# Update on the Management of Febrile Neutropenia

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## Abstract

Febrile neutropenia (FN) is a potentially life-threatening complication of chemotherapy. Supportive measures and diagnostic tools in the management of FN are constantly evolving. Recent evidence has validated the need for risk stratification. With the increasing use of dose-intense chemotherapy and evidence to show the detrimental effects of dose delay in the outcomes of cancer treatment, strategies, including the use of colony-stimulating factors and biosimilars to prevent FN, are being developed. This review is an update on the management of FN in adults undergoing chemotherapy.

## Keywords

Neutropenia, febrile neutropenia, infection, myelosuppression, colony-stimulating factors

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Neutropenic sepsis is a serious and potentially life-threatening complication of cancer chemotherapy. It is the leading cause of infectious complications in patients receiving chemotherapy, accounting for most chemotherapy-associated morbidity and mortality, and compromising treatment outcomes by causing dose reductions and treatment delays. Frequent use of dose-intense and dose-dense chemotherapy, especially in the older population, has escalated the risk of neutropenic sepsis. Prompt recognition and management with antimicrobial therapy reduces mortality but, increasingly, focus is shifting towards prevention using targeted antimicrobial or antifungal prophylaxis and supportive strategies such as the use of growth factors. However, challenges remain with respect to the most appropriate empirical treatment regimen adapted to an evolving and changing epidemiology of infections as well as to resistance rates, the development of early markers of bacterial or fungal infections, the risk stratification of patients and the establishment of targeted empirical or pre-emptive antifungal therapy.[1] This review is an update on the management of febrile neutropenia (FN) in adults and highlights recent developments that are likely to have an impact on patient care.

## Definitions and Risk Factors

FN is a clinical syndrome and, as defined by the Infectious Diseases Society of America (IDSA) and the Immunocompromised Host Society (ICHS), refers to fever in patients who have an absolute neutrophil count (ANC)<0.5 x $10^9$/l or <1 x $10^9$/l that is predicted to fall below 0.5 x $10^9$/l within 48 hours of onset of fever or signs of sepsis. Fever is defined as temperatures of ≥38 °C (100.4 °F) for at least one hour or a single record of ≥38.3 °C (101 °F).[2] The ICHS and other scientific societies have also added, as a criterion of fever, the presence of an oral temperature of ≥38 °C measured twice in 12 hours.[3]

FN represents a medical emergency. Clinical evidence of a focus of infection is present in 20–30 % of febrile episodes, whereas bacteraemia is present in 10–25 % of patients.[2] Prompt initiation of antimicrobial therapy, especially within the first hour of onset of fever, has contributed to a significant reduction in mortality, from 60–70 % in the 1970s to 4–6 % in adults and 0.4–1 % in children currently.[4–6]

In the majority of patients with FN, clinical features are often subtle and minimal. Fever is not blunted, as the necessary pro-inflammatory cytokines are produced by other types of cells (macrophages, lymphocytes, fibroblasts and epithelial and endothelial cells);[7] it may, however, be blunted by the concomitant use of corticosteroids, advanced age or the presence of shock.

The incidence and prognosis of FN is inversely proportional to the degree or depth of neutropenia.[8] The risk of infection increases significantly when the absolute neutrophil count is reduced to <0.1 x $10^9$/l.[9] The duration of neutropenia bears a direct relationship with the risk of infection, response to treatment and complications. It has been estimated that all patients with prolonged grade 4 neutropenia develop an infection. Neutropenia of seven days or less leads to 95 % response rates, compared with 32 % in patients with neutropenia lasting more than 15 days.[1] Factors influencing the frequency of neutropenia include the type and intensity of chemotherapy, nature and extent of disease, use of concomitant radiotherapy, stage of treatment (greater risk in the earlier cycles, especially with induction chemotherapy) and patient-specific factors such as age, performance status and co-morbid conditions.[1] Other factors that increase the potential for complications include mucositis, bleeding diathesis, presence of invasive devices, alteration of the patient flora's by previous antimicrobial therapy, organ dysfunction and agents that affect other arms of the immune system.[10] Genetic factors may also affect patient outcomes.[1]

Patients with neutropenia not related to chemotherapy – e.g., following viral disease or drug toxicity – do not have the same risk of acute infection. Similarly, patients with congenital neutropenia or aplastic anaemia and HIV-positive patients have an increased risk of complications, but a lower relative risk compared with those who are neutropenic post-cytotoxic chemotherapy. This is probably because of maintained mucosal integrity.[11]

The heterogeneity of the FN patient population, which adds to the complexity of patient management, has been increasingly recognised. Many validated prediction models have been developed to distinguish patients falling into different risk categories, and these should be applied during the initial evaluation of patients. While initiating prompt treatment with broad-spectrum antimicrobials is crucial, every effort should be made to exclude fever related to non-infectious causes (drug fever, disease fever, transfusion-related fever, etc.). Febrile episodes during neutropenic periods have an impact on overall survival, probably because of the substantial delays in treatment delivery and the need for dose reductions. A study linking data from the US National Cancer Institute with data from a survey of patients with aggressive non-Hodgkin's lymphoma found a significant association between occurrence of FN, reduction in the number of cycles of CHOP (chemotherapy regimen consisting of cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) and lower five-year overall survival.[12]

## Risk Stratification

Various risk stratification models have been developed for identifying patients at high risk of complications, including the Talcott model and the Multinational Association for Supportive Care in Cancer (MASCC) scoring system. These have been validated in various trials and are useful tools in the management of neutropenic fever.[13–15]

## Clinical Evaluation

A thorough history-taking and clinical examination help to focus subsequent investigations and may provide clues to the site of infection, hence allowing to tailor treatment. Common foci of infection include the lungs (25 %), oropharynx (25 %), skin and soft tissue (15 %), perineum (10 %), gastrointestinal and urinary tract (5 %) and para-nasal sinuses (5 %).[1] Although physical examination may be unremarkable, a thorough search for potential sites of infection – such as the oropharynx, skin and skin folds, axilla, perineum, nails, eyes, sinuses, vascular access sites and lungs – should be performed.

## Laboratory Evaluation

Laboratory evaluation includes investigations that help identify a likely source, microbiological surveillance and surrogate biomarkers of infection.[16] Baseline investigations in all patients should include complete blood count and biochemical tests (liver and renal functions) and two sets of blood cultures. If a central venous catheter (CVC) is present, a set of cultures drawn first from a peripheral vein and then from each CVC lumen is essential for diagnosing catheter-related bloodstream infection. Although not essential to perform, a differential time to positivity between central and peripheral blood cultures of over two hours is strongly suggestive of catheter-related bloodstream infection.[17] It is clear that blood cultures are particularly important, as they may be positive in up to 25 % of febrile episodes.[18]

### Microbiological Diagnosis

Achieving a microbiological diagnosis through culture of body fluids and tissues is important to identify the source of infection and guide antibiotic treatment. However, this must not delay the administration of antibiotics and other supportive measures. The specimens required will depend on the history and likely source of infection. Specimens for further microbiological investigations, including sputum, urine and cerebrospinal fluid (provided there are no contraindications), should be taken if clinically indicated. If appropriate, bronchoalveolar lavage fluid for *Pneumocystis jiroveci (carinii)*, *Mycobacterium* tuberculosis and fungi should be considered in addition to routine bacterial culture. Screening for multidrug-resistant (MDR) pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and MDR gram-negative pathogens, is recommended for infection control purposes.[2] Positive microbiological isolates must all be subjected to standard antibiotic sensitivity testing. *In vitro* fungal susceptibility testing still needs to be clinically interpreted and correlated with clinical outcomes.

### Source Identification and Control

During assessment, it is imperative that adequate attention is given to the identification of the source of sepsis – but the cause of infection may not always be apparent. A chest X-ray should be performed in patients with respiratory signs and symptoms.[2] A high-resolution computed tomography (CT) scan of the lungs may aid the diagnosis of fungal infections. CT scans of other areas should be performed as per clinical indication.[2] Timely debridement of infected tissues is associated with improved outcomes, thus the identification of occult sources of infection (skin and soft tissue, perforated bowel, sinuses) is important. The majority of these diagnoses can be excluded by thorough clinical examination and targeted imaging.

### Biomarkers

Various inflammatory markers have been proposed that may be able to differentiate between infectious and non-infectious causes of a systemic inflammatory response, hence potentially helping manage febrile episodes in patients with neutropenia. Of these, C-reactive protein is frequently used to differentiate between bacterial and non-bacterial causes of fever. Procalcitonin is another marker that may help differentiate between infectious and non-infectious causes of inflammation. However, their use is limited by their lack of sensitivity and specificity.[19]

Molecular nucleic acid-based techniques for identification of pathogens are becoming increasingly available. As yet, none has been validated for use in haematology patients with severe sepsis. These techniques are extremely sensitive at detecting bacterial/fungal DNA in peripheral blood, but it is unclear whether this indicates viable pathogenic organisms circulating in the bloodstream.

Invasive fungal infections (IFIs) may have minimal signs, and cultures are often negative. The detection of circulating fungal antigens or fungal metabolites is being investigated to aid the early diagnosis of IFIs. Among the most promising tests are galactomannan assay and polymerase chain reaction (PCR) for *Aspergillus*. However, physicians must be aware of the potential for false positive and false negative results, and of the fact that these tests do not replace careful microbiological and clinical evaluation. Another test currently under investigation for the early diagnosis of invasive fungal disease is (1,3)-β-D-glucan, which is a component of the cell wall of a variety of fungi. Further clinical studies are needed to validate the regular use of this test in day-to-day clinical practice.[20]

### Continued Assessment for Evidence of Organ Failure

Clinical and laboratory parameters directed towards early and prompt recognition of organ failure including septic shock, renal failure and respiratory failure are paramount in improving outcomes. Serial measurement of renal and liver functions, blood gases and serum lactate is vital. An increased blood lactate concentration may occur in a variety of conditions but, in the context of FN, it has been shown to predict the onset of haemodynamic instability.[21] Moreover, lactate concentration has prognostic significance, with both peak concentration and rate of clearance being associated with mortality.[15]

## Strategies to Reduce Complications in Patients Post-chemotherapy

### Colony-stimulating Factors Including Biosimilars

Primary prophylaxis with growth factors has been recommended for use in high-risk patients with expected long duration of neutropenia (>10 days) and with a high risk of a febrile episode (>20 %).[1,2,22] In patients with acute myeloid leukaemia (AML) who experience FN caused by chemotherapy, the use of colony-stimulating factors (CSFs) does not affect overall survival, but reduces the duration to neutrophil recovery and of hospitalisation.[23,24] There is, however, no consensus over the routine use of granulocyte CSFs (G-CSFs) in the treatment of AML, and clinicians may develop their own guidelines depending on local factors and practice.

In an attempt to improve survival, there is an increasing trend towards the use of dose-dense or dose-intense chemotherapy. A number of trials have shown that the prophylactic use of CSFs avoids treatment delays due to neutropenia.[25,26] For dose-dense or dose-intensive regimens with survival advantage, prophylactic CSFs should be considered.[22] The decision to use prophylactic CSFs is guided by the intention to treat – that is, curative, prolongation of life, or symptom control and palliation. Examples of appropriate use in the curative setting include CHOP or CHOP-like regimens in older patients with aggressive non-Hodgkin's lymphoma.

In Europe, prophylactic treatment with G-CSFs – such as filgrastim (including approved biosimilars), lenograstim or pegfilgrastim – is available to reduce the risk of chemotherapy-induced neutropenia. Clinical evidence shows that filgrastim, lenograstim and pegfilgrastim have comparable clinical efficacy, and the current European Organisation for Research and Treatment of Cancer (EORTC) G-CSF guidelines (see *Figure 1*) allow the use of any of these agents to prevent FN and FN-related complications when indicated.[22] While most G-CSFs, including biosimilars, are administered by a course of daily injections, pegfilgrastim allows once-per-cycle administration. The choice of formulation remains a matter for the individual clinician.

Recently, seven G-CSF filgrastim biosimilars have received approval (see *Table 1*): XM02 in September 2008,[27–30] EP2006 in February 2009[31,32] and PLD108 in June 2010.[33] Filgrastim is widely used; over 7.7 million patients have received it since 1991. The comparability exercise for approval of the filgrastim biosimilars XM02, EP2006 and PLD108 was conducted using filgrastim (Neupogen) as the reference product. Clinical evidence from a meta-analysis indicates that XM02 is similar to filgrastim.[34] Several phase I studies and one phase III study including pharmacodynamic/pharmacokinetic parameters provide evidence that filgrastim EP2006 is similar to filgrastim.[35] Given that biosimilar products are not generic products, a switch from filgrastim to a biosimilar is considered a change in clinical management.[36]

**Figure 1: Algorithm for the Use of Granulocyte Colony-stimulating Factor in Febrile Neutropenia**

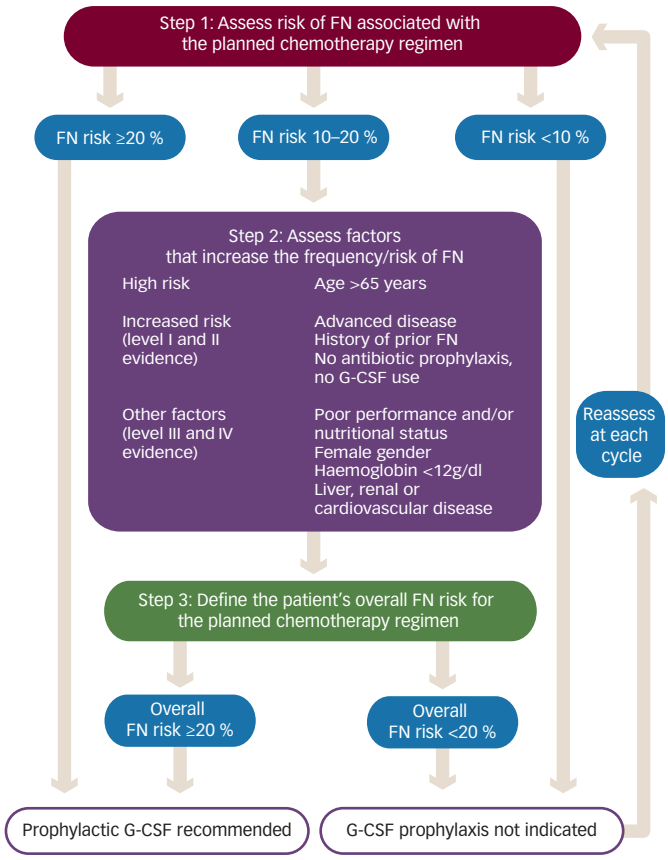


**Table 1: Available Biosimilar Granulocyte Colony-stimulating Factors (G-CSFs)**

| Molecule | International Non-proprietary Name | Brand Name |
|---|---|---|
| XM02 | Filgrastim | Tevagrastim®<br>Ratiograstim®<br>Filgrastim ratiopharm®<br>Biograstim® |
| EP2006 | Filgrastim | Zarzio®<br>Filgrastim Hexal® |
| PLD108 | Filgrastim | Nivestim® |

### Prophylactic Antimicrobials

According to the IDSA guidelines 2010, fluoroquinolone prophylaxis should be considered for high-risk patients expected to have prolonged and profound neutropenia (ANC<0.1 x $10^9$/l for more than seven days). Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered to be roughly equivalent, although levofloxacin is preferred in situations where there is an increased risk of oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli has been recommended. The addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended. Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to be neutropenic for less than seven days. Prophylaxis against *P. jiroveci* pneumonia (cotrimoxazole) should be given to all patients at risk – that is, patients who have had haematopoietic stem cell transplantation (HSCT), patients with lymphoma or chronic lymphocytic leukaemia and patients treated

**Table 2 : Indications for the Addition of Gram-positive Cover to the Initial Empirical Antibiotic Regimen[2]**

| |
|---|
| Severe sepsis |
| Radiological evidence of pneumonia |
| Clinical suspicion of catheter-related sepsis |
| Skin/soft tissue infection |
| Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available |
| Colonisation with MRSA, VRE or penicillin-resistant pneumococci |

*MRSA = methicillin-resistant* Staphylococcus aureus*; VRE = vancomycin-resistant* Enterococcus.

**Table 3: Multiresistant Organisms that are of Potential Importance in Neutropenic Haematology Patients[2]**

| |
|---|
| Extended-spectrum β-lactamase-producing gram-negative bacteria, carbapenemase producing *Klebsiella pneumoniae* and multidrug resistant *Pseudomonas aeruginosa* |
| Viridans streptococci |
| Methicillin-resistant *Staphylococcus aureus* |
| Vancomycin-resistant enterococci |
| Penicillin-resistant *Streptococcus pneumonia* |
| Multiresistant *Acinetobacter* |
| Fluconazole-resistant *Candida* species |

with corticosteroids.[1] The risk of invasive fungal infection is high in patients undergoing allogeneic HSCT and those undergoing intensive remission induction and salvage chemotherapy for acute leukaemia. It has been shown that antifungal prophylaxis reduces the incidence of invasive fungal infections and resulting mortality.[37] Fluconazole prophylaxis is effective and safe in reducing the risk of invasive candidiasis.[38] It is, however, ineffective against moulds. Itraconazole and voriconazole are also effective as antifungal prophylaxis. Posaconazole was found to be superior to fluconazole in the prevention of invasive aspergillosis and also reduced fungal infection-related mortality in patients with graft-versus-host disease.[39] Therefore, posaconazole prophylaxis should be considered for selected patients in whom the risk of invasive aspergillosis is high. Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is less than seven days.[2]

## Therapeutic Considerations

### Initial Empirical Antibiotic Therapy

The prompt administration of empirical antibiotic therapy is essential, because underlying infections can progress rapidly. Factors influencing the selection of an appropriate empirical antimicrobial therapy include the local epidemiology and drug susceptibility patterns of bacterial pathogens, and the exposure of the patient to previous antimicrobial therapy.[40] Initial empirical therapy is primarily directed against bacterial pathogens, because fungal, viral or protozoan aetiology is rarely the cause of infection initially. Resistance patterns in the community, the use of chemoprophylaxis and the type of chemotherapy all influence the local epidemiology. The spectrum of infections in patients with neutropenia has changed significantly in the past four decades. Previously, gram-negative organisms were the predominant isolates. During the 1980s and 1990s, infection with gram-positive organisms became increasingly common. With the widespread use of antibiotic prophylaxis and treatment, infections with drug-resistant organisms are on the rise. Empirical antibiotic therapy should be initiated without delay at the onset of fever.[2] As bacteraemia with gram-negative organisms, especially *Pseudomonas aeruginosa*, is associated with high mortality and morbidity, the initial antibiotic choice is guided by its activity against *Pseudomonas*. The preferred antibiotic should be bactericidal with good activity against *Pseudomonas* and should have minimal toxicity.

High-risk FN patients require inpatient management with intravenous antibiotics. Monotherapy with antipseudomonal agents (meropenem, piperacillin–tazobactam, cefepime, imipenem–cilastatin) has been recommended as first-line treatment. Multiple clinical trials have not demonstrated clear superiority of any single regimen. A suitable and frequently used antibiotic regimen is the combination of piperacillin–tazobactam with an aminoglycoside (e.g., gentamicin). However, a meta-analysis by Paul et al. of 7,807 patients in 47 clinical trials showed an increased incidence of adverse effects with no survival benefit for combination therapy compared with single agents.[41] Other antimicrobials (aminoglycosides, fluoroquinolones and/or vancomycin) may be added to the initial regimen for managing complications (e.g., hypotension and pneumonia) or if antimicrobial resistance is suspected or proven. Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin and soft tissue infection, pneumonia and haemodynamic instability[2] (see *Table 2*). Modifications of the initial empirical therapy may be considered in patients at risk of infection with the antibiotic-resistant organisms listed in *Table 3*, particularly if the patient's condition is unstable or if they have positive blood culture results indicating resistant bacteria.[2]

Emerging antibiotic resistance and/or opportunistic infections with unusual organisms can present challenging problems in immunocompromised patients. Some of these MDR bacteria include MRSA, VRE, extended-spectrum β-lactamase (ESBL)-producing gram-negative bacteria, and carbapenemase-producing organisms including *Klebsiella pneumoniae* carbapenemase (KPC). MDR organisms result mostly from the extensive overuse and misuse of antibiotics. The clinical input from microbiologists is invaluable for the appropriate use of antibiotics. The clinical circumstances are key to making this judgement, including evidence of colonisation with resistant strains, recent antibiotic exposure and, most critically, the local flora of individual units. It is not necessarily the case that the 'newest' antibiotics are the best. Indeed, problems with ever-increasing resistance have led to the re-emergence of some very old antibiotics, notably colistin, which is increasingly being used when other options are unavailable.[42,43] ESBL genes confer a broad range of β-lactam antibiotic resistance among these species, primarily among *Klebsiella* species and *Escherichia coli*. Carbapenemase-producing organisms, including *Klebsiella* species and *P. aeruginosa*, may also cause infections refractory to imipenem or meropenem. Carbapenemase-producing organisms are resistant to all β-lactam antibiotics and may require treatment with colistin or tigecycline.[2] Recognition of these resistant species requires careful interpretation of hospital- and organism-specific antibiograms.

### Fungal Infections

Fungal infections have increasingly been identified as a cause of fever in patients with neutropenia, especially those with prolonged and severe neutropenia following chemotherapy and HSCT. *Candida* and *Aspergillus* are the most common fungal pathogens encountered. *Candida*

infections generally occur during the second or subsequent weeks of neutropenia and *Aspergillus* infection later, during the third and subsequent weeks of neutropenia. Fungal infections do not usually complicate therapies causing short-term neutropenia lasting less than a week. Transplant recipients are at highest risk, because of prolonged significant neutropenia and the presence of other factors compromising immunity – e.g., graft-versus-host disease or corticosteroids.[44] *Candida* may cause fungemia, acute or chronic, disseminated or single-organ disease, with the frequency of infection with non-albicans strains on the rise. Aspergillosis is a lung or paranasal sinus disease initially, but disseminates in 30 % of patients, causing mainly central nervous system disease with a 90 % mortality rate. *Aspergillus* species resistant to amphotericin B, such as *A. terreus* and *A. flavus*, have also emerged as a pathogen. Numerous other fungi are emerging as opportunistic pathogens: *Fusarium* species (sinopulmonary infection, skin lesions, fungaemia), *Mucor* species (sinopulmonary or disseminated disease), *Scedosporuim* species, *Acremoniumi* species, *Trichosporon* species and *Alternaria* species, among others. They tend to present as breakthrough infections because of resistance against many antifungal agents.[45]

High rates of morbidity and mortality associated with fungal infections, the difficulty of diagnosing IFIs early in the course of infection, and the ineffectiveness of treatment when it is delayed have led to the administration of empirical antifungal therapy in patients with antibiotic-resistant fever. Early empiric antifungal therapy has been shown to improve patient outcomes.[1,46]

## Empirical Antifungal Therapy

Empirical antifungal therapy and further investigations for invasive fungal infections should be considered in patients with persistent or recurrent fever after three to five days of antibiotics and whose overall duration of neutropenia is expected to be over seven days.

The choice of antifungal agent is partly determined by the antifungal prophylaxis received by the patient, as this influences the spectrum of IFIs. Patients on fluconazole prophylaxis are at risk of infection with azole-resistant fungi, such as *C. krusei*, *C. glabrata* or moulds. Choosing a specific empirical antifungal for patients already receiving mould-active prophylaxis is more tricky, but a switch to an intravenous antimould agent within a different antifungal class seems rational, based on the evidence that fungal infection breakthroughs may be related to inadequate serum levels following oral voriconazole or posaconazole.[2] In the absence of changes visible on CT, and if serum levels of antimould azole prophylaxis are adequate, continuing the same mould-active prophylaxis may be an acceptable alternative.

Amphotericin B, its lipid formulations and caspofungin have been shown to be equally effective as empirical antifungal therapy in the management of persistent neutropenic fever.[47] In a clinical trial comparing voriconazole with liposomal amphotericin B in the empirical antifungal treatment of neutropenic fever, voriconazole was shown to cause fewer breakthrough fungal infections, but this failed to reach the non-inferiority endpoint compared with liposomal amphotericin B.[48] Its extensive use as treatment or prophylaxis in patients with cancer has been accompanied by reports of an increase in invasive zygomycosis incidence in some centres.[49] Voriconazole is the treatment of choice when there is a strong suspicion of invasive aspergillosis. The optimal duration of empirical antifungal treatment has not been clearly established. If the patient becomes afebrile and the neutrophil count has recovered (>500 cells/mm$^3$), treatment can be discontinued. If the patient is afebrile and stable but neutropenia persists, treatment can be stopped after two weeks of administration. In a patient with unstable FN, treatment should continue until fever and neutropenia resolve.[50]

## Pre-emptive Antifungal Therapy

Increasingly, pre-emptive antifungal therapy is replacing non-selective empirical antifungal therapy based on results of non-culture methods (galactomannan and PCR) and risk stratification efforts.[44] The pre-emptive administration of antifungal agents has been developed to target high-risk neutropenic patients with early invasive fungal disease – selected on the basis of risk factors, clinical presentation, imaging and biological markers – in order to decrease the toxicity, cost and possibly emerging fungal resistance associated with the empirical treatment approach. However, after assessing all the available data, the European Conference on Infections in Leukaemia (ECIL) group has not graded its strength of recommendation for the pre-emptive approach, mainly owing to the lack of defined standard criteria for starting antifungal therapy and the variability of results between studies. Pending definitive scientific evidence, this strategy has to be considered as an experimental approach.

## Treatment of Documented Invasive Fungal Infections

### Candidiasis

The optimal initial treatment for candidaemia in patients with neutropenia previously exposed to azoles is an echinocandin or a liposomal formulation of amphoterecin B (LFAB). Clinicians must be aware that blood culture results positive for yeast may represent infection with *Cryptococcus* species, endemic fungal species or rare yeasts such as *Trichosporon* species. Hence candidaemia needs to be confirmed before committing high-risk neutropenic patients to an echinocandin-based therapy. Once the infection is under control, a change to oral fluconazole or voriconazole is feasible, especially if the *Candida* isolate is azole-susceptible and the patient's neutropenia has resolved. Antifungal therapy should be continued for at least two weeks after the last positive blood culture result in the uncomplicated patient if neutropenia has resolved. Patients with prolonged neutropenia or evidence of metastatic infection should receive four to six weeks of therapy, continued until resolution of infectious signs and neutropenia.[51]

### Aspergillosis

Early diagnosis of invasive aspergillosis is vital in improving clinical outcomes. Voriconazole is considered the drug of choice for most patients with invasive aspergillosis, but liposomal amphoterecin B is a suitable alternative. Posaconazole, itraconazole, echinocandins (e.g., caspofungin) and other LFABs have also demonstrated activity in salvage therapy. Factors that influence the choice of salvage therapy include prior antifungal regimens used, the site of infection, co-morbidities, toxicity profile and efficacy. Many combination antifungal therapies have been tried; however, at the present time, existing data are not sufficient to support the global acceptance of combination therapy as a first-line treatment approach.

The role of adjunct surgery (radical or 'debulking' excision of a dominant fungal lesion) is also potentially useful for managing invasive aspergillosis in selected patients – e.g., young patients with good performance status who are in remission, have a single residual fungal lesion and are candidates for stem cell transplant.[51]

### Zygomycosis and Other Moulds

There are limited data on the primary treatment of zygomycosis. Amphoterecin-based therapy remains the treatment of choice. Posaconazole has been shown to have activity as second-line therapy. Surgical resection of affected tissue and treatment of the underlying illness also contribute to improving patient outcomes. Therapy with triazoles such as voriconazole and posaconazole has been found to be beneficial in small salvage studies for patients with rare fungal infections, e.g., *Scedosporium* and *Fusarium* infections. The optimal therapy for patients with such infections remains undefined.[51]

## Adjuvant Immune Strategies for the Management of Invasive Fungal Infections

Owing to the suboptimal response of immunocompromised patients to antifungal agents, many immune adjunct therapies have been tried aimed at reducing the duration and severity of neutropenia, thus influencing the outcomes of IFIs in these patients. Granulocyte-macrophage-CSFs (GM-CSFs), G-CSFs and recombinant interferon-α enhance the ability of neutrophils to phagocytose fungi and reverse steroid-induced dysfunctions of tissue and alveolar macrophages. Donor granulocyte transfusions and recombinant α-interferon have also been tried in patients with haematological malignancies to enhance immunity. Existing clinical and preclinical data indicate that these approaches may be useful as supportive measures in selected patients until marrow recovery.[51]

## Management of Central Line-associated Bloodstream Infections

The CVC continues to be a major source of bloodstream infections in patients with neutropenia. Central line-associated bloodstream infection (CLABSI) is most commonly caused by colonisers of the skin and mucosa, including coagulase-negative staphylococci, *S. aureus* and *Candida* species. Less common organisms include *Bacillus* species, *Corynebacterium* group JK, enterococci (including VRE), rapidly growing mycobacteria and non-fermenting gram-negative bacilli.[52]

A differential time to positivity >120 minutes on blood culture samples drawn simultaneously from the CVC and a vein is suggestive of CLABSI. For CLABSI caused by *S. aureus*, *P. aeruginosa*, fungi or mycobacteria, in addition to systemic antimicrobial therapy for at least 14 days, catheter removal is recommended. Catheter removal should also be considered in case of tunnel infection or port pocket infection, septic thrombosis, endocarditis, sepsis with haemodynamic instability, and persistent bacteraemia despite appropriate antibiotic therapy for more than 72 hours. For coagulase-negative staphylococci-related cLABsi, the catheter may be salvaged using systemic therapy with or without antibiotic/alcohol lock therapy. Prolonged therapy (four to six weeks) is recommended for complicated cLABsi, such as soft tissue infection, infective endocarditis, septic thrombosis, and bacteraemia or fungaemia persisting for more than 72 hours after catheter removal in a patient who is on appropriate antimicrobials and for *S. aureus* infections.

When catheter removal is not feasible, prolonged systemic antimicrobial therapy will be necessary, especially with *S. aureus* and gram-negative bacteraemia. Anecdotal data suggest that antibiotic lock therapy might be useful in salvaging some of the long-term catheters. However, strategies such as antibiotic lock therapy are currently being studied and cannot be routinely recommended, for the time being, for salvage treatment or prophylaxis.[2]

## Duration of Therapy

Elting and colleagues found that the median time to clinical response in hospitalised patients with cancer is five to seven days, whereas, in low-risk patients, defervescence may be achieved in two days.[53,54] If fever persists after three to five days with no obvious cause, patients should be re-evaluated for occult fungal infection, a deep-seated focus of infection, atypical organisms (viruses, mycobacteria), antibiotic-resistant organisms, suboptimal dosing of antibiotics or non-infectious causes of fever (drug fever, underlying disease, graft-versus-host disease, thrombophlebitis, transfusion reaction, etc.). If no other cause of persistent fever is evident, the next step is the consideration of empirical antifungal therapy, as discussed above.

In patients with a documented focus of infection, the duration of therapy is guided by the organism isolated and site of infection. Appropriate antibiotics should be continued until ANC>0.5 x $10^9$/l or longer if clinically necessary. The duration of antibiotic therapy should be adequate for the effective eradication of the infection. Most bacterial bloodstream infections, soft tissue infections and pneumonias require 10 to 14 days of antibiotic therapy; treatment may therefore extend beyond the resolution of fever and neutropenia. In the absence of any significant impairment of the gastrointestinal function (such as nausea, vomiting, diarrhoea, malabsorption or poor oral intake), an oral antibiotic regimen may be undertaken to complete the full course of therapy.

In patients with persistent unexplained fever, it is recommended that the initial regimen be continued until resolution of the fever and increasing ANC that exceeds 0.5 x $10^9$/l. Alternatively, if an appropriate treatment course has been completed and all signs and symptoms of infection have resolved, oral fluoroquinolone prophylaxis may be resumed in patients who remain neutropenic, until marrow recovery. In low-risk patients who have defervesced after three days of empirical antibiotic therapy, evidence of imminent marrow recovery may allow discontinuation of broad-spectrum antibiotics prior to the ANC reaching 0.5 x $10^9$/l, after administration of a minimum of five days of antibiotic treatment.

Early discontinuation of antibiotic therapy while fever and neutropenia persist is strongly discouraged in high-risk patients. In such cases, carefully searching for a focus of infection and changing antimicrobial on the basis of clinical or microbiological evidence, including the addition of empirical antifungal therapy, must be considered. Patients with profound, prolonged myelosuppression are at high risk of recurrent fever and sepsis and hence, even when no source of infection is identified, antibiotic therapy should be continued until there is evidence of marrow recovery.

## Other Adjuncts to Therapy

Current guidelines do not recommend the use of myeloid CSFs (G-CSFs and GM-CSFs) as adjuncts to antimicrobials for treating established fever and neutropenia, due to the lack of convincing clinical data, cost limitations and possible adverse effects. Several randomised studies have shown a minimal reduction in days of neutropenia, duration of fever and length of hospital stay with the use of CSFs in established FN. However, none of these benefits were statistically significant or showed a survival benefit, and hence the actual clinical benefit of these reductions is not convincing. However, the use of CSFs may be considered in high-risk patients, including those with hypotension or multi-organ failure.[2]

Granulocyte transfusions are not routinely recommended. They may be helpful in documented infections not responding to appropriate treatment, in severe uncontrolled fungal infections and in life-threatening infections such as pneumonia and soft tissue infections, in patients in whom severe neutropenia (<0.1 x $10^9$/l) is expected to persist for more than five to seven days.[55–57] Trials are required to evaluate their effectiveness and define the optimal schedule of administration.

## Conclusion

The effective management of severe neutropenic sepsis clearly remains a major challenge in clinical practice, as increasingly intensive chemoradiotherapy regimens, including HSCT, are used with a curative intent in patients with cancer. Moreover, with changing population demographics, an increasing number of older patients, often frail and with pre-existing co-morbidities, will require chemotherapy and such patients, when rendered neutropenic, are particularly vulnerable to sepsis from a wide range of pathogens. The use of CSFs is required to abrogate neutropenia in these patients. Furthermore, the availability of equally effective G-CSF biosimilars, combined with the search for cost-minimisation strategies, should lead to a more widespread use of these agents. This will hopefully result not only in better patient management, but also in improved patient outcomes. ■


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