

## Antimicrobial Therapy and Prevention in Febrile Neutropenia

a report by

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Infectious complications are the most common cause of morbidity and mortality in cancer patients, particularly in those with chemotherapy-induced neutropenia. Over the past several decades substantial progress has been made in the management of febrile neutropenia (FN). Empirical antibiotic therapy has reduced mortality rates dramatically in the setting of FN and prompt initiation of antimicrobial therapy with broad-spectrum antibiotics at the onset of fever remains the gold standard. Combination therapy with a beta-lactam plus an aminoglycoside has proven to be effective, although related toxicity is of concern. Consequently, there is an increasing use of monotherapy with carbapenems, antipseudomonal penicillins and third- or fourth-generation cephalosporins instead of classic combination therapy.

A marked shift in the spectrum of causative organisms towards a gram-positive predominance has been the main factor influencing therapeutic approaches. Epidemiology of infection is influenced not only by the severity and duration of neutropenia, but also by the intensity of chemotherapy, the use of prophylaxis and/or empirical antibiotic therapy, the use of central venous catheters, environmental factors and duration of the hospital stay, among others.

The detection of epidemiological shifts requires frequent monitoring and surveillance, particularly at centres treating large numbers of patients, as institutional differences can be substantial. For example, in recent years, some hospitals have experienced an increase of infections caused by multidrug-resistant gram-negative bacilli, such as *Acinetobacter* species or *Stenotrophomonas maltophilia*, and gram-positive cocci with increasing resistance to glycopeptides.

Many reports have demonstrated the emergence of gram-positive organisms in patients with neutropenia. They may account for 45–70% of microbiologically documented infections with bacteremia in patients with neutropenia, although

the majority of them are coagulase-negative staphylococci, which have limited virulence. Focusing only on bloodstream infections may result in an misleading picture, as only 15–25% of patients with neutropenia develop a bloodstream infection and bloodstream infections are caused predominantly by gram-positive cocci, whereas infections at most other sites are predominantly gram-negative or polymicrobial. In contrast many gram-negative pathogens are extremely virulent, so empirical therapy must always include coverage for *Pseudomonas aeruginosa* and any other gram-negative organisms that are common within a given institution. Clinicians should therefore consider the entire spectrum of bacterial infection, not only bloodstream infections, when initiating empirical anti-biotic therapy.

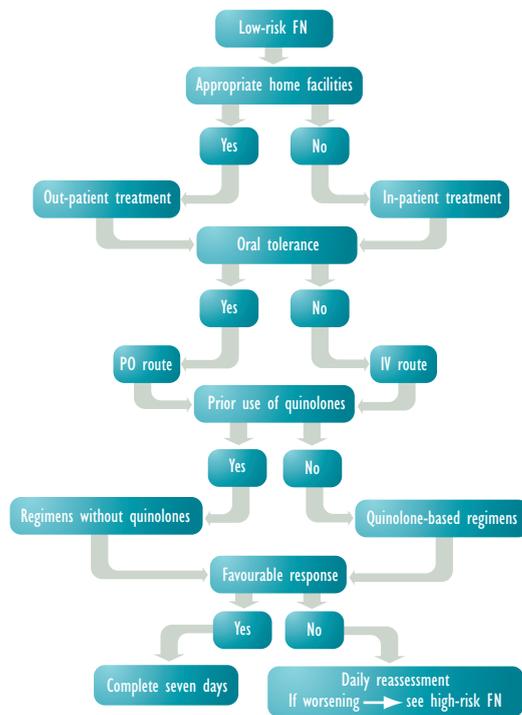
Although overwhelming streptococcal sepsis has raised particular concern, the indiscriminate empirical use of glycopeptides should be discouraged. Treatment with glycopeptides can and should be stopped for those patients whose blood cultures show no growth at 72 to 96 hours. Early empirical antifungal therapy with amphotericin B has been considered a standard practice in cases of persistent fever in high-risk patients despite broad-spectrum antibacterial coverage. Alternatives to amphotericin B (AMB) now exist, including lipid formulations of this drug, and recently licensed antifungal drugs, such as caspofungin and voriconazole, are new options for empirical antifungal therapy that are used increasingly because of their safer toxicity profile. It is critically important that each patient be carefully re-assessed before starting antifungal therapy, because there are many other potential causes for persistent fever, including resistant bacteria and viruses.

There is a growing interest in designing risk-adapted strategies for the management of FN. The administration of parenteral, broad-spectrum empirical antibiotic therapy after the hospitalisation of patients with FN is the accepted standard of care. This approach is effective (with an infection-related mortality rate of less than 10%) but is



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**Figure 1: Algorithm for the Initial Management of Low-risk Febrile Neutropenia**



PO= PerOs(Lr).

expensive and, when applied to all patients with FN, may represent a suboptimal use of resources. Over the past decade, the development of risk stratification models has allowed for the identification of low-risk patients with additional treatment strategies, such as initial hospitalisation followed by early discharge with parenteral or oral antibiotics (sequential therapy) and out-patient treatment with oral antimicrobials. The most attractive option is out-patient treatment

neutropenia (less than 10 days and under 60 years of age) and favourable social and economic environment, with access to prompt medical attention, are relevant prerequisites for considering this approach.

A scoring system for the risk of complications based on the Multinational Association of Supportive Care in Cancer (MASCC) predictive model is gaining increased acceptance. A score  $\geq 21$  of the MASCC index (maximum 26) indicates a low risk. An algorithm for the initial management of low-risk FN is shown in *Figure 1*.

On the other hand, the presence of the clinical site of infection, co-morbid conditions (diabetes mellitus, dehydration and organ failure), a history of documented infection, other causes of immune suppression (asplenia, high-dose steroids, purine analogues and allogeneic haematopoietic stem cell transplantation), and uncontrolled cancer (acute myeloid leukaemia not in complete remission or solid tumour progression in spite of chemotherapy) continue to be an indication for hospital-based antibiotic therapy by an intravenous (IV) route. Monotherapy with a  $\beta$ -lactam (cefepime 2g every eight hours, piperacillin/tazobactam 4.5g every six to eight hours, meropenem 1g every eight hours or imipenem/cilastatin 1g every eight hours) may be the initial choice for most patients. Initial combination therapy may be preferred under some circumstances. Signs of catheter-related infection, known colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA) and severe mucositis are indications for the inclusion of a glycopeptide (vancomycin or teicoplanin) in the

*Treatment with glycopeptides can and should be stopped for those patients whose blood cultures show no growth at 72 to 96 hours.*

for the entire febrile episode, because of several advantages, including important repercussions on economic costs and quality of life, as well as a significant reduction in nosocomial superinfections. Careful selection of patients at a low risk of developing complications, appropriate empirical regimens and the daily monitoring of patients (for response and toxicity) are critical for the success of this approach. Expected duration of

empirical combination. The addition of an aminoglycoside should be considered when the infectious source is other than the central venous catheter, there is colonisation with non-fermenting gram-negative bacilli or treatment with a  $\beta$ -lactam antibiotic has been administered during the previous month. Finally, criteria of severe sepsis at the onset, such as cutaneous hypoperfusion, organ dysfunction, hypotension (systolic arterial pressure

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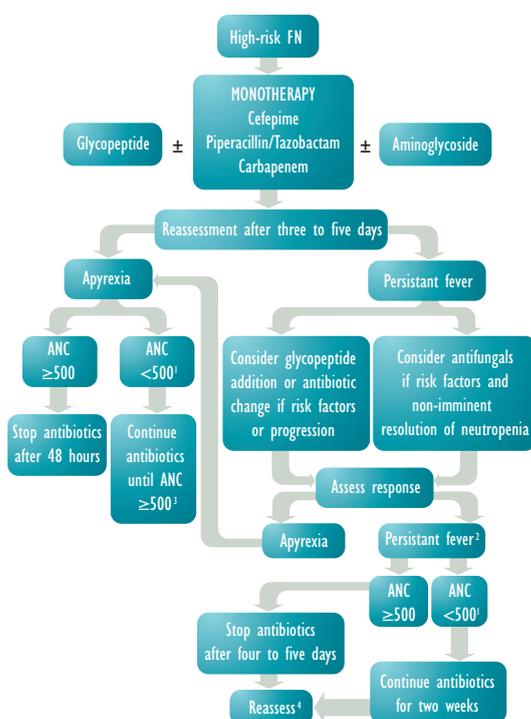
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**Figure 2: Algorithm for the Management of High-risk Febrile Neutropenia**



ANC= absolute neutrophil count.

<90mmHg decreasing >40mmHg from basal value) or lactic acidosis, require the addition of both glycopeptide and aminoglycoside antibiotics. Subsequent treatment will depend on several considerations:

- In the absence of clinical or microbiological documentation, glycopeptide and/or aminoglycoside antibiotics should be discontinued if previously given.

a minimum of 12 to 14 days.

- If fever persists, non-infectious causes and the possibility of stopping antibiotic therapy should be considered, as well as for possible atypical infections.

The algorithm for empirical management of high-risk FN is outlined in *Figure 2*. However, some patients with solid tumour, lymphoma or myeloma treated with chemotherapy regimens producing neutropenia of intermediate duration (seven to 14 days) exhibit a rapid response to the initial antibiotic therapy. In such patients, it would be advisable to administer hospital-based, short-duration IV treatment and subsequent oral therapy at home (sequential therapy).

The practice of antimicrobial prophylaxis has been questioned repeatedly. Although oral prophylaxis against bacterial and fungal infections may decrease the risk of development of infections after bone marrow transplantation or chemotherapy, these practices also promote the emergence of drug-resistant strains (particularly fluoroquinolone-resistant *Escherichia coli* and fluconazole-resistant non-albicans *Candida* species). The use of fluoroquinolones for prophylaxis in high-risk patients with neutropenia has been also associated with the emergence of resistance among *Pseudomonas aeruginosa* isolates (more than 20% at some institutions). The 2002 guidelines from the Infectious Diseases Society of America (IDSA) did not recommend the routine fluoroquinolone prophylaxis during neutropenia. However, this may be considered for high-risk patients in critical periods of time.

*development of risk stratification models has allowed for the identification of low-risk patients with additional treatment strategies.*

- If microbiological documentation is achieved, therapy should be adapted accordingly. Antibiotic changes should not rely only on the persistence of fever. Clinical data should be considered.
- Appropriate duration is not defined. In the setting of severe clinically and/or microbiologically documented infection, antibiotic therapy should be maintained for

In conclusion, a rapid detection of trends in antibiotic resistance patterns of predominant organisms at each institution is of paramount importance for optimal antibiotic selection. ■

*A version of this article containing references can be found in the Reference Section on the website supporting this briefing ([www.touchoncologicaldisease.com](http://www.touchoncologicaldisease.com)).*