Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials

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**Objectives:** To assess the value of empirical anti-Gram-positive antibiotics for the treatment of febrile neutropenia.

**Methods:** Systematic review and meta-analysis of randomized controlled trials comparing antibiotics with anti-Gram-positive spectrum to control or placebo, in addition to the same baseline antibiotic regimen in both arms. We searched MEDLINE, EMBASE, LILACS, the Cochrane Library, conference proceedings, and references. No restrictions on inclusion were imposed. Two reviewers independently applied selection criteria, carried out quality assessment, and extracted the data. Relative risks with 95\% confidence intervals were pooled using the fixed effect model. The primary outcome assessed was all-cause mortality.

**Results:** Thirteen studies met inclusion criteria, including 2392 participants. Glycopeptides were assessed in nine trials. Empirical anti-Gram-positive antibiotics were assessed for the initial treatment in 11 studies, and for persistent fever in two. No significant difference in all-cause mortality was seen [RR 0.86 (0.58–1.26), seven studies, 852 participants]. Overall failure at end of therapy occurred equally [RR 1.00 (0.79–1.27), six studies, 943 participants]. Failure associated with treatment modifications was more frequent in the control arm when empirical initial glycopeptides were assessed [RR 0.70 (0.61–0.80), five studies, 1178 participants]. Bacterial superinfections, mainly Gram-positive, were detected less frequently in the intervention arm. Adverse events were significantly more common with the additional antibiotic, and nephrotoxicity was significantly more common with additional glycopeptides [RR 1.88 (1.10–3.22), six studies, 1282 participants]. No significant heterogeneity was present in these comparisons.

**Conclusions:** The use of glycopeptides can be safely deferred until the documentation of a resistant Gram-positive infection.

**Keywords:** glycopeptides, neutropenic fever, vancomycin, \textit{Staphylococcus aureus}

**Introduction**

Infection is a leading cause of death among cancer patients. Early antibiotic treatment reduces mortality and is standard practice for cancer patients with fever and neutropenia.\textsuperscript{1,2} Selection of antibiotics is based on pathogen occurrences among these patients, and usually includes a β-lactam with broad-spectrum activity against Gram-negative organisms.

In the last few decades, the aetiology of infection among cancer patients has shifted from predominance of Gram-negative to that of Gram-positive bacteria. In multicentre trials conducted by the EORTC, the rate of Gram-positive infections increased from 29\% of single-organism bacteraemias in 1973 to 69\% in 1993.\textsuperscript{3,4} Increased use of indwelling catheters, quinolone prophylaxis, and mucositis induced by more intensive chemotherapy are implicated in these changes.\textsuperscript{5} Currently used β-lactams do not provide adequate coverage for the majority of these Gram-positive infections.

Empirical antibiotic treatment was shown to reduce mortality when Gram-negative infections predominated, infections known

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JAC 436

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to be rapidly fatal. Empirical β-lactam monotherapy, holding broad-spectrum Gram-positive coverage, is currently considered safe despite the rising prevalence of resistant Gram-positive infections. Such practice must rely on evidence showing that mortality is not increased. We carried out a systematic review and meta-analysis of randomized trials assessing the empirical addition of antibiotics with specific activity against staphylococci and other Gram-positive bacteria.

Materials and methods

Inclusion criteria

We included randomized controlled trials comparing a standard antibiotic regimen (‘standard’) with or without the addition of an antibiotic with activity against Gram-positive bacteria (‘intervention’). These were defined as: glycopeptides, 1st generation cephalosporins, penicillinase-resistant penicillins, clindamycin, quinupristin/dalfopristin, and linezolid. Any standard regimen was permitted as long as the same combination or monotherapy was used in both study arms. We included studies assessing empirical intervention, both initially (‘initial therapy’) and at the time of reassessment for persistent fever (‘persistent fever’). Studies reporting efficacy analysis with a dropout rate after randomization above 30% were excluded. Studies are labelled by the first author and year of publication.

Search strategy

We used the search string: (neutropenia OR granulocytopenia OR granulocyte OR granulocyte OR granulopenia OR granulocytopenia OR immune-suppress OR cancer OR neoplasm OR malignancy OR tumor OR leukemia OR lymphoma), combined with specific antibiotic names and classes as defined above, and restricted to clinical trials. Databases searched included CENTRAL (Cochrane Library Issue 1, 2004), MEDLINE, EMBASE, and LILACS, all up to March 2004. In addition, we searched conference proceedings (Interscience Conference on Antimicrobial Agents and Chemotherapy 1995 to 2003, American Society of Hematology 2001 to 2002, Japan Society of Clinical Oncology), on-going clinical trial databases, and all references of included studies. Two reviewers inspected relevant articles and applied inclusion criteria.

Outcomes

The primary outcome assessed was all-cause mortality at end of follow-up. Pre-defined secondary outcomes included overall failure disregarding treatment modifications; failure with modifications and the specific addition of amphotericin; durations of fever, treatment, and hospitalization. We extracted data on the development of resistance as well as the rates of bacterial and fungal superinfection and colonization. We extracted all adverse events and those resulting in treatment discontinuation or fatality.

Data extraction

Two reviewers independently extracted data from included trials. Missing data were sought for all trials and obtained for five. Outcomes were extracted by intention to treat, including all individuals randomized in the outcome assessment. When unavailable, data for available cases were used for the main comparisons, and their effect was assessed through sensitivity analysis.

Quality assessment

Two reviewers independently extracted randomization procedures, blinding, re-entries, intention-to-treat and the number of patients excluded from outcome assessment in studies reporting efficacy analysis. Allocation generation and concealment were classified as A (adequate); B (unclear); C (inadequate), using criteria suggested in the Cochrane handbook. We carried out sensitivity analyses for allocation concealment, based on evidence showing overestimation of effects with inadequate allocation concealment.

Data analysis

Relative risks (RRs) with 95% confidence intervals are reported. Treatment effects across studies were combined using the fixed effect model. The Z statistic was used to test for a significant pooled estimate (i.e. significantly different than 1 at a 95% confidence level). The fixed effect model assumes a common effect for all studies. Heterogeneity was assessed using a χ² test for heterogeneity (Cochran’s Q test), and the I² statistic. The I² statistic estimates the percentage of the variability in effect estimates that is due to heterogeneity rather than chance alone, with values >50% indicating substantial heterogeneity. We carried out subgroup analyses of patients with documented Gram-positive infections. While studies report rates of Gram-positive bacteraemia, outcomes for these patients are usually not reported. We therefore used meta-regression to assess the association between the incidence of Gram-positive bacteraemia and individual study effect estimates (STATA 8 software). Regression coefficients are the estimated increase in the log risk ratio per unit-increase in the covariate, in this case the incidence of Gram-positive bacteraemia. Relative risk ratios (RRR) with 95% confidence intervals are reported. A funnel plot (standard error plotted against odds ratios) was examined to estimate potential selection bias (publication or other), or discrepancies between large and small studies.
Table 1. Table of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year completed</th>
<th>Patients randomized</th>
<th>Re-entries</th>
<th>Exclusions analysis</th>
<th>Comparator antibiotic</th>
<th>Other antibiotics</th>
<th>protocol</th>
<th>Allocation concealment</th>
<th>Allocation generation</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC-1991</td>
<td>1988</td>
<td>891</td>
<td>none</td>
<td>16%</td>
<td>vancomycin</td>
<td>ceftazidime+amikacin</td>
<td>B</td>
<td>A</td>
<td>outcome assessor</td>
<td>double</td>
</tr>
<tr>
<td>Karp et al.</td>
<td>1984</td>
<td>60</td>
<td>none</td>
<td>8%</td>
<td>vancomycin</td>
<td>ticarcillin+gentamicin</td>
<td>A</td>
<td>A</td>
<td>open</td>
<td>double</td>
</tr>
<tr>
<td>Marie et al.</td>
<td>1989</td>
<td>permitted, number unknown</td>
<td>154 episodes evaluated</td>
<td>2%</td>
<td>vancomycin</td>
<td>ceftazidime</td>
<td>B</td>
<td>B</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Ramphal et al.</td>
<td>1988</td>
<td>129</td>
<td>none</td>
<td>29%</td>
<td>teicoplanin</td>
<td>ceftazidime+amikacin</td>
<td>B</td>
<td>A</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Del Favero et al.</td>
<td>1984</td>
<td>54</td>
<td>12</td>
<td>29%</td>
<td>teicoplanin</td>
<td>ceftazidime+amikacin</td>
<td>B</td>
<td>A</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Molina et al.</td>
<td>1992</td>
<td>none</td>
<td>unknown, 36 patients evaluated</td>
<td>unknown, failure</td>
<td>teicoplanin</td>
<td>piperacillin+amikacin</td>
<td>B</td>
<td>B</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Novakova et al.</td>
<td>1987</td>
<td>120</td>
<td>none</td>
<td>ITT for death; 14% for failure</td>
<td>teicoplanin</td>
<td>ceftazidime</td>
<td>B</td>
<td>B</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Lawson et al.</td>
<td>1979</td>
<td>133</td>
<td>none</td>
<td>unknown, 283 episodes evaluated</td>
<td>cefalothin</td>
<td>ticarcillin+tobramycin</td>
<td>A</td>
<td>A</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Verhagen et al.</td>
<td>1985</td>
<td>102</td>
<td>none</td>
<td>ITT</td>
<td>cefalothin</td>
<td>ceftazidime</td>
<td>A</td>
<td>A</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>de Pauw et al.</td>
<td>1983</td>
<td>100</td>
<td>none</td>
<td>ITT</td>
<td>flucloxacillin</td>
<td>ceftazidime</td>
<td>A</td>
<td>A</td>
<td>open</td>
<td></td>
</tr>
<tr>
<td>Menichetti et al.</td>
<td>1983</td>
<td>124</td>
<td>37</td>
<td>ITT for death; 30% for failure</td>
<td>SXT</td>
<td>piperacillin+amikacin</td>
<td>B</td>
<td>A</td>
<td>single</td>
<td></td>
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<tr>
<td><strong>Persistent fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Cometta et al.</td>
<td>2000</td>
<td>165</td>
<td>none</td>
<td>ITT</td>
<td>vancomycin</td>
<td>piperacillin–tazobactam</td>
<td>A</td>
<td>A</td>
<td>double</td>
<td></td>
</tr>
<tr>
<td>Erjavec et al.</td>
<td>1997</td>
<td>114</td>
<td>11</td>
<td>9%</td>
<td>teicoplanin</td>
<td>imipenem</td>
<td>A</td>
<td>A</td>
<td>double</td>
<td></td>
</tr>
</tbody>
</table>

ITT, intention to treat. SXT, trimethoprim/sulfamethoxazole.

*Allocation concealment methods: A, adequate, if participants and the investigators enrolling participants could not foresee assignment. Adequate methods include a priori numbered or coded drug containers of identical appearance prepared by an independent pharmacy; central randomization carried out at a site remote from trial location; and sequentially numbered, sealed, opaque envelopes. B, unclear, if the method was not described.

*Allocation generation methods: A, adequate, if the method used is described and the resulting sequences are unpredictable. Adequate methods include computer generated random numbers, table of random numbers, and drawing of lots or envelopes. B, unclear, if the trial was described as randomized, but the method used for the allocation sequence generation was not described.
Results

We scanned 331 abstracts of which 41 publications were considered for further evaluation (Figure 1). Twenty-one were excluded and seven represented double publications. Two studies were excluded on account of a high percentage of dropouts. An EORTC trial randomized 841 patients and evaluated 419 patients.29 Martino et al. reported outcomes for a 10 month period and 158 patients, of a trial which was conducted for 15 months and included 232 patients.30,31

Thirty trials, randomizing 2392 participants, fulfilled inclusion criteria (Table 1). Eleven studies assessed the ‘initial’ empirical treatment of fever and neutropenia. The antibiotics evaluated were glycopeptides (seven studies), cefalothin (2), flucloxacillin (1), and trimethoprim/sulfamethoxazole (1). Studies assessing glycopeptides were completed between the years 1984 and 1992, while studies assessing other antibiotics were completed before 1985. Two studies, assessing glycopeptides, tested their addition for ‘persistent fever’ after 72 to 96 h of standard treatment. The standard antibiotic regimens are detailed in Table 1. The two ‘persistent fever’ studies excluded patients with catheter-related infections, and another trial excluded patients with any obvious source of infection.45 None of the studies specified septic shock as an exclusion criterion, and all permitted antibiotic prophylaxis before randomization. The rate of single Gram-positive bacteraemia varied from 5.6% to 28.3%. It did not correlate with study year as expected, possibly due to the differing locations and inclusion criteria of the studies included in the review.

Eleven trials described randomization procedures and all were adequately randomized, with adequate allocation concealment described in eight (Table 1). The two studies assessing the addition of glycopeptides for persistent fever were adequately randomized, concealed and double-blinded.

All-cause mortality

No significant difference in all-cause mortality was seen with the addition of antibiotics against Gram-positive infections [RR 0.86 (0.58–1.26), values < 1 favouring the intervention, Figure 2]. Seven studies and 852 participants were assessed. Two studies assessed ‘initial’ glycopeptides, two assessed their addition for ‘persistent fever’, and three trials examined the ‘initial’ addition of other anti-Gram-positive antibiotics. No difference was seen for each sub-category. Heterogeneity was observed between the two studies assessing additional glycopeptides for persistent fever (P = 0.15, I² = 50.7%), but the overall comparison was non-heterogeneous (P = 0.83, I² = 0%).

Six studies including 1420 participants reported infection-related mortality. No difference was seen overall [RR 1.18 (0.72–1.92), I² = 0%]. The sub-category of additional empirical glycopeptides included four studies, of which two did not report overall mortality, and no difference was observed within this sub-category either [RR 1.16 (0.62–2.17), 1030 participants, I² = 0%].

Four studies were not included in the mortality analyses. Three provided no information,41,43,46 and the authors of one reported no significant difference in mortality without providing data.40 Only four studies reported all-cause mortality for patients with documented Gram-positive infections. No significant difference was detected [RR 2.15 (0.56–8.25), 107 participants]. Comparative data for other subgroups were scarce (Gram-positive bacteraemia, one study, 26 participants; Staphylococcus aureus infections, two studies, 15 participants; streptococcal infections, three studies, 53 participants), and no significant difference was found for any of the comparisons.

There was no association between the rate of single-agent Gram-positive bacteraemia and the relative risk for mortality.

![Figure 2](image-url). All-cause mortality. Log scale of relative risks (RR) with 95% confidence intervals (CI), fixed effect model; n, number with outcome; N, total number in group. Studies are identified by the name of first author and year of publication.

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Treatment failure

Overall failure was equivalent in both study arms [RR 1.00 (0.79–1.27)], and in all sub-categories (Figure 3). Ten trials reported failure including treatment modifications in the definition of failure. Significantly more failures were observed in the control arm, the difference originating from studies assessing glycopeptides initially (Figure 4). Amphotericin was added more commonly to the intervention arm in non-blinded trials [RR 1.51 (0.80–2.83), I^2 = 70%, three trials, 976 participants], but not in double-blind studies [RR 0.99 (0.75–1.33), I^2 = 0%, two studies, 225 participants].

Figure 3. Overall failure. Treatment failure with or without treatment modifications.

Figure 4. Failure with modifications. Patients for whom treatment was modified were considered as failures.
The difference in failure with modification was not significant in the subgroup of patients with documented Gram-positive infections [RR 0.79 (0.42–1.48), I² = 12.5%, four studies, 87 patients]. Meta-regression demonstrated no association between the rate of single-organism Gram-positive bacteraemia in the study and the relative risk for failure [RRR 1.001 (0.91–1.07)].

Superinfections

The administration of glycopeptides resulted in a significant reduction in the rate of bacterial superinfections [RR 0.38 (0.24–0.59), I² = 28%, eight studies, 1628 participants] and Gram-positive superinfection [RR 0.21 (0.11–0.37), Figure 5]. Documented fungal superinfections did not differ between the study groups [RR 1.10 (0.69, 1.77), I² = 7%, nine studies, 1637 patients].

No consistent data were available for development of resistance, colonization, and for time to event outcomes.

Adverse events

Addition of anti-Gram-positive treatment resulted in significantly more adverse events (Table 2), mostly dermatological. Glycopeptides were associated with increased nephrotoxicity resulting in harm caused to one of every 37 patients given a glycopeptide.

Sensitivity analyses and selection bias

Repeating the analyses for all-cause mortality and treatment failure using only studies with adequate allocation concealment did not affect results (data not shown). No significant difference in all-cause mortality was seen when analysis was restricted to studies reporting mortality by intention to treat [RR 0.74 (0.48–1.16), five studies]. Intention to treat for failure with modification was carried out for seven studies imputing failure for all dropouts. The treatment effect estimate was smaller than the main comparison [RR 0.85 (0.73–0.99)].

A funnel plot (not shown) showed a symmetric distribution of the studies.

Discussion

The pathogen shift among neutropenic cancer patients towards resistant Gram-positive infections raises the concern whether antibiotics targeting these infections need be added to the empirical treatment of these patients. Current practice is based on results from individual studies that show no advantage to the empirical administration of glycopeptides. These studies are relatively small and may be underpowered to detect differences, particularly in mortality, which is a rare event but the most significant outcome of sepsis. We therefore combined all evidence available from randomized trials assessing the addition of anti-Gram-positive antibiotics.

The empirical addition of antibiotics against Gram-positive infections did not reduce all-cause mortality [RR 0.86 (0.58–1.26)]. In unblinded studies, more treatment modifications were made in the control arm, but overall success was equally achieved. Infection-related mortality did not differ between the study groups. More Gram-positive superinfections were detected in the control arm, but the effects of additional glycopeptides on colonization with resistant microorganisms or selection of resistance could not be assessed. Adverse events were more frequent in the intervention arm, which included an increased rate of nephrotoxicity when the additional antibiotic was a glycopeptide. Thus, no advantage to empirical use of antibiotics against Gram-positive infections was detected, but for a lower rate of Gram-positive superinfections with inadequate data to assess the overall effect of empirical glycopeptides on future resistance.

To maximize our power to detect a significant difference, we merged studies assessing both the initial and the later addition of glycopeptides, and studies assessing other antibiotics with Gram-positive spectra. All studies are empirical in that the intervention was implemented before detection of a causative pathogen. All

Figure 5. Gram-positive superinfections. Superinfections caused by Gram-positive bacteria.
In the same study, the initial administration of vancomycin was not associated with improved ultimate outcome for patients with Gram-positive bacteraemia (418 patients), with the exception of *Streptococcus viridans* bacteraemia (117 patients). In these patients, initial administration of vancomycin was associated with a 14% absolute reduction in mortality \( (P = 0.004) \). This study and current guidelines\(^2\) suggest that centres in which these Gram-positive bacteria are common causes of serious infections, or are commonly associated with penicillin resistance, should consider empirical use of glycopeptides. Other risk factors for viridans streptococcal bacteraemia identified by multivariate analyses in different trials include profound neutropenia, oral mucositis, high dose cytosine arabinoside therapy, prophylaxis with trimethoprim/sulfamethoxazole or fluoroquinolones, and use of antacids or histamine type 2 blockers\(^5\). The presence of one or more of these factors should prompt a careful assessment for the need of empirical glycopeptide therapy.

Catheter-related infections and skin/soft-tissue infections are most commonly caused by Gram-positive bacteria. Centres in which resistance to \( \beta \)-lactams is prevalent should use glycopeptides empirically for these infections\(^2\).

In summary, currently available evidence from randomized controlled trials does not support the need for empirical glycopeptides initially or for persistent fever. Withholding specific treatment against Gram-positive infections pending growth of a resistant Gram-positive organism is safe. Despite more frequent treatment modifications, such practice is associated with fewer adverse events.

Cancer centres need to monitor pathogen prevalences to guide empirical treatment. Future trials assessing empirical glycopeptides are warranted if the spectrum of infections in cancer patients progresses further towards Gram-positive infections. Such trials should adhere to recommendations for their design, analysis and reporting\(^{34,55}\).

### Acknowledgements

We thank Judith E. Karp, Gerald P. Bodey, and Ben E. De Pauw for supplying complementary information for their trials\(^{1,4,12,48-50}\). A detailed protocol of the methodology used for this study was published in The Cochrane Library. The full review will be published in the Cochrane Library.

### Transparency declaration

*Conflicts of interest:* none declared.

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Systematic Review
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American Society for Microbiology, Washington, DC, USA.


