International Journal of Infectious Diseases (2006) **10**(S2) S9–S16

http://intl.elsevierhealth.com/journals/ijid

An evidence based review of the available antibiotic treatment options for neutropaenic patients and a recommendation for treatment guidelines

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KEYWORDS
Febrile;
Neutropenia;
Piperacillin-tazobactam;
Review;
Guidelines

Summary **Objective:** Effective empirical antimicrobial therapy has led to a better outcome for febrile neutropenic patients. Guidelines are based mainly on expert opinion, current practice and some clinical trials. Clinical study evidence and meta-analyses of treatment options are reviewed and a treatment strategy recommended.
Results: Piperacillin-tazobactam, meropenem and imipenem have demonstrated significant superiority over ceftazidime and cefepime. Oral ciprofloxacin plus amoxicillin-clavulanic acid is as effective as IV therapy for low risk patients. In high risk patients, additional aminoglycoside does not improve clinical success but increases nephrotoxicity. In clinically stable patients (no CVC, soft tissue, pulmonary, fungal or viral infection), additional glycopeptide is unnecessary.
The Bonn treatment strategy is oral combination therapy (fluoroquinolone and amoxicillin-clavulanic acid) in low risk patients. Low risk patients who cannot take oral medication or high risk patients without significant skin, soft tissue or CVC infection receive IV monotherapy with piperacillin-tazobactam. Piperacillin-tazobactam has been used for more than a decade with no increase in bacterial resistance.
Conclusion: Antimicrobial therapy selection should be based on several factors including the likely pathogen, local antimicrobial susceptibility patterns, patient infection site, risk assessment, clinical stability, organ dysfunction, previous antimicrobial therapy, and cost.
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Introduction

Progress in the therapy and supportive care of patients with haematological malignancies has led to a gradual improvement in survival rates. Overall, the 5-year survival rate of patients $\leqslant$55 yrs with newly diagnosed acute myeloid leukaemia (AML) treated on Eastern Cooperative Oncology Group (ECOG) protocols has risen from 11% in 1973–1979 to 37% in 1989–1997 [1]. Improvements in mortality and morbidity are associated with the use of more aggressive chemotherapy, but at the cost of more severe side effects, such as neutropenia. The rate and degree of decline in neutrophils and the duration of neutropenia have been shown to influence the risk of infection in AML. Because the immune response is muted, the signs and symptoms of infection may not be apparent and fever is frequently the first, and in most cases, the only sign of infection. Fever during neutropenia is associated with a mortality rate of 5–10%, and more than 80% of AML patients treated with chemotherapy have at least one episode of fever during the neutropenic period [2].

Currently, diagnostic tests are not rapid, sensitive or specific enough to distinguish a microbiological cause

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Table 1
Guidelines for first-line empirical antibiotic therapy of fever in neutropenic patients

Guideline	Low risk patients		High risk patients	
	Monotherapy	Combination therapy	Monotherapy	Combination therapy
Germany (2003) [4]	Ciprofloxacin or levofloxacin	Ofloxacin + amoxicillin-clavulanic acid	Ceftazidime, cefepime, piperacillin-tazobactam, carbapenem	Acylaminopenicillin + AMG, cephalosporin III/IV + AMG
USA – IDSA (2002) [5]	None	Ciprofloxacin + amoxicillin-clavulanic acid	Ceftazidime, cefepime, carbapenem	Acylaminopenicillin + AMG, cephalosporin III/IV + AMG
USA – NCCN (2005) [6]	None	Ciprofloxacin + amoxicillin-clavulanic acid (or clindamycin)	Ceftazidime, cefepime, piperacillin-tazobactam, carbapenem	Acylaminopenicillin + AMG, cephalosporin III/IV + AMG
Spain (2001) [7]	None	Levofloxacin + amoxicillin-clavulanic acid or cefprozil + ciprofloxacin Previous FQ therapy: ceftriaxone + ceftibuten	Ceftazidime, cefepime, piperacillin-tazobactam, carbapenem	None

of fever from other causes. The Gram-positive cocci account for 60–70% of bacteria causing fever with coagulase-negative staphylococci (CoNS) then viridans streptococci (*Streptococcus mitis*, *Streptococcus salivarius* and *Streptococcus millerei*) followed by *Staphylococcus aureus* and *Enterococcus faecium* [3]. Gram-negative bacilli account for the remainder and include *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter* species and *Stenotrophomonas maltophilia*. Prompt administration of effective empirical broad-spectrum antimicrobial therapy is essential for managing febrile neutropenia and has led to an improved outcome.

Clinical classification of neutropenic fever

Definitions of neutropenic fever vary from centre to centre. German guidelines define neutropenic fever as an oral temperature of $\geqslant$38.3°C measured once or $\geqslant$38.0°C sustained for at least 1 hour or measured twice within 12 hours, in a patient with neutropenia defined by a neutrophil count (segments and bands) of $<0.5\times10^9$/L (<500/μL or $<1.0\times10^9$/L (<1000/μL), with a predicted decline to 0.5×10^9/L (500/μL) within the next 2 days [4].

Definition of risk factors

Patients are differentiated into risk categories for antimicrobial therapy according to the duration of neutropenia and the presence of risk factors for serious infection. Patients are classified as at low risk when neutropenia is of short duration ($\leqslant$5 days), there is no infection of the central nervous system (CNS) or central venous catheter (CVC) or pneumonia, there are no signs of sepsis or shock, the ECOG performance status is 0–2, there is no severe comorbidity and there are adequate social, medical and intellectual resources (including ability to take oral medication and adequate fluid). These patients may be considered for oral therapy. Those with neutropenia of longer duration are classified as intermediate (6–9 days) or high risk ($\geqslant$10 days) and are treated with intravenous (IV) therapy.

Guidelines for empirical therapy

Guidelines for empirical therapy of febrile neutropenia have been published in several countries based mainly on expert opinion, current practice and some clinical trials (Table 1). German guidelines recommend empirical monotherapy or combination therapy with antipseudomonal and antistreptococcal agents [4]. Low risk patients suitable for oral therapy may receive ciprofloxacin or levofloxacin as monotherapy or combination therapy with ofloxacin and amoxicillin-clavulanic acid. Intermediate and high risk patients should receive IV monotherapy with ceftazidime, cefepime, piperacillin-tazobactam or a carbapenem or combination therapy with any of these β-lactams plus a single dose of an aminoglycoside (AMG). In severe mucositis or suspected CVC associated infection, a glycopeptide may be added. The regimen is modified after 72–96 hours of therapy if fever persists, with the exception of CoNS infections, which take longer to respond. In intermediate and high risk patients, initial monotherapy may require the addition of an AMG; or initial carbapenem monotherapy may be followed by a fluoroquinolone and/or a glycopeptide. After resolution of fever to <38°C, treatment is continued for 7 days if the neutrophil count is $<1\times10^9$/L (<1000 cells/μL) or 2 days if it is $>1\times10^9$/L (>1000 cells/μL).

The Infectious Diseases Society of America (IDSA) guidelines (2002) recommend oral empirical therapy with ciprofloxacin and amoxicillin-clavulanic acid for low risk patients [5] or IV therapy with either cefepime, ceftazidime or a carbapenem. Piperacillin-tazobactam is also mentioned as an effective monotherapy, but not recommended as there were insufficient data at the time. Combination therapy consists of an AMG (gentamicin, tobramycin, amikacin) together with an antipseudomonal penicillin

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