An evidence-based evaluation of important aspects of empirical antibiotic therapy in febrile neutropenic patients

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ABSTRACT

Febrile neutropenia is still associated with a high mortality rate, making timely and efficient empirical antibiotic therapy absolutely vital. For these reasons, evidence-based guidelines are urgently needed. The guidelines published so far are mainly based on clinical experience and selective citation. This review summarises studies and meta-analyses concerning empirical antibiotic therapy in high-risk neutropenic patients: (1) No benefit results from the addition of an aminoglycoside to the initial empirical therapy. On the contrary, patients who received an aminoglycoside had a significantly higher rate of adverse events, especially nephrotoxicity. (2) The empirical addition of a glycopeptide after 3–4 days of persistent fever was evaluated in two randomised controlled trials. Combined analysis demonstrates that in clinically stable patients without resistant or skin/soft tissue infections, the use of a glycopeptide can be delayed for another 3–4 days. (3) The choice of drugs for monotherapy is currently being evaluated; preliminary results demonstrate that ceftazidime has a significantly inferior response rate (without modification) to other evaluated antibiotics. In conclusion, guidelines should be based on the systematic evaluation of all relevant clinical trials. The analysis of the existing data leads to the recommendation of monotherapy, without aminoglycoside, using piperacillin–tazobactam, cefepime, meropenem or imipenem–cilastin, any of which may be continued for up to 7 days in persistently febrile, clinically stable patients without skin/soft tissue infections. The choice of drug as standard first-line therapy should depend on drug costs, local resistance rates and the potential for resistance induction.

Keywords: Aminoglycosides, fever, glycopetides, neutropenia, piperacillin-tazobactam, review

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INTRODUCTION

More than 80% of patients who have undergone myelosuppressive chemotherapy for acute leukaemia have at least one episode of fever during the period of neutropenia. Despite the empirical use of broad-spectrum antibiotic agents, a fatality rate of 5–10% is seen in most trials. Timely and effective empirical antibiotic therapy is an absolute necessity and has greatly improved the outcome for these patients [1,2].

A series of European Organisation for Research and Treatment of Cancer (EORTC) studies from 1973 to 1993 demonstrated a shift from Gram-negative to Gram-positive organisms in microbiologically documented infections in these patients [3]. The predominant organisms involved are *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci (viridans, group A, *Streptococcus pneumoniae*), *Eschericha coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae*.

This shift was presumed to be due to the introduction of effective prophylaxis with quinolone antibiotics against Gram-negative organisms but the most recent EORTC review of reported episodes of proven single-organism bacteraemias shows that there has been a resurgence of Gram-negative infections. Between 1993 and 2000, the incidence rates of Gram-negative and Gram-positive infections have been roughly the same (12% and 13%, respectively), with a significant increase in the rate of Gram-negative infections (6.5% vs.

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12%, $p < 0.01$) [4]. This recent re-emergence of Gram-negative infections has happened despite the continuing use of quinolone prophylaxis and has been reported by units still using such Gram-negative prophylaxis [5], those which have recently abandoned this approach [6] and those which have never used it [7]. The fluctuating rates of Gram-positive and Gram-negative infections emphasise the need for broad-spectrum antibiotics in the empirical first-line therapy of febrile neutropenia.

Non-bacterial infections are mostly caused by fungi (*Candida* spp. and *Aspergillus* spp.), whereas patients may encounter severe viral (herpes simplex, varicella-zoster, Epstein–Barr virus and cytomegalovirus) and protozoal (*Toxoplasma gondii*) infections after allogeneic stem-cell transplantation [8,9]. However, an identification of the causative agents will be possible only in approximately one-third of patients, so the majority of patients need empirical antibiotic therapy for fever of unknown origin.

CLINICAL PRACTICE GUIDELINES

Recommendations to guide clinical practice in the treatment of these infections have been published in some countries. Whereas two guidelines are available from the USA, only two European guidelines could be found despite an intensive search (via MedLine, Google, and contact with experts in various countries) [9–12].

These guidelines differentiate between low-risk patients, who are likely to receive oral antibiotics, and patients at higher risk, who should be treated in hospital with intravenous antibiotics. This review will consider further the intermediate- or high-risk patients only (usually those with a duration of neutropenia of more than 5 days), as there is a broad consensus on the treatment of low-risk patients.

By definition, where a causative organism is unknown or not suspected on clinical grounds, empirical broad-spectrum antibiotic therapy is recommended. For intermediate- or high-risk neutropenic patients with fever of unknown origin, current guidelines recommend either broad-spectrum monotherapy or combination therapy where an aminoglycoside is added. Table 1 lists the recommended antibiotics from the four published guidelines. In certain risk situations, specific antibiotics are needed (e.g., glycopeptides in the case of central venous line or skin/deep tissue infections) in addition to the empirically chosen antibacterials.

Table 1. Recommendations from clinical practice guidelines for empirical initial antibiotic therapy in neutropenic patients with fever of unknown origin and no particular risk factors

Guideline	Monotherapy	Combination therapy
IDSA (Infectious Disease Society of America) [9]	Ceftazidime	Aminoglycoside + piperacillin–tazobactam/ticarcillin/clavulanate
	Cefepime	Aminoglycoside + cefepime–ceftazidime
	Imipenem–cilastatin	Aminoglycoside + imipenem–cilastatin
	Meropenem	Aminoglycoside + meropenem
	Piperacillin–tazobactam[a]	
NCCN (National Comprehensive Cancer Network) [10]	Ceftazidime	Aminoglycoside + anti-pseudomonal penicillin[b]
	Cefepime	Aminoglycoside + extended-spectrum cephalosporin
	Imipenem–cilastatin	Ciprofloxacin + anti-pseudomonal penicillin
	Meropenem	Double β-lactam
IHO (Infectious Diseases Working Party of the German Society of Hematology and Oncology) [11]	Piperacillin–tazobactam	Aminoglycoside + acylaminopenicillin
	Ceftazidime	
	Cefepime	Aminoglycoside + third- or fourth-generation cephalosporin[c]
	Imipenem–cilastatin	
	Meropenem	
SEQ (Chemotherapy Society of Spain) [12]	Cefepime	Not recommended for routine use
	Meropenem	
	Piperacillin–tazobactam	

[a]Piperacillin–tazobactam has been found to be effective monotherapy.
[b]With or without β-lactamase inhibitor.
[c]Ceftazidime, cefepime, ceftriaxone.

None of these guidelines, however, is evidence-based in the sense that a complete review of the relevant literature was undertaken to formulate the recommendations. Guidance is therefore based mainly on expert opinions and current practice as well as on a selection of clinical trials. Such a review, however, would be a considerable task. Even a very simple PubMed search (key words: [fever OR infection] and neutropen*; limit: randomized controlled trial) revealed 716 citations.

This article will review existing meta-analyses related to this subject and compare these results with the recommendations in the guidelines. As the principles of evidence-based medicine and meta-analysis have not often been applied to infectious diseases, a short introduction to these principles will be given first.

EVIDENCE-BASED MEDICINE AND META-ANALYSIS

David Sackett, one of the pioneers of evidence-based medicine, has defined it as 'the integration of best research evidence with clinical expertise and patient values' [13]. Best research evidence usually refers to randomised controlled trials, but when these are not available, other evidence must be used.

Systematic reviews attempt to minimise bias and random errors by a complete review of published and unpublished data, assessment of possible bias and, as and where appropriate, a quantitative synthesis of independent randomised controlled trials (meta-analysis) [14].

An important example of the advantages of such a quantitative synthesis is reported by Egger *et al.* [14,15]. Lau *et al.* have published a cumulative meta-analysis of the trials of intravenous streptokinase in acute myocardial infarction and demonstrated that a statistically significant combined difference in total mortality of approximately 20% was achieved by 1973 [14,16]. After that date, a further 17 000 patients were enrolled in the placebo arms of subsequent trials (including two that were very large) until the drug was eventually licensed in most countries. Some of the deaths in the placebo arms could have been prevented if the efficacy of the treatment had been recognised earlier. Meta-analysis became routinely available only at the end of the 1970s.

Antman *et al.* correlated in 1992 the evidence of cumulative meta-analysis with the recommendations made by experts in review articles and textbooks [14,17]. They found a 14-year delay before the inclusion of an important therapeutic advance (thrombolytic therapy) in textbooks and review articles and the failure to realise and describe the harmful effects of another intervention (prophylactic use of lidocaine). These alarming findings, however, have not led to a general acceptance of systematic reviews or meta-analysis.

A systematic review should be a carefully planned research project with a clearly formulated question, *a priori* definitions of eligibility criteria for trials to be included, and the relevant outcomes that will be extracted in a written protocol. A comprehensive search for relevant trials (published or unpublished) and an assessment of their methodological quality is necessary. The results of all trials should be displayed graphically, either as the odds ratio (the odds being the ratio of the number of patients with an event to the number of patients without this event) or the relative risk ratio (number of patients with event/total number of patients) of both treatment arms. This graph allows visual examination of the degree of heterogeneity between trials. If possible, a quantitative synthesis should be done which will allow the estimation of the overall effect. Finally, a sensitivity analysis should test the robustness of the combined estimates with respect to the effect of different methodological and clinical variables [18].

THE USE OF AMINOGLYCOSIDES IN EMPIRICAL ANTIBIOTIC THERAPY IN FEBRILE NEUTROPENIC PATIENTS

As shown above, most guidelines for the treatment of fever in neutropenic patients recommend the use of a combination therapy of β-lactam antibiotics with aminoglycosides as a therapeutic alternative to monotherapy with a β-lactam antibiotic alone (Table 1). Many randomised trials have now compared these alternative therapeutic approaches, but there is no consensus on the superiority of one regimen over the other.

Two meta-analyses have explored the use of aminoglycosides for this indication [19–21]. Furno *et al.* analysed 29 trials and 4795 febrile,

neutropenic patients and found no statistically detectable heterogeneity between these trials, although their design and the interventions differed. Overall, the rate of treatment failure was in favour of monotherapy (Peto odds ratio 0.88, 95% confidence interval (CI) 0.78–0.99). A cumulative meta-analysis within this study demonstrated that these effects have remained stable since 1996. Paul *et al.* performed a Cochrane review and included more trials (47 trials, 7807 patients). The main results were not different from those of Furno *et al.* (Table 2), and an analysis of adverse events demonstrated an important difference for the development of renal failure (relative risk 0.49, 95% CI 0.36–0.65; $p < 0.05$). The rate of discontinuation of a study drug was also higher in the combination therapy arms. In the Paul *et al.* study, subgroup analysis differentiated between studies that used the same β-lactam antibiotic in both arms and those using different β-lactams (Table 2). However, monotherapy was at least equivalent to combination therapy in all comparisons. This was independent of the number of daily doses of the aminoglycoside.

In conclusion, there is no therapeutic advantage to using aminoglycosides in the empirical antibiotic therapy of febrile neutropenic patients, but there is clearly a higher rate of adverse events, mainly nephrotoxicity. Long-term ototoxicity is also possible, even with good monitoring of levels. This recommendation does not apply to the treatment of microbiologically documented infections, where combination therapy is generally recommended, e.g., against *Pseudomonas aeruginosa*.

THE USE OF GLYCOPEPTIDES IN EMPIRICAL ANTIBIOTIC THERAPY OF NEUTROPENIC FEVER

It is still standard practice in many centres to modify empirical antibiotic therapy and to add a glycopeptide after a period of persistent fever as short as 48–96 h. This is due to the supposition, perhaps mistaken in view of the recent EORTC data [4], of a predominance of Gram-positive infections, making the use of glycopeptides very attractive. On the other hand, the rising rate of glycopeptide-resistant Gram-positive bacteria makes restriction of the use of these substances necessary [22].

Two randomised clinical trials have evaluated use of an additional glycopeptide vs. placebo in persistently febrile but clinically stable patients with no evidence of resistant or predominantly Gram-positive infections (Table 3) [23–25]. In both trials (one included 114 patients and used teicoplanin, and the other included 165 patients and used vancomycin), the addition of the glycopeptide after 48–96 h did not improve the response rate or the survival rate compared to placebo. In a commentary on the articles in *Cancer Treatment Reviews*, a quantitative synthesis of the two trials was done and no difference for overall survival (Peto odds ratio 0.80; 95% CI 0.33–1.90) or response without modification (Peto odds ratio 1.05; 95% CI 0.66–1.67) could be found [25]. Although the combined trials included only 279 patients, this meta-analysis shows clearly that there is no evidence to support the early use of a glycopeptide in clinically stable patients without evidence of either a resistant organism or a skin/soft tissue infection.

WHICH β-LACTAM ANTIBIOTIC FOR MONOTHERAPY IN FEBRILE NEUTROPENIC PATIENTS?

Table 1 lists the current recommendations in clinical practice guidelines for antibiotic monotherapy. Ceftazidime, cefepime, meropenem, imipenem–cilastatin and piperacillin–tazobactam are listed. The US guidelines do not list pipera-

Table 2. Meta-analysis of β-lactam monotherapy vs. β-lactam–aminoglycoside combination therapy for fever with neutropenia [21]

Monotherapy vs. combination therapy	All-cause fatality	Treatment failure (same β-lactam)	Treatment failure (different β-lactams)
All studies	0.85 (0.72–1.02) ($n = 30$)[a]	1.12 (0.96–1.29) ($n = 9$)	0.87 (0.80–0.93) ($n = 38$)
Patients with haematological malignancy	0.78 (0.58–1.06) ($n = 13$)	0.92 (0.76–1.12) ($n = 4$)	0.83 (0.73–0.96) ($n = 13$)
Patients with severe neutropenia	0.66 (0.35–1.26) ($n = 5$)	1.49 (1.13–1.97) ($n = 2$)	0.94 (0.75–1.18) ($n = 6$)

[a]Relative risk with 95% confidence interval and number of studies reporting the relevant outcome. A relative risk below 1 favours monotherapy.

Table 3. Profile of two randomised trials evaluating the empirical use of glycopeptides in persistently febrile neutropenic patients [23,24]

	Erjavec *et al.* [23]	**Cometta *et al.* [24]**
Initial empirical antibiotic	Imipenem–cilastatin	Piperacillin–tazobactam
Additional glycopeptide	Teicoplanin	Vancomycin
Inclusion criteria	Persistent fever after 72–96 h of initial empirical antibiotic therapy	Persistent fever after 48–62 h of initial empirical antibiotic therapy
Exclusion criteria	Resistant infections, central venous catheter infections, suspected fungal infections, clinical deterioration	Resistant infections, central venous catheter infections, proven fungal or viral infections, pulmonary infiltrates, clinical deterioration
Response without treatment modification	45% vs. 47%[a]	49% vs. 46%
Overall survival	89% vs. 93%	95% vs. 90%

[a]Glycopeptide vs. placebo; all results were not significantly different.

cillin–tazobactam, because of a lack of clinical experience in the U.S.A. at the time of their publication, and the Spanish guidelines do not list ceftazidime. None of the guidelines used a systematic review of published evidence on which to base its recommendations of published evidence.

There is no recent meta-analysis addressing this question. A preliminary analysis of 25 randomised clinical trials with 7274 patients is presented here. In this preliminary analysis, only those trials that were available in electronic databases (randomised clinical trials of one of the above-mentioned antibiotics in each arm, with or without additional aminoglycosides in neutropenic patients) and published up to August 2002 were included. The extracted outcome was a response to the initial empirical antibiotic treatment without modification. Table 4 lists the results of this analysis, which demonstrate the clear and statistically significant inferiority of ceftazidime and point to the equivalence of piperacillin–tazobactam, cefepime, meropenem and imipenem–cilastatin.

We have to emphasise again that this analysis is preliminary and will be continued. However, we think that the inferiority of ceftazidime (with or without additional aminoglycoside) is not an unexpected finding in view of its restricted activity against Gram-positive bacteria [26].

IMPLICATIONS FOR CLINICAL PRACTICE

In view of the above-mentioned data, an evidenced-based recommendation for initial empirical monotherapy with piperacillin–tazobactam, cefepime, meropenem or imipenem–cilastatin in neutropenic patients with fever of unknown origin can be made. The addition of a glycopeptide can be delayed for 6 or 7 days of persistent fever in clinically stable patients without evidence of skin/soft tissue infections and with no microbiological evidence to the contrary. The choice of initial antibiotic may depend on the local hospital resistance rates, the risk of inducing resistant bacteria (which has been frequently reported for

Table 4. Preliminary data of a meta-analysis of β-lactam antibiotic for empirical monotherapy in febrile neutropenic patients

	Patients (trials)	**Odds ratio[a]**	**p**
Carbapenem[b] vs. ceftazidime	3306 (12)	0.75	0.001
Carbapenem vs. cefepime	697 (2)	1.22	0.223
Piperacillin–tazobactam vs. other cephalosporins[c]	391 (2)	0.67	0.049
Piperacillin–tazobactam vs. ceftazidime	1237 (4)	0.67	0.001
Piperacillin–tazobactam vs. cefepime	453 (2)	1.00	0.983
Carbapenem vs. piperacillin–tazobactam	552 (2)	1.22	0.223

[a]An odds ratio below 1 favours the antibiotic named first.
[b]Meropenem or imipenem–cilastatin.
[c]Ceftriaxone or cefpirome.

cephalosporins and carbapenems [26]) and drug acquisition costs. This has led to the choice of piperacillin–tazobactam in EORTC trials and in our institutions, where we can use a broad-spectrum agent while decreasing the overall usage of cephalosporins.

It is difficult for practising clinicians to find and read all relevant clinical randomised trials on a particular subject, but systematic reviews should receive special attention and will be helpful in guiding clinical practice decisions.

IMPLICATIONS FOR RESEARCH AND GUIDELINE DEVELOPMENT

Obviously, more systematic reviews on the treatment of infectious complications in neutropenic patients are needed. These should receive adequate and independent funding. Guideline preparation should include a systematic review to avoid incomplete, misleading or contradictory recommendations.

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