Cochrane meta-analysis: teicoplanin versus vancomycin for proven or suspected infection

Meta-análise Cochrane: teicoplanina *versus* vancomicina para infecções suspeitas ou confirmadas

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ABSTRACT

Objective: To compare efficacy and safety of vancomycin *versus* teicoplanin in patients with proven or suspected infection. **Methods:** Data Sources: Cochrane Renal Group's Specialized Register, CENTRAL, MEDLINE, EMBASE, nephrology textbooks and review articles. Inclusion criteria: Randomized controlled trials in any language comparing teicoplanin to vancomycin for patients with proven or suspected infection. Data extraction: Two authors independently evaluated methodological quality and extracted data. Study investigators were contacted for unpublished information. A random effect model was used to estimate the pooled risk ratio (RR) with 95% confidence interval (CI). **Results:** A total of 24 studies (2,610 patients) were included. The drugs had similar rates of clinical cure (RR: 1.03; 95%CI: 0.98-1.08), microbiological cure (RR: 0.98; 95%CI: 0.93-1.03) and mortality (RR: 1.02; 95%CI: 0.79-1.30). Teicoplanin had lower rates of skin rash (RR: 0.57; 95%CI: 0.35-0.92), red man syndrome (RR: 0.21; 95%CI: 0.08-0.59) and total adverse events (RR: 0.73; 95%CI: 0.53-1.00). Teicoplanin reduced the risk of nephrotoxicity (RR: 0.66; 95%CI: 0.48-0.90). This effect was consistent for patients receiving aminoglycosides (RR: 0.51; 95%CI: 0.30-0.88) or having vancomycin doses corrected by serum levels (RR: 0.22; 95%CI: 0.10-0.52). There were no cases of acute kidney injury needing dialysis. **Limitations:** Studies lacked a standardized definition for nephrotoxicity. **Conclusions:** Teicoplanin and vancomycin are equally effective; however the incidence of nephrotoxicity and other adverse events was lower with teicoplanin. It may be reasonable to consider teicoplanin for patients at higher risk for acute kidney injury.

Keywords: Anti-bacterial agents/adverse effects; Anti-bacterial agents/therapeutic use; Teicoplanin/adverse effects;Teicoplanin/therapeutic use; Vancomycin/adverse effects; Vancomycin/therapeutic use; Kidney/drug effects; Drug eruptions/etiology

RESUMO

Objetivo: Comparar eficácia e toxicidade da teicoplanina e da vancomicina em pacientes com infecção suspeita ou confirmada. **Métodos:** Fontes de dados: *Cochrane Renal Group's Specialized Register*, CENTRAL, MEDLINE, EMBASE, livros de referência e artigos de revisão. Critérios de inclusão: Ensaios clínicos controlados randomizados em qualquer idioma, comparando teicoplanina e vancomicina em pacientes com infecção suspeita ou confirmada. Extração de dados: Dois autores avaliaram a qualidade metodológica dos estudos e extraíram os dados de forma independente. Tentou-se obter dados não publicados diretamente com os autores de cada trabalho. Usou-se um modelo de efeito aleatório para estimar a razão de risco (RR) combinada, com um intervalo de confiança (IC) de 95%. **Resultados:** Foram incluídos 24 estudos (2.610 pacientes). As drogas tiveram taxas semelhantes de cura clínica (RR: 1,03; IC95%: 0,98-1,08), cura microbiológica (RR: 0,98; IC95%: 0,93-1,03) e mortalidade (RR: 1,02; IC95%: 0,79-1,30). A teicoplanina apresentou menores incidências de *rash* cutâneo (RR: 0,57; IC95%: 0,35-0,92), síndrome do homem vermelho (RR: 0,21; IC95%: 0,08-0,59) e eventos adversos em geral (RR: 0,73; IC95%: 0,53-1,00). A teicoplanina reduziu o risco de nefrotoxicidade (RR: 0,66; IC95%: 0,48-0,90). Esse efeito foi consistente em todos os subgrupos, inclusive aqueles com pacientes recebendo aminoglicosídeos concomitantes (RR: 0,51; IC95%: 0,30-0,88) ou com dosagens de vancomicina corrigidas pelo nível sérico (RR: 0,22; IC95%: 0,10-0,52). Não foi encontrado nenhum caso de injúria renal que necessitasse de diálise. **Limitações:** Os estudos não seguiram uma definição padrão de nefrotoxicidade. **Conclusões:** Teicoplanina e vancomicina têm eficácia semelhante; no entanto, o risco de nefrotoxicidade e outros eventos adversos foi menor com teicoplanina. É razoável considerar o uso de teicoplanina para pacientes em risco de desenvolver injúria renal aguda.

Study carried out at Intensive Care Unit at Hospital Israelita Albert Einstein – HIAE, São Paulo (SP), Brazil.

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Received on: March 23, 2011 – Accepted on: Jun 28, 2011

Conflict of interest: none

This article was previously published in electronic format at the Cochrane Library. Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DD, Silva E. Teicoplanin versus vancomycin for proven or suspected infection. Cochrane Database Syst Rev. 2010 Jun 16;(6):CD007022. Review.

Descritores: Agentes antibacterianos/efeitos adversos; Agentes antibacterianos/uso terapêutico; Teicoplanina/efeitos adversos; Teicoplanina/uso terapêutico; Vancomicina/efeitos adversos; Vancomicina/uso terapêutico; Rim/efeitos de droga; Erupção por droga/etiologia

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of bloodstream and other invasive infections worldwide[1,2]. Between 48 and 57% of *S. aureus* isolates from inpatients are resistant to methicillin in United States[3,4] and around 30% in many European countries[5]. 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[6]. Teicoplanin, another glycopeptide, has essentially the same efficacy of vancomycin, and with some advantages, such as once-daily bolus administration, intramuscular use, lack of requirement for routine serum monitoring and possibly less nephrotoxicity[7]. 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[8-13], although others have not found an association[14-16]. 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[8]. 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[17].

Vancomycin might lead to nephrotoxicity due to its effects on proximal tubular cells, where it accumulates inside lysosomes[18,19]. There, it inhibits the activity of many enzymes, such as sphingomyelinase, resulting in vacuolization and necrosis[20]. 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[21].

To date, just one meta-analysis of randomized controlled trials (RCTs) has been published on this issue[7]. 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.

OBJECTIVE

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 intravascular (IV) vancomycin to IV or intramusculra (IM) teicoplanin. 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[22].

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, a similar definition used in the original study was accepted.
- 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. The following sources were searched.

Electronic searches

1. The Cochrane Renal Group specialized register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. CENTRAL and the Cochrane Renal Group's specialized register contain the hand-searched results of conference proceedings from general and specialty 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[23].
2. MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs[23] together with a specific search strategy, developed with input from the Cochrane Renal Group Trial Search Coordinator.
3. EMBASE (from 1980) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs[23] together with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Coordinator.

Check 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 and ES). The search strategy described was used to obtain titles and abstracts of studies that might be relevant to the review. Two authors (DB and 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 sub-studies of included studies were listed under the primary reference, since 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 (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[24].

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[25] and standard χ^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[26]. 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 analyze potential clinical and study quality factors that might influence treatment effects, that is, in an attempt to explain heterogeneity[27,28]. 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 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.

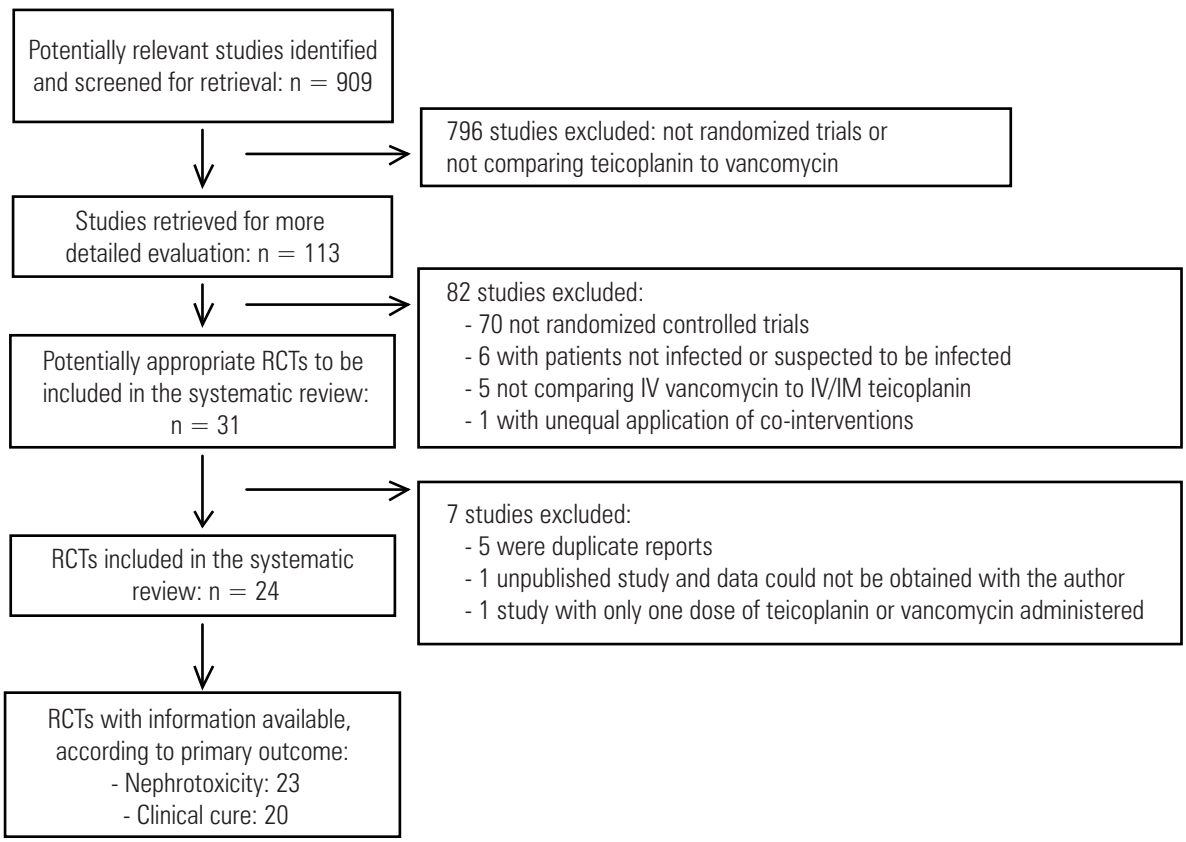
Adverse effects were tabulated and assessed with descriptive techniques. Whenever possible, the pooled RR with 95%CI was calculated for each adverse effect.

All p values reported were two-tailed and values lower than 0.05 were considered significant, except for the χ^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

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[29-31] and excluded studies[32]; one report was a subset of a larger study[33] and one



RCTs: Randomized controlled trials; IV: intravenous; IM: intramuscular

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

study used just one dose of vancomycin or teicoplanin and was excluded[34].

The 24 studies finally included enrolled 2,610 patients. Most were published between 1988 and 2000, with 3 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 pediatric 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 3 doses, then once daily (Table 1). Several schemes of vancomycin were used, varying from 24 to 40 mg/kg/d, divided into 2 to four doses or a fixed dose of 2 g/d divided into 2 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 (Appendix 3). Only 6 out of 24 studies reported allocation concealment. Blinding of participants, healthcare personnel and outcome assessors was adequately described in 5 out of 24 studies. Intention-to-treat analysis was performed in only 7 out of 24 studies. Post-randomization exclusions or losses to follow-up were greater than 10% in 13 out of 24 studies.

In six studies the unit of randomization 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

The main results are summarized in table 2 and in the appendix 4. Teicoplanin reduced the risk of nephrotoxicity (Table 3: RR: 0.66; 95%CI: 0.48-0.90; 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 (Appendix 5: RR: 1.03; 95%CI: 0.98-1.08; I^2 = 0%) as well as microbiological cure (RR: 0.98; 95%CI: 0.93-1.03; 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 neutropenia, catheter-associated infection, *Gram*-positive bacteraemia, endocarditis, bone/joint infection or other *Gram*-positive infections) did not show any evidence of superiority of either vancomycin or teicoplanin for any indication (Appendix 6). 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 6 studies (786 patients). 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 (Appendix 7). A *post-hoc* analysis of nephrotoxicity limited to studies in which all patients had vancomycin administered according to serum levels provided results similar to the overall estimate (RR: 0.22; 95%CI: 0.10-0.52; I^2 = 0%). However, this analysis was based on only 32 nephrotoxic events in 5 studies. Data on other subgroups was unavailable (critically ill patients, kidney failure patients and elderly patients).

The effect of teicoplanin on microbiological cure was similar to vancomycin. Mortality was similar with both antibiotics (RR: 1.02; 95%CI: 0.79-1.3; I^2 = 0%), but due to serious imprecision and poor quality of included studies, this is low quality evidence. Skin rash (RR: 0.57; 95%CI: 0.35-0.92; I^2 = 5%) 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 (RR: 0.73; 95%CI: 0.53-1.0; I^2 = 52%).

Table 1. Characteristics of the studies included

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 neutropenia	Yes	Severe CKD	10 mg/kg BID for 3 doses, than OD	10 mg/kg every 6hs	Moderate renal failure
Charboneau, 1994	56	Adults	Severe Gram-positive infections	Yes	Cr > 2.3 mg/dL	6 mg/kg BID for 3 doses, than OD	24 mg/kg/day in 3 or 4 doses	Increase in serum Cr >0.5 mg/dL
Choi, 1992	44	>15 years	Hematological malignancies + febrile neutropenia	Yes	Cr > 1.5 mg/dL or CrCl < 60 mL/min	400mg BID for 2 doses, than OD	500 mg every 8hs	NS
Chow, 1993	53	Adults	Hickman catheter + febrile neutropenia	Yes	Cr > 2.5 mg/dL	6 mg/kg BID for 3 doses, than OD	14 mg/kg BID	Cr > 1.24 mg/dL
Cony-Makhoul, 1990	65	Adults	Hematologic malignancies + febrile neutropenia	No	NA	6 mg/kg BID for 3 doses, than OD	15 mg/kg BID	NS
Pham Dang, 2001	30	Adults	Joint or bone infection	No	NA	400 mg BID for 3 doses, than OD, IM	Continuous infusion to obtain serum levels between 20-30 mg/L	Increase in serum Cr or anuria
D'Antonio, 2004	154	Adults	Hematologic malignancies + febrile neutropenia	Yes	Cr > 3.0 mg/dL	6 mg/kg BID for 2 days, than OD	15 mg/kg BID	reversible renal toxicity
Figuera, 1996	149	Adults	Hematologic malignancies or BMT + febrile neutropenia	Yes	Cr > 2.5 mg/dL	400mg BID for 3 doses, than OD	1g BID	Cr > 1.5 mg/dL
Fortun, 2001	23	Adults	MRSA right-side endocarditis	Yes	Cr > 2.5 mg/dL	24mg/kg OD in the 1st day, than 12 mg/kg OD	500 mg every 6hs	Moderate increase in SCr
Hedström, 1995	80	Adults	Suspected or proven Gram-positive infection	Yes	CCr < 40 mL/min	400mg BID for 3 doses, than OD	1g BID	Increase in Cr
MMD-09-1992	242	Adults	Catheter-associated bloodstream infection	Unknown	NA	6 mg/kg BID for 3 doses, than OD	15 mg/kg BID	Rise of 0.5 mg/dL or more if baseline SCr< 3mg/dL or rise of 1 mg/dL if baseline Cr > 3 mg/dL.

BMT: bone marrow transplantation; MRSA: Methicillin-resistant Staphylococcus aureus; Cr: creatinine levels; CrCl; creatinine clearance; BID: twice a day; OD: once a day; IM: intramuscular; NA: not applicable; NS: not significant.

Continue...

Table 1. Characteristics of the studies included

MMD-14-1992	106	Adults	Vascular-access-associated bacteremia	Unknown	NA	3 schemes: A) 6 mg/kg BID for 3 doses, than OD; B) 6 mg/kg BID for 9 doses than 6-10 mg/kg OD; C) 10 mg/kg BID.	15 mg/kg BID	Rise of 0.5 mg/dL or more if baseline SCr< 3mg/dL or rise of 1 mg/dL if baseline Cr > 3 mg/dL.
MMD-19-1992	132	Adults	Bacteremia and endocarditis	Unknown	NA	2 schemes: A) For Staphylococcus aureus 30 mg/kg BID for 3 doses, than OD; B) For Streptococcus sp 6mg/kg OD	15 mg/kg BID	Rise of 0.5 mg/dL or more if baseline SCr< 3mg/dL or rise of 1 mg/dL if baseline Cr > 3 mg/dL.
Liu, 1996	45	Adults	MRSA bacteremia	Yes	Cr > 2.5 mg/dL	400mg BID for 3 doses, than OD	500 mg every 6hs	Increase in Cr > 50%
Menichetti, 1994	635	Adults	Hematologic malignancies + febrile neutropenia	Yes	Cr > 1.4 mg/dL	8 mg/kg loading dose, than 6mg/kg OD	15 mg/kg BID	Rise in Cr 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 OD after 2nd day)	1g BID	Increase in Cr > 100%
Nucci, 1998	106	Adults	BMT + febrile neutropenia	No	NA	6 mg/kg BID for 3 doses, than OD	40 mg/kg/d in 1h infusion	Increase in Cr > 0.5 mg/dL or dcrease in CrCl > 50%
Rolston, 1994	64	Adults	Solid neoplasm with suspected or proven Gram-positive bacteremia	Yes	Cr > 3.0 mg/dL	6 mg/kg BID for 3 doses, than OD	15 mg/kg BID	Increase in Cr
Rolston, 1999	240	Adults	Catheter-associated infection with suspected or proven Gram-positive	Yes	Cr > 3.0 mg/dL	6 mg/kg BID for 3 doses, than OD	15 mg/kg BID	Increase in Cr
Sidi, 2000	20	Children	Gram-positive bacteremia + febrile neutropenia	No	NA	10 mg/kg BID for 3 doses, than OD	40 mg/kg/d divided in 3 doses	Increase in Cr > 0.5 mg/dL
Smith, 1989	72	Adults	Hickman catheter-associated infection + hematological malignancies	No	NA	First 11 episodes 400 mg on day 1 than 200 mg OD; thereafter 800 mg on day 1 than 400 mg OD	1g BID	Increase in Cr > 0.5 mg/dL
Van der Auwera, 1991	74	Adults	Solid neoplasm + suspected of proven Gram-positive infection	Yes	Cr > 2.0 mg/dL	First 21 patients 400 mg OD first 3 days than 200 mg OD; thereafter 400mg BID 1st day than 400 mg OD	1g BID	Increase in Cr > 0.5 mg/dL
Van Laethem, 1988	21	Adults	MRSA infection	Yes	Cr > 2.0 mg/dL	400 mg OD	1g BID	NS
Vazquez, 1999	76	Adults	Hematological malignancies+febrile neutropenia	Yes	Cr > 1.5 mg/dL	400 mg BID for 3 doses, than OD	According to serum levels	NS

BMT: bone marrow transplantation; MRSA: Methicillin-resistant Staphylococcus aureus; Cr: creatinine levels; CrCl; creatinine clearance; BID: twice a day; OD: once a day; IM: intramuscular; NA: not applicable; NS: not significant.

Table 2. Summary of findings for the main comparison

Outcomes	Illustrative comparative risk		Relative effect (95%CI)	Number of participants (studies)	Quality of evidence (GRADE)
	Presumed risk	Corresponding risk			
	Control	Teicoplanin versus vancomycin			
Nephrotoxicity	92 per 1,000	61 per 1,000 (44-83)	RR 0.66 (0.48-0.9)	2,596 (23 studies)	Moderate
Clinical cure or improvement	730 per 1,000	752 per 1,000 (715-788)	RR 1.03 (0.98-1.08)	1,703 (20 studies)	Moderate
Microbiological cure	850 per 1,000	833 per 1,000 (790-875)	RR 0.98 (0.93-1.03)	914 (16 studies)	Moderate
Renal failure needing dialysis	See comment	See comment	Not estimable	606 (3)	See comment
Mortality	103 per 1,000	105 per 1,000	RR 1.02 (0.79-1.3)	1,565 (16 studies)	Low
Skin rash	60 per 1,000	34 per 1,000 (21-55)	RR 0.57 (0.35-0.92)	1,823 (18 studies)	Moderate
Total adverse events	184 per 1,000	103 per 1,000	RR 0.56 (0.33-0.95)	880 (11 studies)	Very low

95%CI: 95% Confidence Interval; RR: Risk Ratio.
Comment: only six studies reported this outcome. No event was observed, therefore no pooled effect could be estimated.
GRADE Scoring system: 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.

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 in which vancomycin administration was guided by serum levels.

Skin 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. Some 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[33,35,36]. Teicoplanin, even at higher doses, does not penetrate the vegetations; thus, success may be achieved only for small vegetations or when aminoglycosides are associated[37]. The totality of evidence from RCTs regarding endocarditis suggests teicoplanin is similar to vancomycin; however, a small study[38] had discrepant results, which were unfavorable 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,

Table 3. Pooled data for rate of nephrotoxicity of vancomycin and teicoplanin

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	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]
Hedstr?m 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)				

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[39]. 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. 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 out of 24 studies and on clinical cure from 20 out of 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[40]. 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[41]. 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[42]. 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[7]. In that study, both drugs achieved similar probabilities of clinical cure (72.7% for teicoplanin *versus* 77.2% for vancomycin); nonetheless, 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 ten 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 relation between dose and its clinical efficacy[36,43]. 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, doubling this dose for endocarditis[36]. Initial studies with teicoplanin used a much lower dose, generally half of that currently used[31,44,45]. 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[46].

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[39]. Teicoplanin is as efficacious as vancomycin regarding clinical and microbiological cure, although it is associated with a lower risk of nephrotoxicity and skin 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. Nevertheless, antibiotics to treat MRSA and other *Gram*-positive infections are widely used in the intensive care

setting. The effects 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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Appendix 1. Electronic search strategies

Database	Electronic search strategies
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$.tw. 5. targo?id.tw. 6. or/1-5 7. Vancomycin/ 8. VANCOMYCIN DERIVATIVE/ 9. vancomycin$.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): randomization method described it would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
- Unclear (B): randomization stated but no information on method used is available.
- Inadequate (C): method of randomization 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 (randomized patients 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.

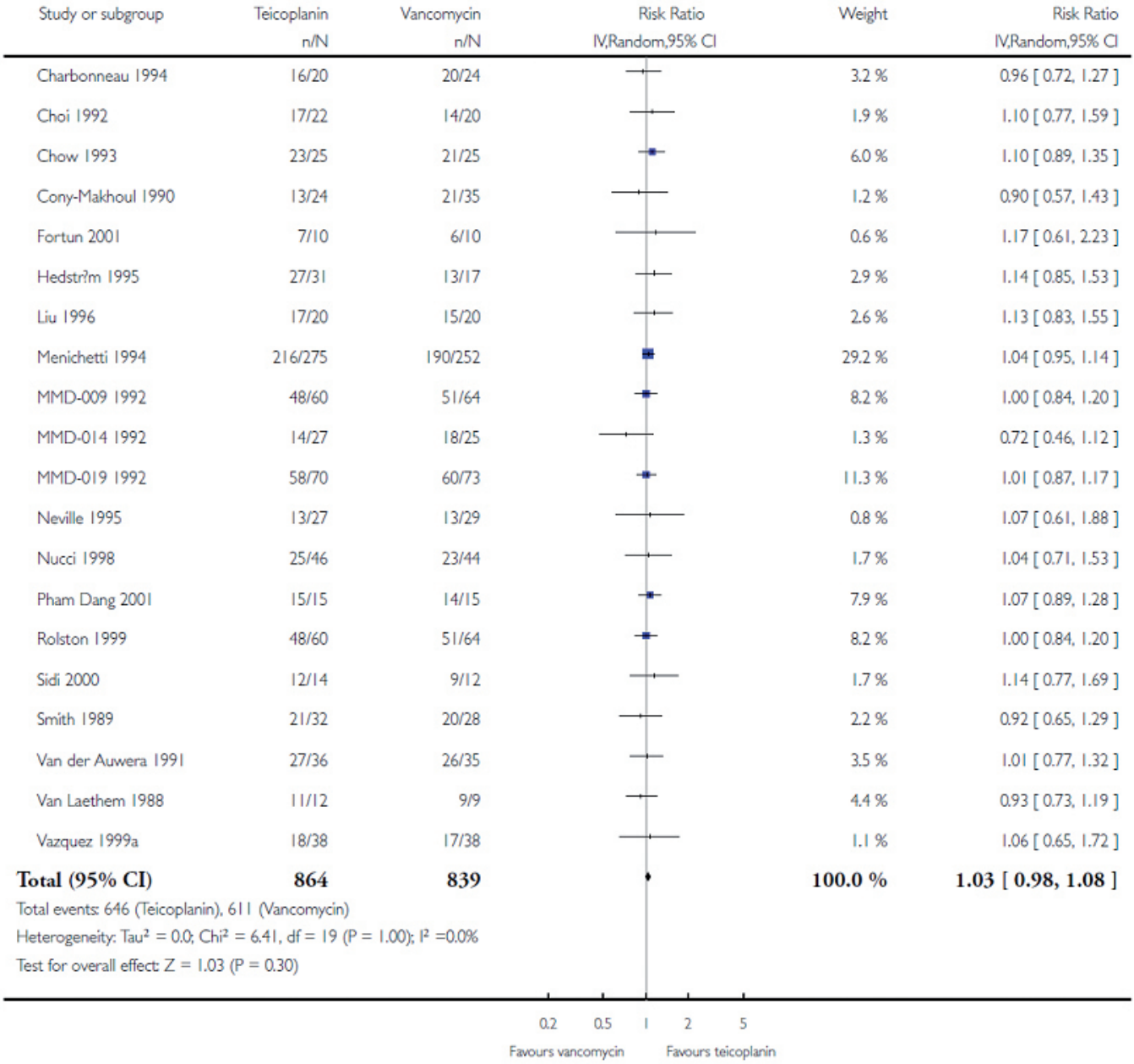
Appendix 3. Methodological characteristics of included studies

Study	Allocation concealment	Blinding			ITT analysis	Exclusion from analysis	Unit of analysis
		Investigators	Participants	Outcome assessors			
Auperin, 1997	Unclear	Unclear	Unclear	Unclear	Yes	3%	Patients
Charboneau, 1994	Unclear	No	No	Unclear	No	9%	Patients
Choi, 1992	Unclear	No	No	No	Yes	0%	Patients
Chow, 1993	Unclear	Yes	Yes	Unclear	No	6%	Patients
Cony-Makhoul, 1990	Unclear	No	No	Unclear	No	9%	Infection episode
Pham Dang, 2001	Adequate	No	No	Unclear	Yes	0%	Patients
D'Antonio, 2004	Unclear	Inadequate	Inadequate	Unclear	No	19%	Patients
Figuera, 1996	Unclear	No	No	Unclear	No	15%	Infection episode
Fortun, 2001	Unclear	No	No	No	No	13%	Patients
Hedström, 1995	Unclear	Inadequate	Unclear	Inadequate	No	40%	Patients
MMD-09-1992	Unclear	Yes	Yes	Yes	No	48%	Patients
MMD-14-1992	Unclear	Yes	Yes	Yes	No	51%	Patients
MMD-19-1992	Unclear	Yes	Yes	Yes	No	51%	Patients
Menichetti, 1994	Adequate	No	No	Yes	No	17%	Patients
Neville, 1995	Unclear	No	No	No	No	4%	Infection episode
Nucci, 1998	Unclear	No	Unclear	Unclear	No	15%	Patients
Rolston, 1994	Adequate	Yes	Yes	Yes	No	28%	Patients
Rolston, 1999	Adequate	Yes	Yes	Yes	No	48%	Patients
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%	Patients
Van Laethem, 1988	Unclear	No	No	No	Yes	0%	Patients
Vazquez, 1999	Adequate	Unclear	Unclear	Unclear	Yes	0%	Patients

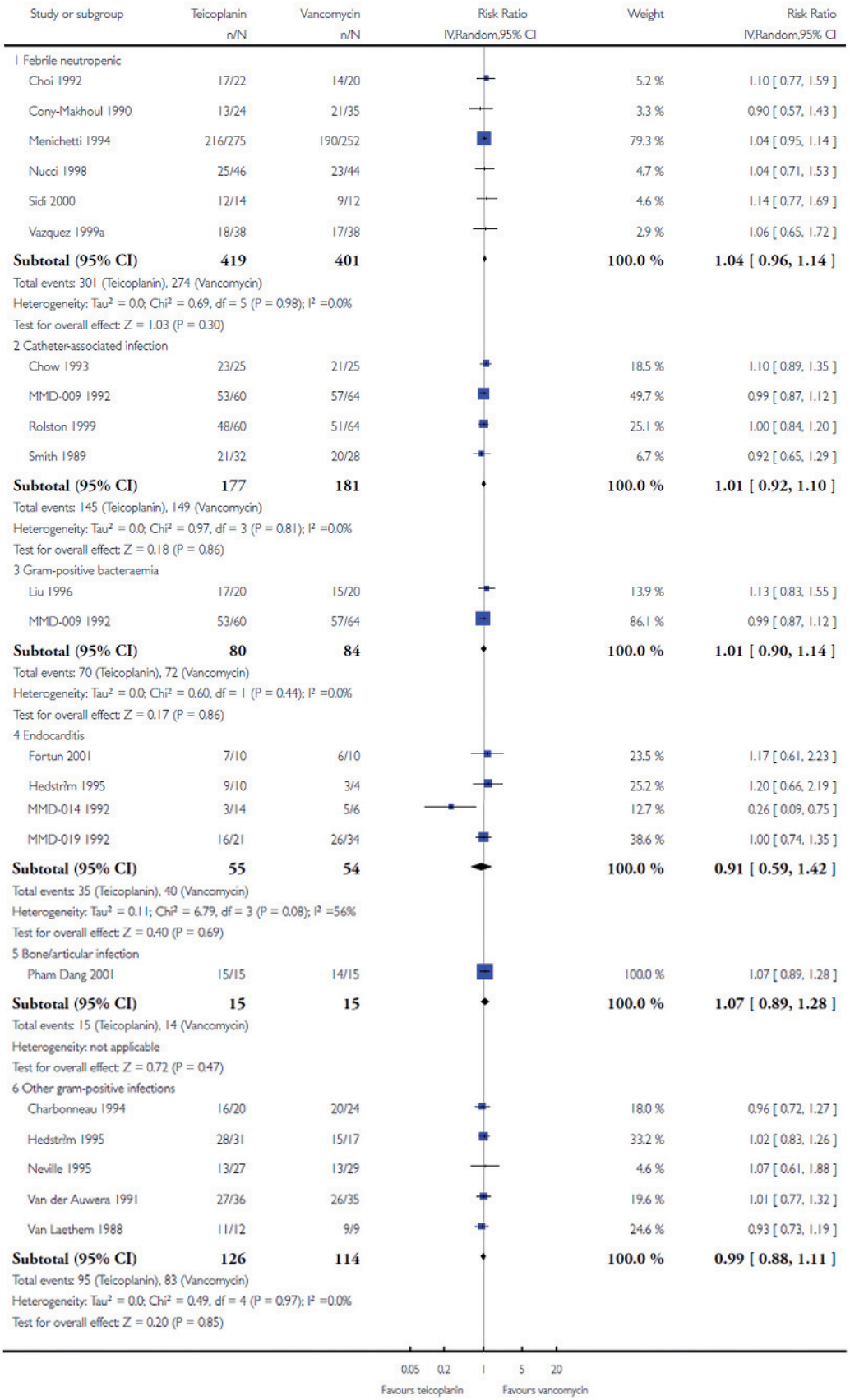
Appendix 4. Summary of findings for the main comparison

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]

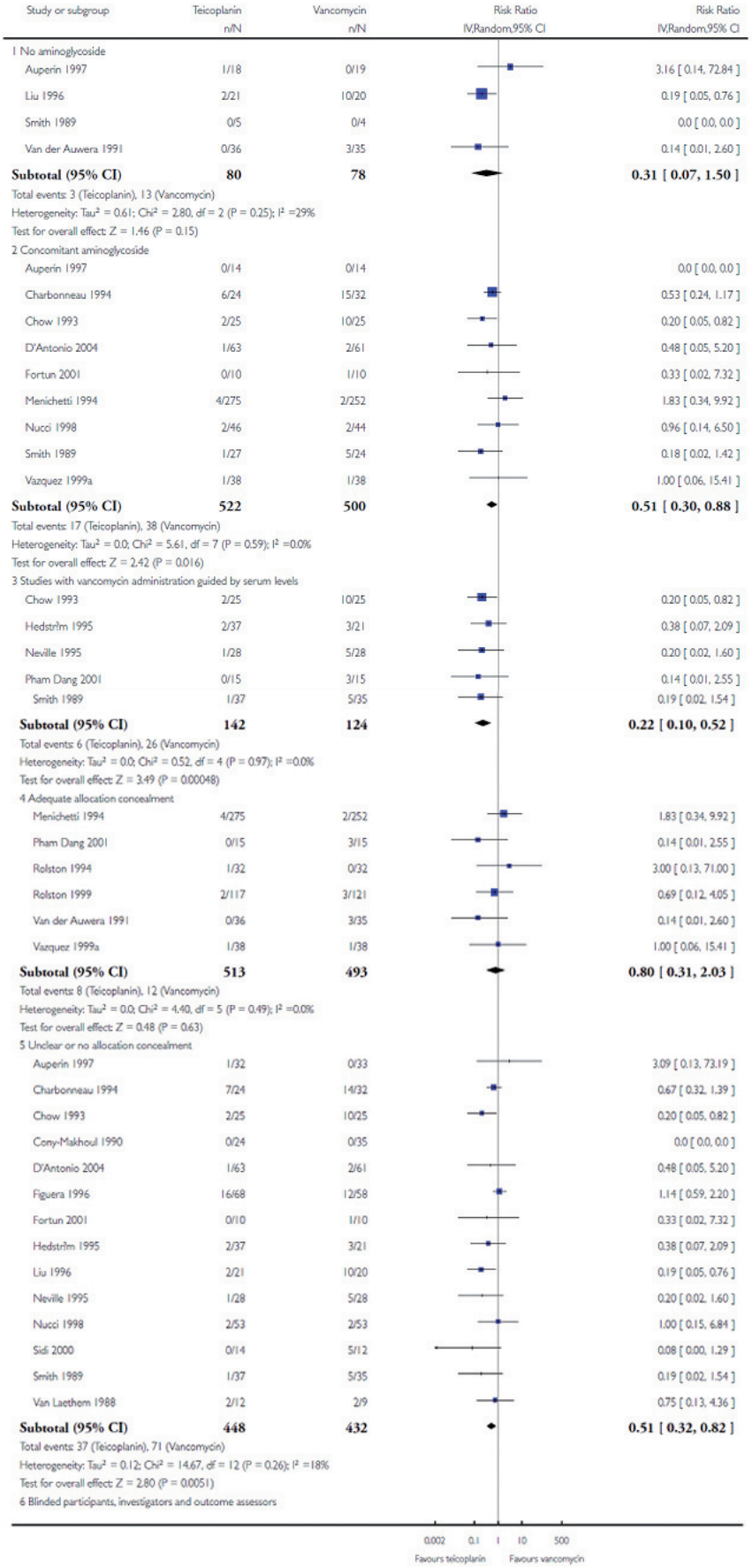
Appendix 5. Pooled analysis of rates of clinical cure or improvement for vancomycin and teicoplanin



Appendix 6. Rates of clinical cure according to indication for antibiotics



Appendix 7. Rates of nephrotoxicity according to study characteristics



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Appendix 7. Rates of nephrotoxicity according to study characteristics