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 ≤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. 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.

Currently, diagnostic tests are not rapid, sensitive or specific enough to distinguish a microbiological cause of infection.
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 milleri) followed by Staphylococcus aureus and Enterococcus faecium. 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 ≥38.3°C measured once or ≥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 x 10^9/L (≤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 (≥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. 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. 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.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Low risk patients</th>
<th>Combination therapy</th>
<th>High risk patients</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany (2003)</td>
<td>Ciprofloxacin or levofloxacin</td>
<td>Ofloxacin + amoxicillin-clavulanic acid</td>
<td>Cefazidime, cefepime, piperacillin-tazobactam, carbapenem</td>
<td>Acylaminopenicillin + AMG, cephalosporin III/IV + AMG</td>
</tr>
<tr>
<td>USA - IDSA (2002)</td>
<td>None</td>
<td>Ciprofloxacin + amoxicillin-clavulanic acid</td>
<td>Cefazidime, cefepime, carbapenem</td>
<td>Acylaminopenicillin + AMG, cephalosporin III/IV + AMG</td>
</tr>
<tr>
<td>USA - NCCN (2005)</td>
<td>None</td>
<td>Ciprofloxacin + amoxicillin-clavulanic acid (or clindamycin)</td>
<td>Cefazidime, cefepime, piperacillin-tazobactam, carbapenem</td>
<td>Acylaminopenicillin + AMG, cephalosporin III/IV + AMG</td>
</tr>
<tr>
<td>Spain (2001)</td>
<td>None</td>
<td>Levofoxacin + amoxicillin-clavulanic acid or cefprozil + ciprofloxacin</td>
<td>Cefazidime, cefepime, piperacillin-tazobactam, carbapenem</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 1
Guidelines for first-line empirical antibiotic therapy of fever in neutropenic patients
(ticarcillin-clavulanic acid or piperacillin-tazobactam), ceftazidime or carbapenem.

The European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada suggest that vancomycin should not generally be used as empirical therapy because of the association between its excessive use in hospitals and the emergence of vancomycin-resistant enterococci (VRE). Alternatives requiring more study include teicoplanin (not available outside Europe), linezolid or quinupristin-dalfopristin. Low risk patients on IV therapy who have no subsequent complications can be changed after 48 hours to oral ciprofloxacin and amoxicillin-clavulanic acid, and all patients who become afebrile in 3-5 days continue the same therapy. In persistent fever, the patient is reassessed at day 3. If there is no clinical deterioration the same therapy is continued, but when there is progression of the infection or clinical instability, the therapy should be changed with the addition of an antifungal agent empirically if the patient is still febrile after 5 days. If the patient is afebrile and clinically stable, therapy can be stopped when the neutrophil count exceeds $0.5 \times 10^9/L$ ($\geq 500/\mu L$) for 2 consecutive days and the patient has been afebrile for $\geq 48$ hours. If the patient is afebrile and still neutropenic but clinically stable therapy can be stopped after 5-7 days.

More recent US guidelines have been compiled by the National Comprehensive Cancer Network (2005). Low risk patients receive oral combination therapy only with ciprofloxacin and amoxicillin-clavulanic acid (or clindamycin when there is penicillin allergy). The Panel recommends 3 evidence-based approaches to IV therapy. Firstly, monotherapy with piperacillin-tazobactam, a carbapenem (imipenem-cilastatin or meropenem) or a cephalosporin (ceftazidime or cefepime), though recent studies have shown that some Gram-negative bacilli, including *Pseudomonas aeruginosa*, are developing resistance to ceftazidime. Secondly, combination therapy of an AMG together with either an antipseudomonal penicillin (with or without a β-lactamase inhibitor) or an extended-spectrum antipseudomonal cephalosporin. Ciprofloxacin with an antipseudomonal penicillin can also be given. Thirdly, monotherapy or combination therapy plus IV vancomycin. The Panel recommends quinupristin-dalfopristin, linezolid and daptamycin limited to specific situations such as the involvement of a vancomycin-resistant enterococcus or when vancomycin is not an option.

Initial empirical therapy in clinically unstable patients should comprise a combination of a carbapenem, an AMG and vancomycin, depending on local susceptibility patterns, and a cephalosporin or penicillin with either an AMG or ciprofloxacin, if there is a history of infection due to *Pseudomonas aeruginosa*. Therapy can be stopped for patients who become afebrile for at least 24 h soon after initiation of therapy if neutropenia has resolved. Patients who become afebrile but remain neutropenic should receive therapy until neutrophil recovery. Patients who remain neutropenic with no focus of infection and are afebrile for 7-14 days may either discontinue therapy or change to oral therapy until neutropenia resolves. Persistent fever is reassessed after 4 days therapy, and recurrent fever may require a change in therapy or the addition of an antifungal agent.

Spanish guidelines (2001) recommend oral therapy for low risk patients not previously given fluoroquinolone therapy. Therapy can consist of levofloxacin and amoxicillin-clavulanic acid, or ciprofloxacin and cefprozil. Ceftriaxone and cefitubten with or without teicoplanin is recommended for those previously treated with a fluoroquinolone. Initial IV monotherapy with cefepime, piperacillin-tazobactam, meropenem or imipenem is recommended. Additional antimicrobial agents are recommended for several indications. Addition of a glycopeptide (vancomycin or teicoplanin) is indicated for CoNS infection or a CVC infection, amikacin for colonisation with the Gram-negative bacilli, *Pseudomonas aeruginosa* or *Acinetobacter* spp., a glycopeptid (vancomycin or teicoplanin) and amikacin for septic shock, and initial treatment with aztreonam or amikacin and a glycopeptide when there is allergy to penicillin. If infection is due to *Pseudomonas aeruginosa* amikacin or ciprofloxacin is added to the initial regimen and/or fever persists after 3-5 days treatment and no microbiologically defined infection is found, an aminoglycoside or glycopeptide or both are added. If fever persists for 5-7 days addition of an antifungal (ampoterican B) is considered.

**Evidence based evaluation of combination versus monotherapy**

The Cochrane Review of 15 randomised controlled trials of oral versus IV therapy found that oral fluoroquinolone monotherapy or combination therapy produced comparable results. The analysis did not produce any data to support any particular regimen but suggested it was prudent to employ a combination of a fluoroquinolone with a second antibiotic active against Gram-positive organisms. Oral empirical therapy with ciprofloxacin and amoxicillin-clavulanic acid was found to be as safe and as effective as IV therapy for low risk patients. However, most guidelines recommend combination therapy with a β-lactam plus an AMG as an alternative to a β-lactam alone. Many studies have compared the two approaches, but there is no consensus on the superiority of one over the other (Table 2).

**Aminoglycosides, clinical outcomes: survival and adverse reactions**

A systemic review of clinical trials compared the efficacy of monotherapy with combinations containing AMG. A meta-analysis of pooled data from 4795 febrile neutropenic episodes in 29 clinical trials and a subset of 1029 bacteraemic episodes was carried out by both Peto fixed and Der Simonian and Laird random effects models. No statistical heterogeneity between the trials was detected. The outcome measure was clinical treatment failure defined as modification of the initially allocated regimen or death during treatment. The pooled odds ratio (OR)
of clinical failure with monotherapy versus combination therapy for all febrile episodes was 0.88 (95% CI: 0.78–0.99; p < 0.05) by the fixed effects model and 0.87 (95% CI: 0.80–0.93) by the more conservative random effects model. For bacteraemic episodes, the pooled OR was 0.70 (95% CI: 0.54–0.92; p < 0.05) by the fixed effects model and 0.72 (95% CI: 0.54–0.95) by the random effects model. There was a tendency to favour monotherapy in all of the subgroup analyses and there was a higher rate of adverse events, mainly nephrotoxicity, in the combination therapy groups. It was concluded that monotherapy was as effective as combination therapy with AMG. The relative risk (RR) of treatment failure with monotherapy was reduced overall by 12% and by 30% for bacteraemic episodes.

A second meta-analysis of data from 7807 patients in 47 clinical trials comparing the efficacy of β-lactam monotherapy versus combination therapy with a β-lactam plus an AMG was carried out using an intent to treat (ITT) approach. RR s were pooled with the random effects model. The outcome measure was all-cause fatality. The mean all-cause fatality was 6.2% and overall, there was no significant difference between monotherapy and combination therapy (RR 0.85, 95% CI: 0.72–1.02; ns). For success of treatment there was a significant advantage for monotherapy (0.92, 95% CI: 0.85–0.99). In 5 trials using the same β-lactam antibiotic in both arms, there was no significant difference between monotherapy and combination therapy (0.73, 95% CI: 0.49–1.08) but there was a major advantage for monotherapy in trials comparing different β-lactams (0.87, 95% CI: 0.80–0.93). There was a small advantage for monotherapy when data for treatment failure was combined from all 47 studies (RR 0.92, 95% CI: 0.85–0.99; ns), but significant heterogeneity was detected among the trials. There was no significant difference in treatment failure between monotherapy and combination therapy in 9 trials that compared the same β-lactam in both arms (RR 1.12, 95% CI: 0.96–1.29; ns). However, there was significant benefit for monotherapy in trials comparing different beta-lactams (0.87, 95% CI: 0.80–0.93). There was also a significant advantage for monotherapy for patients with documented infection and haematological malignancies. In the combination treatment group, adverse events were significantly more common with an important difference in the development of renal failure (0.49, 95% CI: 0.36–0.65) that was not influenced by single daily administration of AMG. Discontinuation of therapy because of an adverse event was also more common (0.57, 95% CI: 0.36–0.91). It was concluded that there is no clinical advantage for combination therapy which is associated with a significantly higher rate of adverse events, mainly nephrotoxicity. Hence monotherapy with a broad-spectrum β-lactam antibiotic should be regarded as standard care in patients with febrile neutropenia.

### Glycopeptides: summary of meta-analyses

Gram-positive cocci are the most commonly identified cause of infection of febrile neutropenic patients, and the β-lactams and carbapenems employed for empirical therapy lack in-vitro activity against many of the species involved. Hence many clinicians consider that glycopeptides should be used empirically. Indeed, empirical modification of the therapy regimen is still standard practice in many centres, most frequently with a glycopeptide, on the basis of persistent fever for a period as short as 48-96 hours. There is considerable debate about the use of empirical glycopeptides because of the growing awareness of the development of resistance among enterococci, *Staphylococcus aureus* and CoNS, the potential for nephrotoxicity and their high cost.

Most guidelines stress that vancomycin should not be considered as a routine component of initial empirical therapy, but its use should be limited to certain indications including clinically defined CVC infections (usually caused by CoNS); high level β-lactam resistance, Gram-positive bacteraemia, known colonisation with β-lactam-resistant pneumococci or methicillin-resistant *Staphylococcus aureus* (MRSA), previous prophylaxis with fluoroquinolones.

### Table 2

Evidence based studies of first-line empirical antibiotic therapy of fever in neutropenic patients

<table>
<thead>
<tr>
<th>References</th>
<th>Trials (patients)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral vs IV therapy</td>
<td>Vidal et al. 8, Innes et al. 9, Kern et al. 10, Freifeld et al. 11</td>
<td>15</td>
</tr>
<tr>
<td>Monotherapy vs combination + AMG</td>
<td>Furno et al. 12</td>
<td>29 (4795)</td>
</tr>
<tr>
<td>β-lactam monotherapy vs β-lactam–AMG combination therapy</td>
<td>Paul et al. 13</td>
<td>47 (7807)</td>
</tr>
<tr>
<td>Cefepime monotherapy vs comparators</td>
<td>Paul et al. 14</td>
<td>33</td>
</tr>
<tr>
<td>Empirical use of glycopeptides</td>
<td>Wade and Glasmacher 15</td>
<td>2 (279)</td>
</tr>
</tbody>
</table>
such as ciprofloxacin or cotrimoxazole (trimethoprim-sulfamethoxazole), or the presence of hypotension or septic shock.

In a double-blind study of 763 neutropenic patients, 165 remained febrile after 48-60 hours of empirical piperacillin-tazobactam monotherapy and were randomly allocated vancomycin (86 episodes) or placebo (79) as additional therapy. Resolution of fever was observed in 82/86 (95%) vancomycin and 73/79 (92%) placebo treated episodes. Overall, resolution of fever without any modification of therapy occurred in 458/677 episodes (68%) with a median time to defervescence of 4.3 days (95%CI: 3.5-5.1 days).

Adverse events definitely or probably associated with study medication were seen for 9 patients (10%) treated with vancomycin and included rash (3), purpura (2), nephrotoxicity (2), lip swelling (1) and red man syndrome (1); and for 3 given placebo (4%) including pseudomembranous colitis, diarrhoea and rash.

In a second double-blind study, neutropenic patients who remained febrile after 72-96 hours of empirical imipenem monotherapy were randomised to additionally receive teicoplanin (56 patients) or placebo (58) 17. Resolution of fever within 72 hours occurred in 25 teicoplanin (44.6%) and 27 placebo treated patients (46.6%).

A small meta-analysis of the two trials showed that in 279 patients, no difference for resolution of fever without modification of therapy was found (Peto OR 0.795; 95% CI: 0.466-1.605; p = 0.605) or in infectious disease related mortality (Peto OR 1.984; 95% CI: 0.467-4.188; p = 0.312) 17. The evidence suggests that initial empirical therapy can be continued, and the addition of a glycopeptide is unnecessary, for clinically stable patients who do not have a CVC, soft tissue or pulmonary infection, a fungal or viral infection.

**Piperacillin-tazobactam: combination versus monotherapy**

One multicentre, double-blind, placebo-controlled trial has compared empirical piperacillin-tazobactam monotherapy and piperacillin-tazobactam and amikacin combination therapy for 364 and 369 patients, respectively 18. Piperacillin-tazobactam monotherapy was as effective as combination therapy according to all efficacy parameters examined. The overall success rate was similar in each treatment arm; monotherapy (49%) and combination therapy (53%), [95% CI: 11.3; p = 0.2]. The overall distribution of time to defervescence and to failure was similar (p = 0.6 and 0.9, respectively). Treatment success in the ITT population for monotherapy was 49% and combination therapy 51% (p = 0.6). Monotherapy was discontinued for 2 patients because of skin rash and gastrointestinal disturbance, and combination therapy for 5 patients because of skin rash (2), nephrotoxicity (2) and hypersensitivity (1). The study concluded that empirical monotherapy with piperacillin-tazobactam was as efficacious as the combination of piperacillin-tazobactam and an AMG for the treatment of high-risk, febrile neutropenic patients.

Data from consecutive cohorts of neutropenic patients with haematological malignancies at the University of Bonn treated with piperacillin-tazobactam monotherapy or piperacillin-tazobactam plus gentamicin have demonstrated a similar result. The response rate with or without modification was 57% in monotherapy patients versus 54% in combination therapy patients (p = 0.774) 19.

**Treatment options for monotherapy**

Current guidelines recommend ceftazidime, piperacillin-tazobactam, imipenem and meropenem for empirical monotherapy. Ceftazidime is not recommended in the Spanish guidelines and in the USA, piperacillin-tazobactam is not recommended in IDSA guidelines (2002) because of lack of clinical experience, but is recommended in later NCCN guidelines (2005).

In a meta-analysis and systemic review of randomised, controlled trials, the main analysis of all-cause mortality comparing cefepime with a comparator showed that there was a non-significant tendency in the subgroups in favour of the comparator 10. However, there was a significantly higher mortality rate associated with cefepime than with other β-lactams (ceftazidime, carbapenems and piperacillin-tazobactam); 96 versus 66 deaths, respectively (RR 1.44, 95% CI: 1.06-1.94; p = 0.02). There were no methodological problems, no statistical heterogeneity and no publication bias (symmetrical funnel plot) and the effect is consistent in studies with adequate allocation concealment or generation and ITT analysis. A higher mortality rate was associated with a lower dose of cefepime (<6g/day), [RR 2.01, 95%CI: 0.87-5.08] and a significant mortality difference was also seen in full dose studies [RR 1.73, 95%CI: 1.12-2.66].

A further meta-analysis currently includes 37 studies and 8676 febrile neutropenic patients 21. The main outcome was response without treatment modification, and a survival difference was not identified. The analysis included published survival data only, whereas the meta-analysis of Paul et al. 20 included additional data retrieved from authors. Significant heterogeneity between trials was not detected. Ceftazidime was found to be inferior to piperacillin-tazobactam, meropenem and imipenem-cilastatin (RR for failure of treatment without modification 0.88, 95%CI: 0.83-0.92). There was a clear advantage for piperacillin-tazobactam use in comparison to ceftazidime (RR 0.81, 95%CI: 0.72-0.91; p = 0.04) and the same trend was seen in comparison to cefepime (0.94, 95%CI: 0.86-1.03; p = 0.93) 22-26,14,27,28. Overall there was a significant advantage for piperacillin-tazobactam compared to all cephalosporins (0.89, 95%CI: 0.83-0.95; p = 0.19), with 11% reduction of the RR of treatment failure (Table 3).

In a randomised, open label, controlled study, first line monotherapy with piperacillin-tazobactam in 265 febrile neutropenic patients was compared to cefepime in 263 patients 20. At end of treatment, the clinical success rate in ITT patients was significantly superior in patients treated with piperacillin-tazobactam (45.3%) than cefepime (35.9%), p = 0.04. Adverse events in
Table 3
Clinical trials with piperacillin-tazobactam in neutropenic patients: relative risk of treatment failure without modification

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Cephalosporin III (n/N)</th>
<th>Piperacillin-tazobactam (n/N)</th>
<th>RR (fixed) 95% CI</th>
<th>Favours PipTaz over ceph III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Piperacillin-tazobactam versus ceftazidime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cometta et al. 1995²²</td>
<td>132/342</td>
<td>168/364</td>
<td>0.84 (0.70, 0.99)</td>
<td>+</td>
</tr>
<tr>
<td>Marie et al. 1995²³</td>
<td>37/94</td>
<td>54/94</td>
<td>0.69 (0.50, 0.93)</td>
<td>+</td>
</tr>
<tr>
<td>Hess et al. 1998²⁴</td>
<td>40/48</td>
<td>39/48</td>
<td>1.03 (0.85, 1.23)</td>
<td>-</td>
</tr>
<tr>
<td>Marie et al. 1999²⁵</td>
<td>52/114</td>
<td>83/133</td>
<td>0.73 (0.57, 0.93)</td>
<td>+</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>598</td>
<td>639</td>
<td>0.81 (0.72, 0.91)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Piperacillin-tazobactam versus cefepime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bohme et al. 1998²⁶</td>
<td>19/49</td>
<td>22/51</td>
<td>0.90 (0.56, 1.44)</td>
<td>+</td>
</tr>
<tr>
<td>Cornely et al. 2001¹⁴</td>
<td>68/177</td>
<td>70/176</td>
<td>0.97 (0.74, 1.25)</td>
<td>+</td>
</tr>
<tr>
<td>Sanz et al. 2002²⁷</td>
<td>212/432</td>
<td>222/435</td>
<td>0.96 (0.84, 1.10)</td>
<td>+</td>
</tr>
<tr>
<td>Bow et al. 2003²⁸</td>
<td>155/263</td>
<td>172/265</td>
<td>0.91 (0.79, 1.04)</td>
<td>+</td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>921</td>
<td>927</td>
<td>0.94 (0.86, 1.03)</td>
<td>+</td>
</tr>
<tr>
<td>Overall total (95% CI)</td>
<td>1519</td>
<td>1566</td>
<td>0.89 (0.83, 0.95)</td>
<td>+</td>
</tr>
</tbody>
</table>

both treatment groups were most frequently rash and diarrhoea. It was concluded that piperacillin-tazobactam monotherapy was as safe and at least as efficacious as cefepime.

**Treatment strategy at the University of Bonn**

The clinical classification of neutropenic fever used in Bonn differs slightly from that used in most guidelines (Figure 1). Patients are initially categorised as low or high risk. High risk patients are differentiated into those with clinically or microbiologically defined infection whereby the focus of infection can be determined (pneumonia, neutropenic enterocolitis, urinary tract infection, skin and soft tissue infection or a CVC infection) and those with unexplained fever. Treatment can be adapted according to whether this information is available, but it is not necessary for empirical therapy. The criteria for oral therapy are similar to the German guidelines. In Bonn, a patient with an expected duration of neutropenia of less than five days, who is clinically stable and has not received very intensive chemotherapy, may receive oral therapy. Oral therapy has been shown to be effective for patients with 5–10 days neutropenia after a more intensive course of chemotherapy for lymphoma.

A low risk patient able to take oral therapy receives a fluoroquinolone and amoxicillin-clavulanic acid (or sul- tamicillin). IV monotherapy with piperacillin-tazobactam is administered to those patients who are unable to take oral medication and to high risk patients when a glycopeptide is not required. A glycopeptide is added if there is clinically significant skin and soft tissue or CVC infection. If fever is not resolved after 3–4 days of therapy, the patient is re-evaluated and a CT scan is performed. When the patient is stable, with no pulmonary infiltrates and no soft tissue infection, therapy is continued for 7–8 days, and then changed to a different regimen if the patient remains clinically stable.

Piperacillin-tazobactam has been used as initial monotherapy in Bonn for more than 10 years with no increase of bacterial resistance despite its intensive use (Figure 2). The susceptibility rates in 2005 for *Escherichia coli* were 97%, *Pseudomonas aeruginosa* (90%), *Klebsiella pneumoniae* (94%) and *Serratia marcescens* (87%), [Molitor E, personal communication].

![Figure 1. Initial empirical antimicrobial therapy in neutropenic fever in the Department of Haematology and Oncology, University of Bonn.](image-url)
Choice of monotherapy

Piperacillin-tazobactam, meropenem or imipenem are good choices for initial empirical antibiotic therapy as they have demonstrated significant superiority over ceftazidime and cefepime.

Ultimately the selection of initial antimicrobial therapy should take into account local circumstances including the most common potential infecting pathogen for the neutropenic populations and local antimicrobial susceptibility patterns, the patient’s infection risk assessment, the site of infection, clinical stability, medication allergy, organ dysfunction and previous antimicrobial therapy as well as cost. Careful selection may enhance efficacy and should minimise the incidence of adverse events and reduce bacterial resistance.

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References


