Role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomised controlled trials

Konstantinos Z Vardakas, George Samonis, Stavroula A Chrysanthopoulou, Ioannis A Bliziotis, Matthew E Falagas

We did a meta-analysis of randomised controlled trials studying glycopeptides as part of the initial empirical treatment of febrile neutropenic patients with a beta-lactam and with or without an aminoglycoside. 14 randomised controlled trials that studied 2413 patients were included in the analysis. A better outcome regarding treatment success, without modification of the initial regimen, was accomplished with the inclusion of a glycopeptide in the empirical therapy; this better outcome applied to the full set of studied patients (OR=1·63, 95% CI 1·17–2·28), as well as in three important subsets of patients—those with microbiologically documented infections (2·03, 1·39–2·97), patients with bacteraemia (1·80, 1·23–2·63), and patients with severe neutropenia, defined as a white blood cell count below 100 cells/µL (2·24, 1·15–4·39). However, mortality was not different in the compared groups (0·67, 0·42–1·05). Overall treatment success was not different if a glycopeptide was added to the antimicrobial regimen in the case of continuation of fever 72 hours or more after the start of treatment (1·02, 0·68–1·52). Also, the inclusion of a glycopeptide in the empirical regimen did not lead to a difference regarding time to defervesence. Adverse effects (4·98, 2·91–8·55), including nephrotoxicity (2·10, 1·12–3·95), were more common in the group receiving a glycopeptide as part of the empirical treatment. In conclusion, our meta-analysis suggests that there are good reasons why glycopeptides should not be routinely used as part of the initial empirical treatment of febrile neutropenic patients.

Introduction

Infection presenting as fever—alone or with other symptoms—is one of the most common complications in patients receiving chemotherapy for malignant diseases. Empirical administration of broad-spectrum antibiotics, usually beta-lactam monotherapy or in combination with an aminoglycoside, has been a traditionally used therapy for such patients. However, since the early 1980s there have been substantial changes in the different types of bacteria isolated from febrile neutropenic patients.

Gram-positive bacteria have become a very common cause of infection in neutropenic patients. The use of indwelling central venous catheters, the increasing intensity of anticancer chemotherapy, and the use of specific anti-infective prophylaxis against Gram-negative bacteria in neutropenic patients are the basic reasons leading to this change. These developments, combined with the growing problem of antimicrobial resistance among staphylococcal, enterococcal, and streptococcal isolates, raised the issue of administration of glycopeptides as part of the first-line empirical treatment in febrile neutropenic patients. Another fact in support of the inclusion of a glycopeptide in the empirical antimicrobial regimen of febrile neutropenic patients was the publication of cases of fulminant bloodstream infections with Gram-positive bacteria in patients receiving antibiotics with coverage mainly against Gram-negative bacteria.

Therefore, whether a glycopeptide should be included in the empirical antimicrobial regimen in febrile neutropenic patients is an important question. Several randomised controlled trials examined the role of glycopeptides in this patient population. In this meta-analysis we pooled data from relevant randomised controlled trials to review the available evidence regarding the advantages and disadvantages of the addition of a glycopeptide as part of the empirical treatment of febrile neutropenic patients.

Methods

Data sources

Relevant randomised controlled trials for our meta-analysis were identified from searches of PubMed (January 1950 to October 2004), Current Contents, the Cochrane central register of randomised controlled trials, and references from relevant articles, including review papers. Search terms included “aminoglycoside”, “febrile”, “fever”, “glycopeptides”, “granulocytopenia”, “granulocytopenic”, “lactam”, “neutropenia”, “neutropenic”, “teicoplanin”, and “vancomycin”.

Study selection

Two independent reviewers searched the literature and examined the identified relevant randomised controlled trials for further evaluation of data on effectiveness and toxicity. A study was considered eligible if it was a randomised, controlled clinical trial, if it studied the role of glycopeptides as part of empirical treatment with a beta-lactam—with or without an aminoglycoside—for the treatment of febrile neutropenic patients, if it assessed the effectiveness, toxicity, or mortality of both therapeutic regimens, and if it was done in hospitalised patients (not in an outpatient setting). No restriction in language was set. Trials with both blind and unblind design were included in the analysis. Experimental trials
Table 1: Characteristics of randomised controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference Year of publication</th>
<th>Total quality score (points)</th>
<th>Glycopeptide group</th>
<th>Non-glycopeptide group</th>
<th>Previous antimicrobial prophylaxis</th>
<th>Study population</th>
<th>ITT, episodes or patients (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micoczi8 1993</td>
<td>3</td>
<td>Piperacillin 4 g q6h, amikacin 7.5 mg/kg q12h, teicoplanin 7 mg/kg q12h for three doses, then 7 mg/kg q24h</td>
<td>Piperacillin 4 g q6h, tazobactam 500 mg q6h, amikacin 7.5 mg/kg q12h</td>
<td>Ciprofloxacin, norfloxacine, or co-trimoxazole</td>
<td>Leukaemia and lymphoma</td>
<td>126</td>
</tr>
<tr>
<td>Pico7 1993</td>
<td>2</td>
<td>Ceftazidime 1 g q12h, vancomycin 500 mg q12h</td>
<td>Ceftazidime 1 g q12h or ceftazidime 1 g q12h and amikacin 7.5 mg/kg q12h</td>
<td>No data</td>
<td>Leukaemia, lymphoma, and solid tumours</td>
<td>102</td>
</tr>
<tr>
<td>Bossetz7 1992</td>
<td>2</td>
<td>Ceftazidime 1 g q12h, vancomycin 1 g q12h</td>
<td>Imipenem 1 g q8h</td>
<td>No data</td>
<td>Leukaemia, solid tumours, lymphoma, others</td>
<td>87</td>
</tr>
<tr>
<td>Kelsey7 1992</td>
<td>2</td>
<td>Aztreonam 2 g q6h, vancomycin 1 g q12h</td>
<td>Piperacillin 4 g q6h, gentamicin 120 mg loading dose, then 80 mg q12h</td>
<td>No data</td>
<td>Mostly leukaemia</td>
<td>61</td>
</tr>
<tr>
<td>Martino11 1992</td>
<td>2</td>
<td>Piperacillin 100 mg/kg q12h, amikacin 7.5 mg/kg q12h, teicoplanin 10 mg/kg q12h for five doses, then 10 mg/kg q24h</td>
<td>Piperacillin 100 mg/kg q12h, amikacin 7.5 mg/kg q12h</td>
<td>Ciprofloxacin, norfloxacine, or co-trimoxazole</td>
<td>Leukaemia and lymphoma</td>
<td>174</td>
</tr>
<tr>
<td>Riikonen15 1991</td>
<td>2</td>
<td>Ceftazidime 50 mg/kg q8h, vancomycin 400 mg q12h</td>
<td>Ceftazidime 25 mg/kg q12h, vancomycin 7.5 mg/kg q12h</td>
<td>Quinolones or co-trimoxazole</td>
<td>Leukaemia and lymphoma, bone marrow transplantation, aplastic anaemia</td>
<td>89</td>
</tr>
<tr>
<td>EORTC13 1991</td>
<td>3</td>
<td>Ceftazidime 25 mg/kg q6h, amikacin 7.5 mg/kg q12h, vancomycin 7.5 mg/kg q6h</td>
<td>Ceftazidime 25 mg/kg q12h, amikacin 7.5 mg/kg q12h</td>
<td>No data</td>
<td>Leukaemia, lymphoma, or solid tumour</td>
<td>120</td>
</tr>
<tr>
<td>Novakova14 1991</td>
<td>2</td>
<td>Ceftazidime 2 g q8h, vancomycin 20 mg/m2 q6h</td>
<td>Ceftazidime 2 g q12h</td>
<td>Ciprofloxacin or co-trimoxazole</td>
<td>Leukaemia and lymphoma, or solid tumour</td>
<td>89</td>
</tr>
<tr>
<td>Karp20 1986</td>
<td>5</td>
<td>Ticarcillin 45 mg/kg q6h, gentamicin 5 mg/kg q6h, vancomycin 500 mg q6h</td>
<td>Ticarcillin 45 mg/kg q4h, gentamicin 5 mg/kg q 6h</td>
<td>No data</td>
<td>Leukaemia</td>
<td>60</td>
</tr>
</tbody>
</table>

Note: ITT=intention to treat; q6h, q12h, q24h=every 6, 12, or 24 hours.

and trials focusing on pharmacokinetic and/or pharmacodynamic parameters were excluded. Trials in which the initial regimen included additional antimicrobials (antifungal, antiviral, or other antibiotics apart from those given for prophylaxis before the febrile episode) were also excluded. Trials in which the use of glycopeptides was second-line therapy, those examining antimicrobial agents other than beta-lactams, aminoglycosides, and glycopeptides, and those that compared vancomycin with teicoplanin—ie, those that had the same beta-lactam in both study arms and were comparing different glycopeptides—were also excluded.

**Data extraction**

The following data were extracted from each study: year of publication, clinical setting, patient population, number of patients, antimicrobial agents and doses used, mortality, clinical and microbiological outcomes, and toxicity outcomes. Data were extracted by two independent reviewers. Any disagreement between the two reviewers was resolved by consensus in meetings with authors. A quality review of each randomised controlled trial was done to include details of randomisation, generation of random numbers, details of double-blinding procedure, information on withdrawals, and concealment of allocation. One point was awarded for the specification of each criterion; the maximum score for a study is 5. High-quality randomised controlled trials scored more than 2 points, while low-quality randomised controlled trials scored 2 or less points, according to reported methodology.

**Outcomes**

The overall treatment success (defined as survival of the patient and disappearance of all symptoms and signs) without the need for any modification of the initial regimen, all-cause mortality, and adverse effects due to study regimens were considered as primary outcome measures for this meta-analysis. The primary outcomes were also analysed in the subset of studies that included exactly the same drugs in both study arms (except for the inclusion, or not, of a glycopeptide as part of the empirical treatment of febrile neutropenic patients). Treatment success without modification of the initial regimen was also analysed in four important subsets of patients—those with microbiologically documented...
infections, patients with bacteraemia, patients with bacteraemia due to Gram-positive bacteria, and patients with severe neutropenia (white blood cell count below 100 cells/µL). The addition of any antimicrobial (antibacterial, antiviral, or antifungal) agent, and/or the discontinuation of any agent from the initial regimen because of continuing symptoms and/or signs of infection was considered as modification of the initial regimen. All-cause mortality was analysed based on the reported data for mortality during the study period or during the neutropenic episode. Nephrotoxicity was defined as any rise in serum creatinine concentration or an effect on other laboratory or clinical parameters considered to represent nephrotoxicity by the study authors. Treatment success with the addition of a glycopeptide at a later phase (not as part of the empirical regimen) in patients with continuing fever and/or other symptoms of infection, the time to defervescence, and superinfections were considered as secondary outcomes.

Data analysis and statistical methods
Statistical analyses were done using the “Meta-analyst” software (Joseph Lau, Tufts University School of Medicine, Boston, MA). The heterogeneity between randomised controlled trials was assessed by using a random effects model. For all analyses, results from the fixed effects model are presented only when there was no heterogeneity between randomised controlled trials; otherwise results from the random effects model are presented.

Results
Selected randomised controlled trials
We identified 32 published randomised controlled trials21–26 that were done in febrile neutropenic patients treated with various combinations of glycopeptides, beta-lactams, and aminoglycosides. Of these trials, six were excluded because glycopeptides were used only as second-line therapy and not as part of the initial empirical regimen;21–26 two because more than one beta-lactam was used in one or both study arms;27,28 five because the same glycopeptide was part of the empirical treatment in both study arms;29–33 and four because they compared the effectiveness of vancomycin against teicoplanin.34-37 In addition, one trial was excluded because it compared the outcome of patients with soft tissue infections and bacteraemia treated with vancomycin with the outcome of patients with infection.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Bacteraemia success n (%)</th>
<th>Bacteraemia documented infection n (%)</th>
<th>Microbiologically documented infection n (%)</th>
<th>Success with the addition of glycopeptide n (%)</th>
<th>Treatment success n (%)</th>
<th>Secondary outcomes n (%)</th>
<th>Time to defervescence days (SD)</th>
<th>Adverse effects n (%)</th>
<th>Nephrotoxicity n (%)</th>
<th>Mortality n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micozzi25</td>
<td>34/56 vs 24/58 (61 vs 41)</td>
<td>17/18 vs 6/18 (94 vs 53)</td>
<td>14/14 vs 5/14 (100 vs 36)</td>
<td>NA</td>
<td>34/56 vs 35/58 (61 vs 60)</td>
<td>NA</td>
<td>NA</td>
<td>5 vs 5</td>
<td>0·56 vs 0·58 (0 vs 0)</td>
<td>0·58 vs 0·58 (0 vs 0)</td>
<td>3·56 vs 3·58 (5 vs 5)</td>
</tr>
<tr>
<td>Picó26</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
<tr>
<td>Bosaray27</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA</td>
<td>NA vs NA</td>
<td>1·14 vs 1·43 (2 vs 2)</td>
<td>NA vs NA</td>
<td>2·44 vs 0·43 (5 vs 6)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
<tr>
<td>Kelley26</td>
<td>15·29 vs 16·29 (57 vs 55)</td>
<td>5·15 vs 5·15 (33 vs 33)</td>
<td>4·10 vs 4·10 (40 vs 40)</td>
<td>5·15 vs 5·15 (33 vs 33)</td>
<td>NA vs NA</td>
<td>3·29 vs 2·29 (10 ws 7)</td>
<td>NA vs NA</td>
<td>5·29 vs 3·29 (17 vs 10)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
<tr>
<td>Martino28</td>
<td>45·75 vs 42·83 (60 vs 53)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>45·75 vs 55·55 (60 vs 60)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>2·75 vs 0·83 (3 vs 0)</td>
<td>0·75 vs 0·83 (0 vs 0)</td>
<td>5·75 vs 4·83 (7 vs 5)</td>
<td></td>
</tr>
<tr>
<td>Ramphal29</td>
<td>39·64 vs 21·63 (61 vs 33)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>39·64 vs 33·63 (62 vs 52)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>19·64 vs 6·63 (30 vs 10)</td>
<td>7·64 vs 6·63 (11 vs 10)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
<tr>
<td>EORTC30</td>
<td>28·87 vs 377·37 (232 vs 370)</td>
<td>79·116 vs 68·123 (68 vs 53)</td>
<td>48·67 vs 29·68 (72 vs 43)</td>
<td>98·137 vs 80·141 (72 vs 57)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>42·377 vs 50·370 (11 vs 14)</td>
<td>NA vs NA</td>
<td>24·377 vs 9·370 (6 vs 2)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
<tr>
<td>Novakova31</td>
<td>33·52 vs 25·53 (61 vs 49)</td>
<td>10·20 vs 7·18 (50 vs 39)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>33·52 vs 32·51 (61 vs 63)</td>
<td>14·57 vs 9·51 (27 vs 18)</td>
<td>NA vs NA</td>
<td>3·18 (0·9) vs 3·5 (0·8)</td>
<td>4·57 vs 3·51 (8 vs 6)</td>
<td>7·66 vs 9·60 (12 vs 15)</td>
<td></td>
</tr>
<tr>
<td>Riikonen32</td>
<td>26·44 vs 37·45 (59 vs 82)</td>
<td>5·20 vs 6·8 (50 vs 75)</td>
<td>4·9 vs 6·8 (44 vs 75)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>4·84 vs 4·0 a (7 vs 6)</td>
<td>3·44 vs 0·45 (7 vs 6)</td>
<td>0·44 vs 0·45 (0 vs 0)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td></td>
</tr>
<tr>
<td>Viscoli33</td>
<td>75·98 vs 63·95 (77 vs 66)</td>
<td>16·26 vs 6·25 (62 vs 52)</td>
<td>8·18 vs 6·35 (66 vs 56)</td>
<td>27·41 vs 23·41 (71 vs 58)</td>
<td>NA vs NA</td>
<td>40·66 vs 38·65 (71 vs 58)</td>
<td>11·30 vs 9·9 (11 vs 9)</td>
<td>34·98 vs 4·95 (35 vs 4)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
<tr>
<td>Meunier34</td>
<td>25·39 vs 29·24 (64 vs 67)</td>
<td>5·7 vs 5·11 (43 vs 45)</td>
<td>4·9 vs 8·15 (44 vs 53)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>7·17 vs 1·85 (22 vs 16)</td>
<td>NA vs NA</td>
<td>0·93 vs 0·36 (0 vs 0)</td>
<td>0·53 vs 0·48 (0 vs 0)</td>
<td>0·53 vs 0·48 (0 vs 0)</td>
<td>0·53 vs 0·48 (0 vs 0)</td>
</tr>
<tr>
<td>Shinpō35</td>
<td>45·53 vs 30·48 (85 vs 62)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>10·3 vs 15·1 (18 vs 22)</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
<td>NA vs NA</td>
</tr>
</tbody>
</table>

Table 2: Outcome data from the selected randomised controlled trials for the meta-analysis

Outcomes are reported for the glycopeptide vs the non-glycopeptide group. SD=standard deviation; NA=not applicable
in other body sites and bacteraemia treated without vancomycin. Thus, 14 randomised controlled trials were included in our meta-analysis.7–20

The main characteristics of the analysed randomised controlled trials are shown in table 1. The mean quality score of the included randomised controlled trials was 2·64 (in a scale from 0–5). The quality of seven randomised controlled trials was high (≥3), while the quality of seven randomised controlled trials was low (≤2). All studied patients had an absolute neutrophil count of 1000 cells/µL or less or an expected decrease of neutrophil count to 1000 cells/µL or less within 24–48 hours from enrolment. Neutropenia, in all patients, was the result of previous cytostatic chemotherapy for treatment of haematological malignancies, solid tumours, or bone marrow transplantation. The duration of neutropenia varied in different trials, but there was no imbalance of the duration of neutropenia between the compared treatment groups in the individual trials.

**Anti-infective prophylaxis**

Anti-infective prophylaxis during the period of neutropenia until the development of fever and enrolment to the study was used in patients of seven trials. Ciprofloxacin and sulfamethoxazole-trimethoprim (co-trimoxazole), alone or in combination, were used for anti-infective prophylaxis in four7,11,13,14 and six trials,7,10,11,13–15 respectively. Other drugs used for prophylaxis included norfloxacin, neomycin, amphotericin B (or other antifungal), and colistin for gut decontamination. In one study, prophylaxis was used but the drugs were not reported.20 The patients should not have taken any antibiotic other than those given for anti-infective prophylaxis for at least 4 days before enrolment (4 days to 3 weeks in different trials). In two trials, no information regarding the use of prophylaxis was reported.

**Administration of study drugs**

The dosages of the administered drugs are shown in table 1. All drugs were administered intravenously. Vancomycin and teicoplanin was administered in nine7,10,12,13,17,18,20 and five7,11,14,17,19 trials, respectively. The beta-lactam was the same in both study arms in 11 trials. In seven of them, ceftazidime was used,8,12,14,16,17,19 in two piperacillin was used,7,11 and ticarcillin was used in two.10,19 In two trials, patients in the glycopeptide study arm received ceftazidime and vancomycin while patients in the other study arm received imipenem.10,19 In one trial, patients in the glycopeptide study arm received aztreonam and vancomycin while patients in the other study arm received piperacillin and gentamicin.13 An aminoglycoside was part of the empirical treatment in both study arms in six trials.7,11,13,16–18 In addition, in three trials, an aminoglycoside was given only in the study arm of patients who did not receive a glycopeptide.8,10,16 Amikacin was used in seven of the trials and gentamicin in two. Thus, the regimens were exactly the same (except for the inclusion, or not, of a glycopeptide as part of the empirical treatment) in the compared study arms in six of the 14 trials that were included in our analysis.11–14,18,20

**Treatment success without modification of the empirical treatment**

The major studied outcomes that were included in the meta-analysis are shown in table 2. Data about treatment success without modification of the initial regimen was reported in 11 of the trials.7,10–19 The odds ratios for treatment success in the individual randomised controlled trials, as well as the pooled odds ratio, are presented in figure 1. The addition of a glycopeptide to the empirical treatment was associated with better treatment success without modification of the initial regimen (1812 episodes, random effects model, OR=1.63, 95% CI 1.17–2.28).

Figure 2 presents data from individual trials and pooled data regarding treatment success for four subsets of patients—those with microbiologically documented infections, those with bacteraemia, those with bacteraemia due to Gram-positive bacteria, and those with severe neutropenia. In general, treatment success without modification of the empirical regimen was better with the inclusion of a glycopeptide in the initial regimen of febrile neutropenic patients; treatment success for patients with microbiologically documented
infections (493 episodes, fixed effects model, six trials; 7,10,13,14,16,18 2.03, 1.39–2.97), patients with bacteraemia (457 episodes, fixed effects model, eight trials; 9,13,14,16,17,19 2.24, 1.54–3.95). By contrast, when patients with bacteraemia were excluded, treatment success without modification of the initial regimen was not different between the two groups (1655 episodes, fixed effects model, 1.12–2.63). Also, treatment success without modification of the initial regimen was not different between the two groups for patients with Gram-positive bacteraemia (242 episodes, random effects model, six trials; 7,10,13,15,16,19 2.16, 0.73–6.45).

Mortality
All-cause mortality during the study period or the period of neutropenia (based on the reported data) was available in nine trials.7,8,10,12,13,14,16–18 In the remaining five trials, only the sum of deaths in both study arms is reported, without specific statements about mortality in each study arm11,13,19 or only mortality associated with infection, or for a subset of patients was reported.11,19 These studies were excluded from the mortality analysis. Figure 3 presents data from individual trials and pooled data regarding mortality. There was no statistically significant difference in mortality between the two compared groups of febrile neutropenic patients—ie, those who received a glycopeptide as part of the empirical regimen or those who did not (1073 patients, fixed effects model, 0.67, 0.42–1.05).

Adverse effects
Data regarding adverse effects were reported for 12 trials. However, only data about adverse effects of different types but not the total number of patients that exhibited them was reported in four trials.9,10,13,14,16 Therefore, these trials were excluded from the analysis for adverse effects. The addition of a glycopeptide as part of the empirical treatment was associated with more adverse effects (figure 4; 883 patients, fixed effects model, 4.98, 2.91–8.55). Specific data for nephrotoxicity was reported for eight trials.7,8,11,13–15,17,18 The addition of a glycopeptide was also associated with more nephrotoxicity (1508 patients, fixed effects model, 2.10, 1.23–3.95).

Time to defervescence
Time to defervescence was reported in four trials. Data about the mean and standard deviation of the distributions of time to defervescence was provided for two trials;14,15 the mean, median, and range was provided for one;7 in one trial only the mean was provided.7 Subsequently, data about the time to defervescence could not be pooled except for two trials in which mean and standard deviation were provided. The analysis of these results did not show any difference regarding time to defervescence between groups of febrile neutropenic patients taking, or not, a glycopeptide as part of the empirical treatment (data not shown).

Superinfections
Data about superinfections were reported for four trials.7,10,13,14,16 The inclusion, or not, of a glycopeptide as part of the empirical treatment regimen for febrile neutropenic patients did not have an effect on the development of superinfections (1188 episodes, random effects model, 1.18, 0.71–1.98). One trial did not separate fungal and bacterial infections.7 The rest of the relevant trials differentiated between fungal and bacterial infections7,13,14,16 but only one reported specific data about secondary infections due to Gram-positive bacteria.13 The total number of
bacterial superinfections (in the trials with relevant data reported) was 19 and 29 for the glycopeptide and the non-glycopeptide group, respectively; the total number of fungal superinfections was 28 and 21 for the glycopeptide and non-glycopeptide group, respectively.

Sensitivity analyses

Trials with the same regimen in the study arms

A sub-analysis of six trials in which patients in the compared study arms received the same regimen, except for the inclusion, or not, of a glycopeptide, as part of the initial empirical regimen was also done.11–14,19–20 Treatment success without modification of the empirical regimen was better in the group of patients receiving the glycopeptide (1182 episodes, fixed effects model, 1·98, 1·55–2·53). There was no difference regarding mortality (405 patients, fixed effects model, 1·02, 0·52–2·00). Nephrotoxicity was more common in the group of patients receiving the glycopeptide (1014 patients, fixed effects model, 2·30, 1·17–4·54).

Randomised controlled trials using antipseudomonal penicillins and carbapenems

A sensitivity analysis was done for five trials7,10–11,18,20 that used antimicrobial agents in both groups that are more frequently used nowadays, compared with the period during which the trials included in our meta-analysis were conducted. Treatment success without modification of the empirical regimen was better for the glycopeptide group (431 episodes, fixed effects model, 1·76, 1·18–2·61). However, there was no significant difference between the two groups for bacteraemia (66 episodes, random effects model, 5·27, 0·17–166·14), Gram-positive bacteraemia (48 episodes, random effects model, 5·83, 0·13–264·78), and mortality (431 episodes, fixed effects model, 0·95, 0·39–2·32). Development of adverse effects (330 episodes, fixed effects model, 2·22, 0·63–7·80) and nephrotoxicity (376 episodes, fixed effects model, 0·99, 0·10–9·65) were not different between the two groups.

Randomised controlled trials not allowing re-entrance of the same patient to the study

A separate analysis was done for those trials that did not allow re-entrance of a patient to the study. Treatment success without modification of the empirical regimen was better for the glycopeptide group (1598 episodes, fixed effects model, 1·85, 1·49–2·29). However, there was no difference between the two groups in terms of treatment success without modification of the empirical regimen in patients with bacteraemia (378 episodes, fixed effects model, 5·27, 0·17–166·14) and Gram-positive bacteraemia (216 episodes, random effects model, 2·60, 0·87–7·78), as well as no difference in mortality (851 episodes, fixed effects model, 0·81, 0·47–1·38). Development of adverse effects (737 episodes, fixed effects model, 5·47, 3·00–9·99), and nephrotoxicity (1204 episodes, fixed effects model, 2·35, 1·15–4·83) were more common in the glycopeptide group.

Treatment success with modification of the empirical treatment

Results concerning the treatment success with the addition of a glycopeptide (for patients in the study arm that did not receive a glycopeptide initially) were reported for four trials.7,11,12,14 No difference between the two groups was found regarding this outcome (502 episodes, fixed effects model, 1·02, 0·71–1·46). A further analysis was done including only those trials that permitted the introduction of a glycopeptide to the empirical treatment in patients who remained febrile for 72 hours or more. Treatment success was not different between the two groups (three trials,7,11–12, 399 episodes, fixed effects model, 1·02, 0·68–1·52). Only one trial of those that allowed modification of treatment according to criteria other than persistent fever reported data on treatment success after the modification of therapy.14

Analysis of subsets of randomised controlled trials

Because of the influence of one trial with a large number of patients on the results of our study,13 we did an analysis of pooled data that excluded this trial. In this subset analysis, the addition of a glycopeptide in the empirical treatment was associated with better treatment success without modification of the initial regimen (1065 episodes, random effects model, 1·48, 1·14–1·92).

Discussion

Our meta-analysis evaluated the role of glycopeptides as part of the initial empirical treatment regimen
Review

(consisting of a beta-lactam with or without an aminoglycoside) of febrile neutropenic patients. An interesting finding is that the inclusion of a glycopeptide in the empirical antimicrobial treatment of these patients results in better outcome as far as treatment success without modification of the initial regimen is concerned. This finding applies to the full set of studied patients, as well as to three important subsets of patients—those with microbiologically documented infections, patients with bacteraemia, and patients with severe neutropenia. However, the overall mortality was the same in the compared groups of patients. In addition, the inclusion of a glycopeptide in the empirical antimicrobial regimen did not reduce the time to defervescence.

Despite the observed better outcome regarding treatment success without modification of the initial regimen, the results of our meta-analysis do not support the routine inclusion of a glycopeptide in the initial empirical therapeutic regimen in febrile neutropenic patients in terms of the effect on all-cause mortality, which was not reduced in patients who received a glycopeptide. Furthermore, adverse effects, including nephrotoxicity, were more common in patients receiving a glycopeptide as part of the empirical treatment than in patients who did not receive it. Although the nephrotoxicity observed in the studied patients can be partly attributed to the concurrent use of aminoglycosides in some of the analysed trials, it should be noted that the use of aminoglycosides was more common in the non-glycopeptide group.

The addition of a glycopeptide in the subset of patients with continuing fever 72 hours after the initiation of the empirical treatment or in patients with clinical evidence of infection due to Gram-positive bacteria led to similar treatment success to that obtained with the inclusion of a glycopeptide as part of the initial empirical regimen of all the patients. In addition, a double-blind, placebo-controlled randomised trial was specifically designed to assess whether the addition of vancomycin in neutropenic patients with fever persisting for 48–60 hours after the initiation of empirical piperacillin-tazobactam monotherapy would reduce the time to defervescence; the results failed to demonstrate any benefit of the introduction of vancomycin in patients with persistent fever.38

There may be subsets of febrile neutropenic patients with specific risk factors who may benefit from the inclusion of a glycopeptide in the empirical regimen, such as patients with history of infection due to Gram-positive bacteria, clinical evidence for catheter-related infection, evidence for infections due to Gram-positive bacteria resistant to the initial empirical regimen (especially staphylococcal, enterococcal, and streptococcal species), hypotension or evidence of cardiovascular impairment, and use of antibacterial prophylaxis without coverage against Gram-positive bacteria.39,40 However, no randomised controlled trial was designed specifically to study the effectiveness and safety of the inclusion of a glycopeptide in the initial regimen of febrile neutropenic patients with these risk factors. In addition, analyses of subsets of patients with one or more of these risk factors were not generally reported in the published papers of the relevant trials.

Our meta-analysis has limitations. First, all randomised controlled trials that were included in our study were conducted before 1994. Since then, several
changes in practice have occurred. Antipseudomonal penicillins and carbapenems are more frequently used as first-line empirical treatment in febrile neutropenic patients. These drugs were used only in five of 14 trials included in our meta-analysis. In addition, the use of aminoglycosides has been considerably reduced during the past decade in several parts of the world. Also, the use of prophylaxis against bacterial infections (mainly with quinolones) and treatment in the outpatient setting are more frequently employed in neutropenic patients. However, reports of meticillin-resistant and even vancomycin-resistant Gram-positive bacteria have increased. Moreover, there have been reports for excess mortality associated with bacteremia due to beta-haemolytic streptococci when patients were not treated with vancomycin in the initial regimen. Despite the fact that the Infectious Diseases Society of America (IDSA) guidelines discourage the use of glycopeptides as part of the empirical regimen in febrile neutropenic patients, vancomycin is probably still frequently incorporated in the empirical therapy of this population.

Second, the lack of blindness—in most of the randomised controlled trials included in the analysis—could have facilitated modification of treatment in patients who did not receive a glycopeptide in the initial empirical regimen more frequently compared with those that did not receive it, especially at a time when the IDSA guidelines recommended the incorporation of vancomycin in the empirical treatment of febrile neutropenia if fever persisted for more than 3–5 days. Third, most trials did not stratify patients according to the severity of neutropenia, a potentially important determinant of outcome of febrile neutropenic patients. Fourth, the study drugs (beyond the inclusion, or not, of a glycopeptide in the empirical regimen) were not exactly the same in the compared trial arms in all trials that were included in this meta-analysis; however, no different results were found in a subset of trials in which the same drugs (except for the glycopeptide) were given in patients in the compared study arms. Finally, the results of our meta-analysis are influenced considerably by one of the selected randomised controlled trials, due to the large number of patients included in that study. However, it is interesting that the remaining 13 trials that were included in our study also showed similar results in the analysis of pooled data.

In conclusion, the results of our meta-analysis provide further evidence in support of guidelines published by the IDSA, the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), and the Japanese guidelines, which were primarily based on the findings of the trial done by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada. These guidelines do not suggest the inclusion of a glycopeptide in the routine, initial empirical regimen of febrile neutropenic patients.

Conflicts of interest
We declare that we have no conflicts of interest.

References
27 Granowetter L, Wells H, Lange BJ. Cefazidime with or without vancomycin vs. cefotaxim and gentamicin as the initial therapy of the febrile neutropenic pediatric cancer patient. *Pediatr Infect Dis J* 1988; 7: 165–70.