

**MANAGEMENT OF FEBRILE NEUTROPENIA IN ONCOLOGY PRACTICE**Suhag V.<sup>1</sup>, Sunita B.S.<sup>2</sup>, Sarin A.<sup>3</sup>, Dutta V.<sup>4</sup>, Singh A.K.<sup>5</sup>, Goyal P.<sup>6</sup> and Dubey A.P.<sup>7</sup><sup>1</sup>HOD Radiation Oncology, Army Hospital (R&R) Delhi-110010 (India)<sup>2</sup>MD DNB Pathology, Classified Specialist, Army Hospital (R&R) Delhi-110010 (India)<sup>3</sup>Consultant Radiodiagnosis and Radiotherapy, HOD Oncology Centre, Command Hospital (SC), Pune, India<sup>4</sup>Consultant Pathology and Oncopathology, HOD Pathology and Lab Sciences, Army Hospital (R&R) Delhi-110010 (India)<sup>5</sup>Senior Advisor Radio-diagnosis and Imaging, Army Hospital (R&R) Delhi-110010 (India)<sup>6</sup>Senior Resident Radiation Oncology, Army Hospital (R&R) Delhi-110010 (India)<sup>7</sup>Senior Resident Medical Oncology, Army Hospital (R&R) Delhi-110010 (India)**\*Correspondence for Author: Prof. Suhag V.**

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**ABSTRACT**

Febrile neutropenia (FN) is a frequent, serious complication of intensive chemotherapy regimens both in hematology and solid cancers. Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because signs and symptoms of inflammation typically are attenuated. It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly in order to avoid progression to a sepsis syndrome and possibly death. Due to the potential for life-threatening complications, the development of FN in patients receiving cancer chemotherapy traditionally prompted hospitalization and i.v. antimicrobial therapy, but there is convincing published evidence that an identifiable subset of patients can be safely treated as outpatients. It is crucial to assess the risk of serious complications in patients with neutropenic fever, since this assessment will dictate the approach to therapy, including the need for inpatient admission, intravenous (IV) antibiotics, and prolonged hospitalization. High-risk neutropenic patients are those with an absolute neutrophil count (ANC) <500 cells/microL expected to last >7 days or evidence of ongoing comorbid conditions. Despite major advances in prevention and treatment, febrile neutropenia (FN) remains one of the most concerning complications of cancer chemotherapy, and is a major cause of morbidity, healthcare resource use and compromised efficacy resulting from delays and dose reductions in chemotherapy. Here we review the latest recommendations for management of FN; issued by Infectious Diseases Society of America (IDSA), European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN); which are considered standard of care in Oncology practices.

**KEYWORDS:** Cancer, fever, neutropenia, antibiotic therapy.**INTRODUCTION**

The incidence of cancer is raising and the treatments are increasingly aggressive. Consequently, general practitioners, emergency departments, hematologists and oncologists are regularly facing a severe side-effect of cytotoxic therapy, febrile neutropenia (FN). FN is a serious complication of chemotherapy because it can be quickly fatal and causes a temporary or definitive cessation of treatment. Febrile neutropenia (FN) is considered as a medical emergency. It causes significant economic loss, morbidity and mortality to the patients. Early detection, prompt initiation of empiric antibiotics leads to effective management of this condition. Hematological malignancies constitutes around 70-80% FN cases, whereas 5-30% of episodes are due to solid tumors. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500/ $\mu$ L, or less than 1000/ $\mu$ L

with an anticipated decline to less than 500/ $\mu$ L in the next 48-hour period. Neutropenic fever is a single oral temperature of 38.3° C (101° F) or a temperature of greater than 38.0° C ( 100.4° F) sustained for more than 1 hour in a patient with neutropenia. Infections in neutropenic patients can progress rapidly, leading to hypotension and/or other life-threatening complications.<sup>[1,2]</sup> Categorizing neutropenic patients as being at high risk or low risk for infection according to presenting signs and symptoms, underlying cancer, type of therapy, and medical comorbidities has become essential to the treatment algorithm. Risk stratification is a recommended starting point for managing patients with fever and neutropenia.<sup>[1-3]</sup>

A major advance in the management of febrile neutropenia (FN) has been the stratification of the population of adult patients with FN for the risk of

complications and death. Using validated reliable predictive instruments, such as the Multinational Association for Supportive Care in Cancer score, it is possible to identify a population of 'low-risk' patients, who can benefit from simplified and less expensive therapeutic approaches (e.g., orally administered antimicrobial therapy and early home return). Prevention of FN by the use of granulopoietic colony-stimulating factor (G-CSF) has been successfully applied to patients at 'high risk' of developing FN.<sup>[4,5]</sup> Mortality from FN has diminished steadily but remains significant. Overall mortality rates are ~5% in patients with solid tumours (1% in low-risk patients) and as high as 11% in some haematological malignancies.<sup>[6-8]</sup>

### GENERAL PRINCIPLES

Fever in a neutropenic patient should be considered a medical emergency. Broad-spectrum antibacterials should be given as soon as possible (within 60 minutes of triage) and at full doses, adjusted for renal and/or hepatic function. In addition, the diagnostic evaluation should be obtained quickly. The aim of empiric therapy is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infection in neutropenic patients. The following general principles apply:<sup>[1,2,6,9]</sup>

- Antibiotics are usually administered empirically but should always include appropriate coverage for suspected or known infections. Even when the pathogen is known, the antibiotic regimen should provide broad-spectrum empiric coverage for the possibility of other pathogens, unlike the treatment strategy adopted in many immunocompetent hosts.
- In high-risk patients, antibiotics should generally be administered intravenously in a hospital setting.
- Initial antibiotic selection should be guided by the patient's history, allergies, symptoms, signs, recent antibiotic use and culture data, and awareness of the susceptibility patterns of institutional nosocomial pathogens
- Ideally, antibiotics should be bactericidal.
- Clinical response and culture and susceptibility results should be monitored closely, and therapy should be adjusted in a timely fashion in response to this information.

Febrile neutropenic patients should be monitored frequently with respect to vital signs (blood pressure, heart rate, respiratory rate, and temperature), performance status (the clinical burden of the neutropenic fever syndrome), and the ability to achieve adequate oral intake in the presence of oral or gastrointestinal mucositis. Temporarily holding administration of systemic chemotherapy should be considered during the management of the sepsis syndrome until the patient stabilizes. Attention to fluid and electrolyte management is important given the dehydrating effects of fever, vomiting, and/or diarrhea. Urine output of >0.5 mL/kg per hour should be

maintained. Afebrile neutropenic patients with new signs or symptoms that are consistent with infection should be evaluated and managed as if they are febrile<sup>1,2</sup>. Common gram-positive pathogens include coagulase-negative staphylococci, staphylococcus aureus, enterococcus species, viridans group streptococci, streptococcus pneumoniae, streptococcus pyogenes etc. Common gram-negative pathogens include escherichia coli, klebsiella species, pseudomonas aeruginosa, citrobacter species, acinetobacter species, and stenotrophomonas maltophilia.<sup>[10]</sup>

If an infectious source of fever is identified, antibiotics should be continued for at least the standard duration indicated for the specific infection (eg, 14 days for Escherichia coli bacteremia); antibiotics should also continue at least until the absolute neutrophil count (ANC) is  $\geq 500$  cells/microL or longer if clinically indicated.

### INITIAL EVALUATION

A detailed history should be taken including the nature of the chemotherapy given, prior prophylactic antibiotic, concomitant steroid use, recent surgical procedure and presence of allergies. It is important to check the clinical record for past positive microbiology, in particular previous presence of antibiotic-resistant organisms or bacteraemia, in order to guide therapy. Urgent full blood count to ascertain the neutrophil level along with other relevant clinical investigations are crucial in guiding early management. Two sets of blood cultures from a peripheral vein and any indwelling venous catheters should be taken. In addition, sputum, urine, skin swabs and stool specimens where clinically indicated should be sampled, before the prompt institution of empirical broad-spectrum antimicrobial therapy.<sup>[1,2,6]</sup>

### RISK ASSESSMENT

The initial clinical evaluation focuses on assessing the risk of serious complications. This risk assessment dictates the approach to therapy, including the need for inpatient admission, IV antibiotics, and prolonged hospitalization.<sup>[11]</sup>

- Low-risk patients are defined as those who are expected to be neutropenic with ANC <500 cells/microL for  $\leq 7$  days and those who have no active comorbidities or evidence of significant hepatic or renal dysfunction. Most patients receiving chemotherapy for solid tumors are considered to be low-risk for complications requiring hospitalization or prolonging hospitalization. Afebrile neutropenic patients who have new signs or symptoms suggestive of infection should be evaluated and treated as high-risk patients. Low-risk patients should receive initial oral or IV empirical antibiotic doses in a clinic or hospital setting; they may be transitioned to outpatient oral or IV treatment if they meet specific clinical criteria.<sup>[12-15]</sup>

- Most experts consider high-risk patients to be those with anticipated prolonged ( $\geq 7$  days duration) and profound neutropenia with ANC  $< 100$  cells/mm<sup>3</sup> following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy.<sup>[1,6]</sup>

Two validated assessment tools recommended for identifying patients at low risk for FN complications are the Talcott classification system and the Multinational Association for Supportive Care in Cancer (MASCC) risk index; the MASCC index is superior in terms of sensitivity and negative predictive value but has lower specificity.

### ORAL THERAPY FOR LOW-RISK CASES

A recent review has concluded that inpatient oral antibacterial therapy can be safely substituted for conventional intravenous treatment in some low-risk FN patients, namely those who are haemodynamically stable, who do not have acute leukaemia or evidence of organ failure, who do not have pneumonia, an indwelling venous catheter or severe soft tissue infection. Single-agent quinolones are not inferior to combinations (quinolone with amoxicillin plus clavulanic acid) but the latter are preferred given the rise in Gram-positive FN episodes. Oral quinolone therapy should not be used in patients who have taken a quinolone antibacterial as prophylaxis. The safety of early change to oral combinations in afebrile patients after 48 h on i.v. therapy is preferred by many physicians. The possibility of exclusive oral outpatient management for low-risk FN cases has become increasingly appealing on the grounds of patient convenience, economy and reduction in the incidence of nosocomial infections, but about 20% of cases required later re-admission.<sup>[6,16]</sup>

### HIGH-RISK PATIENTS

Initiation of monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam is preferred. Many experts avoid ceftazidime monotherapy because of rising resistance rates among gram-negative bacteria and its limited activity against gram-positive bacteria, such as streptococci, compared with newer alternatives. The dosing of these agents for patients with normal renal function are:

- Cefepime – 2 g IV every eight hours
- Meropenem – 1 g IV every eight hours
- Imipenem-cilastatin – 500 mg IV every six hours
- Piperacillin-tazobactam – 4.5 g IV every six to eight hours
- Ceftazidime – 2 g IV every eight hours
- Other antibiotics (eg, aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen in patients with complicated

presentations (eg, hypotension and/or mental status changes), focal findings (eg, pneumonia or cellulitis), or if antimicrobial resistance is suspected or proven. Most penicillin-allergic patients tolerate cephalosporins, but those with a history of an immediate-type hypersensitivity reaction (eg, hives and bronchospasm) should be treated with a combination that avoids  $\beta$ -lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin.<sup>[2,3,6]</sup>

### ADDITION OF GRAM-POSITIVE COVERAGE

Routine addition of gram-positive antibiotic coverage to the initial empiric antibiotic regimen has not been associated with significant clinical benefit. The risk of promoting resistance among enterococci and *Staphylococcus aureus* is an important reason to avoid empiric vancomycin use.<sup>[17]</sup> Gram-positive coverage with Vancomycin and other agents should be added in patients with any of the following findings<sup>[18,19]</sup>:

- Hemodynamic instability or other signs of severe sepsis
- Pneumonia
- Positive blood cultures for gram-positive bacteria
- Suspected central venous catheter (CVC)-related infection
- Skin or soft tissue infection
- Severe mucositis in patients who were receiving prophylaxis with a fluoroquinolone lacking activity against streptococci and in whom ceftazidime is being used as empiric therapy.

Empiric gram-positive coverage is particularly important for patients who are colonized with methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococcus, or penicillin- or ceftriaxone-resistant streptococci who become hemodynamically unstable or develop bacteremia with gram-positive cocci.<sup>[20,21]</sup>

Vancomycin is used most commonly when an agent with specific gram-positive activity is indicated. Linezolid is an alternative for patients intolerant of vancomycin. However, a concern with linezolid is that it may cause myelosuppression, typically after two or more weeks of therapy. Daptomycin is another alternative to vancomycin, but it has been less well studied and should not be used for pulmonary infections because it is inactivated by surfactant and therefore does not achieve sufficiently high concentrations in the respiratory tract.<sup>[22,23]</sup>

### MODIFICATION TO INITIAL REGIMEN

Modifications to the initial regimen should be considered for patients at risk for infection with antibiotic-resistant organisms, patients who are clinically unstable, and patients with positive blood cultures that are suggestive of a resistant infection. Risk factors for infections caused by resistant bacteria include previous infection or colonization by the organism and/or treatment in a

hospital with high rates of resistance. These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum  $\beta$ -lactamase (ESBL)-producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC).<sup>[24-26]</sup> Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity. For MRSA: Consider early addition of vancomycin, linezolid, or daptomycin. For VRE: Consider early addition of linezolid or daptomycin. For ESBLs: Consider early use of a carbapenem. For KPCs: Consider early use of polymyxin-colistin or tigecycline.<sup>[7]</sup> In addition, we suggest that anaerobic coverage be included if there is evidence of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intraabdominal infection (including neutropenic enterocolitis [typhlitis]), pelvic infection, or anaerobic bacteremia.<sup>[1,3,6]</sup>

An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is felt to be adequate. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured. If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source.<sup>[6]</sup>

#### **ADDITION OF AN ANTIFUNGAL/ ANTIVIRAL AGENT**

An empiric antifungal agent should be added after four to seven days in high-risk neutropenic patients who are expected to have a total duration of neutropenia >7 days who have persistent or recurrent fever and in whom reassessment does not yield a cause. The rationale for this approach is that undiagnosed fungal infection was found in early studies in many patients who died during prolonged neutropenia.<sup>[27]</sup> The incidence of fungal infection (especially those caused by *Candida* or *Aspergillus* spp) rises after patients have experienced more than seven days of persistent neutropenic fever. In patients who are clinically unstable or have a suspected fungal infection, antifungal therapy should be considered even earlier than what is recommended for empiric therapy. Resolution of fever occurs in approximately 40 to 50 percent of patients given antifungal therapy. The choice of agent for empiric antifungal therapy depends upon which fungi are most likely to be causing infection, as well as the toxicity profiles and cost. The current guidelines for empiric antifungal therapy recommend amphotericin B deoxycholate, a lipid formulation of amphotericin B, caspofungin, voriconazole, or itraconazole as suitable

options for empiric antifungal therapy in neutropenic patients.<sup>[1,7,23,28]</sup>

Voriconazole or a lipid formulation of amphotericin B are preferred in patients with pulmonary findings suggestive of an invasive mold infection due to higher failure rates with caspofungin in preventing and treating invasive aspergillosis, which is the most common cause of mold infections.<sup>[29,30,31]</sup> Most experts prefer voriconazole if aspergillosis is thought to be most likely, but if mucormycosis is suspected, an amphotericin B formulation should be given since voriconazole has no activity against the agents of mucormycosis. Most centres prefer a lipid formulation of amphotericin B rather than amphotericin B deoxycholate in order to minimize toxicity.<sup>[1,7,29,32]</sup>

Herpes simplex virus (HSV)-seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis.<sup>23</sup> Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease. Routine treatment of respiratory syncytial virus infection in neutropenic patients with upper respiratory disease should not be given.<sup>[1,6,33-36]</sup>

The dosing of the various antifungal agents recommended above is as follows:

- Caspofungin – Loading dose of 70 mg IV on day one, then 50 mg IV once daily
- Voriconazole – Loading dose of 6 mg/kg IV every 12 hours on day one, followed by 4 mg/kg IV every 12 hours
- Amphotericin B lipid complex – 5 mg/kg IV once daily
- Liposomal amphotericin B – 3 to 5 mg/kg IV once daily

#### **CATHETER REMOVAL**

Central venous catheter (CVC)-related infections are common in patients with neutropenic fever. If blood cultures drawn from the CVC become positive at least 120 minutes before peripheral blood cultures drawn at the same time, then the CVC is likely to be the source of the bacteremia.<sup>[1]</sup> In addition to antibiotics, CVC removal is recommended for patients with catheter-related bloodstream infections caused by *S. aureus*, *P. aeruginosa*, *Candida* species, other fungi and rapidly growing nontuberculous mycobacteria. Antibiotics should be administered for a minimum of 14 days following catheter removal and clearance of blood cultures. Catheter removal is also recommended for tunnel infection, port pocket infection, septic thrombosis, endocarditis, sepsis with hemodynamic instability, and bloodstream infection that persists despite  $\geq 72$  hours of therapy with appropriate antibiotics, even when pathogens other than those described above are isolated. A prolonged duration of treatment of four to six weeks is

recommended for patients with complicated CVC-associated infections, such as those with deep tissue infection, endocarditis, septic thrombosis, or persistent bacteremia or fungemia occurring >72 hours following catheter removal in a patient receiving appropriate antimicrobial therapy. For CVC-associated bacteremia caused by coagulase-negative staphylococci, the CVC may be retained; in this setting, patients are treated with systemic antibiotics with or without antibiotic lock therapy.<sup>[1,37-43]</sup>

#### TAKE-HOME MESSAGE<sup>[1,3,6]</sup>

(1) Risk stratification allows the identification of a subset of patients who may be safely managed as outpatients given the right health care environment. (2) Antibacterial prophylaxis for high-risk patients who remain neutropenic for  $\geq 7$  days prevents infections and decreases mortality. (3) Empirical management of febrile neutropenia with a single antipseudomonal beta-lactam results in the same outcome and less toxicity than combination therapy using aminoglycosides. (4) Vancomycin should not be used routinely empirically either as part of the initial regimen or for persistent fever, but rather should be added when a pathogen that requires its use is isolated. (5) Empirical antifungal therapy should be added after 4 days of persistent fever in patients at high risk for invasive fungal infection (IFI); the details of the characterization as high risk and the choice of agent remain debatable. (6) Preemptive antifungal therapy in which the initiation of antifungals is postponed and triggered by the presence, in addition to fever, of other clinical findings, computed tomography (CT) results, and serological tests for fungal infection is an acceptable strategy in a subset of patients. (8) Monotherapy is recommended as the first choice for initial empirical therapy of febrile neutropenia, but local epidemiological and antibiotic susceptibility data are now considered pivotal to design a correct management strategy.

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