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Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DDG, Silva E.
Teicoplanin versus vancomycin for proven or suspected infection.
Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD007022.
DOI: 10.1002/14651858.CD007022.pub2.

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[Intervention Review]

Teicoplanin versus vancomycin for proven or suspected infection

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Editorial group: Cochrane Renal Group.
Publication status and date: New, published in Issue 6, 2010.
Review content assessed as up-to-date: 29 March 2010.

Citation: Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DDG, Silva E. Teicoplanin versus vancomycin for proven or suspected infection. *Cochrane Database of Systematic Reviews* 2010, Issue 6. Art. No.: CD007022. DOI: 10.1002/14651858.CD007022.pub2.

ABSTRACT

Background

Vancomycin and teicoplanin are commonly used to treat gram-positive infections, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). There is uncertainty regarding the effects of teicoplanin compared to vancomycin on kidney function with some previous studies suggesting teicoplanin is less nephrotoxic than vancomycin.

Objectives

To investigate the efficacy and safety of vancomycin versus teicoplanin in patients with proven or suspected infection.

Search methods

We searched the Cochrane Renal Group's Specialised Register, CENTRAL, MEDLINE, EMBASE, reference lists of nephrology textbooks, review articles with relevant studies and sent letters seeking information about unpublished or incomplete studies to investigators involved in previous studies.

Selection criteria

We searched for randomised controlled trials (RCTs) in any language comparing teicoplanin to vancomycin for patients with proven or suspected infection.

Data collection and analysis

Two authors independently evaluated methodological quality and extracted data using standardised data extraction forms. Study investigators were contacted for information not available in the original manuscripts. Random effects model was used to estimate the pooled risk ratio (RR) with 95% confidence interval (CI).

Main results

We included 24 studies (2,610 patients) in this review. Teicoplanin reduced the risk of nephrotoxicity compared to vancomycin (RR 0.66, 95% CI 0.48 to 0.90).The effects of teicoplanin or vancomycin were similar for clinical cure (RR 1.03, 95% CI 0.98 to 1.08), microbiological cure (RR 0.98, 95% CI 0.93 to 1.03) and mortality (RR 1.02, 95% CI 0.79 to1.30). Six studies reported no cases

of acute kidney injury (AKI) needing dialysis. Adverse events were less frequent with teicoplanin including cutaneous rash (RR 0.57, 95% CI 0.35 to 0.92), red man syndrome (RR 0.21, 95% CI 0.08 to 0.59) and total adverse events (RR 0.73, 95% CI 0.53 to 1.00). A lower risk of nephrotoxicity with teicoplanin was observed in patients either with (RR 0.51, 95% CI 0.30 to 0.88) or without aminoglycosides (RR 0.31, 95% 0.07 to 1.50), and also when vancomycin dosing was guided by serum levels (RR 0.22, 95% CI 0.10 to 0.52).

Authors' conclusions

Teicoplanin and vancomycin are both effective in treating those with proven or suspected infection; however the incidence of adverse effects including nephrotoxicity was lower with teicoplanin. There were no cases of AKI needing dialysis. It remains unclear whether the differential effect on kidney function should influence which antibiotic be prescribed, although it may be reasonable to consider teicoplanin for patients at higher risk for AKI needing dialysis.

PLAIN LANGUAGE SUMMARY

Teicoplanin versus vancomycin for proven or suspected infection

One of the most common bacteria responsible for human diseases is *Staphylococcus aureus*, which causes mainly skin, lung and blood infections. In many cases, especially in infections acquired inside a hospital, usual antibiotics are ineffective and more aggressive drugs are needed. Teicoplanin and vancomycin are both effective against this bacteria, however, there is a concern that vancomycin may be more toxic, especially for the kidneys. This review identified 24 studies enrolling 2,610 patients comparing teicoplanin and vancomycin in those with either proven or suspected infection. Teicoplanin was as effective as vancomycin for treating infections caused by *Staphylococcus aureus* with similar results for clinical cure, microbiological cure and death. However, there were less adverse events (skin rash and red man syndrome) and it caused significantly less damage to the kidneys.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Teicoplanin versus vancomycin for proven or suspected infection

Patient or population: patients with proven or suspected infection
Settings:
Intervention: Teicoplanin versus vancomycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Teicoplanin versus vancomycin				
Nephrotoxicity	**Medium risk population**		**RR 0.66** (0.48 to 0.9)	2596 (23 studies)	⊕⊕⊕◯ **moderate**[1]	
	92 per 1000	**61 per 1000** (44 to 83)				
Clinical cure or improvement	**Medium risk population**		**RR 1.03** (0.98 to 1.08)	1703 (20 studies)	⊕⊕⊕◯ **moderate**[1]	
	730 per 1000	**752 per 1000** (715 to 788)				
Microbiological cure	**Medium risk population**		**RR 0.98** (0.93 to 1.03)	914 (16 studies)	⊕⊕⊕◯ **moderate**[1]	
	850 per 1000	**833 per 1000** (790 to 875)				
Renal failure needing dialysis[2]	See comment	See comment	Not estimable[2]	606 (3)	See comment	
Mortality	**Medium risk population**		**RR 1.02** (0.79 to 1.3)	1565 (16 studies)	⊕⊕◯◯ **low**[3]	

	103 per 1000	**105 per 1000** (81 to 134)			
Cutaneous rash	**Medium risk population**		**RR 0.57** (0.35 to 0.92)	1823 (18 studies)	⊕⊕⊕○ **moderate**[1]
	60 per 1000	**34 per 1000** (21 to 55)			
Total adverse events	**Medium risk population**		**RR 0.56** (0.33 to 0.95)	880 (11 studies)	⊕○○○ **very low**[1,3,4]
	184 per 1000	**103 per 1000** (61 to 175)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] All studies have flaws in one or more of the following methodological quality domains: allocation concealment, blinding or intention-to-treat analysis. While the unit of randomisation was the patient in all trials, most considered the number of infection episodes as the unit of analysis.
[2] Only six studies reported this outcome. No event was observed, therefore no pooled effect could be estimated.
[3] 95% confidence interval around the best estimate of effect includes both negligible effect (relative risk reduction (RRR) less than 25%).and appreciable benefit or appreciable harm.
[4] I2 compatible with important heterogeneity of individual trials' effects. This may have been caused by different definitions used for this outcome between trials.

BACKGROUND

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of bloodstream and other invasive infections worldwide (Bubacz 2007; Rioux 2007). Between 48% and 57% of *S. aureus* isolates from inpatients are resistant to methicillin in United States (NNIS 2004; Wisplinghoff 2004) and around 30% in many European countries (Voss 1994). Vancomycin remains the drug of choice for the treatment of infections caused by MRSA; however one of the major limitations for its use is its potential nephrotoxicity (Maclayton 2007). Teicoplanin, another glycopeptide, has essentially the same efficacy of vancomycin with some advantages such as once-daily bolus administration, intramuscular use, lack of requirement for routine serum monitoring and possibly less nephrotoxicity (Wood 2000). However teicoplanin is more expensive.

There is uncertainty as to whether vancomycin causes permanent or temporary kidney damage. Many studies have shown an increased risk of kidney failure after vancomycin treatment (Bailie 1988; Cheung 1986; Downs 1989; Hidayat 2006; Kralovicova 1997; Sidi 2000), although others have not found an association (Bhatt-Mehta 1999; Vazquez 1999b; Wenisch 1996). In fact, adverse kidney effects were common with earlier vancomycin preparations, but the significance of this problem is less well established with current purified formulations (Bailie 1988). Furthermore, other factors such as association with nephrotoxic drugs, especially aminoglycosides, and different nephrotoxicity definitions may have blurred the real impact of vancomycin on kidney function in some previous studies (Rybak 1990).

Vancomycin might lead to nephrotoxicity due to its effects on proximal tubular cells where it accumulates inside lysosomes (Beauchamp 1992; Sokol 1991). There, it inhibits the activity of many enzymes, such as sphingomyelinase, leading to vacuolization and necrosis (Beauchamp 1990). As aminoglycosides accumulate in the same cells and are also nephrotoxic, using both drugs simultaneously may lead to a faster and more severe loss of kidney function (Duffull 1994).

To date, just one meta-analysis of randomised controlled trials (RCTs) has been published on this issue (Wood 1996). The authors found no difference between vancomycin and teicoplanin regarding clinical or bacteriological response. However, 10.7% of vancomycin treated patients developed nephrotoxicity compared to 4.8% of those treated with teicoplanin ($P < 0.001$). Nevertheless, methods used to conduct this meta-analysis were poorly reported, seriously hindering interpretation of its results.

OBJECTIVES

This systematic review of RCTs aimed to investigate the efficacy and safety of vancomycin compared to teicoplanin in patients with proven or suspected infection.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) comparing intravenous (IV) teicoplanin to IV or intramuscular (IM) vancomycin. The first period of randomised cross-over studies were also be included. Studies were considered for inclusion regardless of their publication status, language, blinding, size, duration of patient follow-up, or their primary objectives and reported outcomes.

RCTs in which there were no relevant or adverse events in both the treatment and control groups were excluded because these studies provide no information on the magnitude of the treatment effect (Whitehead 1991).

Types of participants

Inclusion criteria

- Patients of all ages with suspected or proven gram-positive infection.

Exclusion criteria

- Use of teicoplanin or vancomycin for prophylaxis (rather than for suspected or proven infection).

Types of interventions

- At least one arm allocated to receive IV or IM teicoplanin and another arm to receive IV vancomycin.

Types of outcome measures

Primary outcomes

- Nephrotoxicity: An elevation of serum creatinine (SCr) greater than or equal to twice the basal level or urine output less than 0.5 mL/kg/h over a 12 hour period. In case data were not available according to this definition and after contacting authors, we accepted a similar definition used in the original study.
- Clinical cure: Patients who showed resolution or significant improvement of signs and symptoms by the end of study drug treatment.

Secondary outcomes

- Acute kidney injury (AKI) needing renal replacement therapies;
- Microbiological cure defined as a negative culture from a material in which it had been previously positive;
- Mortality;
- Infusion reactions;
- Other adverse events reported in the studies.

Search methods for identification of studies

The search strategy included all languages. We searched the following sources.

Electronic searches

1. The Cochrane Renal Group specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL and the Cochrane Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective. Therefore we did not specifically search conference proceedings. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings (Renal Group 2010).
2. MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) together with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Co-ordinator.
3. EMBASE (from 1980) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) together with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Co-ordinator.

See Appendix 1 for search terms used.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Assessment of study eligibility

The review was undertaken by five authors (AC, AG, DB, CA, ES). The search strategy described was used to obtain titles and abstracts of studies that might be relevant to the review. Two authors (DB, CA) independently selected the abstracts identified in our search. If any of the authors considered a citation might possibly include a relevant RCT the full text article was assessed. After obtaining the full text articles, each potential was evaluated independently by two authors (groups of two formed by AC, AG, DB, CA or ES). In the case of a disagreement, the authors discussed the reasons for their decisions. If the disagreement was not resolved during this process, a third author would make the final decision (AC or ES or AG). In case of any doubts about the study design (e.g. observational study compared to RCTs), the author of the publication was contacted.

Data extraction

Data extraction was carried out independently by AC and ES using standard data extraction forms. Disagreements were resolved by consensus. Studies reported in non-English language were translated before assessment. Duplicate publications or substudies of included studies were listed under the primary reference as they may have provided information on relevant outcomes not available in the original publication. Any further information required from the original author was requested by written correspondence.

Study quality

The quality of studies included was assessed independently by AC and ES without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussions aimed at a consensus.

Quality checklist

We assessed the following criteria (see Appendix 2).

- Allocation concealment
- Blinding ((participants, investigators, outcome assessors and data analysis)
- Intention-to-treat
- Completeness of follow-up

Statistical assessment

Dichotomous data (e.g. AKI needing dialysis or nephrotoxicity as defined above) from all included RCTs was combined to estimate the pooled risk ratio (RR) with 95% confidence interval (CI) using a random-effects model (Der Simonian 1986).

The analyses were based on intention-to-treat data from the individual studies whenever possible. Every effort was made to obtain complete information about patients' outcomes, including contacting authors. However, we did not include in the denominator patients with no follow-up.

The presence of heterogeneity across studies was evaluated using I^2 statistics (Higgins 2003) and standard Chi^2 tests for homogeneity

for each outcome analysis. An I^2 value represents the percentage of total variation across studies due to heterogeneity rather than chance. We considered an I^2 value less than 25% as low and an I^2 value more than 75% as high. We looked for potential publication bias and other biases associated with small study effects by constructing funnel plots (Egger 1997). Funnel plots are simple scatter plots of the treatment effects obtained from individual studies on the vertical axis (for example, log OR) against some measure of study size on the horizontal axis (for example, Standard error of log OR).

We had originally planned to carry out univariate and multivariate random-effects meta-regression models to analyse potential clinical and study quality factors that might influence treatment effects, that is, in an attempt to explain heterogeneity (Altman 2003; Thompson 1999). The following variables were to be considered: standard error of log odds ratio, publishing status (MEDLINE indexed or not), study quality (generation of allocation sequence, allocation sequence concealment, follow-up, intention-to-treat analysis), definition of nephrotoxicity, dose adjustment guided by vancomycin serum measurement, clinical sub-groups (critically ill patients, kidney failure patients, elderly patients or concomitant aminoglycoside use). However, as we have not found substantial heterogeneity for any of the primary outcomes, meta-regression was not performed. We conducted simple sub-group analyses instead (serum vancomycin-guided dose adjustment and concomitant aminoglycoside use). We had the planned to look to other sub-groups (according to age or baseline kidney function), but that was not feasible because we were unable to obtain appropriate data.

Adverse effects were tabulated and assessed with descriptive techniques. Whenever possible, the pooled RR with 95% CI was calculated for each adverse effect.

All P values reported were two-tailed and values lower than 0.05 were considered significant, except for the Chi^2 test for homogeneity. This method has low sensitivity for detecting heterogeneity using few studies, therefore we considered a P value lower than 0.10 as statistically significant.

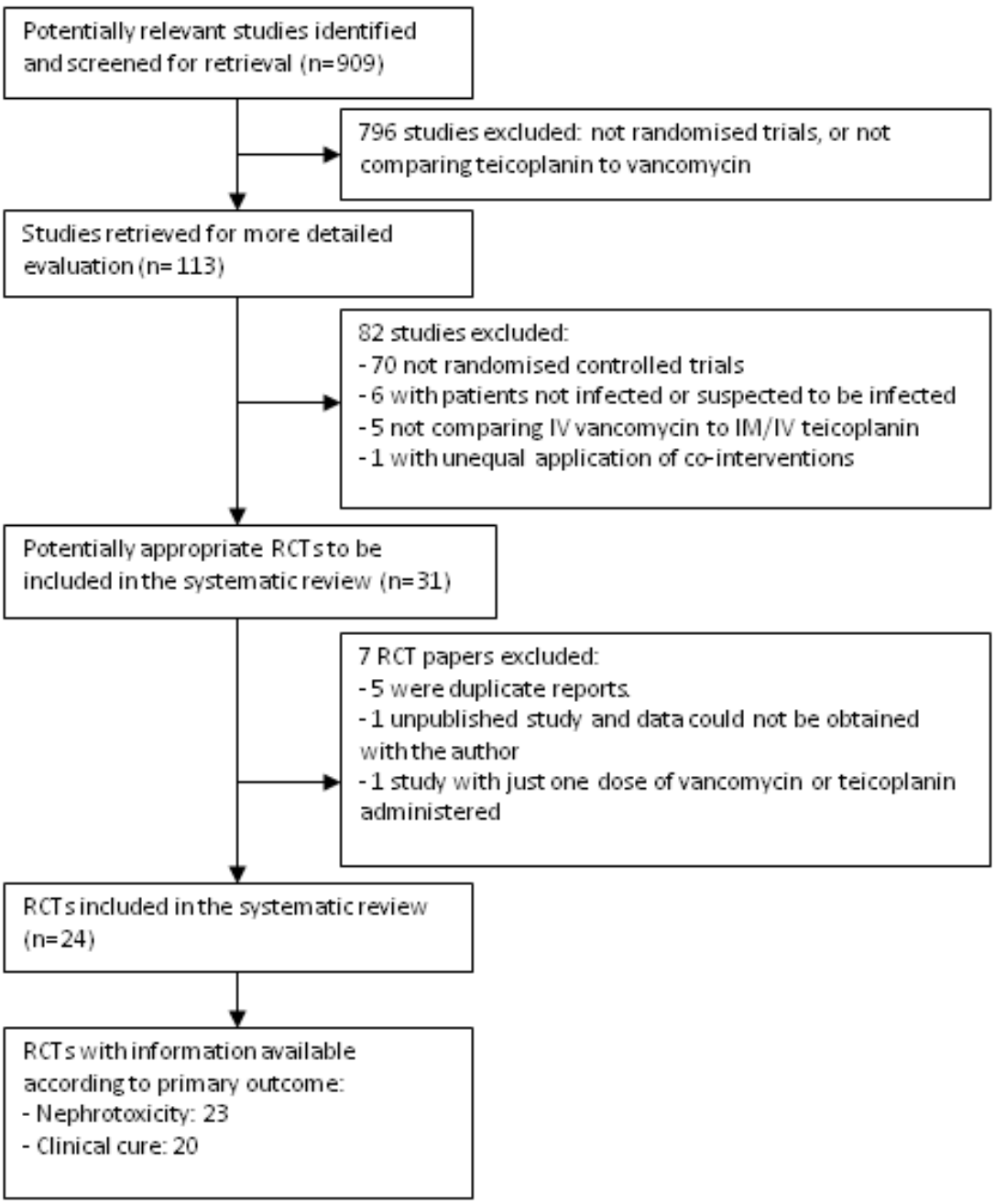
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We initially identified 909 potentially relevant studies (Figure 1). After evaluating their abstracts (or titles) we excluded 796 reports because they were not RCTs or did not compare teicoplanin to vancomycin. The full-text articles of the remaining 113 studies were evaluated, with a further 82 considered ineligible. This left 31 potentially relevant RCTs. Five reports were duplicate publications of included (Chow 1993 (2); Figuera 1996; Van der Auwera 1991) and excluded studies (Menichetti 1992); one report was a subset of a larger study (MMD-009 1992) and one study used just one dose of vancomycin or teicoplanin and was excluded (Rybak 1992).

Figure 1. Selection of studies for inclusion in the systematic review of teicoplanin versus vancomycin for proven or suspected infection



The 24 studies finally included enrolled 2,610 patients. Most were published between 1988 and 2000, with three studies published between 2001 and 2004 (Table 1). The median sample size was 72 patients, ranging from 20 to 635. Most evaluated adults, with only two studies including paediatric patients. Ten of 24 studies evaluated febrile neutropenic patients, the remaining included several other infections related or probably related to gram-positive bacteria. Sixteen studies did not include patients with previously elevated SCr, although cut-off levels for exclusion varied. Definitions of nephrotoxicity were also not uniform across the studies.
Most studies administered 6 to 10 mg/kg of teicoplanin IM or IV every 12 hours for three doses, then once daily (Table 1). Several schemes of vancomycin were used, varying from 24 to 40 mg/kg/d, divided into two to four doses or a fixed dose of 2 g/d divided into two to four doses. Vancomycin was adjusted according to serum levels in seven studies, although only for selected patients in two of these.

Risk of bias in included studies

In general, the quality of included studies was poor (Table 2). Only 6/24 studies reported allocation concealment. Blinding of participants, healthcare personnel and outcome assessors was adequately described in 5/24 studies. Intention-to-treat analysis was performed in only 7/24 studies. Post-randomisation exclusions or losses to follow-up were greater than 10% in 13/24 studies.
In six studies the unit of randomisation and analysis was an infection episode. That is, the same patient could be included twice or more in the study. This is inappropriate because statistical methods used assume independency of observations.

Effects of interventions

See: **Summary of findings for the main comparison** Teicoplanin versus vancomycin for proven or suspected infection
Teicoplanin reduced the risk of nephrotoxicity (Analysis 1.1: RR 0.66, 95% CI 0.48 to 0.90; I^2 = 10%). Ordering the studies according to the year of publication data, did not suggest a pattern of decreasing nephrotoxicity related to vancomycin in the more recent studies. Clinical cure was similar with teicoplanin or vancomycin (Analysis 1.2: RR 1.03, 95% CI 0.98 to 1.08; I^2 = 0%). Funnel plots for nephrotoxicity or clinical cure did not suggest either a small studies' effect or reporting bias (graphs not shown in this manuscript).
We did not carry out meta-regression analysis because there was no evidence of substantial heterogeneity between the study results for the main endpoints (nephrotoxicity and clinical cure). Sub-group analyses according to clinical indication (febrile neutropenic, catheter-associated infection, gram-positive bacteraemia, endocarditis, bone/articular infection or other gram-positive infections) did not show any evidence of superiority of either vancomycin or teicoplanin for any indication (Analysis 1.10). With respect to nephrotoxicity, subgroup analysis suggested no difference in the treatment effect for the comparisons of studies with adequate allocation concealment versus unclear or no allocation concealment (test for subgroup differences P = 0.56), studies with blinding of participants, healthcare personnel and outcome assessors and studies with unclear or no blinding (test for subgroup differences P = 0.70) and studies with versus without intention-to-treat analysis (test for subgroup differences P = 0.48).
Data on AKI with an indication for dialysis was available in only six studies (786 patients) (Summary of findings for the main comparison). No patient in either the vancomycin or teicoplanin group needed dialysis, therefore it was impossible to estimate the RR. There was no evidence of a higher nephrotoxic effect of vancomycin compared to teicoplanin in patients receiving concomitant aminoglycosides (Analysis 1.11.2). A *post-hoc* analysis of nephrotoxicity limited to studies where all patients had vancomycin administered according to serum levels provided results similar to the overall estimate (Analysis 1.11.3: RR 0.22, 95% CI 0.10 to 0.52; I^2 = 0%). However, this analysis was based on only 32 nephrotoxic events in five studies. Data on other subgroups was unavailable (critically ill patients, kidney failure patients, elderly patients).
The effect of teicoplanin on microbiological cure was similar to vancomycin (Summary of findings for the main comparison). Mortality was similar with both antibiotics (Analysis 1.5), but due to serious imprecision and poor quality of included studies, this is low quality evidence. Cutaneous rash (Analysis 1.6) and red man syndrome were observed much less often with teicoplanin than with vancomycin. The incidence of any adverse effect was 27% lower with teicoplanin, although heterogeneity was very high (Analysis 1.9).

DISCUSSION

Summary of main results

In this systematic review and meta-analysis, we found a similar effect of teicoplanin compared to vancomycin on clinical and microbiological cure. However the RR of nephrotoxicity was reduced by 34% when using teicoplanin. This represents a number needed to harm of 25 (assuming a risk of nephrotoxicity with vancomycin of 9%). The reduced nephrotoxicity of teicoplanin compared to vancomycin was similarly observed in patients with or without aminoglycosides, and also in studies where vancomycin administration was guided by serum levels.

Cutaneous rash, red man syndrome and total adverse events were also less common with teicoplanin than vancomycin. Mortality was similar with both drugs, but the total number of deaths was low. Thus, there is inadequate precision in the estimate of effect on mortality.

Overall completeness and applicability of evidence

The results of this systematic review are applicable to most patients for whom teicoplanin or vancomycin is being considered for treatment of a gram-positive infection, in particular due to MRSA. However some groups of patients may not have been adequately represented in this review. Most studies excluded patients with kidney failure and none included only critically ill patients. Data specific for the subgroups of kidney failure, critically ill or elderly patients were not available from the publications of the original studies and could not be obtained from the authors.

Data on AKI needing dialysis was available in only six studies, but no patient (0/786) developed this complication in either antibiotic group. Thus, it was not possible to evaluate whether the lower risk of nephrotoxicity with teicoplanin than with vancomycin translates into a lower risk of AKI requiring dialysis. The absence of cases needing dialysis is most likely explained by the selection of patients at lower risk for this event, for instance under-representation of previous kidney failure or critically ill patients. Also, vancomycin-induced nephrotoxicity is mild. However, it is possible that progression to dialysis may be precipitated by vancomycin among higher risk patients.

Comparative evaluations of clinical cure according to clinical site showed a consistent effect for the sites of infection/indications evaluated. Previous studies suggest that the failure rate in endocarditis may be unacceptable with teicoplanin at usual doses (6 mg/kg every 12 hours for 3 doses, then once a day) compared to vancomycin (MMD-009 1992; Wilson 1994). Teicoplanin even at higher doses does not penetrate the vegetations, thus, success may be achieved only for small vegetations or when aminoglycosides are associated (Cremieux 1989). The totality of evidence from RCTs regarding endocarditis suggests teicoplanin is similar to vancomycin; however a small study (MMD-014 1992) had discrepant results, which were unfavourable to teicoplanin. This resulted in large inconsistent (I^2 = 52%) between-study effects. Thus it is not possible to conclude on the efficacy of teicoplanin for this condition.

Quality of the evidence

The RCTs included in this review are generally small and only a few are free of methodological problems, thereby increasing the risk of biased results. There was low heterogeneity between estimates of effect from the included studies for all outcomes, except occurrence of any adverse event. This last result is probably a consequence of the very different definitions of "any adverse event" used in the primary studies.

The quality of the evidence regarding the effect of teicoplanin compared to vancomycin on nephrotoxicity is moderate according to the GRADE system (Summary of findings for the main comparison), (GRADE 2004). Limitations in design of primary studies downgraded the quality of evidence. The GRADE quality of evidence is also moderate for the evaluation of clinical cure (Summary of findings for the main comparison). The level of evidence was downgraded due to methodological limitations of primary studies.

Potential biases in the review process

In order to ensure a high degree of internal and external validity, we followed a systematic approach for study identification, selection, data abstraction and analysis. We searched for all relevant studies using sensitive and validated search strategies in several bibliographic databases. Studies were included independent of publication status or language. Original investigators were contacted, and some, but not all, contributed additional information. Data on the main outcome nephrotoxicity was obtained from 23/24 studies and on clinical cure from 20/24 studies. We looked for and found no evidence of reporting or small studies' bias using funnel plots for these outcomes.

Limitations in this review include the lack of a uniform definition of nephrotoxicity in the original studies. In fact, until recently there was not a universally recognized definition of AKI and several definitions were used in the literature (Kellum 2002). The current definition of AKI proposed by the Acute Kidney Injury Network (AKIN) includes an elevation of at least 0.3 mg/dL in baseline levels of creatinine or a 50% increase in two different measurements, or a urine output lower than 0.5 mL/kg/h for over 6 hours (Mehta 2007). The AKIN definition had not been published when we prepared this review's protocol. Therefore, we defined nephrotoxicity in our review according to the "Injury" component of the RIFLE criteria for AKI (Bellomo 2004). However, we were unable to obtain data on nephrotoxicity according to our definition from the study authors. Therefore, we abstracted nephrotoxicity data as defined in the original studies, with the most common definition being an increase in SCr > 0.5 mg/dL above baseline. In spite of no uniformity in the definition of this outcome, there was no evidence of substantial heterogeneity among studies regarding the effect of teicoplanin versus vancomycin on nephrotoxicity.

Agreements and disagreements with other studies or reviews

One meta-analysis evaluating teicoplanin versus vancomycin was previously published, however the author did not report any structured method for study identification, selection and analysis (Wood 1996). In that study, both drugs achieved similar probabilities of clinical cure (72.7% for teicoplanin versus 77.2% for

vancomycin), however teicoplanin had significantly less adverse events (21.9% versus 13.9% P = 0.0003), especially less nephrotoxicity (4.8% versus 10.7% P = 0.0005). A formal approach was followed in the present review and 10 additional studies were included. Despite these differences, we found similar results for clinical cure (74.3% versus 72.0%) and nephrotoxicity (4.7% versus 9.2%).

A recurrent issue in the literature on teicoplanin is the relationship between dose and its clinical efficacy (Finch 2005; Wilson 1994). Currently the recommended dose is 6 mg/kg (or 400 mg) every 12 hours for 3 doses, then 6 mg/kg (or 400 mg) once daily, with double this dose being needed for endocarditis (Wilson 1994). Initial studies with teicoplanin used a much lower dose, generally half of that currently used (Neville 1995; Van der Auwera 1991; Van Laethem 1988). Most studies in this review used the current larger dose (400 mg/kg every 12 hours for 3 doses, then once daily), or changed to the larger dose during the study. The results of these studies present a very similar and consistent effect of teicoplanin versus vancomycin on clinical or microbiological cure. Recently a loading dose of 6 mg/kg every 12 hours for 4 doses, then once daily has been recommended to speedily achieve optimal concentrations of serum teicoplanin (Brink 2008).

AUTHORS' CONCLUSIONS

Implications for practice

This review summarizes the best available evidence on the use of teicoplanin versus vancomycin for infected or suspected to be infected patients. The overall quality of evidence across all comparisons is low to moderate using the GRADE system (GRADE 2004). Teicoplanin is as efficacious as vancomycin regarding clinical and microbiological cure, although it is associated with a lower risk of nephrotoxicity and cutaneous rash. Since no patient on either antibiotic required dialysis, the effect of teicoplanin compared to vancomycin on this outcome could not be determined. Thus it remains unclear whether teicoplanin has a clinically relevant advantage over vancomycin, although it may be reasonable to consider teicoplanin a better choice for patients at higher risk for AKI needing dialysis.

There is no consistent evidence of efficacy of teicoplanin compared to vancomycin for treating endocarditis. Therefore, teicoplanin cannot be currently recommended for this condition.

Implications for research

Investigators should conduct studies to evaluate antibiotics for gram-positive infections with a sound design and adequate power to evaluate outcomes relevant to patients. Studies with vancomycin should report the incidence of AKI needing dialysis. Future studies involving vancomycin should use serum levels to guide dose adjustments. This review showed that the risk of nephrotoxicity was also higher in patients receiving vancomycin guided by serum levels, but this analysis was based on only a few events from four studies.

No RCT evaluated vancomycin versus teicoplanin exclusively in critically ill patients. We were also unable to obtain data specific for this subgroup in our review. However, antibiotics to treat MRSA and other gram-positive infections are widely used in the intensive care setting. The effect of vancomycin versus teicoplanin in patients with previous kidney injury are also unclear from the available evidence. Thus, studies involving critically ill and kidney injury patients are necessary. Finally, adequately powered RCTs are warranted to evaluate the efficacy of teicoplanin compared to vancomycin for the treatment of endocarditis.

ACKNOWLEDGEMENTS

- We would like to thank the referees for their editorial advice during the preparation of this protocol. We are especially indebted to Dr A. Peter Wilson for his thoughtful suggestions and for providing us with additional unpublished data of teicoplanin versus vancomycin studies.

- We would like to thank the following colleagues for kindly providing additional unpublished data on their studies: Drs Pascale Cony-Makhoul et al., Domenico D'Antonio et al., Dr Sidi and Emmanuel Roilides et al, and Dr. Sven Hedström et al.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Auperin 1997

Methods	• Study design: RCT
Participants	• Patients < 18 years with solid neoplasm, neutropenia (< 500/mm³) and fever • Age (median): Teicoplanin (8); vancomycin (8) • Males: Teicoplanin (20/32); vancomycin (21/33)
Interventions	• Teicoplanin ○ 10 mg/kg every 12 h for 3 doses, then OD • Vancomycin ○ 10 mg/kg every 6 h ○ Vancomycin dose adjustment guided by serum levels: NS
Outcomes	• Hours of sleep • Costs. • Follow-up: from randomisation to discharge from paediatric oncology ward or starting of new chemotherapy • Definitions ○ Nephrotoxicity: Reported, but definition NS ○ Clinical cure: Data not reported
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	No information regarding blinding, however this would not bias this evaluation
Blinding? Clinical cure	Unclear	No information regarding blinding.
Incomplete outcome data addressed? All outcomes	Yes	ITT: Follow-up losses (2), nephrotoxicity event (1).

Charbonneau 1994

Methods	• Study design: RCT
Participants	• Patients ≥18 years, admitted to ICU or department of infections disease for severe gram-positive infection • Age (mean): Teicoplanin (56.8), vancomycin (56.4) • Males: Teicoplanin (15/24), vancomycin (21/32)
Interventions	• Teicoplanin ○ 6 mg/kg every 12 h for 3 doses, then OD • Vancomycin ○ 24 mg/kg/d divided in 2 or 3 daily doses ○ Vancomycin dose adjustment guided by serum levels: Yes • Concomitant aminoglycoside use: All patients received netilmicin (4.5 mg/kg/d)
Outcomes	• Authors did not specify primary outcomes • Outcomes reported ○ Nephrotoxicity, clinical cure and microbiological cure • Follow-up: NS (probably during the period of treatment) • Definitions ○ Nephrotoxicity: Four different definitions for nephrotoxicity were used. We abstracted data according to the following nephrotoxicity definition. ◇ 0.5 mg/dL increase if the baseline value < 3 mg/dL ○ Clinical cure: Defined as cure or improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	No	Analysis per-protocol. 5/56 exclusions to follow-up or losses

Choi 1992

Methods	• Study design: RCT
Participants	• Haematological patients ≥ 15 years with febrile neutropenia • Age (mean): Teicoplanin (35), vancomycin (29) • Males: Teicoplanin (7/22), vancomycin (9/20)

Choi 1992 (*Continued*)

Interventions	• Teicoplanin
	  ○ 400 mg every 12 h for 2 doses, then OD
	• Vancomycin
	  ○ 500mg every 8 hours.
	  ○ Vancomycin dose adjustment guided by serum levels: NS
	• Concomitant aminoglycoside use: No.
	• All patients received ceftazidime and aztreonam

Outcomes	• Clinical cure and adverse events
Notes	• Article in Korean, only abstract in English. It was translated to Portuguese to allow quality assessment and data extraction.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	Yes	Yes

Chow 1993

Methods	• Study design: RCT
Participants	• Patients ≥ 18 years with neutropenia (< 500/mL) and fever; all with Hickman catheters • Exclusions: Cr > 2.5 mg/dL • Age (median): Teicoplanin (40), vancomycin (38) • Males: Teicoplanin (11/25), vancomycin (15/25)

Interventions	• Teicoplanin
	  ○ 6 mg/kg every 12 h for 3 doses, then OD alternated with placebo
	• Vancomycin
	  ○ 4 mg/kg every 12 h. All patients also received amphotericin and piperacillin
	  ○ Vancomycin dose adjustment guided by serum levels: Yes
	• Concomitant aminoglycoside use: All patients received tobramycin

Outcomes	• Primary outcomes; NS • Pharmacokinetic and several clinical outcomes were evaluated • Definitions:

Chow 1993 (*Continued*)

	○ Nephrotoxicity: Cr > 1.24 mg/dL ○ Clinical cure or improvement ◇ Cure: Fever and all clinical signs resolved with eradication of the infecting micro-organisms if isolated and without change of the study regimen ◇ Improvement: Oral temperature fell below 38°C and all other signs and symptoms had partially resolved within 48 hours
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Yes
Blinding? Clinical cure	Yes	Yes
Incomplete outcome data addressed? All outcomes	No	No

Cony-Makhoul 1990

Methods	• Study design: RCT
Participants	• Patients ≥ 16 years with acute leukaemia after chemotherapy or multiple myeloma after high dose cyclophosphamide, and < 500 neutrophils/mm³ and fever despite ceftazidime • Age (mean): Teicoplanin (51.5), vancomycin (45.0) • Males: Teicoplanin (15/22), vancomycin (17/34)
Interventions	• Teicoplanin ○ 6 mg/kg every 12 h for three doses then OD • Vancomycin ○ 30 mg/kg/d, divided into two daily doses. ○ Vancomycin dose adjustment guided by serum levels: NS • Concomitant aminoglycoside use: Patients not responding to the study antibiotics received an aminoglycoside (number not reported)
Outcomes	• Primary outcomes: NS. • Efficacy outcomes: Clinical cure and microbiological cure • Safety outcomes: Cutaneous, renal and hepatic toxicity • Definitions: ○ Nephrotoxicity: NS ○ Clinical cure: Apyrexia after 48 h

Cony-Makhoul 1990 (*Continued*)

Notes	The unit of randomisation and analysis was an infection episode, instead of a patient

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 6/65 patients.

D'Antonio 2004

Methods	• Study design: RCT
Participants	• Haematological malignancy with neutropenia and persisting fever after ceftazidime and amikacin, plus bacteraemia due to gram-positive cocci • Age mean: Teicoplanin (41.5), vancomycin (37.2) • Males: Teicoplanin (29/63), vancomycin (29/61)

Interventions	• Teicoplanin
	  ○ 6 mg/kg every 12 h for 2 days, then OD
	• Vancomycin
	  ○ 30 mg/kg/d divided into 2 daily doses
	  ○ Vancomycin dose adjustment guided by serum levels: NS
	• Concomitant aminoglycoside use: All patients (amikacin)
	• All patients received amikacin and ceftazidime

Outcomes	• Primary outcome: NS. • Outcomes evaluated were therapeutic success and costs Definitions: • Therapeutic success: Negative cultures after 96 h • Nephrotoxicity: Reversible renal toxicity (not further specified). • Clinical cure: Data not reported
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

D'Antonio 2004 (*Continued*)

Blinding? Nephrotoxicity	Yes	It is unclear whether this study was blinded. However, this is unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	Unclear	The study is described as double-blind, but procedures used to achieve blinding are NS
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 30/154 patients

Figuera 1996

Methods	• Study design: RCT
Participants	• Cr > 2.5 mg/dL • Age (median): Teicoplanin (35), vancomycin (39) • Males: Teicoplanin (36/68), vancomycin (35/58)
Interventions	• Teicoplanin ○ 400 mg every 12 h for 3 doses, then OD • Vancomycin ○ 1g every 12 h ○ Vancomycin dose adjustment guided by serum levels: No • All patients also received imipenem 500 mg every 6 hours • Concomitant aminoglycoside use: A sub-group of patients received amikacin (number of patients in each study arm NS)
Outcomes	• Primary outcome: NS • Outcomes reported: Fever resolution (primary and secondary response) • Definitions ○ Fever resolution ◇ Primary response: Fever resolution and negative of cultures within 72 h (48 h for blood cultures) ◇ Secondary response: Response after association of amikacin or amphotericin, except for patients whose response occurred simultaneously with resolution of neutropenia or addition of other antibiotics ○ Nephrotoxicity: SCr > 1.5 mg/dL. ○ Clinical cure: Data not collected because it was incompletely reported (data available for just part of the patients)
Notes	The unit of randomisation and analysis was an infection episode, instead of a patient

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear

Figuera 1996 (*Continued*)

Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 23/149 patients

Fortun 2001

Methods	• Study design: RCT
Participants	• Parenteral drug abusers with methicillin-susceptible *S. aureus* right-side endocarditis • Exclusions: SCr > 2.5 mg/dL • Age (mean): Teicoplanin (31), vancomycin (25) • Males: Teicoplanin (10/10), vancomycin (9/10)
Interventions	• Teicoplanin ○ 24 mg/kg OD on the 1st day, then 12 mg/kg OD • Vancomycin ○ 500 mg every 6 h ○ Vancomycin dose adjustment guided by serum levels: NS • Concomitant aminoglycoside use: All patients also received gentamicin.
Outcomes	• Primary outcome: NS • Outcomes reported: Clinical and microbiological cure, adverse effects • Definitions ○ Nephrotoxicity: "moderate elevation in SCr levels". ○ Clinical cure: "microbiological eradication and satisfactory clinical response"
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	Yes	ITT analysis. Lost to follow-up 3/23 patients.

Hedström 1995

Methods	• Study design: RCT (patients randomised with a 2:1 chance of receiving teicoplanin versus vancomycin)
Participants	• Patients with severe infections definitely or probably caused by gram-positive bacteria • Age (mean): Teicoplanin (58), vancomycin (62) • Males: Teicoplanin (36/53), vancomycin (17/27)

Interventions	• Teicoplanin
	  ○ 400 mg every 12 h for 3 doses, then OD
	• Vancomycin
	  ○ 1 g every 12
	  ○ Vancomycin dose adjustment guided by serum levels: Yes
	• Concomitant aminoglycoside use: 17/48 patients

Outcomes	• Primary outcome: NS
	• Reported outcomes: Microbiological cure and adverse events
	• Definitions
	  ○ Nephrotoxicity: "elevation of SCr" (no further details)
	  ○ Clinical cure: Cure or improvement (no further details)

Notes	• Publication as abstract • Data extracted from Astra Arcus AB on file clinical report.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Although it is not stated whether the study was blinded, this is unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 32/80 patients

Liu 1996

Methods	• Study design: RCT
Participants	• Adults >18 years with proven MRSA bacteraemia • Age (mean): Teicoplanin (71.3, vancomycin (67.2) • Males: Teicoplanin (16/20), vancomycin (19/20)

Liu 1996 (*Continued*)

Interventions	• Teicoplanin ○ 400 mg every 12 h for 3 doses, then OD. • Vancomycin ○ 500 mg every 6 h. ○ Vancomycin dose adjustment guided by serum levels: NS • Concomitant aminoglycoside use: No
Outcomes	• Primary outcomes: Clinical efficacy and adverse events. Definitions: • Nephrotoxicity: Elevation of SCr > 50% above baseline • Clinical cure: Clinical signs of infection eradication at the end of follow-up or subsidence of clinical signs and symptoms but incomplete resolution of infection.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	The study is not described as blinded. However this is unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	Unclear	The study is not described as blinded
Incomplete outcome data addressed? All outcomes	No	Not addressed

Menichetti 1994

Methods	• Study design: RCT
Participants	• Haematological malignancies, neutropenia (<1,000/mm³), and fever in the absence of an obvious noninfectious cause. No parenteral antibiotics for > 4 days before randomisation. • Exclusion: Cr > 1.4 mg/mL • Age (mean): Teicoplanin (44), vancomycin (42) • Males: Teicoplanin (158/275), vancomycin (132/252)
Interventions	• Teicoplanin ○ 8 mg/kg loading dose, then 6 mg/kg OD. • Vancomycin ○ 15 mg/kg every 12 h. ○ Vancomycin dose adjustment guided by serum levels: NS • All patients received amikacin and ceftazidime. • Concomitant aminoglycoside use: All patients used amikacin.

Menichetti 1994 (*Continued*)

Outcomes	• Primary outcomes: Clinical efficacy and adverse events. • Definitions: ○ Nephrotoxicity: Elevation of SCr above the normal range when other causes of nephrotoxicity (hypotension, hypovolaemia) or other nephrotoxic drugs had been excluded. ○ Clinical cure: Success was resolution of fever and clinical signs of infection and eradication of the infecting micro-organism without a change in the allocated antibacterial therapy. The response had to be maintained for > 4 days after the discontinuation of therapy.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Yes
Blinding? Nephrotoxicity	No	The definition of nephrotoxicity in this study was according to Cr levels plus an investigator assessment of whether other causes could be excluded. Therefore, the unblinded nature of study might have influenced outcome assessment
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 108/635 patients

MMD-009 1992

Methods	• Study design: RCT
Participants	• Patients with vascular-access-associated bacteraemia caused by gram-positive bacteria.
Interventions	• Teicoplanin ○ 6 mg/kg every 12 h for 3 doses, then OD alternated with placebo • Vancomycin ○ 15 mg/kg every 12 ○ Vancomycin dose adjustment guided by serum levels: Yes • Concomitant aminoglycoside use: Yes
Outcomes	• Primary outcomes: Data unavailable Definitions: • Nephrotoxicity: Rise ≥ 0.5 mg/dL if baseline SCr < 3 mg/dL, or ≥ 1 mg/dL if baseline SCr ≥ 3 mg/dL. • Clinical cure: NS

MMD-009 1992 (*Continued*)

Notes	• Authors: Kulmala HK, Heilman CJ, Kuzma RJ, et al. • Data on file, Marion Merrell Dow.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Study blinded
Blinding? Clinical cure	Yes	Study blinded
Incomplete outcome data addressed? All outcomes	No	Not ITT

MMD-014 1992

Methods	• Study design: RCT
Participants	• Non-vascular access bacteraemia
Interventions	• Teicoplanin i) 6 mg/kg every 12 h for 3 doses then OD ii) 6 mg/kg every 12 h for 9 doses then 6-10 mg/kg OD iii) 10 mg/kg every 12 h due to low teicoplanin serum levels • Vancomycin ○ 15 mg/kg every 12 h ○ Vancomycin dose adjustment guided by serum levels: NS • Concomitant aminoglycoside use: NS
Outcomes	• Primary outcomes: Data unavailable Definitions: • Nephrotoxicity: Rise ≥ 0.5 mg/dL if baseline SCr < 3 mg/dL, or a rise ≥ 1 mg/dL if baseline SCr ≥ 3 mg/dL. • Clinical cure: NS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Blinding? Nephrotoxicity	Yes	Blinded
Blinding? Clinical cure	Yes	Blinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Only 52/106 patients randomised were analysed.

MMD-019 1992

Methods	• Study design: RCT
Participants	• Bacteraemia and endocarditis
Interventions	• Teicoplanin i) 30 mg/kg every 12 h for 3 doses then OD for *S. aureus* endocarditis ii) 6 mg/kg OD for *Streptococcus* sp endocarditis • Vancomycin • 15 mg/kg every 12 h ○ Vancomycin dose adjustment guided by serum levels: NS • Concomitant aminoglycoside use: NS
Outcomes	• Primary outcomes: Data unavailable Definitions: • Nephrotoxicity: Rise ≥ 0.5 mg/dL if baseline SCr < 3 mg/dL, or a rise ≥ 1mg/dL if baseline SCr ≥ 3 mg/dL • Clinical cure: NS
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Blinded
Blinding? Clinical cure	Yes	Blinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Only 143/293 patients randomised were analysed.

Neville 1995

Methods	• Study design: RCT
Participants	• Suspected or proven gram-positive infection • Exclusions: SCr ≥1.69 mg/dL • Age (median): Teicoplanin (38), vancomycin (32) • Males: Teicoplanin (15/26), vancomycin (14/28)
Interventions	• Teicoplanin ○ 400 mg OD (some patients received 200 mg/d from the 2nd day) • Vancomycin ○ 1g every 12 h ○ Vancomycin dose adjustment guided by serum levels: Yes • Some patients (numbers not stated) also received azlocillin and amphotericin. • Concomitant aminoglycoside use: Some patients (numbers not stated) received netilmicin
Outcomes	• Primary outcomes: NS • Other outcomes: Clinical and microbiological response; adverse effects Definitions: • Nephrotoxicity: 100% increase in SCr above baseline • Clinical cure: Patients who became symptom-free were graded as ○ Cured: Resolution of signs and symptoms at the end of study drug treatment, and these did not recur ○ Improvement: Lessening of signs and symptoms, but without complete resolution of infection
Notes	The unit of randomisation and analysis was an infection episode, instead of a patient

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Not blinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 2/56 patients.

Nucci 1998

Methods	• Study design: RCT
Participants	• Leukaemia or lymphoma submitted to bone marrow transplantation; ≥12 years, with neutropenia and fever, no antibiotics in the last 7 days, life expectancy > 72 h • Age (median): Teicoplanin (31), vancomycin (37) • Males: Teicoplanin (28/53), vancomycin (37/53)
Interventions	• Teicoplanin ○ 6 mg/kg every 12 h for 3 doses, then OD • Vancomycin ○ 40 mg/kg/d in 1 hour infusion ○ Vancomycin dose adjustment guided by serum levels: NS • All patients received amikacin and ceftazidime; 42% received quinolones and 49% amphotericin B. • Concomitant aminoglycoside use: All patients received amikacin
Outcomes	• Primary outcomes: Success of antibiotic therapy and toxicity Definitions: • Clinical cure (success): Normalisation of temperature, plus resolution of all clinical and microbiological signs • Nephrotoxicity: Increase in SCr > 0.5 mg/dL above baseline or a 50% decrease in CrCl.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. Exclusions or losses to follow-up in 16/106 patients

Pham Dang 2001

Methods	• Study design: RCT
Participants	• Osteo-articular or bone infection needing surgical treatment; patients had to be receiving an anti-staphylococcal drug and had confirmed MRSA infection • Age (mean): Teicoplanin (64), vancomycin (62) • Males: Teicoplanin (7/15), vancomycin (10/15)

Pham Dang 2001 (*Continued*)

Interventions	• Teicoplanin ○ 400 mg every 12 h for 3 doses, then OD, IM • Vancomycin ○ Continuous infusion to obtain serum levels between 20-30 mg/L ○ Vancomycin dose adjustment guided by serum levels: Yes • Concomitant aminoglycoside use: Teicoplanin (10/15), vancomycin (10/15)
Outcomes	• Primary outcome: Cost Definitions: • Nephrotoxicity: Elevation of SCr (no further information) or anuria • Clinical cure: Data not reported
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis. No patient was lost to follow-up or excluded from analysis

Rolston 1994

Methods	• Study design: RCT
Participants	• Cancer patients, with suspected or proven gram-positive bacteraemia; age ≥18 years • Age (median): Teicoplanin (39), vancomycin (36) • Males: Teicoplanin (13/21), vancomycin (13/25)
Interventions	• Teicoplanin ○ 6 mg/kg every 12 h for 3 doses, then OD • Vancomycin ○ 15 mg/kg, 12/12 h ○ Vancomycin dose adjustment guided by serum levels: Yes • Some patients (numbers not stated) received amikacin, aztreonam, ceftazidime and metronidazole. • Concomitant aminoglycoside use: Some patients (numbers not stated) received amikacin.

Rolston 1994 (*Continued*)

Outcomes	• Primary outcomes: NS • Evaluated outcomes: Microbiological cure and toxicity Definitions: • Clinical cure: Not evaluated • Nephrotoxicity: Increase in SCr > 0.5 mg/dL above baseline
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate
Blinding? Nephrotoxicity	Yes	Blinded
Blinding? Clinical cure	Yes	Blinded
Incomplete outcome data addressed? All outcomes	Unclear	Unclear

Rolston 1999

Methods	• Study design: RCT
Participants	• Hospitalised patients with clinically suspected or microbiologically documented bacteraemia secondary to vascular access-associated infection caused by gram-positive bacteria • Exclusion: SCr > 3 mg/dL (and other exclusion criteria) • Age (mean): Teicoplanin (50), vancomycin (50) • Males: Teicoplanin (43/60), vancomycin (42/64)
Interventions	• Teicoplanin ○ 6 mg/kg every 12 h for 3 doses, then OD • Vancomycin ○ 15 mg/kg 12/12 h ○ Vancomycin dose adjustment guided by serum levels: Yes (for patients with impaired kidney function) • Some patients (numbers not stated) received aminoglycosides, ceftazidime, ticarcillin, piperacillin, aztreonam, timentin and/or metronidazole. • Concomitant aminoglycoside use: Some patients (numbers not stated) received gentamicin, amikacin, tobramycin, netilmicin.
Outcomes	• Primary outcomes: NS • Evaluated outcomes: Clinical cure, microbiological cure and toxicity Definitions:

Rolston 1999 (*Continued*)

	• Clinical cure: Cure or improvement: signs and symptoms of infection resolved, or reduction of symptoms. • Nephrotoxicity: Elevation of SCr (no further details).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate
Blinding? Nephrotoxicity	Yes	Blinded
Blinding? Clinical cure	Yes	Blinded
Incomplete outcome data addressed? All outcomes	No	Not ITT (the authors state the study was ITT, but many randomised patients were excluded from the analyses). Losses to follow-up or exclusions were 116/240 patients

Sidi 2000

Methods	• Study design: RCT
Participants	• Paediatric patients (2-15 years) with gram-positive bacteraemia (isolated on blood culture), neutropenia (< 1000 granulocytes) and fever

Interventions	• Teicoplanin
	  ○ 10 mg/kg every 12 h for 3 doses, then OD
	• Vancomycin
	  ○ 40 mg/kg/d (divided in three doses)
	  ○ Vancomycin dose adjustment guided by serum levels: NS
	• All patients received netilmicin, ceftazidime, 15.6% also received amphotericin
	• Concomitant aminoglycoside use: All patients received netilmicin.

Outcomes	• Primary outcomes: NS • Evaluated outcomes: Clinical cure, microbiological cure, toxicity Definitions: • Clinical cure: Afebrile on 3rd to 4th day • Nephrotoxicity: Increase of SCr $\geq$ 0.5 mg/dL above baseline.
Notes	• Some patients randomised to vancomycin received teicoplanin instead, because previous red man syndrome due to vancomycin. The manuscript reports data from these patients together with the teicoplanin group. For this review we obtained data from the authors for patients who followed the original randomisation allocation. • The unit of randomisation and analysis was an infection episode, instead of a

Sidi 2000 (*Continued*)

	patient.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	Not adequate
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	Yes	Data addresses

Smith 1989

Methods	• Study design: RCT
Participants	• Hickman catheter-associated infections in patients with haematological malignancies. • Age (mean): Teicoplanin (40), vancomycin (45) • Males: Teicoplanin (15/32), vancomycin (14/28)
Interventions	• Teicoplanin ○ The first 11 episodes in 10 patients randomised to receive teicoplanin were treated with 400 mg of teicoplanin dose on day 1 and 200 mg IV once daily on following days. Subsequent episodes were treated with 800 mg of teicoplanin on day 1 and 400 mg OD on following days. • Vancomycin ○ 1g every 12 h ○ Vancomycin dose adjustment guided by serum levels: Yes • Some patients received piperacillin (82%), cephalosporins (3%) • Concomitant aminoglycoside use: 85% received gentamicin
Outcomes	• Primary outcomes: NS • Evaluated outcomes: Clinical cure, microbiological cure, toxicity Definitions: • Clinical cure: Complete response was resolution of fever and complete resolution of soft tissue infection with eradication of the infecting organism at 72 hours. • Nephrotoxicity: increase of SCr > 0.5 mg/dL above baseline associated with the study drug and not attributable to other events or systemic hypotension.
Notes	The unit of randomisation and analysis was an infection episode, instead of a patient

Risk of bias

Smith 1989 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear
Blinding? Nephrotoxicity	No	Unblinded
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	No	Not ITT. The number of losses to follow-up or exclusions were 12/72 patients

Van der Auwera 1991

Methods	• Study design: RCT
Participants	• Non-neutropenic patients hospitalised mainly for cancer with a clinically suspected or microbiologically proven infection due to a gram-positive bacterium and presenting fever. • Exclusion: Cr > 2 mg/dL (and other exclusions) • Age (median): Teicoplanin (59), vancomycin (62) • Males: Teicoplanin (16/37), vancomycin (23/37)
Interventions	• Teicoplanin ○ First 21 patients randomised to teicoplanin, received 400 mg IV OD (approximately 6 mg/kg) (infused over 30 min) for the first 3 days and then 200 mg IV OD until 3 days of apyrexia. Thereafter, patients received 400 mg three times/d IV on day 1 then 400 mg OD. • Vancomycin ○ 1g every 12 h ○ Vancomycin dose adjustment guided by serum levels: Yes • Concomitant aminoglycoside use: No
Outcomes	• Primary outcomes: NS • Evaluated outcomes: Clinical cure, microbiological cure, toxicity Definitions: • Clinical cure ○ Cure: Complete resolution of signs and symptoms of infection was recorded as a clinical cure ○ Improvement: Incomplete resolution (no persistence of fever but wound not yet healed) which did not require additional antimicrobial agents (follow-up of 2 weeks) was considered to be a clinical improvement. • Nephrotoxicity: Increase in SCr ≥ 0.5 mg/dL above baseline.
Notes	

Risk of bias

Van der Auwera 1991 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate
Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	Yes	Incomplete outcome data addressed

Van Laethem 1988

Methods	• Study design: RCT
Participants	• Adults hospitalised in surgical wards or ICU with MRSA isolated from previous normally sterile sites or from relevant sites plus clinical signs of infection • Exclusion: SCr > 2 mg/dL • Age (mean): Teicoplanin (56), vancomycin (69) • Males: Teicoplanin (9/12), vancomycin (6/9)
Interventions	• Teicoplanin ○ 400 mg OD • Vancomycin ○ 1g every 12 h ○ Vancomycin dose adjustment guided by serum levels: NS • Concomitant aminoglycoside use: NS
Outcomes	• Primary outcomes: NS • Evaluated outcomes: Clinical cure and adverse effects Definitions: • Clinical cure ○ Cure: Complete resolution of signs and symptoms of infection was recorded as a clinical cure ○ Improvement: Clinical signs/symptoms of infection subsided, but without complete resolution • Nephrotoxicity: NS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear

Van Laethem 1988 (*Continued*)

Blinding? Nephrotoxicity	Yes	Unblinded nature of study unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	No	Unblinded
Incomplete outcome data addressed? All outcomes	Yes	Incomplete outcome data addressed

Vazquez 1999a

Methods	• Study design: RCT
Participants	• Adults > 18 years, with haematological malignancies under treatment, neutropenia (neutrophils < 500/mm³) and fever resistant to the combination of piperacillin/tazobactam and amikacin. • Exclusion: Cr > 1.5mg/dL • Age (mean): Teicoplanin (51), vancomycin (47) • Males: Teicoplanin (15/38), vancomycin (21/38)
Interventions	• Teicoplanin ○ 400 mg every 12 h for 3 doses, then OD • Vancomycin ○ Doses between 200 mg and 3,900 mg/d administered in intervals between 6 and 48 hours according to a nomogram [Fernández de Gatta MM, et al. Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. *Clinical Pharmacy*. 12(7):515-20, 1993] ○ Vancomycin dose adjustment guided by serum levels: Yes • All patients received amikacin and piperacillin-tazobactam • Concomitant aminoglycoside use: All patients used amikacin
Outcomes	• Primary outcomes: Clinical efficacy, cost and toxicity Definitions: • Clinical efficacy was evaluated according to whether or not apyrexia was obtained (success/failure) after 48h (primary success or failure), after 7 days (secondary success or failure) or at the conclusion of aplasia (definitive success or failure). • Nephrotoxicity: NS
Notes	The unit of randomisation and analysis was an infection episode, instead of a patient

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Adequate

Vazquez 1999a (*Continued*)

Blinding? Nephrotoxicity	Yes	It is impossible to tell from the manuscript whether the study was blinded, but this is unlikely to affect evaluation of nephrotoxicity
Blinding? Clinical cure	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	Yes	Incomplete outcome data addressed

Cr - creatinine; CrCl - creatinine clearance; ICU - intensive care unit; IM - intramuscular; ITT - intention-to-treat; IV - intravenous; MRSA - methicillin-resistant *S. aureus;* NS - not stated; OD - once a day; SCr - serum creatinine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abad 2000	Not RCT
Adinolfi 1991	Not RCT
Altoparlak 2004	Not RCT
Arda 2005	Not RCT
Beytout 1988	Not RCT
Biavasco 1989	Not RCT
Blans 2001	Not RCT
Borja 1994	Not RCT
Bouffet 1994	Not RCT
Bouza 1997	Not RCT
Bowley 1988	Not IV vancomycin versus IM or IV teicoplanin (both administered only in peritoneum cavity)
Bricker 2005	Not RCT
Brumfitt 1986	Not RCT
Brunet 1990	Not RCT
Bucaneve 1999	Not RCT

(*Continued*)

Cercendado 1995	Not RCT
Chadwick 2000	Not RCT
Cheesbrough 1990	Not RCT
Cobo 1995	Not RCT
Cobo 1996	Not RCT
Codina 2000	Patients not infected or suspected to be infected
Daschner 1995	Not RCT
Davey 1996	Not RCT
de Lalla 1989	Not IV vancomycin versus IM or IV teicoplanin (both administered orally)
de Lalla 1992	Not IV vancomycin versus IM or IV teicoplanin (both administered orally)
Del Bene 1986	Not RCT
Dykhuizen 1995	Patients not infected or suspected to be infected
Eckert 2005	Not RCT
Egerer 1999	Not RCT
Felmingham 1987	Not RCT
Fietta 1986	Not RCT
Finch 2005	Not RCT
Garcia-Quetglas 1997	Not RCT
Guay 2004	Not RCT
Hallgren 2001	Not RCT
Haverkorn 1993	Not RCT
Jansen 1995	Not RCT
Jensen 1995	Patients not infected or suspected to be infected
Klaus 1995	Not IV vancomycin versus IM or IV teicoplanin (both administered intraperitoneally)

(*Continued*)

Knowles 1993	Not RCT
Kroh 1992	Not RCT
Lagast 1986	Not RCT
Lakovlev 1999	Not RCT
Leclercq 1988	Not RCT
Ley 1996	Not RCT
Matsumoto 1990	Not RCT
May 1998	Not RCT
Menichetti 1992	Not RCT
Moller 1997	Patients not infected or suspected to be infected
Montalar 2002	Not RCT
Muller-Wiefel 1999	Not RCT
Munoz 1997	Not RCT
Nathwani 1998	Not RCT
Peters 1983	Not RCT
Plosker 2005	Not RCT
Porta 1986	Not RCT
Portoles 2006	Not RCT
Robertson 1999	Not RCT
Rybak 1992	This study was initially included according to our predefined eligibility criteria. However, this study evaluated the risk of red man syndrome after only one dose of teicoplanin or vancomycin, therefore we excluded it
Rybak 1993	Not RCT
Sahai 1990	Patients not infected or suspected to be infected
Salaria 2001	Not RCT
Schaefer 1999	Not RCT

(*Continued*)

Schaison 1993	Co-interventions not equally applied to both vancomycin and teicoplanin groups
Schmitz 1998	Not RCT
Scotton 2002	Not RCT
Sheikh 1994	Not RCT
Shlaes 1989	Not RCT
Shlaes 1995	Not RCT
Stanley 1994	Not RCT
Togneri 2005	Not RCT
Tsakris 2002	Not RCT
Van Bambeke 2004	Not RCT
Van der Auwera 1987	Patients not infected or suspected to be infected
Van der Auwera 1996	Not RCT
Weinberg 1993	Not RCT
Wenisch 1996	Not IV vancomycin versus IM or IV teicoplanin (both administered orally)
Wilcox 1993	Not RCT
Williams 1984	Not RCT
Wood 1996	Not RCT
Wood 2000	Not RCT
Zhao 2003	Not RCT

Characteristics of ongoing studies *[ordered by study ID]*

Akan 2007

Trial name or title	Comparison of Teicoplanin and Vancomycin in terms of efficacy and side effect profile during initial antibiotic treatment of febrile neutropenic patients at high risk for gram positive infection: multi-center, prospective, randomized study
Methods	National, multi-center, prospective, two-armed, randomized, phase IV clinical study

Akan 2007 (*Continued*)

Participants	• In neutropenic and febrile patients with hematological or solid tumors: ○ Absolute neutrophil counts (ANC) of less than or equal to 500/mm3 in peripheral blood, were considered as neutropenia. ○ Patients with absolute neutrophil counts between 500 and 1000/mm3, that was expected to fall below 500/mm3 in the next 24 hours due to chemotherapy, were also considered as neutropenic • In order for a patient to be considered febrile, body temperature measured by oral or axillary method should be over 38.30C once or over 38.00C twice in at least half an hour intervals in a 12 hour period. • Patients were included in the study in their first fever attack of febrile neutropenic episodes. Therefore patients who were afebrile for at least 3 days after the empirical treatment of previous febrile attack have been included in the study.
Interventions	Teicoplanin • Dose: Loading dose in adults was 400 mg intravenous injection every 12 hours for first 3 doses, and maintenance dose was 400 mg once daily. Loading dose in children aged 2-16 years was 10 mg/kg intravenous injection every 12 doses for first 3 doses, and maintenance dose was 10 mg/kg/day. • Administration: Diluted teicoplanin was administered intravenously by rapid injection within 3-5minutes or by slow infusion within 30 minutes Vancomycin • Dose: The dose for children over 2 years of age was 10 mg/kg every 6 hours. • Administration: Vancomycin was administered as 1 gr. every 12 hours by slow infusion (at least in one hour) intravenously. Duration of treatment: 5-21 days Duration of observation: 21 days
Outcomes	Primary Outcome Measures • The primary efficacy parameter will be the response • Time Frame: 4 to 6 days after study drug discontinuation. ○ Designated as safety issue: No Secondary Outcome Measures • Safety will be assessed for all randomized patients who received at least one dose • Time Frame: 1 month after the last dose of the drug ○ Designated as safety issue: Yes
Starting date	18-Jan-2005
Contact information	Dr Hamdi Akan Ankara University, Faculty of Medicine, Ibn-i Sina Hospital, Department of Hematology
Notes	Study code: M000507_6004

DATA AND ANALYSES

Comparison 1. Teicoplanin versus vancomycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nephrotoxicity	21	2596	Risk Ratio (IV, Random, 95% CI)	0.66 [0.48, 0.90]
2 Clinical cure or improvement	20	1703	Risk Ratio (IV, Random, 95% CI)	1.03 [0.98, 1.08]
3 Microbiological cure	16	914	Risk Ratio (IV, Random, 95% CI)	0.98 [0.93, 1.03]
4 Acute kidney injury needing dialysis	6	786	Risk Ratio (IV, Random, 95% CI)	Not estimable
5 Mortality	16	1565	Risk Ratio (IV, Random, 95% CI)	1.02 [0.79, 1.30]
6 Cutaneous rash	18	1823	Risk Ratio (IV, Random, 95% CI)	0.57 [0.35, 0.92]
7 Diarrhoea	4	225	Risk Ratio (IV, Random, 95% CI)	0.43 [0.17, 1.10]
8 Red man syndrome	11	818	Risk Ratio (IV, Random, 95% CI)	0.21 [0.08, 0.59]
9 Total adverse events	11	1561	Risk Ratio (IV, Random, 95% CI)	0.73 [0.53, 1.00]
10 Clinical cure according to indication	20		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 Febrile neutropenic	6	820	Risk Ratio (IV, Random, 95% CI)	1.04 [0.96, 1.14]
10.2 Catheter-associated infection	4	358	Risk Ratio (IV, Random, 95% CI)	1.01 [0.92, 1.10]
10.3 Gram-positive bacteraemia	2	164	Risk Ratio (IV, Random, 95% CI)	1.01 [0.90, 1.14]
10.4 Endocarditis	4	109	Risk Ratio (IV, Random, 95% CI)	0.91 [0.59, 1.42]
10.5 Bone/articular infection	1	30	Risk Ratio (IV, Random, 95% CI)	1.07 [0.89, 1.28]
10.6 Other gram-positive infections	5	240	Risk Ratio (IV, Random, 95% CI)	0.99 [0.88, 1.11]
11 Nephrotoxicity according to study characteristics	21		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.1 No aminoglycoside	4	158	Risk Ratio (IV, Random, 95% CI)	0.31 [0.07, 1.50]
11.2 Concomitant aminoglycoside	9	1022	Risk Ratio (IV, Random, 95% CI)	0.51 [0.30, 0.88]
11.3 Studies with vancomycin administration guided by serum levels	5	266	Risk Ratio (IV, Random, 95% CI)	0.22 [0.10, 0.52]
11.4 Adequate allocation concealment	6	1006	Risk Ratio (IV, Random, 95% CI)	0.80 [0.31, 2.03]
11.5 Unclear or no allocation concealment	14	880	Risk Ratio (IV, Random, 95% CI)	0.51 [0.32, 0.82]
11.6 Blinded participants, investigators and outcome assessors	3	514	Risk Ratio (IV, Random, 95% CI)	0.69 [0.37, 1.29]
11.7 Unclear or no blinding of participants, investigators and outcome assessors	18	1584	Risk Ratio (IV, Random, 95% CI)	0.54 [0.35, 0.82]
11.8 Intention-to-treat analysis	6	289	Risk Ratio (IV, Random, 95% CI)	0.43 [0.15, 1.23]

11.9 Not intention-to-treat analysis	15	1809	Risk Ratio (IV, Random, 95% CI)	0.62 [0.43, 0.89]

Analysis 1.1. Comparison 1 Teicoplanin versus vancomycin, Outcome 1 Nephrotoxicity.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 1 Nephrotoxicity

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Van Laethem 1988	2/12	2/9		0.75 [0.13, 4.36]
Smith 1989	1/37	5/35		0.19 [0.02, 1.54]
Cony-Makhoul 1990	0/24	0/35		0.0 [0.0, 0.0]
Van der Auwera 1991	0/36	3/35		0.14 [0.01, 2.60]
MMD-009 1992 (1)	53/346	64/342		0.82 [0.59, 1.14]
Chow 1993	2/25	10/25		0.20 [0.05, 0.82]
Rolston 1994	1/32	0/32		3.00 [0.13, 71.00]
Menichetti 1994	4/275	2/252		1.83 [0.34, 9.92]
Charbonneau 1994	7/24	14/32		0.67 [0.32, 1.39]
Neville 1995	1/28	5/28		0.20 [0.02, 1.60]
Hedström 1995	0/53	1/27		0.17 [0.01, 4.11]
Figuera 1996	16/68	12/58		1.14 [0.59, 2.20]
Liu 1996	2/21	10/20		0.19 [0.05, 0.76]
Auperin 1997	1/32	0/33		3.09 [0.13, 73.19]
Nucci 1998	2/53	2/53		1.00 [0.15, 6.84]
Rolston 1999	2/117	3/121		0.69 [0.12, 4.05]
Vazquez 1999a	1/38	1/38		1.00 [0.06, 15.41]
Sidi 2000	0/14	5/12		0.08 [0.00, 1.29]
Fortun 2001	0/10	1/10		0.33 [0.02, 7.32]
Pham Dang 2001	0/15	3/15		0.14 [0.01, 2.55]
D'Antonio 2004	1/63	2/61		0.48 [0.05, 5.20]
Total (95% CI)	**1323**	**1273**	◆	**0.66 [0.48, 0.90]**

Total events: 96 (Teicoplanin), 145 (Vancomycin)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 21.03$, df = 19 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 2.63 (P = 0.0086)

Test for subgroup differences: Not applicable

(1) This is the aggregate nephrotoxicity data for Marion Merrel Dow studies 009, 014 and 019. This data was not available for individual studies.

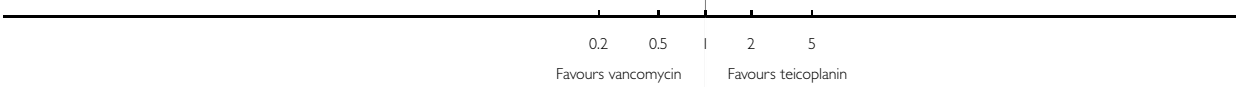
Analysis 1.2. Comparison 1 Teicoplanin versus vancomycin, Outcome 2 Clinical cure or improvement.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 2 Clinical cure or improvement

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Charbonneau 1994	16/20	20/24		3.2 %	0.96 [0.72, 1.27]
Choi 1992	17/22	14/20		1.9 %	1.10 [0.77, 1.59]
Chow 1993	23/25	21/25		6.0 %	1.10 [0.89, 1.35]
Cony-Makhoul 1990	13/24	21/35		1.2 %	0.90 [0.57, 1.43]
Fortun 2001	7/10	6/10		0.6 %	1.17 [0.61, 2.23]
Hedström 1995	27/31	13/17		2.9 %	1.14 [0.85, 1.53]
Liu 1996	17/20	15/20		2.6 %	1.13 [0.83, 1.55]
Menichetti 1994	216/275	190/252		29.2 %	1.04 [0.95, 1.14]
MMD-009 1992	48/60	51/64		8.2 %	1.00 [0.84, 1.20]
MMD-014 1992	14/27	18/25		1.3 %	0.72 [0.46, 1.12]
MMD-019 1992	58/70	60/73		11.3 %	1.01 [0.87, 1.17]
Neville 1995	13/27	13/29		0.8 %	1.07 [0.61, 1.88]
Nucci 1998	25/46	23/44		1.7 %	1.04 [0.71, 1.53]
Pham Dang 2001	15/15	14/15		7.9 %	1.07 [0.89, 1.28]
Rolston 1999	48/60	51/64		8.2 %	1.00 [0.84, 1.20]
Sidi 2000	12/14	9/12		1.7 %	1.14 [0.77, 1.69]
Smith 1989	21/32	20/28		2.2 %	0.92 [0.65, 1.29]
Van der Auwera 1991	27/36	26/35		3.5 %	1.01 [0.77, 1.32]
Van Laethem 1988	11/12	9/9		4.4 %	0.93 [0.73, 1.19]



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Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Vazquez 1999a	18/38	17/38		1.1 %	1.06 [0.65, 1.72]
Total (95% CI)	**864**	**839**		**100.0 %**	**1.03 [0.98, 1.08]**

Total events: 646 (Teicoplanin), 611 (Vancomycin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.41$, df = 19 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Teicoplanin versus vancomycin, Outcome 3 Microbiological cure.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 3 Microbiological cure

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Charbonneau 1994	17/23	21/29		2.4 %	1.02 [0.73, 1.42]
Chow 1993	12/13	9/9		4.9 %	0.94 [0.75, 1.18]
Cony-Makhoul 1990	5/14	12/17		0.4 %	0.51 [0.24, 1.09]
D'Antonio 2004	55/63	56/61		17.8 %	0.95 [0.84, 1.07]
Figuera 1996	20/25	19/20		5.3 %	0.84 [0.68, 1.05]
Fortun 2001	8/10	9/10		1.9 %	0.89 [0.61, 1.29]
Hedström 1995	15/17	7/8		2.6 %	1.01 [0.74, 1.38]
Liu 1996	17/20	15/20		2.6 %	1.13 [0.83, 1.55]
Menichetti 1994	46/50	45/52		14.2 %	1.06 [0.93, 1.22]
MMD-009 1992	49/58	55/64		11.8 %	0.98 [0.85, 1.14]
Neville 1995	10/14	7/9		1.1 %	0.92 [0.57, 1.49]
Pham Dang 2001	15/15	14/15		7.9 %	1.07 [0.89, 1.28]

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Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Rolston 1994	19/21	24/25		10.1 %	0.94 [0.80, 1.11]
Rolston 1999	49/60	55/64		10.7 %	0.95 [0.81, 1.11]
Smith 1989	17/21	14/16		3.3 %	0.93 [0.70, 1.22]
Van der Auwera 1991	28/36	23/35		2.9 %	1.18 [0.88, 1.59]
Total (95% CI)	**460**	**454**		**100.0 %**	**0.98 [0.93, 1.03]**

Total events: 382 (Teicoplanin), 385 (Vancomycin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.69$, df = 15 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 0.78 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Teicoplanin versus vancomycin, Outcome 4 Acute kidney injury needing dialysis.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 4 Acute kidney injury needing dialysis

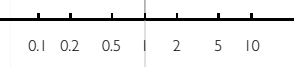
Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Cony-Makhoul 1990	0/24	0/35		0.0 [0.0, 0.0]
D'Antonio 2004	0/63	0/61		0.0 [0.0, 0.0]
Fortun 2001	0/10	0/10		0.0 [0.0, 0.0]
Menichetti 1994	0/275	0/252		0.0 [0.0, 0.0]
Pham Dang 2001	0/15	0/15		0.0 [0.0, 0.0]
Sidi 2000	0/14	0/12		0.0 [0.0, 0.0]
Total (95% CI)	**401**	**385**		**0.0 [0.0, 0.0]**

Total events: 0 (Teicoplanin), 0 (Vancomycin)

Heterogeneity: $Tau^2 =$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

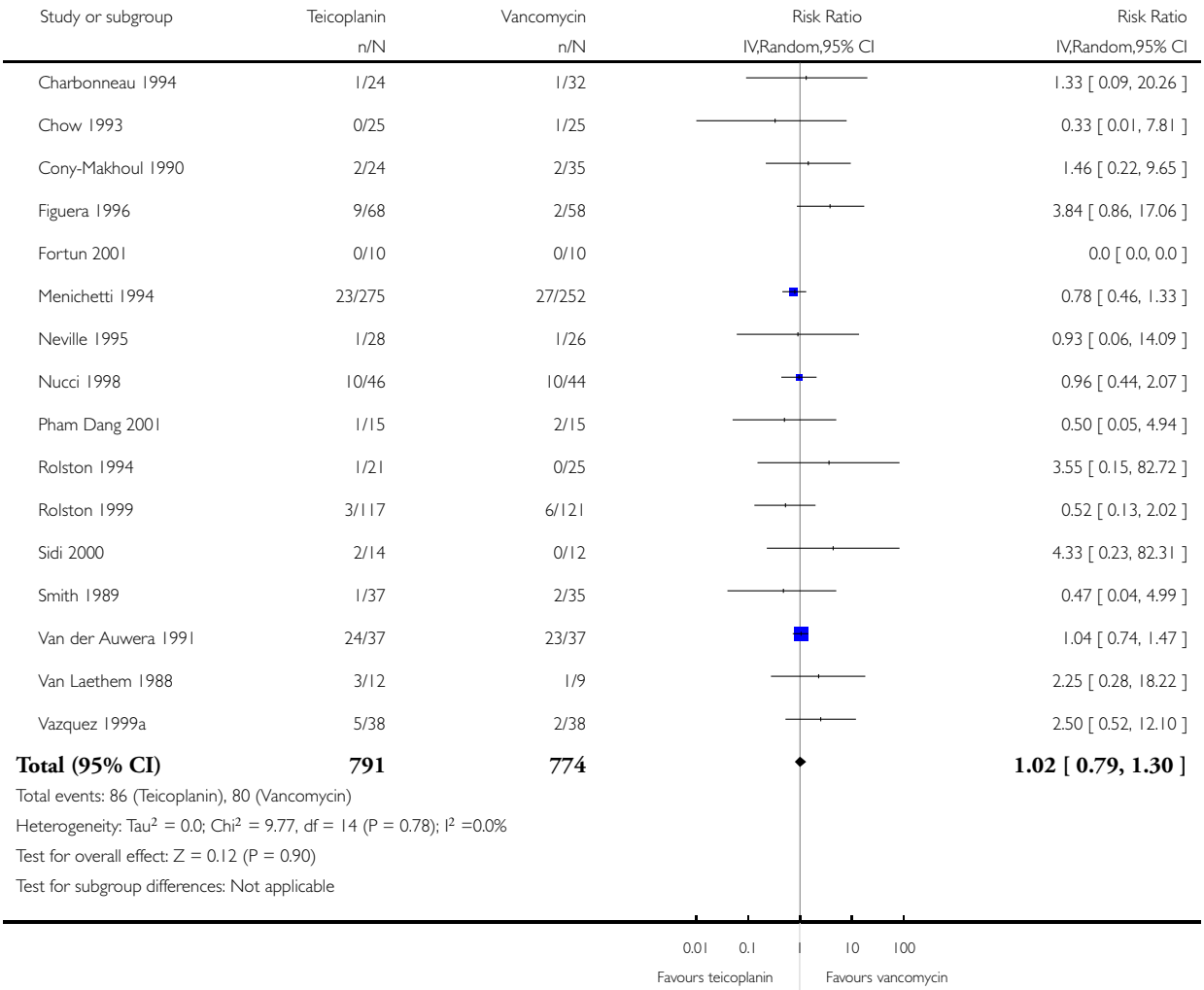


Analysis 1.5. Comparison 1 Teicoplanin versus vancomycin, Outcome 5 Mortality.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 5 Mortality



Analysis 1.6. Comparison 1 Teicoplanin versus vancomycin, Outcome 6 Cutaneous rash.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 6 Cutaneous rash

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Auperin 1997	0/32	2/33		0.21 [0.01, 4.13]
Charbonneau 1994	0/24	1/32		0.44 [0.02, 10.35]
Choi 1992	0/22	4/20		0.10 [0.01, 1.77]
Chow 1993	0/25	1/25		0.33 [0.01, 7.81]
Cony-Makhoul 1990	0/24	0/35		0.0 [0.0, 0.0]
D'Antonio 2004	5/63	5/61		0.97 [0.29, 3.18]
Figuera 1996	5/68	2/58		2.13 [0.43, 10.58]
Fortun 2001	3/10	1/10		3.00 [0.37, 24.17]
Hedström 1995	0/53	1/27		0.17 [0.01, 4.11]
Liu 1996	1/21	2/20		0.48 [0.05, 4.85]
Menichetti 1994	4/275	15/252		0.24 [0.08, 0.73]
Neville 1995	1/28	1/28		1.00 [0.07, 15.21]
Nucci 1998	2/53	3/53		0.67 [0.12, 3.83]
Rolston 1994	1/32	5/32		0.20 [0.02, 1.62]
Rolston 1999	6/117	4/121		1.55 [0.45, 5.36]
Sidi 2000	0/14	2/12		0.17 [0.01, 3.29]
Smith 1989	1/37	4/35		0.24 [0.03, 2.01]
Van der Auwera 1991	0/36	4/35		0.11 [0.01, 1.94]
Total (95% CI)	**934**	**889**		**0.57 [0.35, 0.92]**

Total events: 29 (Teicoplanin), 57 (Vancomycin)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 16.89$, df = 16 (P = 0.39); $I^2 = 5\%$

Test for overall effect: Z = 2.31 (P = 0.021)

Analysis 1.7. Comparison 1 Teicoplanin versus vancomycin, Outcome 7 Diarrhoea.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 7 Diarrhoea

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Cony-Makhoul 1990	1/24	7/35		21.5 %	0.21 [0.03, 1.59]
Rolston 1994	0/32	2/32		9.8 %	0.20 [0.01, 4.01]
Sidi 2000	0/14	3/12		10.7 %	0.12 [0.01, 2.18]
Vazquez 1999a	4/38	5/38		57.9 %	0.80 [0.23, 2.75]
Total (95% CI)	**108**	**117**		**100.0 %**	**0.43 [0.17, 1.10]**

Total events: 5 (Teicoplanin), 17 (Vancomycin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.43$, df = 3 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 1.77 (P = 0.077)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Teicoplanin versus vancomycin, Outcome 8 Red man syndrome.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 8 Red man syndrome

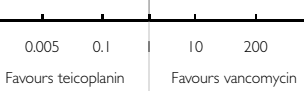
Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Chow 1993	0/25	1/25		0.33 [0.01, 7.81]
Cony-Makhoul 1990	0/24	0/35		0.0 [0.0, 0.0]
Liu 1996	0/21	1/20		0.32 [0.01, 7.38]
Neville 1995	0/28	2/28		0.20 [0.01, 3.99]
Nucci 1998	0/53	1/53		0.33 [0.01, 8.00]
Pham Dang 2001	0/15	3/15		0.14 [0.01, 2.55]
Rolston 1994	0/32	1/32		0.33 [0.01, 7.89]
Rolston 1999	0/117	1/121		0.34 [0.01, 8.38]
Sidi 2000	0/14	0/12		0.0 [0.0, 0.0]
Smith 1989	0/37	4/35		0.11 [0.01, 1.89]
Vazquez 1999a	0/38	4/38		0.11 [0.01, 1.99]
Total (95% CI)	**404**	**414**		**0.21 [0.08, 0.59]**

Total events: 0 (Teicoplanin), 18 (Vancomycin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.88$, df = 8 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 2.98 (P = 0.0029)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 Teicoplanin versus vancomycin, Outcome 9 Total adverse events.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 9 Total adverse events

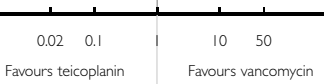
Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Charbonneau 1994	7/24	17/32		10.4 %	0.55 [0.27, 1.11]
Choi 1992	3/22	5/20		4.7 %	0.55 [0.15, 2.00]
Chow 1993	2/25	11/25		4.1 %	0.18 [0.04, 0.74]
Fortun 2001	3/10	2/10		3.5 %	1.50 [0.32, 7.14]
Hedström 1995	26/53	11/27		13.2 %	1.20 [0.71, 2.05]
Liu 1996	4/21	12/20		7.3 %	0.32 [0.12, 0.82]
Menichetti 1994	9/275	20/252		9.4 %	0.41 [0.19, 0.89]
MMD-009 1992	32/118	37/122		15.8 %	0.89 [0.60, 1.33]
MMD-014 1992	13/50	17/56		11.8 %	0.86 [0.46, 1.58]
MMD-019 1992	48/147	39/146		16.6 %	1.22 [0.86, 1.74]
Nucci 1998	2/53	4/53		3.1 %	0.50 [0.10, 2.61]
Total (95% CI)	**798**	**763**		**100.0 %**	**0.73 [0.53, 1.00]**

Total events: 149 (Teicoplanin), 175 (Vancomycin)

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 20.74$, df = 10 (P = 0.02); $I^2 = 52\%$

Test for overall effect: Z = 1.93 (P = 0.053)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 Teicoplanin versus vancomycin, Outcome 10 Clinical cure according to indication.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 10 Clinical cure according to indication

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Febrile neutropenic					
Choi 1992	17/22	14/20		5.2 %	1.10 [0.77, 1.59]
Cony-Makhoul 1990	13/24	21/35		3.3 %	0.90 [0.57, 1.43]
Menichetti 1994	216/275	190/252		79.3 %	1.04 [0.95, 1.14]
Nucci 1998	25/46	23/44		4.7 %	1.04 [0.71, 1.53]
Sidi 2000	12/14	9/12		4.6 %	1.14 [0.77, 1.69]
Vazquez 1999a	18/38	17/38		2.9 %	1.06 [0.65, 1.72]
Subtotal (95% CI)	**419**	**401**		**100.0 %**	**1.04 [0.96, 1.14]**
Total events: 301 (Teicoplanin), 274 (Vancomycin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$, df = 5 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 Catheter-associated infection					
Chow 1993	23/25	21/25		18.5 %	1.10 [0.89, 1.35]
MMD-009 1992	53/60	57/64		49.7 %	0.99 [0.87, 1.12]
Rolston 1999	48/60	51/64		25.1 %	1.00 [0.84, 1.20]
Smith 1989	21/32	20/28		6.7 %	0.92 [0.65, 1.29]
Subtotal (95% CI)	**177**	**181**		**100.0 %**	**1.01 [0.92, 1.10]**
Total events: 145 (Teicoplanin), 149 (Vancomycin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 3 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.18 (P = 0.86)					
3 Gram-positive bacteraemia					
Liu 1996	17/20	15/20		13.9 %	1.13 [0.83, 1.55]
MMD-009 1992	53/60	57/64		86.1 %	0.99 [0.87, 1.12]
Subtotal (95% CI)	**80**	**84**		**100.0 %**	**1.01 [0.90, 1.14]**
Total events: 70 (Teicoplanin), 72 (Vancomycin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.17 (P = 0.86)					
4 Endocarditis					
Fortun 2001	7/10	6/10		23.5 %	1.17 [0.61, 2.23]
Hedström 1995	9/10	3/4		25.2 %	1.20 [0.66, 2.19]

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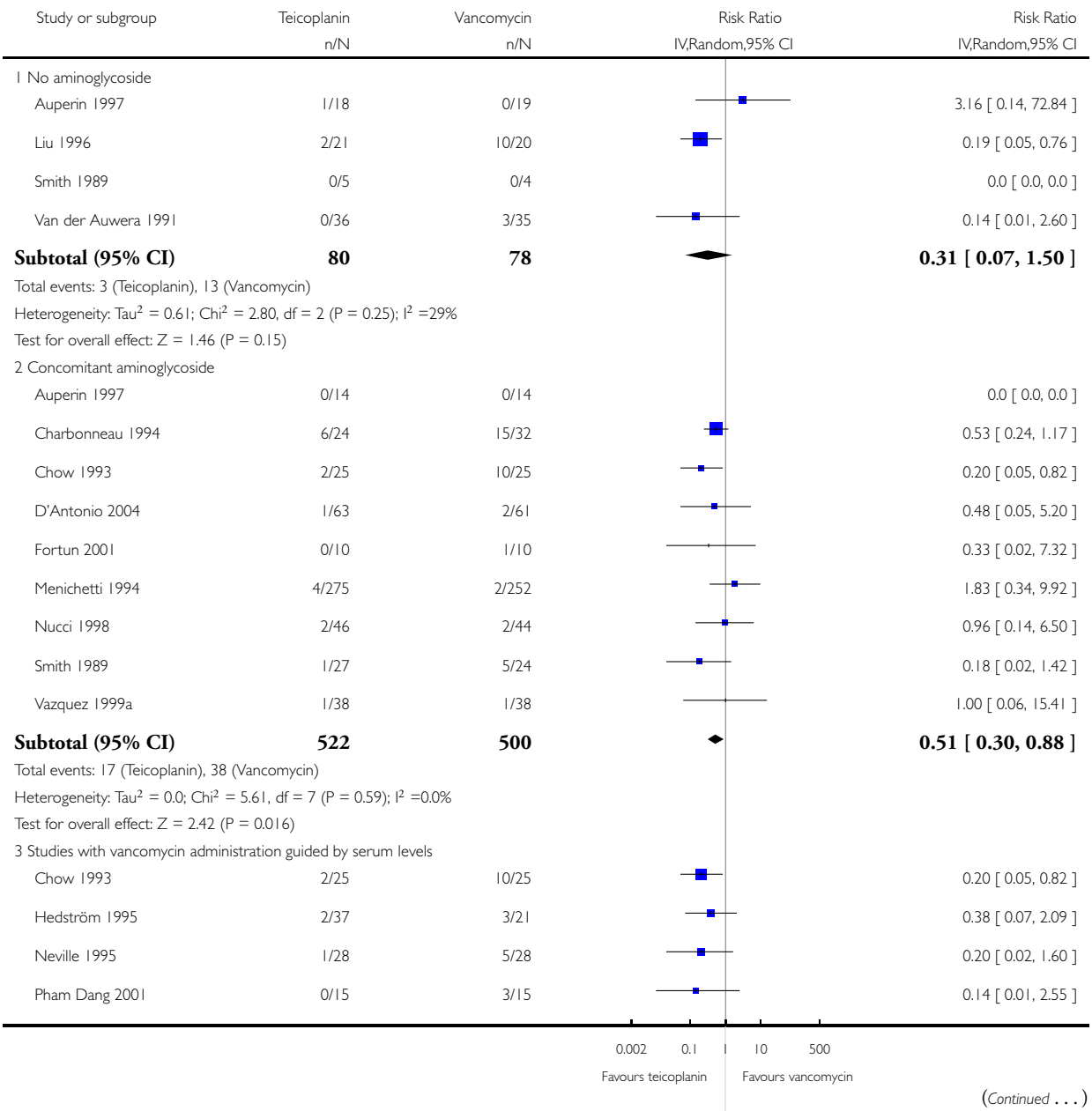
Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
MMD-014 1992	3/14	5/6		12.7 %	0.26 [0.09, 0.75]
MMD-019 1992	16/21	26/34		38.6 %	1.00 [0.74, 1.35]
Subtotal (95% CI)	**55**	**54**		**100.0 %**	**0.91 [0.59, 1.42]**
Total events: 35 (Teicoplanin), 40 (Vancomycin)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 6.79$, df = 3 (P = 0.08); $I^2 = 56\%$					
Test for overall effect: Z = 0.40 (P = 0.69)					
5 Bone/articular infection					
Pham Dang 2001	15/15	14/15		100.0 %	1.07 [0.89, 1.28]
Subtotal (95% CI)	**15**	**15**		**100.0 %**	**1.07 [0.89, 1.28]**
Total events: 15 (Teicoplanin), 14 (Vancomycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
6 Other gram-positive infections					
Charbonneau 1994	16/20	20/24		18.0 %	0.96 [0.72, 1.27]
Hedström 1995	28/31	15/17		33.2 %	1.02 [0.83, 1.26]
Neville 1995	13/27	13/29		4.6 %	1.07 [0.61, 1.88]
Van der Auwera 1991	27/36	26/35		19.6 %	1.01 [0.77, 1.32]
Van Laethem 1988	11/12	9/9		24.6 %	0.93 [0.73, 1.19]
Subtotal (95% CI)	**126**	**114**		**100.0 %**	**0.99 [0.88, 1.11]**
Total events: 95 (Teicoplanin), 83 (Vancomycin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.49$, df = 4 (P = 0.97); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.20 (P = 0.85)					

Analysis 1.11. Comparison 1 Teicoplanin versus vancomycin, Outcome 11 Nephrotoxicity according to study characteristics.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 11 Nephrotoxicity according to study characteristics



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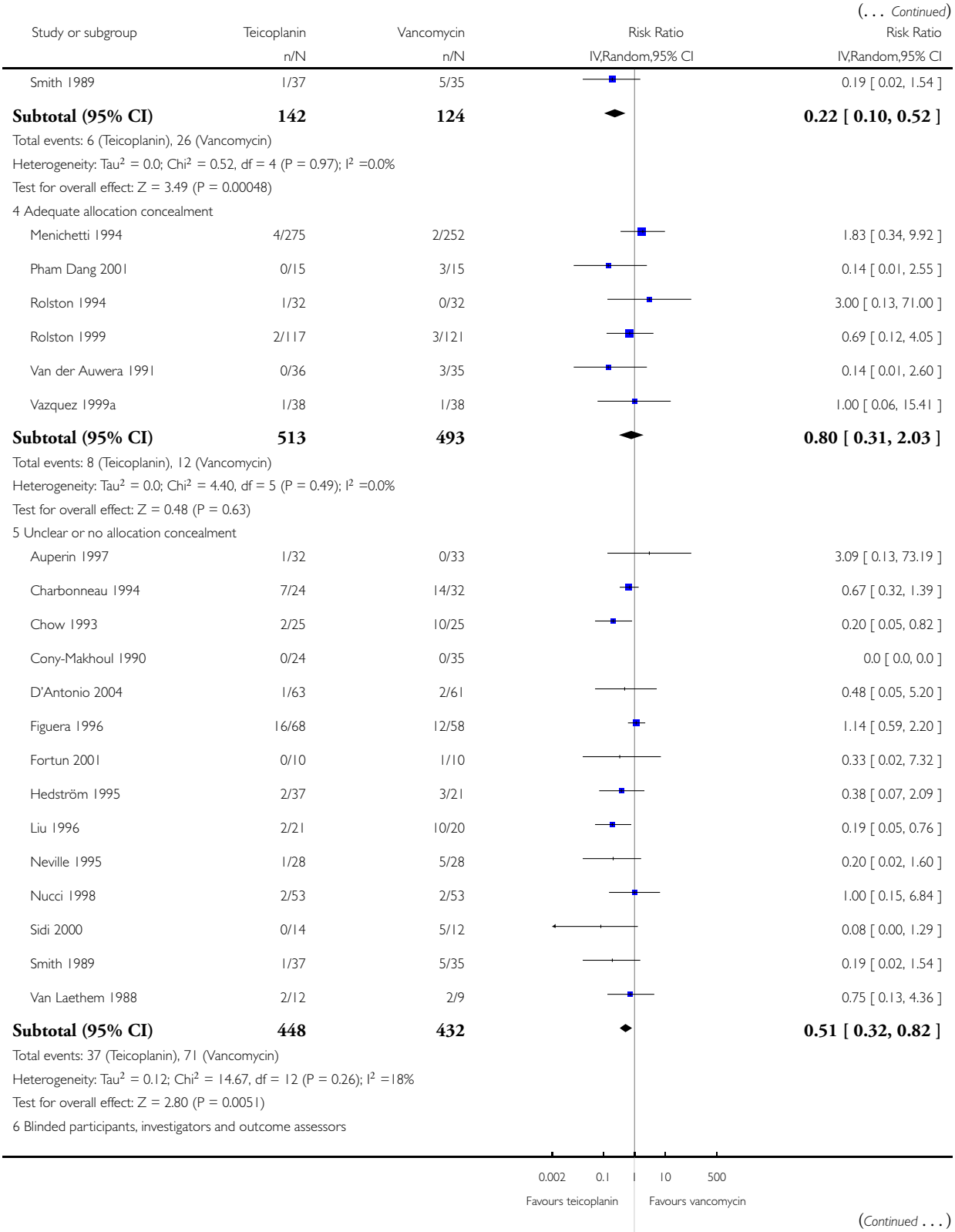

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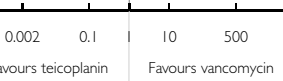
Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
MMD-009 1992	12/111	17/101		0.64 [0.32, 1.28]
Rolston 1994	1/32	0/32		3.00 [0.13, 71.00]
Rolston 1999	2/117	3/121		0.69 [0.12, 4.05]
Subtotal (95% CI)	**260**	**254**		**0.69 [0.37, 1.29]**
Total events: 15 (Teicoplanin), 20 (Vancomycin)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.87$, df = 2 (P = 0.65); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.16 (P = 0.24)				
7 Unclear or no blinding of participants, investigators and outcome assessors				
Auperin 1997	1/32	0/33		3.09 [0.13, 73.19]
Charbonneau 1994	7/24	14/32		0.67 [0.32, 1.39]
Chow 1993	2/25	10/25		0.20 [0.05, 0.82]
Cony-Makhoul 1990	0/24	0/35		0.0 [0.0, 0.0]
D'Antonio 2004	1/63	2/61		0.48 [0.05, 5.20]
Figuera 1996	16/68	12/58		1.14 [0.59, 2.20]
Fortun 2001	0/10	1/10		0.33 [0.02, 7.32]
Hedström 1995	2/37	3/21		0.38 [0.07, 2.09]
Liu 1996	2/21	10/20		0.19 [0.05, 0.76]
Menichetti 1994	4/275	2/252		1.83 [0.34, 9.92]
Neville 1995	1/28	5/28		0.20 [0.02, 1.60]
Nucci 1998	2/53	2/53		1.00 [0.15, 6.84]
Pham Dang 2001	0/15	3/15		0.14 [0.01, 2.55]
Sidi 2000	0/14	5/12		0.08 [0.00, 1.29]
Smith 1989	1/37	5/35		0.19 [0.02, 1.54]
Van der Auwera 1991	0/36	3/35		0.14 [0.01, 2.60]
Van Laethem 1988	2/12	2/9		0.75 [0.13, 4.36]
Vazquez 1999a	1/38	1/38		1.00 [0.06, 15.41]
Subtotal (95% CI)	**812**	**772**		**0.54 [0.35, 0.82]**
Total events: 42 (Teicoplanin), 80 (Vancomycin)				
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 18.41$, df = 16 (P = 0.30); $I^2 = 13\%$				
Test for overall effect: Z = 2.85 (P = 0.0043)				
8 Intention-to-treat analysis				
Auperin 1997	1/32	0/33		3.09 [0.13, 73.19]
Pham Dang 2001	0/15	3/15		0.14 [0.01, 2.55]
Sidi 2000	0/14	5/12		0.08 [0.00, 1.29]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Teicoplanin n/N	Vancomycin n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Van der Auwera 1991	0/36	3/35		0.14 [0.01, 2.60]
Van Laethem 1988	2/12	2/9		0.75 [0.13, 4.36]
Vazquez 1999a	1/38	1/38		1.00 [0.06, 15.41]
Subtotal (95% CI)	**147**	**142**		**0.43 [0.15, 1.23]**
Total events: 4 (Teicoplanin), 14 (Vancomycin)				
Heterogeneity: Tau² = 0.0; Chi² = 4.79, df = 5 (P = 0.44); I² =0.0%				
Test for overall effect: Z = 1.57 (P = 0.12)				
9 Not intention-to-treat analysis				
Charbonneau 1994	7/24	14/32		0.67 [0.32, 1.39]
Chow 1993	2/25	10/25		0.20 [0.05, 0.82]
Cony-Makhoul 1990	0/24	0/35		0.0 [0.0, 0.0]
D'Antonio 2004	1/63	2/61		0.48 [0.05, 5.20]
Figuera 1996	16/68	12/58		1.14 [0.59, 2.20]
Fortun 2001	0/10	1/10		0.33 [0.02, 7.32]
Hedström 1995	2/37	3/21		0.38 [0.07, 2.09]
Liu 1996	2/21	10/20		0.19 [0.05, 0.76]
Menichetti 1994	4/275	2/252		1.83 [0.34, 9.92]
MMD-009 1992	12/111	17/101		0.64 [0.32, 1.28]
Neville 1995	1/28	5/28		0.20 [0.02, 1.60]
Nucci 1998	2/53	2/53		1.00 [0.15, 6.84]
Rolston 1994	1/32	0/32		3.00 [0.13, 71.00]
Rolston 1999	2/117	3/121		0.69 [0.12, 4.05]
Smith 1989	1/37	5/35		0.19 [0.02, 1.54]
Subtotal (95% CI)	**925**	**884**		**0.62 [0.43, 0.89]**
Total events: 53 (Teicoplanin), 86 (Vancomycin)				
Heterogeneity: Tau² = 0.04; Chi² = 14.15, df = 13 (P = 0.36); I² =8%				
Test for overall effect: Z = 2.61 (P = 0.0090)				

ADDITIONAL TABLES

Table 1. Characteristics of studies comparing vancomycin to teicoplanin for proven or suspected infection

Study	N	Age group	Patients	Exclusion if previous kidney injury	Definition of previous kidney injury	Teicoplanin dose	Vancomycin dose	Definition of nephrotoxicity
Auperin 1997	67	Children	Solid neoplasm + febrile neutropenic	Yes	Severe CKD (no further details)	10 mg/kg BID for 3 doses, then OD	10 mg/kg, every 6 h	Moderate renal insufficiency (no further details)
Charbonneau 1994	56	Adults	Severe gram-positive infection	Yes	Cr > 2.3 mg/dL	6 mg/kg BID for 3 doses, then OD	24mg/kg/day, divided in 2 or 3 doses	Increase in SCr > 0.5 mg/dL (if baseline value <3 mg/dL)
Choi 1992	44	>15 y	Haematological malignancies + febrile neutropenic	Yes	Cr > 1.5 mg/dL or CrCl < 60 mL/min	400 mg BID for 2 two doses, then OD	500 mg every 8hs	NS
Chow 1993	53	Adults	Hickman catheter + febrile neutropenic	Yes	Cr > 2.5 mg/dL	6 mg/kg BID for 3 doses, then OD	14 mg/kg, BID	Cr > 1.24 mg/dL
Cony-Makhoul 1990	65	Adults	Haematological malignancies + febrile neutropenic	No	NA	6 mg/kg BID for 3 doses, then OD	15mg/kg/d, BID	NS
Pham Dang 2001	30	Adults	Articular or bone infection	No	NA	400 mg BID for 3 doses, then OD, IM	Continuous infusion to obtain serum levels between 20-30 mg/L	Increase in SCr (no further details) or anuria
D'Antonio 2004	154	Adults	Haematological malignancies + febrile neutropenic	Yes	Cr > 3 mg/dL	6 mg/kg BID for 2 days, then OD	15 mg/kg/d, BID	Reversible renal toxicity (no further details)
Figuera 1996	149	Adults	Haematological malignancies or BMT + febrile neu-	Yes	Cr > 2.5 mg/dL	400 mg BID for 3 doses, then OD	1 g, BID	SCr > 1.5 mg/dL

Table 1. Characteristics of studies comparing vancomycin to teicoplanin for proven or suspected infection (*Continued*)

			tropenic					
Fortun 2001	23	Adults	MRSA right-side endocarditis	Yes	Cr >2.5 mg/dL	24mg/kg OD in the 1st day, then 12mg/kg OD	500 mg, every 6 h	Moderate increase in SCr
Hedström 1995	80	Adults	Suspected or proven Gram-positive infection	Yes	CrCl < 40 mL/min	400mg BID for 3 doses, then OD	1 g, BID	Increase in SCr (no further details)
MMD-009 1992	242	Adults	Catheter-associated bloodstream infection	Unknown	NA	Teicoplanin: 6mg/kg BID for 3 doses, then OD	15 mg/kg, BID	Rise of 0.5 mg/dL or more if baseline SCr < 3 mg/dL, or a rise of 1 mg/dL or more if baseline SCr ≥ 3 mg/dL
MMD-014 1992	106	Adults	Vascular-access-associated bacteraemia	Unknown	NA	Several schemes: a)6 mg/kg BID for 3 doses then OD b) 6 mg/kg BID for 9 doses then 6-10 mg/kg OD c) 10mg/kg BID	15 mg/kg, BID	Rise of 0.5 mg/dL or more if baseline SCr < 3 mg/dL, or a rise of 1 mg/dL or more if baseline SCr ≥ 3 mg/dL
MMD-019 1992	132	Adults	Bacteraemia and endocarditis	Unknown	NA	Two schemes: a) 30 mg/kg every 12 h for 3 doses then OD for *S. aureus* endocarditis; b) 6 mg/kg OD for *Streptococcus* sp endocarditis	15 mg/kg, BID	Rise of 0.5 mg/dL or more if baseline SCr < 3 mg/dL, or a rise of 1 mg/dL or more if baseline SCr ≥ 3 mg/dL
Liu 1996	45	Adults	MRSA bacteraemia	Yes	Cr > 2.5 mg/dL	400 mg BID for 3 doses, then OD	500 mg every 6 h	Increase in SCr > 50%

Table 1. Characteristics of studies comparing vancomycin to teicoplanin for proven or suspected infection (*Continued*)

Menichetti 1994	635	Adults	Haematological malignancies + febrile neutropenic	Yes	Cr > 1.4 mg/dL	8 mg/kg loading dose, then 6 mg/kg OD	15 mg/kg BID	Rise of SCr above normal range
Neville 1995	56	Adults	Suspected or proven gram-positive infection	Yes	Cr >1.7 mg/dL	400 mg OD (some patients 200 mg/d after 2nd day)	1g, 12/12 h	Increase in SCr > 100%
Nucci 1998	106	Adults	BMT + febrile neutropenic	No	NA	6 mg/kg BID for 3 doses, then OD	40 mg/kg/d in 1 h infusion	Increase in SCr > 0.5 mg/dL or decrease of CrCl ≥ 50%
Rolston 1994	64	Adults	Solid neoplasm with suspected or proven gram-positive bacteraemia	Yes	Cr > 3 mg/dL	6 mg/kg BID for 3 doses, then OD	15 mg/kg, BID	Increase in SCr > 0.5 mg/dL
Rolston 1999	240	Adults	Catheter-associated infection due to suspected or proven gram-positive	Yes	Cr > 3 mg/dL	6 mg/kg BID for 3 doses, then OD	15 mg/kg, BID	Increase in SCr (no further details)
Sidi 2000	20	Children	Gram-positive bacteraemia + febrile neutropenic	No	NA	10mg/kg BID for 3 doses, then OD	40 mg/kg/d, divided in 3 doses	Increase in SCr > 0.5 mg/dL
Smith 1989	72	Adults	Hickman catheter associated infection + haematological malignancy	No	NA	First 11 episodes, 400 mg on day 1, then 200 mg OD; thereafter, 800 mg on day 1, then 400 mg OD	1g, BID	Increase in SCr > 0.5 mg/dL not attributable to other events

Table 1. Characteristics of studies comparing vancomycin to teicoplanin for proven or suspected infection (*Continued*)

Van der Auwera 1991	74	Adults	Solid neoplasm + suspected or proven gram-positive infection	Yes	Cr > 2.0 mg/dL	First 21 patients 400mg OD first 3 days, then 200mg OD; thereafter, 400 mg TID 1st day, then 400 mg OD	1g, BID	Increase in SCr > 0.5 mg/dL
Van Laethem 1988	21	Adults	MRSA infection	Yes	Cr > 2.0 mg/dL	400 mg OD	1g, BID	NS
Vazquez 1999a	76	Adults	Haematological malignancies + febrile neutropenic	Yes	Cr > 1.5 mg/dL	400 mg BID for 3 doses, then OD	According to serum levels (no further details)	NS

BID - twice a day; CKD - chronic kidney disease; Cr - creatinine; CrCl - creatinine clearance; NA: not applicable; OD - once a day; NS - not stated; SCr - serum creatinine

Table 2. Methodological characteristics of studies comparing vancomycin to teicoplanin for proven or suspected infection

Study	Allocation concealment	Blinding			ITT analysis	Exclusions from analysis	Unit of analysis
		Investigators	Participants	Outcome assessors			
Auperin 1997	Unclear	Unclear	Unclear	Unclear	Yes	3%	Patient
Charbonneau 1994	Unclear	No	No	Unclear	No	9%	Patient
Choi 1992	Unclear	No	No	No	Yes	0%	Patient
Chow 1993	Unclear	Yes	Yes	Unclear	No	6%	Patient
Cony-Makhoul 1990	Unclear	No	No	Unclear	No	9%	Infection episode
Pham Dang 2001	Adequate	No	No	Unclear	Yes	0%	Patient
D'Antonio 2004	Unclear	Inadequate	Inadequate	Unclear	No	19%	Patient

Table 2. Methodological characteristics of studies comparing vancomycin to teicoplanin for proven or suspected infection (*Continued*)

Figuera 1996	Unclear	No	No	Unclear	No	15%	Infection episode
Fortun 2001	Unclear	No	No	No	No	13%	Patient
Hedström 1995	Unclear	Inadequate	Unclear	Inadequate	No	40%	Patient
Liu 1996	Unclear	No	No	Unclear	No	11%	Patient
MMD-009 1992	Unclear	Yes	Yes	Yes	No	48%	Patient
MMD-014 1992	Unclear	Yes	Yes	Yes	No	51%	Patient
MMD-019 1992	Unclear	Yes	Yes	Yes	No	51%	Patient
Menichetti 1994	Adequate	No	No	Yes	No	17%	Patient
Neville 1995	Unclear	No	No	No	No	4%	Infection episode
Nucci 1998	Unclear	No	Unclear	Unclear	No	15%	Patient
Rolston 1994	Adequate	Yes	Yes	Yes	No	28%	Patient
Rolston 1999	Adequate	Yes	Yes	Yes	No	48%	Patient
Sidi 2000	Inadequate	No	No	Unclear	Yes	0%	Infection episode
Smith 1989	Unclear	No	No	No	No	17%	Infection episode
Van der Auwera 1991	Adequate	No	No	Unclear	Yes	4%	Patient
Van Laethem 1988	Unclear	No	No	No	Yes	0%	Patient
Vazquez 1999a	Adequate	Unclear	Unclear	Unclear	Yes	0%	Infection episode

ITT - intention-to-treat

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Teicoplanin, this term only 2. (teicoplanin*):ti,ab,kw in Clinical Trials 3. (teichomycin*):ti,ab,kw in Clinical Trials 4. (targocid*):ti,ab,kw or (targosid*):ti,ab,kw in Clinical Trials 5. (1 OR 2 OR 3 OR 4) 6. MeSH descriptor Vancomycin, this term only 7. MeSH descriptor Vancomycin Resistance, this term only 8. (vancomycin*):ti,ab,kw in Clinical Trials 9. (diatracin*):ti,ab,kw in Clinical Trials 10. (vancocin*):ti,ab,kw in Clinical Trials 11. (vancomicin*):ti,ab,kw in Clinical Trials 12. (vanco-cell* or vanco-saar*):ti,ab,kw in Clinical Trials 13. (lyphocin*):ti,ab,kw in Clinical Trials 14. (vancamycin*):ti,ab,kw in Clinical Trials 15. (vancoled*):ti,ab,kw in Clinical Trials 16. (vancococin*):ti,ab,kw in Clinical Trials 17. (6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16) 18. (5 AND 17)
MEDLINE	1. Teicoplanin/ 2. teicoplanin$.tw. 3. teichomycin.tw. 4. targo?id.tw. 5. or/1-4 6. Vancomycin/ 7. Vancomycin Resistance/ 8. vancomycin$.tw. 9. diatracin$.tw. 10. vancocin$.tw. 11. vancomicin$.tw. 12. (vanco-cell or vanco-saar).tw. 13. lyphocin$.tw. 14. vancamycin$.tw. 15. vancoled$.tw. 16. vanococin$.tw. 17. or/6-16 18. and/5,17
EMBASE	1. Teicoplanin/ 2. TEICOPLANIN DERIVATIVE/ 3. teicoplanin$.tw. 4. teichomycin$.tw. 5. targo?id.tw. 6. or/1-5

(*Continued*)

	7. Vancomycin/ 8. VANCOMYCIN DERIVATIVE/ 9. vancomycin$.tw. 10. diatracin$.tw. 11. vancocin$.tw. 12. vancomicin$.tw. 13. (vanco-cell or vanco-saar).tw. 14. lyphocin$.tw. 15. vancamycin$.tw. 16. vancoled$.tw. 17. vanococin$.tw. 18. or/7-17 19. and/6,18

Appendix 2. Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
- Unclear (B): Randomisation stated but no information on method used is available.
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

Blinding

- Blinding of investigators: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).
- Blinding of participants: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).
- Blinding of outcome assessors: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).
- Blinding of data analysis: Yes/no/not stated/ Unclear or inadequate (if the study was described as double blind, but the method of blinding was not described or is not compatible with blinding).

The above were considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment.(Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed upon study assessment.
- Not stated.

Completeness of follow-up

Proportions of participants excluded or lost to follow-up.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 6, 2010

Date	Event	Description
14 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review - AC, AG, DB, CA, ES
- Screening of titles and abstracts - DB, CA
- Assessment for inclusion - AC, AG, DB, CA, ES
- Quality assessment - AC, ES
- Data extraction - AC, ES, AG, DB, CA
- Data entry into RevMan - AC
- Data analysis - AC, AG, DB, CA, ES
- Disagreement resolution - AC, ES, AG

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects; *therapeutic use]; Drug Eruptions [etiology]; Kidney [*drug effects]; Methicillin-Resistant Staphylococcus aureus; Randomized Controlled Trials as Topic; Staphylococcal Infections [*drug therapy]; Teicoplanin [adverse effects; *therapeutic use]; Vancomycin [adverse effects; *therapeutic use]

MeSH check words

Humans