
ii. Separate blood culture sets can be achieved by venipuncture of both arms. If the patient has a indwelling central venous catheter (CVC), one pair should be drawn from a peripheral vein and at least one from the CVC. The diagnostic yield of this approach can be increased by taking blood sample from each lumen of a CVC and by taking three pairs of blood cultures
iii. Other samples for cultures (Urine, stool, sputum, BAL, swabs and other body fluids) should be taken as per patients' symptoms.

b. Repeat baseline laboratory tests described above
c. Serum lactate in selected cases
d. Biomarkers such as procalcitonin, serum Galactomannan, serum Beta-D glucan (if indicated)
e. ***Imaging studies***

i. HRCT scan of the lungs is recommended in the case of respiratory tract symptoms
ii. CT PNS should be done if there is nasal congestion or signs and symptoms of sinusitis
iii. Echocardiography, If clinically indicated
iv. Abdominal ultrasonography In patients with Gastrointestinal complaints or laboratory abnormalities. An abdominal CT scan is an alternative if neutropenic enterocolitis is suspected.

6. Things to avoid

a. Urinary catheterization should not be performed (unless clinically indicated)

b. Vaginal or rectal examinations and suppositories and enemas are **CONTRAINDICATED** in neutropenic patients.

c. Consider removal of CV line if hypotension occurs with line use and with no other identifiable cause, evidence of local line associated soft tissue infection or persistent fever with no other focus.

Treatment of Neutropenic Patients

a. Intravenous fluids, antibiotic therapy and all prescribed medical treatment must be commenced immediately without waiting for results from investigations, aiming for a **door-to-needle / fever to needle time of less than one hour**.

b. Diuretics and anti-hypertensive medications should be reviewed/ withheld during this episode.

c. Check the patient's records for previous infection with multidrug resistant organisms, aspergillosis, *Clostridium difficile* and previous exposure to broad spectrum antibiotics.

d. Antimicrobial agents for empirical first-line therapy

Table 1

Risk Assessment for Patients with Febrile Neutropenia[3,5]

Low Risk (no high-risk factors and most of the following):	High Risk (any factor listed below):
• MASCC risk index score of ≥ 21 • Outpatient status at time of development of fever • No concomitant acute comorbid illness • Anticipated short duration of severe neutropenia (≤ 100 cells/mcL for fewer than seven days) • Good performance status (ECOG 0–1) • No hepatic or renal insufficiency	• MASCC risk index score < 21 • Inpatient status at time of development of fever • Significant medical comorbidity or clinically unstable[a] • Allogeneic HSCT • Anticipated prolonged severe neutropenia (≤ 100 cells/mcL for seven days or longer) • Hepatic insufficiency (5 × ULN for aminotransferases) • Renal insufficiency (CrCl < 30 mL/min) • Uncontrolled/progressive cancer[b] • Pneumonia or other complex infections at clinical presentation • Treatment with alemtuzumab (Campath, Genzyme) • Mucositis grade 3–4

[a]Hypotension, pneumonia, new-onset abdominal pain, or neurological changes (as specified by the Infectious Diseases Society of America).
[b]Leukemia not in complete remission or patients without leukemia with evidence of disease progression after more than two courses of chemotherapy.

CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; HSCT = hematopoietic stem cell transplantation; MASCC = Multinational Association for Supportive Care in Cancer; ULN = upper limit of normal.

i. In high-risk patients, the spectrum of first-line antibacterial agents should include gram-negative enterobacteria, P. aeruginosa, S. aureus, and streptococci, while local epidemiology must be taken into account.

ii. Antimicrobial must be administered within 1 hour of fever onset.

iii. As per AFBMTC antibiogram results obtained in 2020, following is recommended as suitable first line antibiotics

High risk neutropenia (deescalating strategy)

a. *Clinically stable* with no Previous ESBL or MDR organism: Piperacillin-Tazobactum **OR** Cefepime **PLUS** AMIKACIN 15 mg/kg/day.
If *previous ESBL or MDR organism:* Meropenem (adults 1 g TDS, pediatrics 20 mg/kg TDS) OR Imipenem cilastatin 500mg IV 06 hourly.

b. *Clinically unstable (hypotension, hypoxia):* Meropenem (adults 1 g TDS, pediatrics 20 mg/kg TDS) OR Imipenem cilastatin 500mg IV 06 hourly **PLUS** AMIKACIN 15 mg/kg/day

c. *Previous infection with VRE, surveillance culture positive for VRE, MRSA,*

severe sepsis: **ADD** Teicolplanin (adult dose <70 kg , 400 mg every 12 hourly for 3 doses then 400 mg once daily, >70 kg require 6 mg/kg every 12 hourly for 3 doses and then once daily. For children 10 mg/kg every 12 hours for 3 doses, followed by 6 to 10 mg/kg once daily **OR** Linezolid 600 mg BD for adults and 10 mg/kg TDS for children < 12 years

d. *Previous infection with Carbapamanese resistant organism(CRE) /stool surveillance sample positive for CRE/ severe sepsis refractory to combination therapy* : **ADD** Colomycin

e. *Previous invasive fungal infection / PNS involvement* ***: ADD*** *empirical antifungal*

Low risk Neutropenia (Escalating strategy)

1. Clinically stable (Previous no ESBL or MDR organism): Piperacillin-Tazobactum **OR** Cefepime

2. Clinically stable (Previous ESBL or MDR organism): Meropenem **OR** Imipenem

3. Clinically unstable (hypotension, hypoxia): Meropenem **OR** Imipenem **PLUS** AMIKACIN

e. Re-evaluation of patients after 72-96 hours of first-line empirical antibacterial therapy

i. A thorough physical examination must be repeated, with inspection of the oropharynx, skin lesions with particular attention to venous access and puncture sites and the perianal region, as well as tenderness of paranasal sinuses or other signs of upper airway infection
ii. Obtain new blood cultures if new clinical instability develops
iii. Other microbiological cultures are only useful if clinical signs or symptoms indicate a possible site of infection.
iv. Serum Galactomannan, Beta-D glucan, pro-calcitonin should be sent (if not sent earlier)
v. After ≥ 96 h of persistent or recurrent fever despite therapy, a high resolution pulmonary and para nasal sinus CT scan (HRCT chest and PNS) may be performed, even if there are no sinopulmonary symptoms
vi. Other imaging procedures are indicated according to clinical signs or symptom of a localized infection
vii. Consider viral PCRs including Multiplex PCR for resp. Viruses, PCR for CMV and EBV

viii. Patients who demonstrate a gradual improvement in fever curve do not require extensive work-up or change in antimicrobials despite continuous fevers.

ix. Patients who initiated on Teicoplanin or an aminoglycoside for hemodynamic instability should have these therapies discontinued 72 hours after clinical stability and cultures do not identify organisms requiring aminoglycosides (maintain broad-spectrum anti-pseudomonal), or if an alternative source of infection is identified that does not require continued Teicoplanin or aminoglycoside therapy.

x. If fever curve not improving (i.e gradually lower and less frequent fever spikes) for >96 hours without defined etiology, evaluate for other sources of fever like drug fevers, mucositis, GVHD, venous thromboembolism, fever due to active malignancy/disease fever etc

f. <u>Modifying antibiotic treatment in non-responders after 72- 96 hours</u>

i. If a causative pathogen has been isolated, the empirical antibacterial approach should be changed to targeted therapy.

ii. Pre-emptive antimicrobial treatment is chosen/ added according to the spectrum of microorganisms typically involved in the respective clinically documented infection (Table 2).

Clinical signs and symptoms	Frequently involved pathogens
Erythema and/or pain at venous access	Coagulase-negative staphylococci
Mucosal ulcers	Alpha-hemolytic streptococci, *Candida* spp.
Single point-like skin lesions	Gram-positive cocci, *Candida* spp.
Necrotizing skin lesions	*Pseudomonas aeruginosa*, filamentous fungi
Diarrhea, meteorism	*Clostridium difficile*
Enterocolitis, perianal lesions	Polymicrobial (incl. anaerobes)
Lung infiltrates ± sinusitis	Filamentous fungi, *Pneumocystis jirovecii*
Retinal infiltrates	Candidemia

i. Usually, changes in antibiotic regimen are not necessary if clinical conditions are stable. If no signs or symptoms of clinical deterioration (e.g. septic shock, confusion, worsening respiratory function) are present, slow response to antibiotic treatment should be considered, particularly if accompanied by improvement in inflammatory markers such as C-reactive protein, or procalcitonin (particularly for Gram-negative bloodstream infections).

ii. Routine addition of antibiotics against resistant Gram-positives (glycopeptides) has not been shown effective.

iii. A modification or escalation of antimicrobial therapy only because of persistent elevation of inflammatory laboratory parameters has not been successful as well.

iv. Results of galactomannan performed either in screening or at the onset of fever, once available should guide antifungal treatment.

v. A change of antimicrobial therapy with addition of an antifungal is recommended in patients with recurrent or persisting fever and clinical deterioration, instability, or localized signs of infection.

vi. Less frequent agents, such as legionella, mycobacteria, and nonbacterial infections (viral, fungal and parasitic) should be considered in differential diagnosis and tested for, based on clinical presentation and patient's past exposure.

g. Empirical antifungal treatment in high-risk patients

i. For high-risk patients without prior systemic antifungal prophylaxis, ***mould-active empirical antifungal therapy (Amphotericin vs. voriconazole) is recommended, if fever persists for ≥ 96 h*** or if fever relapses despite adequate antibacterial therapy.

ii. For patients receiving oral voriconazole prophylaxis, switch to another mould-active agent (amphotericin-B) for empirical antifungal therapy is recommended.

iii. Liposomal Amphotericin B is preferred in patients with severe sepsis, multi-organ dysfunction, Mucor mycosis.

iv. IV voriconazole can be considered for patients in which amphotericin cannot be administered due to side effects or intolerance

h. Empirical antiviral treatment

Empirical antiviral therapy in febrile neutropenic patients without signs or symptoms typical for a viral infection is not recommended

** **Antibiotic therapy should not be de-escalated or discontinued in patients with persistent fevers, hemodynamic instability or clinical instability thought to be secondary to bacterial infection.**

i. Adjunctive measures

Granulocyte colony-stimulating factor: Its use can be considered to reduce duration of neutropenia in patients who are at high risk for infection-associated complications. High risk features include

i. expected prolonged (more than 10 days) and profound neutropenia (less than 0.1×10^9/L),

ii. age more than 65 years,

iii. uncontrolled primary disease,

iv. pneumonia,

v. hypotension and multi-organ dysfunction (sepsis syndrome),

vi. invasive fungal infection

vii. hospitalization at the time of fever development.

GCSF should only be used following discussion with treating consultant.

j. Duration of empirical antimicrobial therapy after defervescence

i. Empirical antibacterial therapy can be safely discontinued after 72 h of apyrexia provided patient remained hemodynamically stable since the onset of fever , irrespective of the neutrophils count. *Oral step-down is illogical.*

ii. For culture positive infection, treat as per infectious organism

k. General Guidelines for In-Patient Care

i. Protective isolation measures must be taken in accordance with Infection Control Policy.

ii. Educate patient and relatives about the need to avoid visitors

iii. Careful hand washing is the single most important action for the health care professional, patient, patient and attendants, in preventing cross infection.

iv. Fresh flower, plants should not be placed in the patient's room as pathogens could flourish in stagnant water.

v. Food may be a source of infection. Avoid unprepared / raw fresh fruit, raw vegetable, raw egg, dry fruit. Relatives must be informed of food restrictions when bringing food into the ward.

vi. Filtered tap water is recommended for patients.

vii. Face cloths should be avoided and disposable wipes/ masks should be used.

viii. Patients must be encouraged to wash/shower atleast once daily

ix. The rooms should be cleaned daily and all surfaces wiped clean with dis-infectant.

x. Use of alcohol based hand rub is mandatory before examining patient

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Name:	Age/Sex:
Disease:	Status:
Risk stratification for Neutropenia:	Low/ High
Candidate for Neutropenic Regime	Escalating/deescalating
Previous history	Bacterial colonization Resistant bacterial infections Prolong antimicrobial use
Clinical examination:	B.P Pulse R/R Temp SPO2 Systemic Examination:
Survillance tests:	MRSA/ VRE/ CRE
Lab Investigations: CRP PCT Serum Lactate Blood cultures Beta D glucan/Serum Galactomannan Other specimen for cultures	
Imaging Studies: CXR CT scan	
Treatment Initiated:	Started on Stopped
Imipenum/Meropenum Piperacillin Tazobactum Amikacin Teicoplanin Colomycin Anti fungal Antiviral	