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UNIVERSIDAD
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FACULTAD DE MEDICINA
UNIVERSIDAD DE CANTABRIA

GRADO EN MEDICINA.

TRABAJO FIN DE GRADO.

EFICACIA DE LA TEICOPLANINA COMPARADA CON LA DE LA VANCOMICINA. REVISIÓN SISTEMÁTICA DE ENSAYOS CLÍNICOS RANDOMIZADOS.

EFFICACY OF TEICOPLANIN COMPARED TO VANCOMYCIN. SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS.

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Santander, Junio 2017.

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ABSTRACT.

Objective: To compare the efficacy of teicoplanin with that of vancomycin in patients with proven or suspected infection.

Methods: We performed a systematic review and meta- analysis of published randomized controlled trials which compared teicoplanin with vancomycin. We searched Medline, Cochrane central, text books and previous meta- analyses. We extracted data by means of a standardized form. We used a random effect model to estimate the pooled risk ratio (RR) with 95% confidence interval (CI) as computed with MetaAnalyst free software.

Results: We initially identified 166 potentially relevant studies. After exclusion of ineligible articles, the final data set consisted of 23 reports which had included 1851 patients. The random-effects model meta-analysis gave a relative effect of teicoplanin not significantly different from that of vancomycin (RR: 1.008; 95%CI: 0.972-1.045). We found no significant heterogeneity between the trials. We performed several sensitivity analyses, all of which provided similar results.

Conclusions: Our analysis confirms the reports of those of previous meta-analyses that focused on other outcomes of the comparison of vancomycin and teicoplanin, but which reported summarized results of clinical efficacy. It can be confidently concluded that teicoplanin and vancomycin are equally effective.

Keywords: Anti-bacterial agents/therapeutic use; Teicoplanin/ therapeutic use; Vancomycin/ therapeutic use; efficacy.

RESUMEN.

Objetivo: Comparar la eficacia de la vancomicina y la teicoplanina en pacientes con sospecha de infección o infección confirmada.

Métodos: Fuente de datos: Realizamos una revisión sistemática y meta- análisis de ensayos clínicos randomizados que comparaban teicoplanina con vancomicina. Realizamos la búsqueda en Medline, Cochrane central, libros de texto y meta análisis previos. Extraíamos los datos con ayuda de un modelo estandarizado. Usamos un modelo de efectos aleatorios para estimar el riesgo relativo agregado (RR) con un intervalo de confianza (IC) del 95% realizado con el software MetaAnalist.

Resultados: Se identificaron inicialmente 166 estudios potencialmente relevantes. Tras excluir los artículos inelegibles resultaron 23 artículos que incluían 1851 pacientes. El modelo de efectos aleatorios de meta- análisis concluyó un efecto relativo de la teicoplanina no significativamente diferente a la vancomicina (RR: 1.008; 95%CI: 0.972-1.045). No se halló heterogeneidad significativa entre ensayos. Se realizaron múltiples análisis de sensibilidad, que aportaron resultados similares.

Conclusiones: Se confirman los resultados de meta análisis previos centrados en otros aspectos de la comparación entre vancomicina y teicoplanina. Se puede afirmar que la teicoplanina y vancomicina son igualmente efectivas.

Palabras clave: Agentes antimicrobianos; Teicoplanina/ Uso terapéutico; Vancomicina/ Uso terapéutico; eficacia.

INTRODUCTION.

Staphylococcus aureus (SA) is a major bacterial pathogen in humans, due to its high incidence [as shown by the fact that it was the second most common bacterial isolate overall and in community–acquired infections, and the third most common in nosocomial infections in the Spanish Study on Hospital Infections (1)] and to its high attributable mortality even under the best treatment circumstances (2). In addition, SA has proved to be a sturdy, resilient and adaptable organism, having shown particular ability to develop resistance to commonly used-first lines antibiotics. Widespread SA resistance to penicillin had appeared soon after the introduction of this antibiotic. In 1959 methicillin, a synthetic penicillin-derivative resistant to degradation by SA penicillinase, was licensed in England to treat penicillin-resistant *SA* infections. It was not very late after that, in 1961 that the first known methicillin-resistant SA (MRSA) isolates were reported in a British study, and from 1961 to 1967 there were infrequent hospital outbreaks in Western Europe and Australia (3). The first United States hospital outbreak of MRSA occurred at the Boston City Hospital in 1968. From 1968 to the mid-1990s the percentage of *SA* infections that were caused by MRSA increased steadily, and MRSA became recognized as an endemic pathogen. In 1974, 2% of hospital-acquired *SA* infections could be attributed to MRSA. The rate had increased to 22% by 1995, and by 1997 the percent of hospital *SA* infections attributable to MRSA had reached 50%. In Spain, the history did not differ much from that described above, with just a few-years delay: the proportion of MRSA isolates was 18% in 1995 and reached 50% by 2009 (4).

MRSA was clearly a nosocomial pathogen in the earlier phases of its epidemiologic development, but a transition to its implantation in the community was finally documented. The first report of community-associated MRSA (CA-MRSA) occurred in 1981, and in 1982 there was a large outbreak of CA-MRSA among intravenous drug users in Detroit, Michigan (3). Additional outbreaks of CA-MRSA were reported through the 1980s and 1990s, including outbreaks among Australian Aboriginal populations that had never been exposed to hospitals. In the mid-1990s there were scattered reports of CA-MRSA outbreaks among US children. While hospital acquired MRSA rates stabilized between 1998 and 2008, CA-MRSA rates continued to rise. Again the events in Spain paralleled or followed those described in US and Great Britain. In 2013 we performed a cross-sectional study to assess the prevalence of nasopharyngeal colonization by SA and MRSA in a population of high-school student, with null or minimal contact with the healthcare system, in our area. We found that over 40% of SA isolates were in fact MRSA, a finding that supports previous observations and the notion that MRSA has become a major community health-related issue.

The cornerstone of treatment of MRSA has been, for several decades, vancomycin. Vancomycin is a branched tricyclic glycosylated non ribosomal peptide produced by the Actinobacteria species *Amycolatopsis orientalis. V*ancomycin acts by inhibiting proper cell wall synthesis in Gram-positive bacteria. [Due to the different mechanism by which Gram-negative bacteria produce their cell walls and the various factors related to entering the outer membrane of Gram-negative organisms, vancomycin is not active against them (except some non- gonococcal species of *Neisseria*)]. The large hydrophilic molecule is able to form hydrogen bond interactions with the

terminal D- alanyl- D- alanine moieties of the NAM/ NAG-peptides. Under normal circumstances, this is a five-point interaction. This binding of vancomycin to the D-Ala-D-Ala prevents cell wall synthesis of the long polymers of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG) that form the backbone strands of the bacterial cell wall, and it prevents the backbone polymers that do manage to form from cross-linking with each other. Only a few Gram-positive bacteria are intrinsically resistant to vancomycin: *Leuconostoc* and *Pediococcus* species, but these organisms rarely cause diseases in humans. Most *Lactobacillus* species are also intrinsically resistant to vancomycin, with the exception of *L. acidophilus* and *L. delbruekii*, which are sensitive. Other Gram-positive bacteria with intrinsic resistance to vancomycin include *Erysipelothrix rhusiopathiae*, *Weissella confusa*, and *Clostridium innocuum*. However, most clinically relevant Gram-positive bacteria remain susceptible to vancomycin despite its long record of use in clinical practice since its first introduction in human therapeutics in 1954. Vancomycin remains the first-line agent in every single disease caused by MRSA in the current practice guidelines about management of patients with infections caused by MRSA of the Infectious Diseases Society of America (5). This persistency in the top ranks of treatment guidelines is unquestionably due to its resiliency, and not at all to its convenience. Rather, vancomycin is an uncomfortable, uneasy and unsafe drug, calling for a replacement ever since its unavoidable expansion which paralleled that of SARM.

The first consistent alternative to vancomycin to be introduced in clinical practice was teicoplanin. Teicoplanin (formerly known as teichomycin A), obtained from the actinomycete Actinoplanes teychomiceticus, isolated from soil in India in 1978, is actually a mixture of related glycopeptides analogues with a basic structure characterized by a linear heptapetide, the distinct carbohydrates D-mannose and D-glycosamine, and acyl residue that carries various fatty acids, which define members of the teicoplanin complex. Teicoplanin has a molecular weight estimated as 1900 Da. It inhibits cell wall synthesis by a mechanism similar to that of vancomycin, although with some differences which turn out in some small but appreciable differences also in the MICs of some bacteria for teicoplanin and for vancomycin (6). The favorable pharmacokinetic properties of teicoplanin allow administration by intravenous bolus or by the intramuscular route (7). Despite its theoretical potential and the encouraging results of early development-phase studies, teicoplanin was not licensed for its use in the USA. Consequently, it is not mentioned in the IDSA treatment guidelines. Furthermore, a large registration randomized controlled trial to demonstrate its clinical efficacy was never required…nor performed; and North American clinical investigators had neither the availability of the commercial drug to eventually perform independent trials, nor the interest in it. There is a large number of published papers regarding the efficacy and safety of teicoplanin, generated in other countries, but most of them are anecdotal reports, case series and uncontrolled trials at the best. A number of small randomized controlled trials comparing the safety and efficacy of teicoplanin and of vancomycin have been published, however, as well as a couple of medium sized, well performed double-blind RCT. Altogether, a confident conclusion regarding the relative safety and efficacy of teicoplanin and vancomycin could be expected from an aggregated analysis of these data. This hypothesis has not passed unnoticed to other groups of investigators. We have found five meta-analyses performed previously.

The first one dates from 1996 (8). By that time, less than half the RCT on the subject had been published, and they were those of lesser quality. Another meta-analysis is published in Chinese (9), while a third one is published in English, but only trials which included only Chinese patients were analyzed (10). A fourth study focused its main analysis in mortality (11). The last one was focused on nephrotoxicity and it was published in a non-indexed local Brazilian journal (12). In consideration of these limitations we believed that a new meta- analysis focusing in the clinical efficacy of teicoplanin as compared with that of vancomycin was warranted

OBJECTIVE.

This systematic review of RCTs aimed to focus on the investigation of the efficacy of teicoplanin, as compared to that of vancomycin, in patients with proven or suspected infection.

METHODS.

Criteria for considering studies for this review: Types of studies. We included only RCTs comparing intravascular (IV) vancomycin to IV or intramuscular (IM) teicoplanin.

Studies were considered for inclusion regardless of their publication status, language (except Chinese), 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.

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).

- Trials on pharmacokinetic parameters.

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:

- Clinical cure: patients who showed resolution or significant improvement of signs and symptoms by the end of study drug treatment.

Secondary outcomes:

- Microbiological outcomes: We recorded "microbiological cure" data, defined as a negative culture from a material in which it had been previously positive, but we neither analyzed them nor present them here.

- Safety data: we did not collect safety data.

Search methods for identification of studies:

With the above specifications in mind, we followed the "PICO" scheme to define our search strategy, as follows:

- P (patients). Blank.
- I (intervention): teicoplanin.
- C (comparator): vancomycin.
- O (outcome): clinical cure.

Which lead us to the specific terms searched: "teicoplanin" AND "vancomycin" AND "randomized trial OR randomized controlled trial"

The search strategy included all languages, but we did not include articles in Chinese. We searched the following sources.

Electronic searches:

- The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. CENTRAL contains the hand-searched results of conference proceedings from general and specialty meetings. This is reported to be an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (12). With this information in mind, we did not specifically search conference proceedings, for which purpose we would have been otherwise unable to complete.

- MEDLINE (from 1966) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs.

Searching other resources:

- Reference lists of infectious diseases textbooks, review articles and relevant studies.

- References of previously published meta-analyses.

Data collection and analysis:

Assessment of study eligibility.

The review was undertaken by the first author (AT). The search strategy described was used to obtain titles and abstracts of studies that might be relevant to the review. The author independently selected the abstracts identified in our search. If the author considered that a citation might possibly include a relevant RCT the full text article was assessed. After obtaining the full text articles, each potential study was evaluated. The author discussed every step with the director (SE). If disagreement emerged and was not resolved during this process, the final decision would rely on the latter (SE).

Data extraction.

Data extraction was carried out independently by AT using standard data extraction forms. Studies reported in non-English language were not translated before assessment.

Duplicate publications or sub-studies of included studies were reviewed and deleted, since none provided information on relevant outcomes not available in the original publication.

Study quality.

The quality of studies included was assessed independently by AT without blinding to authorship or journal using the Cochrane risk-of-bias tool (13). We calculated the Jadad-score, also, for each individual study, but this scoring provided less discriminative capacity and added no significant information to that of the Cochrane tool, and its results are not presented here.

Quality checklist.

The Cochrane risk-of-bias tool includes the following items:

- Patient selection: sequence generation and allocation concealment;

- Trial execution and outcome assessment: blinding (participants, investigators, outcome assessors and data analysis);

- Information: completeness of follow-up, intention-to-treat, report of mortality;

- Report: completeness of report.

Statistical assessment.

Our analysis was aimed at comparing the efficacy of two drugs, and we chose risk ratio of success as the outcome variable. Individual risk ratios (RR) were directly specified or easily calculated from all included RCTs and they were combined to estimate the pooled (RR) with 95% confidence interval (CI) using a random-effects model. For the purpose of calculating RR we used the raw data

presented in the articles in order to standardize the results under the intention-to-treat principle, as it was not regularly used across the studies. We did include in the denominator all patients reported by the authors, unless clear specifications in the text precluded it.

The presence of heterogeneity across studies was evaluated using I2 statistics and standard χ2 tests for homogeneity for the outcome analysis. An I2 value represents the percentage of total variation across studies due to heterogeneity rather than chance. We considered an I2 value less than 25% as low and an I2 value more than 75% as high. We looked for potential publication bias and other biases associated with small study effects by constructing funnel plots. Funnel plots are simple scatter plots of the treatment effects obtained from individual studies on the vertical axis (in our case: RR) against some measure of study size on the horizontal axis (for example, standard error RR).

As we have not found substantial heterogeneity for our primary outcome, meta-regression was not required. We conducted sensitivity sub-group analyses instead.

All p values reported were two-tailed and values lower than 0.05 were considered significant, except for the χ2 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 166 potentially relevant studies (Figure 1. Trial flow-chart). After evaluating their abstracts (or titles) we excluded 123 reports because they were not randomized clinical trials or did not compare teicoplanin with vancomycin. The full-text articles of the remaining 43 studies were evaluated when available, with a further nine considered ineligible. This left 34 potentially relevant randomized clinical trials. Other ten reports were excluded because they were duplicate publications of included and excluded studies; or a subset of a larger study. Finally, we decided not to include another trial which was clearly an outlier by any consideration: it was written in French (which we considered not even a minor drawback); but it reported a trial to assess the comparative costs associated with treatment with teicoplanin versus vancomycin; the report allows for a consideration of the trial as a low-quality one, with a particular flaw in the use and/or report of the intention-to-treat principle; and in line with this problem, we estimated a relative risk for success with vancomycin of 3.75, very far from those calculated for the remaining 23 trials included (14).

The 23 studies finally included enrolled 1851 patients (15- 37). Most were published between 1990 and 2000, with 3 studies published between 2001 and 2009 (Table 1). The median sample size was 82 patients, ranging from 20 to 527. Only three studies included just pediatric patients; most evaluated adults, and 6 evaluated both adults and pediatric patients. Thirteen of 23 studies evaluated febrile neutropenic patients, the remaining included several other infections related or probably related to Gram-positive bacteria: catheter-associated

infection, Gram-positive bacteraemia, endocarditis, bone/joint infection or other Gram-positive infections.

Several schemes of vancomycin were used, going 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. When it comes to teicoplanin, most studies administered 6 to 10 mg/kg IM or IV, every 12 hours, for 3 doses, then once daily. Table 1 includes the additional antibiotics that were added to the therapy in every study. The most frequent treatments selected were ceftazidime, amikacine, netilmicine, and piperacillin (w/wo tazobactam), and antifungal agents depending on the clinical cases.

Many studies did not include patients with previously elevated serum creatinine levels, although cut-off levels for exclusion varied. Definitions of nephrotoxicity were also not uniform across the studies. However, in this meta-analysis we do not evaluate adverse effects, but efficacy, so there's no further information in terms of toxicity.

Effects of interventions

The main results are summarized in Table 1. Clinical cure was similar with teicoplanin or vancomycin (RR: 1.008; 95%CI: 0.972-1.045).

We evaluated for each study sequence generation, allocation concealment, blinding execution, blinding detection of outcome, mortality reporting; the attrition; and fullness of report. Results of our risk-of–bias evaluation are available at Figure 2.

Calculated study weights were:

-   Akan H. : 2.105%.
-   Auperin A. : 42.541%.
-   Chartonneau P : 1.156%.
-   Choi JY. : 1.107%.
-   Cony Makhoul P. : 0.709%.
-   D'antonio D. : 5.629%.
-   Figuera A. : 2.181%.
-   Fortun J. : 0.352%.
-   Kureishi A. : 3.470%.
-   Liu C. : 1.511%.
-   Menichetti F. : 16.829%.
-   Neville LO. : 0.908%.
-   Nucci M. : 0.963%.
-   Rolston KVI. : 5.765%.
-   Rolston KV : 4.725%.
-   Sidi V. : 3.790%.
-   Smith SR. : 1.107%.
-   Van der Auwera P.: 2.011%.
-   Van Laethen Y. : 2.517%.
-   Vazquez L. : 0.624%.

Figure 1. Trial flow. Selection process of studies for inclusion in the systematic review of teicoplanin versus vancomycin for proven or suspected infection.
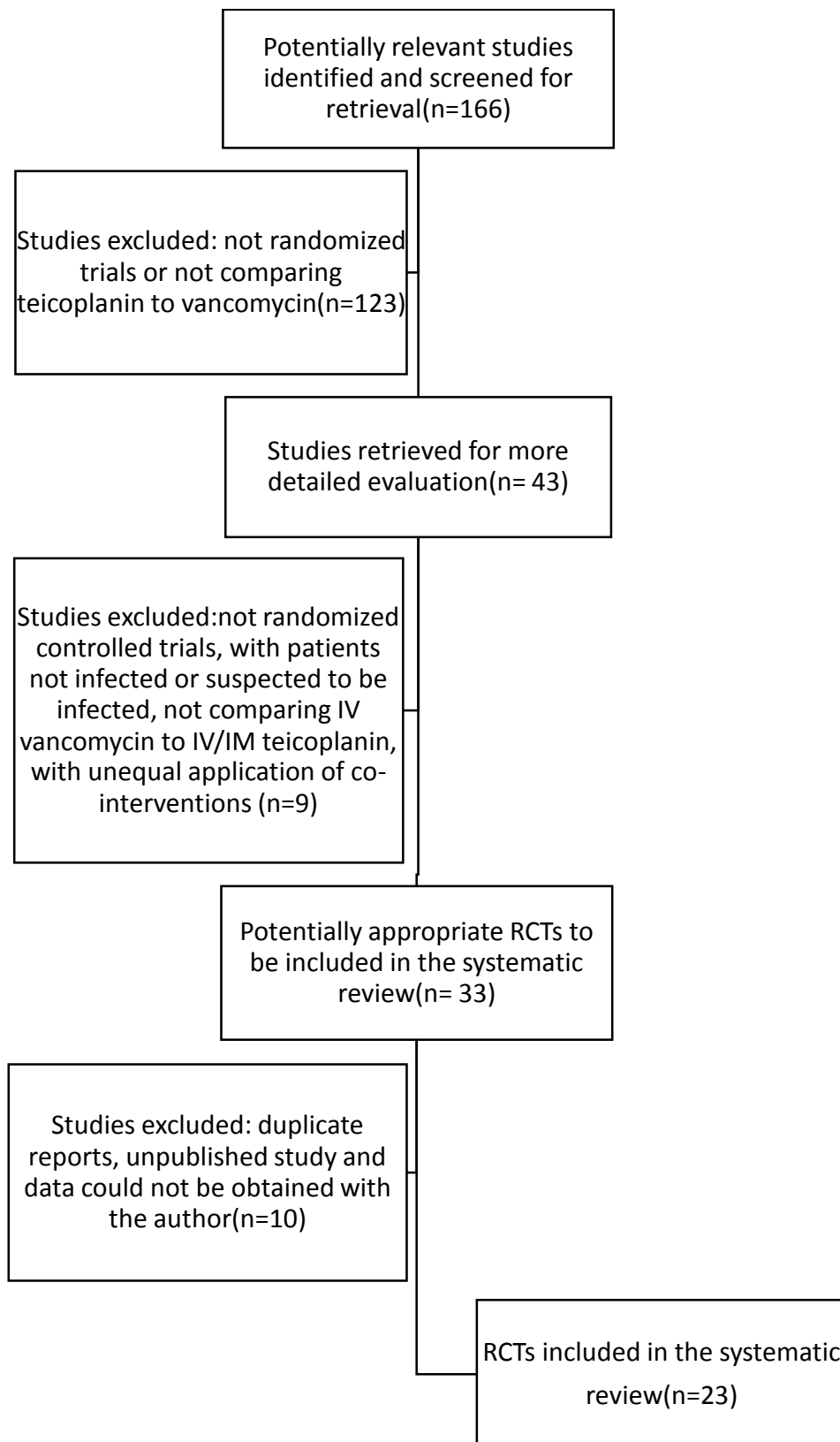
Author.	Journal.	Year.	Theme.	Subjects.	Other treatments.	N (T).	N (V).	T (C+M).	V (C+M).
Akan H.	EU Clin Trials Registry 2014- 004628-23.	2009	Neutropenics.	Mixed.	+ Cefta + Amika.	97	93	54/97	48/93
Auperin A.	Med Mal Infect.	1997	Neutropenics.	<18years.	+ Ceftacidime.	32	33	32/32	33/33
Chartonneau P	Intensive care med.	1994	Gram positives infection.	Adults.	Netilmicine.	24	32	16/23	20/28
Choi JY.	J Korean Soc Chemother.	1992	Neutropenics.	>15years.	¿?	22	20	17/22	14/20
Cony Makhoul P.	Br J Haematol.	1990	Neutropenics.	Adults.	+ Cefta (+AG+ AnfoB).	24	35	13/24	21/35
D'antonio D.	Chemotherapy.	2004	Neutropenics. Hematologics. G+.	Adults.	+ Cefta + Amika.	69	68	55/69	56/68
Figuera A.	Rev Clin Esp.	1996	Neutropenics.	>13years.	+ Imipenem.	57	51	37/57	36/51
Fortun J.	CID.	2001	Right endocarditis (S. Aureus).	Adults.	+ Gentamicine.	10	10	07-oct	06-oct
Gerard M.	ICAAC.	1987	Hem/Onc. Stafilococcus infection.	¿?	¿?	21	19	13/18	14/17
Hedstrom SA.	7th ECCMID.	1995	G+ (suspected or confirmed).	Adults.	¿?	31	17	27/31	13/17
Klaus G.	Advances Perit- Dis.	1995	Peritoneal dyalisis infection.	Children.	Ceftacidime.	24	22	20/21	22/22
Kureishi A.	AAC.	1991	Neutropenics.	Adults.	+ Pip. + Tobr.	25	25	23/25	21/25
Liu C.	Clin Drug Invest.	1996	Bacteriemia por SARM.	Adults.	-	20	20	17/20	15/20
Menichetti F.	AAC.	1994	Neutropenics. Hematologics.	>14 years.	+ Cefta + Amika.	275	252	216/275	190/252
Neville LO.	Int JAA.	1995	G+ (suspected or confirmed).	>14 years.	As indicated.	18	19	13/17	13/19
Nucci M.	Oncol. Reports.	1998	Neutropenics.	>12 years.	+ Cefta + Amika.	53	53	31/46	23/46
Rolston KVI.	JID.	1994	Neutropenics, Oncologic G+.	Adults.	As indicated.	21	25	19/21	24/25
Rolston KVI.	J Infect Chemother.	1999	Catheter infection (G+).	Adults.	Cefta ±Anti G(-).	60	64	48/60	51/64
Sidi V.	J chemother.	2000	Neutropenics. G+ bacteriemia.	Children.	+ Cefta + netilmicine.	31	21	29/31	18/21
Smith SR.	AAC.	1989	Haematological, Hickman catheter.	Adults.	Pip+ Gent 24/28g.	28	32	22/32	20/34
Van der Auwera	AAC.	1991	M.O. onc., neutropenics, G+ infection.	Adults.	-	36	35	27/36	26/35
Van Laethen Y.	J Antimicrob Chemother.	1988	SARM infections.	Mixed.	-	12	9	11-dic	09-sep
Vazquez L.	Haematologica.	1999	Neutropenics. Hematologics.	Adults.	+ Pip/ Taz+ Amika.	38	38	18/38	17/38

Table 1. Characteristics of the studies included. Cefta: ceftazidime; Pip/Taz: Piperacillin/Tazobactem; Amika: amikacine; Genta: gentamicine; Tobr: tobramicine; AG: aminoglucoside; AnfoB: anfotericineB; SARM: S. Aureus Meticilin resistant; Hem: hematologic patients; Onc: oncologic patients. N: number of patients; V: Vancomycin; T: Teicoplanin; C+ M: Cure+ Improvement.

Author.	Journal.	Sequence Generation.	Allocation concealment.	Blind execcution.	Blind detection.	Mortality detection.	Attrition.	Report.
Akan H.	EU Clin Trials Registry 2014- 004628-23.	Unclear R	Unclear R	High R	Low R	Low R	High R	Low R
Auperin A.	Med Mal Infect	Unclear R	Unclear R	Unclear R	Unclear R	Low R	Low R	High R
Chartonneau P	Intensive care med.	Unclear R	Unclear R	High R	High R	Low R	Low R	Low R
Choi JY.	J Korean Soc Chemother.	Unclear R	Unclear R	High R	Unclear R	Unclear R	Bajo R	Unclear R
Cony Makhoul P.	Br J Haematol	Unclear R	Unclear R	High R	High R	Low R	Low R	Low R
D'antonio D.	Chemotherapy	Unclear R	Unclear R	High R	High R	High R	Low R	Low R
Figuera A.	Rev Clin Esp	Alto R	High R	High R	High R	Low R	Low R	High R
Fortun J.	CID	Unclear R	Unclear R	Low R	Alto R	Low R	Low R	Low R
Gerard M.	ICAAC	Unclear R	Unclear R	Unclear R	Unclear R	Unclear R	Unclear	Unclear R
Hedstrom SA.	7th ECCMID	Unclear R	Unclear R	High R	High R	Unclear R	High R	Unclear R
Klaus G.	Advances Perit- Dis	Unclear R	Unclear R	High R	Low R	Low R	Low R	High R
Kureishi A.	AAC.	Low R	Low R	Low R	Low R	Low R	Low R	Low R
Liu C.	Clin Drug Invest.	Low R	Unclear R	High R	Alto R	Low R	Low R	Low R
Menichetti F.	AAC	Low R	Low R	Low R	Bajo R	Low R	Low R	Low R
Neville LO.	Int JAA.	Low R	Unclear R	High R	High R	Low R	High R	Low R
Nucci M.	Oncol. Reports.	Low R	Unclear R	Low R	Bajo R	Low R	Low R	Low R
Rolston KVI.	J Infect Chemother.	Low R	Low R	Low R	Low R	Low R	High R	Low R
Rolston KVI.	JID	Low R	Low R	Low R	Bajo R	Low R	Low R	Low R
Sidi V.	J. Chemother.	Unclear R	High R	High R	Low R	Low R	Low R	High R
Smith SR.	AAC	Unclear R	Unclear R	High R	High R	Low R	Low R	Low R
Van der Auwera P.	AAC	Unclear R	Low R	High R	Bajo R	Low R	Low R	Low R
Van Laethen Y.	J Antimicrob Chemother.	Unclear R	Unclear R	High R	High R	Low R	Low R	Low R
Vazquez L.	Haematologica	Unclear R	Low R	Unclear R	Bajo R	Low R	Low R	High R

Table 2. Summary of findings for the main comparison. Low R: Low Risk; Unclear R: Unclear Risk, High R: High risk.

To represent the results of the meta- analysis we created a forest plot (Figure 2). This graphic represents the results of the randomized controlled trials. In the first column there are both author and publication year; the last two columns show the microbiological and clinical rates of each group of patients [those treated with vancomycin (Ctrl) and those treated with teicoplanin (Trt)]. Then we can see the estimated RR for every study with its respective 95% confidence interval (CI). In the graphic representation, a logarithmic scale is used to represent the relative risk: the confidence interval of each trial is represented as a line within which the point estimated of relative risk is marked by a black square. The conclusion of the analysis is a relative risk of 1.008 (95% CI: 0.972; 1.045; p=0.997), which means no significant differences are found between teicoplanin versus vancomycin treatment in different clinical situations.
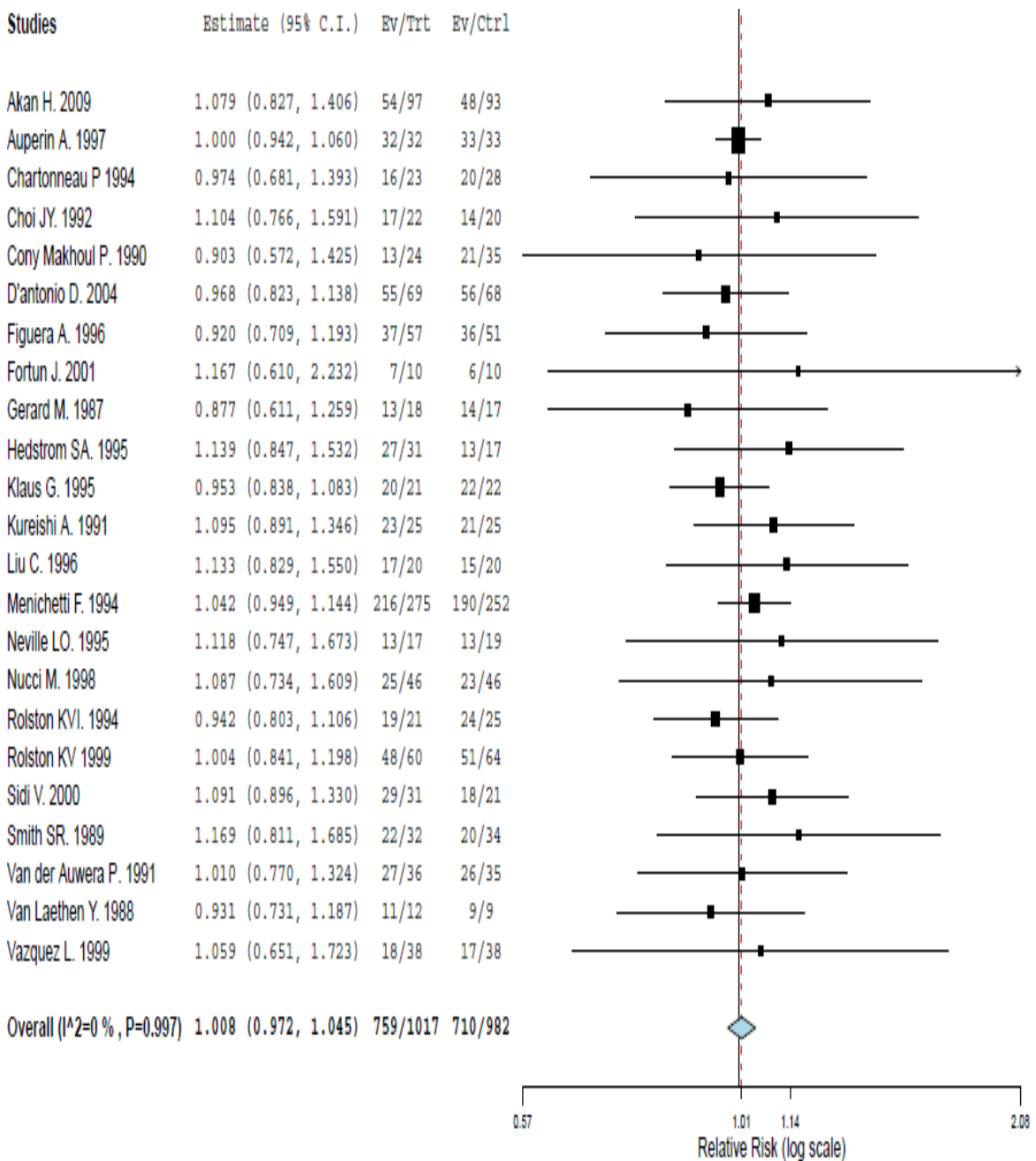
Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Akan H. 2009	1.079 (0.827, 1.406)	54/97	48/93
Auperin A. 1997	1.000 (0.942, 1.060)	32/32	33/33
Chartonneau P 1994	0.974 (0.681, 1.393)	16/23	20/28
Choi JY. 1992	1.104 (0.766, 1.591)	17/22	14/20
Cony Makhoul P. 1990	0.903 (0.572, 1.425)	13/24	21/35
D'antonio D. 2004	0.968 (0.823, 1.138)	55/69	56/68
Figuera A. 1996	0.920 (0.709, 1.193)	37/57	36/51
Fortun J. 2001	1.167 (0.610, 2.232)	7/10	6/10
Gerard M. 1987	0.877 (0.611, 1.259)	13/18	14/17
Hedstrom SA. 1995	1.139 (0.847, 1.532)	27/31	13/17
Klaus G. 1995	0.953 (0.838, 1.083)	20/21	22/22
Kureishi A. 1991	1.095 (0.891, 1.346)	23/25	21/25
Liu C. 1996	1.133 (0.829, 1.550)	17/20	15/20
Menichetti F. 1994	1.042 (0.949, 1.144)	216/275	190/252
Neville LO. 1995	1.118 (0.747, 1.673)	13/17	13/19
Nucci M. 1998	1.087 (0.734, 1.609)	25/46	23/46
Rolston KVI. 1994	0.942 (0.803, 1.106)	19/21	24/25
Rolston KV 1999	1.004 (0.841, 1.198)	48/60	51/64
Sidi V. 2000	1.091 (0.896, 1.330)	29/31	18/21
Smith SR. 1989	1.169 (0.811, 1.685)	22/32	20/34
Van der Auwera P. 1991	1.010 (0.770, 1.324)	27/36	26/35
Van Laethen Y. 1988	0.931 (0.731, 1.187)	11/12	9/9
Vazquez L. 1999	1.059 (0.651, 1.723)	18/38	17/38
Overall (I^2=0 % , P=0.997)	1.008 (0.972, 1.045)	759/1017	710/982

Relative Risk (log scale)
0.57 1.01 1.14 2.08

Figure 2. Forest plot. All studies included. (RR: 1.008; 95%CI: 0.972-1.045).

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The next step was to create the leave-one-out forest plot (Figure 3). This analysis is similar to the cumulative forest plot made before, except that instead of adding all studies at a time, each study is hold out in turn. This intends to show up influential studies. The results did not change the previous conclusions. We obtained an overall relative risk of 1.013 (95% CI: 0.975-1.052); as Figure 3 shows, all intervals crossed the "one" (neutral effect) axis.
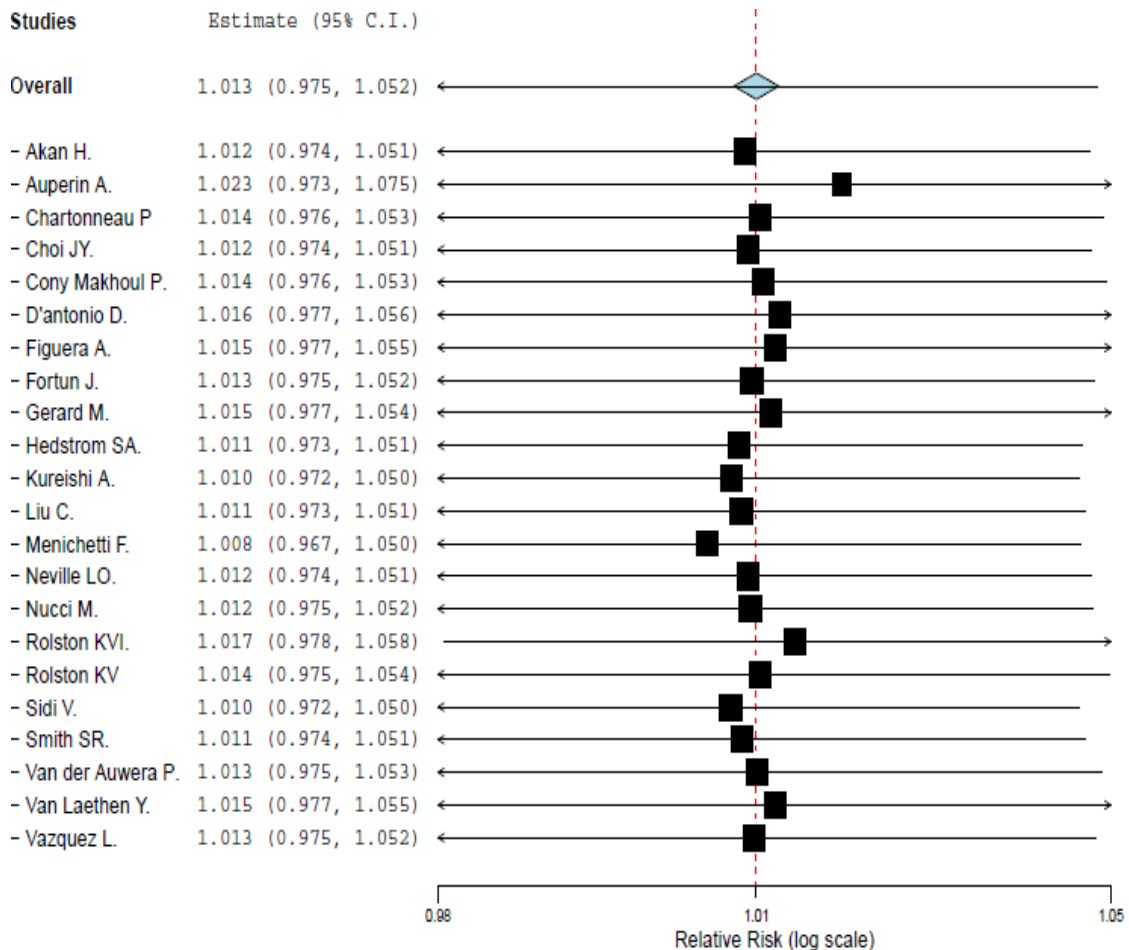

Figure 3. Leave one out forest plot. (RR: 1.013; 95%CI: 0.975-1.052)

We performed a series of sensitivity analysis. This means subgroup meta-analysis that may underscore differences between groups. The procedure for subgroup meta-analysis is the same as for standard meta-analysis except that a categorical variable must be selected. We created different categories including: children (less than 12 years old); persons>12 years; adults>18 years; MRSA infestions and febrile neutropenia. None of them showed any evidence of superiority of either vancomycin or teicoplanin for any indication. (Figure 4. Figure 5. Figure 6. Figure 7.).
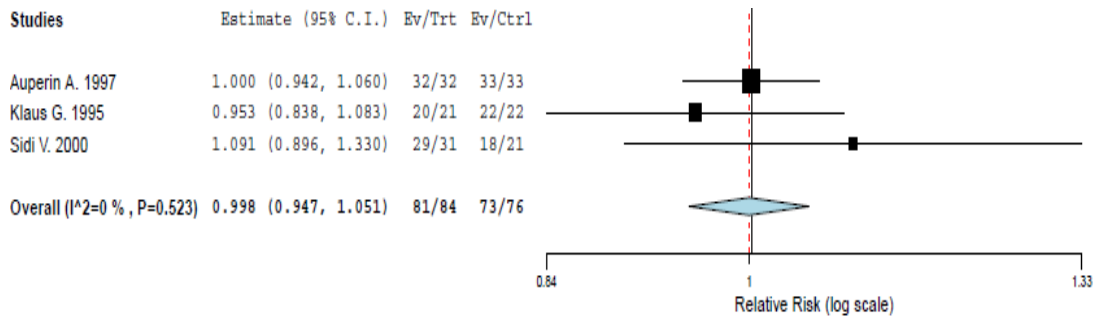
Figure 4. Forest plot, children. (RR: 0.998; 95%CI: 0.947-1.051)

Three studies included just children [Auperin A. et al (15); Klaus G. et al (16); and Sidi V. et al (17)]. In this subgroup no significant differences are found between teicoplanin and vancomycin. (RR: 0.998; 95%CI: 0.947-1.051). (Figure 4.)
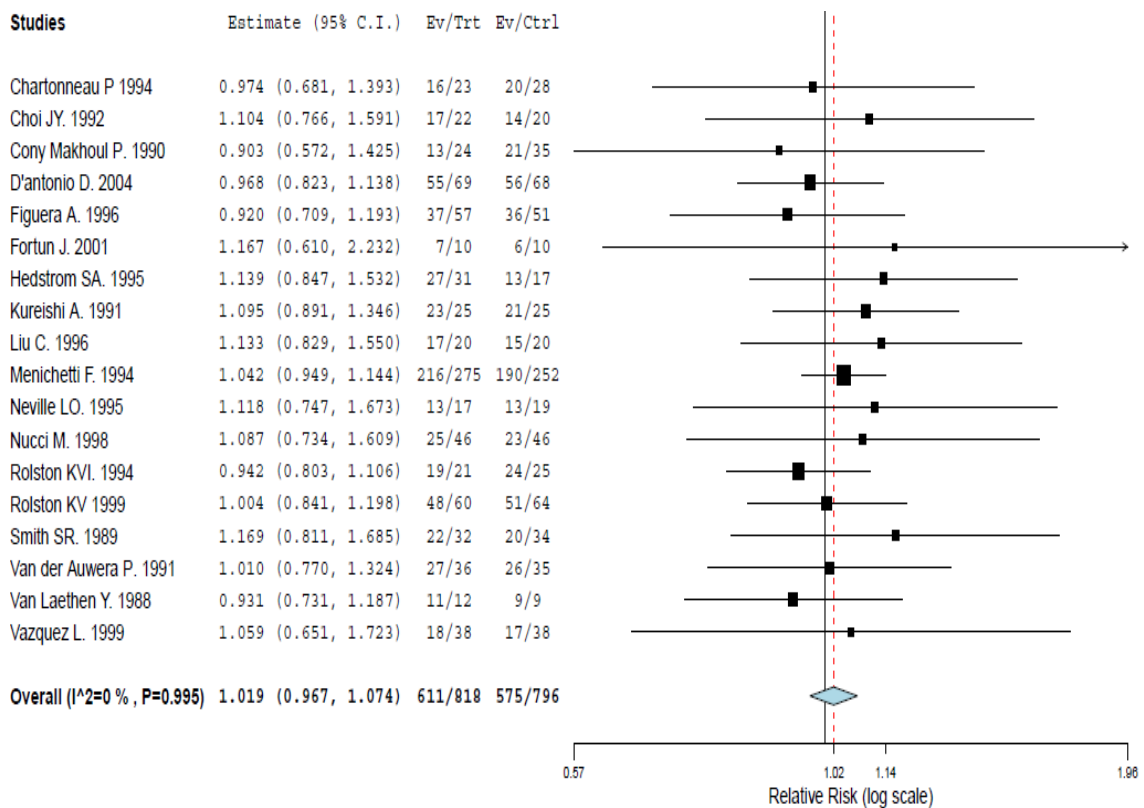

Figure 5. Forest plot. >12 years old. (RR: 1.019; 95%CI: 0.967-1.074).

Eighteen studies included patients with 12 years old and more [Chartonneau P. et al (18); Choi JY. et al (19); Cony Makhoul P. et al (20); D'antonio D. et al (21); Figuera A. et al (22); Fortún J. et al (24); Hedstrom SA. et al (23); Kureishi A. et al (25); Liu C. et al (26); Menichetti F. et al (27); Neville LO. et al (28); Nucci M. et al (29); Rolston KVI (30). et al; Rolston KVI. et al (31); Smith SR. et al (32); Van der Auwera P. et al (33); Van Laethen Y. et al (34); Vázquez L. et al (35)]. Neither this subgroup showed significant differences between teicoplanin and vancomycin. (RR: 1.019; 95%CI: 0.967-1.074). (Figure 5.)
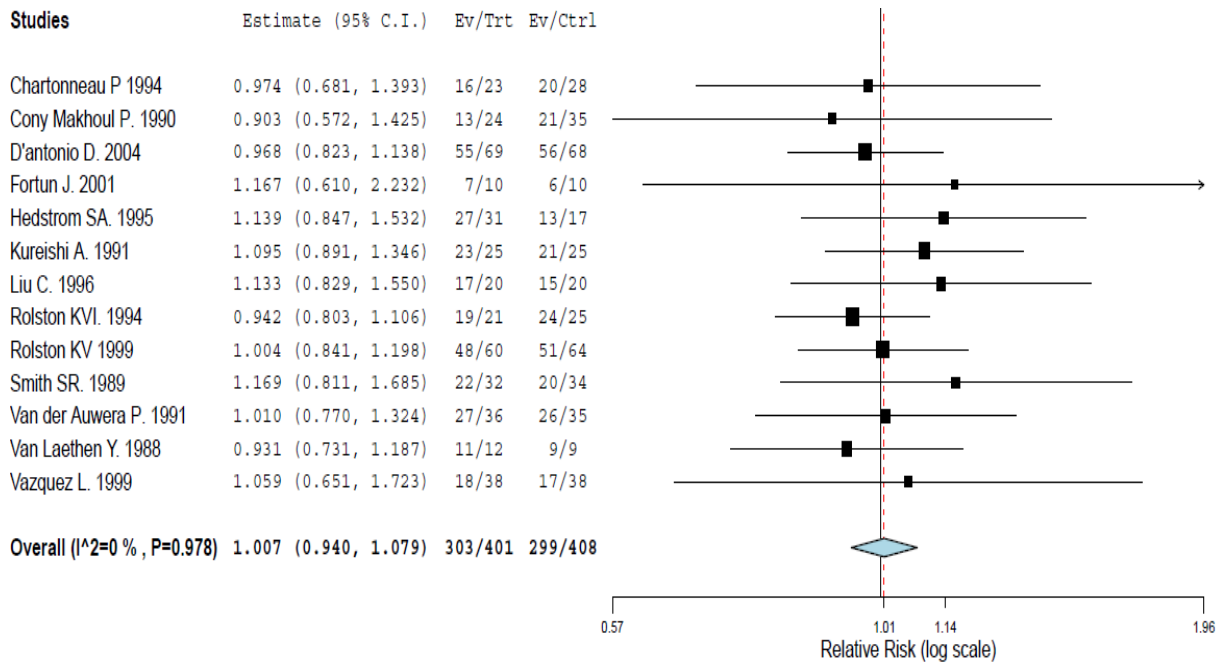
Figure 6. Forest plot >18 years old. (RR: 1.007; 95%CI: 0.940-1.079).

When taking just patients older than years old and more thirteen studies were analyzed. [Chartonneau P. et al (18); Cony Makhoul P. et al (20); D'antonio D. et al (21); Fortún J. et al (24); Hedstrom SA. et al (23); Kureishi A. et al (25); Liu C. et al (26); Rolston KVI. et al (30); Rolston KVI. et al (31); Smith SR. et al (32); Van der Auwera P. et al (33); Van Laethen Y. et al (34); Vázquez L. et al(35)]. This confirmed that vancomycin and teicoplanin are comparable when treating adults. (RR: 1.007; 95%CI: 0.940-1.079) (Figure 6).
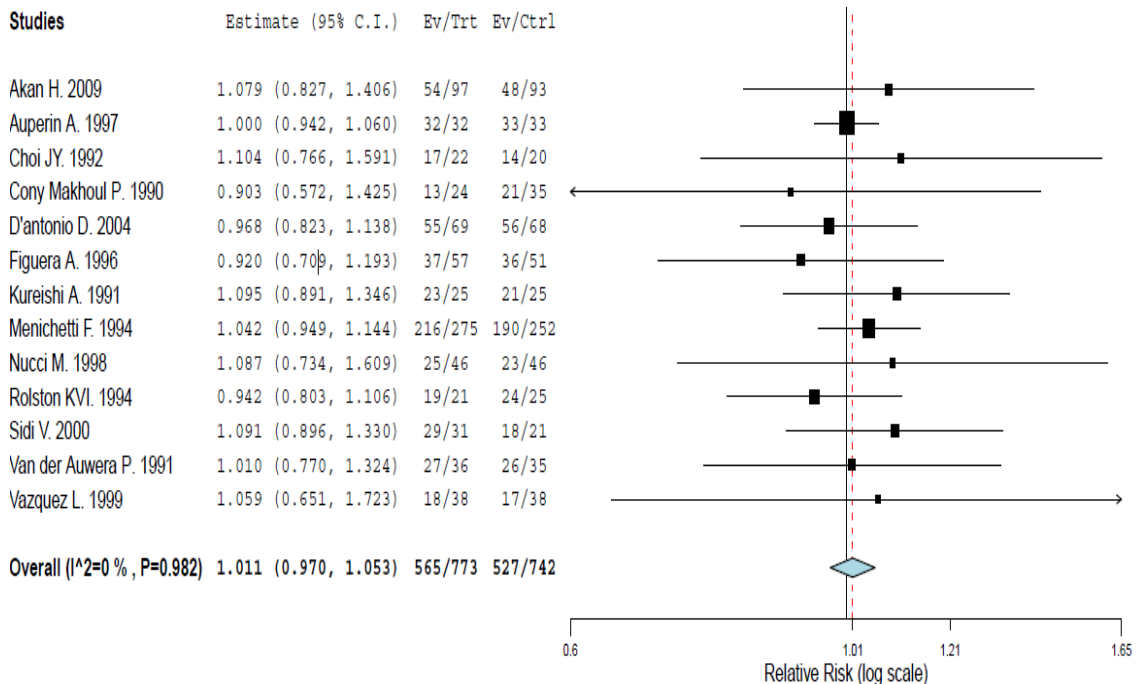
Figure 6. Forest plot. Febrile neutropenics. (RR: 1.011; 95%CI: 0.970-1.053).

Next subgroup we analyzed was febrile neutropenics, including thirteen studies [Akan H. et al (36); Auperin A. et al (15); Choy JY. et al (19); Cony Makhoul P. et al (20); D' Antonio D. et al (21); Figuera A. et al (22); Kureishi A. et al (25); Menichetti F. et al (27); Nucci M. et al (29); Rolston KVI. et al (30); Sidi V. et al (17); Van der Awera P. Y. et al (33); Vázquez L. et al (35); Akan H. et al. (36)]. Teicoplanin and vancomycin showed equivalent efficacy when treating febrile neutropenics (RR: 1.011; 95%CI: 0.970-1.053). (Figure 6).

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Chartonneau P 1994	0.974 (0.681, 1.393)	16/23	20/28
D'antonio D. 2004	0.968 (0.823, 1.138)	55/69	56/68
Fortun J. 2001	1.167 (0.610, 2.232)	7/10	6/10
Hedstrom SA. 1995	1.139 (0.847, 1.532)	27/31	13/17
Liu C. 1996	1.133 (0.829, 1.550)	17/20	15/20
Neville LO. 1995	1.118 (0.747, 1.673)	13/17	13/19
Rolston KVI. 1994	0.942 (0.803, 1.106)	19/21	24/25
Rolston KV 1999	1.004 (0.841, 1.198)	48/60	51/64
Sidi V. 2000	1.091 (0.896, 1.330)	29/31	18/21
Van der Auwera P. 1991	1.010 (0.770, 1.324)	27/36	26/35
Van Laethen Y. 1988	0.931 (0.731, 1.187)	11/12	9/9
Overall (I^2=0 % , P=0.963)	1.007 (0.938, 1.080)	269/330	251/316

Relative Risk (log scale)

Figure 7. Forest plot, MRSA infection. (RR: 1.007; 95%CI: 0.938-1.080).

To finalize with the sensitivity analysis we selected the eleven studies that included MRSA infection [Chartonneau. et al (18); D' Antonio D. et al (21); Fortún J. et al (24); Hedstrom. et al (23); Liu C. et al (26); Neville LO. et al (28); Rolston KVI. et al (30); Rolston KVI. et al (31); Sidi V. et al (17); Van der Auwera P. Y. et al (33); Van Laethen Y. et al (34). Teicoplanin seems to be as effective as vancomycin in the antibiotic therapy in MRSA infections (RR: 1.007; 95%CI: 0.938-1.080) (Figure 7).

Figure 8 shows the representation of our evaluation of the quality of the studies analyzed by means of the Cochrane risk-of-bias tool. Overall, the studies performed well in the reporting-related items, but more poorly in the guaranteeing of randomization and blinding.
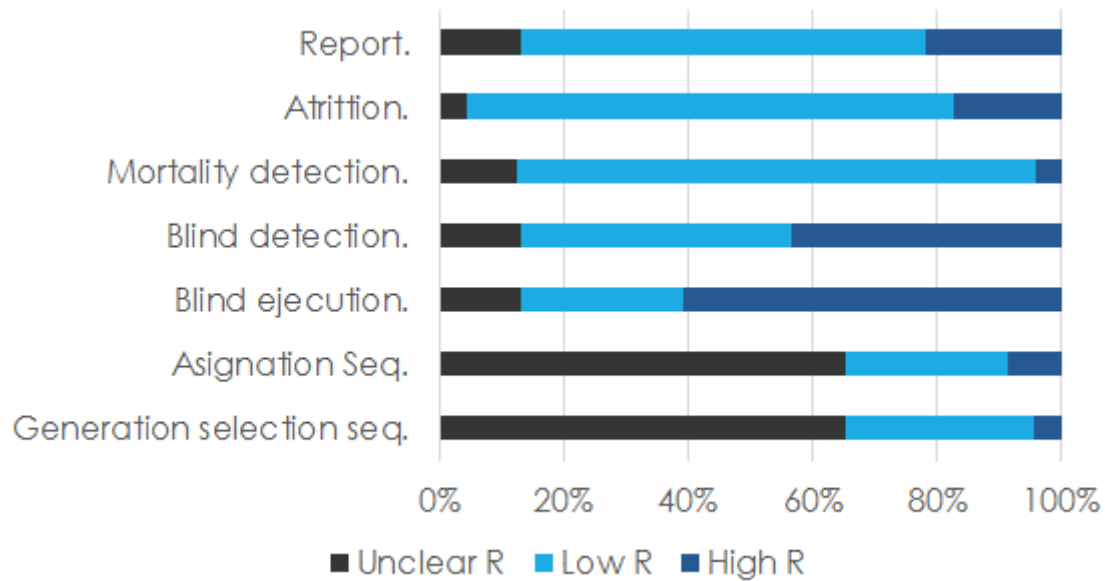
Figure 8. Bar diagram showing the percentage of studies within each of one categories of risk of bias, according to the Cochrane Handbook for Systematic Reviews recommendations.

Results study by study.

Most of the studies selected to be included in this meta-analysis did not just compare vancomycin and teicoplanin in terms of effectiveness but also compared other items such as toxicity, mortality or efficiency. It was not the end point of our study to analyze those factors but just to focus on clinical efficacy. However, we considered interesting to summarize the principal conclusions and characteristics of them with the purpose of having a qualitative perspective of some other differences between the two glycopeptides.

In the study published by Van Laethen et al. in the Journal of Antimicrobial Chemotherapy, twenty-one patients were included in an open randomized study comparing vancomycin 1 g bd with teicoplanin 400 mg daily in severe methicillin-resistant *Staphylococcus aureus* infections. The median duration of therapy was I5 days for vancomycin and 21 days for teicoplanin. The infections treated, included septicaemia, osteomyelitis, bronchopneumonia, cellulitis and acute pyelonephritis. The cure rate was seven of twelve in the teicoplanin group and six of nine in the vancomycin group, with four and three cases, respectively, of improvement and one failure in the teicoplanin group. Transient renal impairment occurred in two cases with both regimens; superinfection and colonization in three patients and one patient, respectively, with both regimens. (34)

The study published by P. Chartonneau et al. in Intensive Care Medicine was a prospective, randomized multicentre study conducted in order to evaluate the potentially superior tolerability profile of teicoplanin plus netilmicin compared with vancomycin plus netilmicin in patients in ICUs. A total of 56 patients were enrolled into the study. Twenty-four patients were included in the teicoplanin plus netilmicin group and thirty-two patients were randomized to receive vancomycin plus netilmicin. Septicaemia was the most common infection and most infections

were caused by Staphylococcus aureus or coagulase-negative staphylococci. Clinical and bacteriological efficacy was similar: clinical success was achieved in 80% of the patients in the teicoplanin group compared with 83 % in the vancomycin group. The bacteriological response rates were 81 and 84%, respectively. Adverse events were reported in 24 patients: 7 (29%) in the teicoplanin group and 17 (53%) in the vancomycin group (p>0.05). Nephrotoxicity was reported as an adverse event in 21 patients: 6 (25%) in the teicoplaningroup and 15 (47%) in the vancomycin group (p = 0.09). They concluded that teicoplanin is an efficacious, well-tolerated and convenient antibiotic for the treatment of Gram- positive infection in ICU patients. (18)

Smith SR et al. published a Randomized Prospective Study Comparing Vancomycin with Teicoplanin in the Treatment of Infections Associated with Hickman Catheters in the Antimicrobial agents and Chemotherapy journal. 72 episodes of suspected or proven Hickman-catheter-associated infection occurring in 59 patients with various hematological disorders were selected. Patients were assigned to treatment with either vancomycin or teicoplanin in a randomized non-blinded prospective study. Of 60 episodes evaluable for response, 28 were treated with vancomycin and 32 were treated with teicoplanin. Sixteen infective episodes were microbiologically documented in the vancomycin group, and twenty-one were in the teicoplanin group. Microbiologically and clinically documented infections treated with vancomycin had an 80% response rate, compared with a 69% response rate for those treated with teicoplanin (P = 0.316). Adverse events occurred in nine (25%) of the episodes in the vancomycin group, compared with three (8%) in the teicoplanin group (P = 0.044). The results were that Teicoplanin may provide an effective alternative to vancomycin in the treatment of Hickman catheter- associated infection in patients with hematological malignancies. (32)

The study of Cony- Makhoul et al. published in British Journal of Haematology is a prospective study that compares the efficacy and toxicity of vancomycin versus teicoplanin as second-line empiric therapy for infection in neutropenic patients. They chose a sample of 151 adult leukaemic patients hospitalized for intensive chemotherapy. When the patients became febrile, they received ceftazidime and if fever persisted more than 48-72 hours they were randomly assigned to receive ceftazidime combined with either vancomycin or teicoplanin. When fever persisted further, an aminoglycoside antibiotic and/or amphotericin B were usually added. 59 patients had persistent (or recurrent) fever despite administration of ceftazidime and received either vancomycin (n = 35) or teicoplanin (n=24). The main characteristics of patients and infection were similar in both arms. The treatment was considered as a success 60% of patients treated with vancomycin compared to 54% of patients of the teicoplanin. No major toxic effects were found in either group. The preliminary results didn't show any difference between both treatments as second-line antibiotic therapy in leukaemicpatients with severe and prolonged granulocytopenia. (20)

Van der Auwera P. et al published in the Antimicrobial Agents and Chemotherapy a randomized study of Vancomycin versus Teicoplanin for the treatment of Gram-Positive Bacterial Infections in immunocompromised Hosts. Seventy-four immunocompromised patients with severe infection due to gram-positive organisms were randomized to receive either vancomycin or teicoplanin. The

most frequent pathogen was Staphylococcus epidermidis, followed by Staphylococcus aureus; and the infections were 46 bacteremias (39 associated with central catheters), 24 skin and soft tissue infections (3 with bacteremia), and 7 others (mainly bronchopneumonia). Microbiological erradication was obtained in 23 of 35 evaluable patients treated with vancomycin (65.7%) and 28 of 36 patients treated with teicoplanin (77.8%). Clinical cure and improvement were obtained in 26 of 35 patients (74.3%) and 27 of 36 patients (75.0%), respectively. No significant side effects were observed with teicoplanin, in contrast to reversible increases in serum creatinine and skin rashes with vancomycin. (33)

The study published by D' Antonio D et al in the Microbiology Chemotherapy, is a prospective, randomized, double-blind trial on 124 febrile patients with hematological malignancies to compare teicoplanin with vancomycin as an addition to the initial empiric amikacin-ceftazidime regimen after documented bacteremia due to gram-positive cocci. Rates of therapeutic success were 55/63 (87.3%) in the teicoplanina group and 56/61 (91.8%) in the vancomycin group. Thirteen patients experienced an adverse drug reaction, but without any significant difference in the two arms. (21)

Vazquez L. et al. published in Haematologica a randomized, prospective study to evaluate the efficacy, safety and cost comparing of teicoplanin and vancomycin as second-line empiric therapy for infection in neutropenic patients, after the failure of empirical treatment with a combination of piperacillin/ tazobactam and amikacin. Seventy-six febrile episodes from 66 patients with hematologic malignancies under treatment, neutropenia (neutrophils <500/mm3) and fever (38°C twice or 38.5°C once) resistant to the combination piperacillin/ tazobactam and amikacin were included in the study. Primary success of second-line therapy was obtained in 35 cases (46%) with no significant difference between vancomycin (17/38) and teicoplanina arms (18/38). No difference in renal or hepatic toxicity related to the antibiotic therapy was observed. They concluded that teicoplanin and vancomycin can be administered in neutropenic hematologic patients with similar efficacy and direct costs. (35)

Menichetti F. et al. published in the Antimicroblal agents and chemotherapy about the efficacy and toxicity of teicoplanin and vancomycin in the initial empirical antibiotic regimen in febrile, neutropenic patients with hematologic malignancies. It was a prospective, randomized, unblinded, multicenter trial in the setting of 29 hematologic units in tertiary-care or university hospitals. A total of 635 consecutive febrile patients with hematologic malignancies and chemotherapy-induced neutropenia were randomly assigned to receive intravenously amikacin plus ceftazidime plus either teicoplanin at 6 mg/kg of body weight once daily or vancomycin at 1 g twice daily. An efficacy analysis was done for 527 evaluable patients: 275 treated with teicoplanin and 252 treated with vancomycin. Overall, successful outcomes were recorded for 78% of patients who received teicoplanin and 75% of those who were randomized to vancomycin. The most common pathogens isolated were coagulase-negative staphylococci (42%), Staphylococcus aureus (27%), and streptococci (21%). The overall responses to therapy of gram-positive bacteremias were 92% for teicoplanin and 87% for vancomycin. Side effects were mainly represented by skin rash (3.2 and 8% of teicoplanin and vancomycin treated patients, respectively) and nephrotoxicity (1.4 and 0.8% for the teicoplanin and vancomycin groups, respectively). The

conclusion was that when used for initial empirical antibiotic therapy in febrile, neutropenic patients, teicoplanin was at least as efficacious as vancomycin, but it was associated with fewer side effects. (27)

Rolston KI et al. published about the treatment of Gram-Positive Bacteremia in Patients with Cancer using Vancomycin or Teicoplanin in de JID journal. It is a prospective, randomized, double-blind study. At enrollment, both groups were comparable in age, sex, underlying hematologic or neoplastic disorder, baseline renal functions, and incidence of neutropenia. Treatment was successful in 19 (90%) of 21 patients who received teicoplanin and 24 (96%) of 25 who received vancomycin. Adverse reactions occurred more often in the vancomycin group (31%) than in the teicoplanin group (9%; P = .06) and were primarily cutaneous or gastrointestinal. In conclusion, teicoplanin was better tolerated than vancomycin, and no statistically significant difference in efficacy was detected with the sample size in this study. (31)

Nucci M. et al. made a clinical prospective randomized trial performed to compare teicoplanin and vancomycin as part of the empirical antibiotic therapy of febrile neutropenic cancer. Fifty-three patients were randomized to receive ceftazidime (100 mg/kg daily every 8 h), amikacin (15 mg/kg daily every 8 h) and teicoplanin (6 mg/kg once a day) and 53 other patients received ceftazidime, amikacin (same dosages) and vancomycin (30 mg/kg/day every 6 h). In 99 evaluable episodes, the success rates were 54% for patients receiving teicoplanin and 52% for patients receiving vancomycin. The response rates were similar for patients with documented or not infections. There were no differences in renal toxicity or cutaneous side effects between the two groups. Teicoplanin seems to be well tolerated and as effective as vancomycin in the empirical antibiotic therapy of fever in neutropenic cancer patients. (29)

Figuera A. published a comparative study of teicoplanin versus vancomycin both combined with imipenem for the initial empirical treatment of neutrophenic fever. 126 episodes of febrile neutropenia in patients with haematological malignancies or bone marrow transplantation. One group received imipenem plus vancomycin and the other imipenem plus teicoplanin. Similar percentage of clinical response was reported (55% and 68% respectively) and also in those microbiologically documented (54% and 34.5% respectively). In some cases it was necessary to add a sequential empiric use of amikacin followed by amphotericin B to assure an adequate overall control of infection in the patients with prolonged severe neutropenia. In any case, no significant differences were observed in the clinical response or in toxicity between the combination of imipenem with any of the two glycopeptides, for the initial empiric therapy of febrile neutropenia. (22)

Kureishi A. et al. published in Antimicrobial agents and chemotherapy a prospective, randomized, and double-blind study comparing teicoplanin with vancomycin in the initial management of febrile neutropenic patients. Patients also received piperacillin and tobramycin. Of 53 patients enrolled, 50 were judged to be evaluable. At enrollment, both groups were comparable in age, sex, renal function, underlying hematologic condition, and concurrent therapy. 25 received teicoplanin and 25 received vancomycin. Empirical antimicrobial therapy resulted in the cure of or improvement in 23 (92%) teicoplanin patients and 21 (84%) vancomycin patients. Failures occurred with two vancomycin patients but no

teicoplanin patients and clinical response was indeterminate for two patients in each group. Adverse reactions occurred significantly more often in the vancomycin group and required the termination of the study regimens. Nephrotoxicity was observed more frequently in the vancomycin group. The conclusion was that teicoplanin in the dosage employed was tolerated better than vancomycin in the empirical treatment of fever and neutropenia in our patient population. (25)

In the Study published by Rolston KV. Et al. in J. Infect Chemother, a total of 240 patients with suspected bacteremia or septicemia secondary to vascular Access-associated gram- positive infection were enrolled in a multicenter trial in 47 centers in the United States and Canada, comparing teicoplanin with vancomycin. The pathogens most often isolated were coagulase-negative staphylococci (64 patients) and Staphylococcus aureus (60 patients).Clinical cure and improvement was achieved in 48 (80.0%) of 60 patients for teicoplanin and 51 (79.7%) of 64 patients for vancomycin. "Intent-to-treat" analysis also showed similar efficacy for the two glycopeptides. Eradication was achieved in 49 (81.7%) of 60 patients for teicoplanin and 55 (85.9%) of 64 patients for vancomycin. Adverse events were reported by 32 (27, 4%) of 117 patients receiving teicoplanin and 37 (30,6%) of 121 patients receiving vancomycin. It is concluded that teicoplanin and vancomycin show equivalent efficacy and tolerance in vascular access- associated bacteremia/septicemia caused by gram-positive pathogens. (30)

The study published by Neville L. O. et al in the international Journal of Antimicrobial Agents is a prospective, randomized study of 56 patients comparing teicoplanin with vancomycin for suspected or proven severe Gram- positive infection. The majority of infections were soft tissue infections and a significantly higher number of Hickman catheter. Of these, 18 episodes in 17 patients (teicoplanin) and 19 episodes in 18 patients (vancomycin) gave an evaluable clinical response. Bacteriological elimination rates were similar in both groups (71% teicoplanin; 78% vancomycin). Significantly more patients given vancomycin experienced adverse events (7 teicoplanin; 16 vancomycin). This caused treatment to be discontinued in 4 cases, compared with only one receiving teicoplanin. Teicoplanin and vancomycin show similar clinical and bacteriological efficacy and teicoplanin is significantly less toxic and easier to use in patients with severe infection. (28)

Sidi V. et al. published in the Journal of Chemotherapy a clinical trial to compare the efficacy and safety of teicoplanin and vancomycin in 32 children for 52 Gram-positive bacteremias during malignancy-associated neutropenia. Patients mainly suffered from hematological malignancies. Twenty-five episodes were treated with teicoplanin and 21 with vancomycin; plus ceftazidime and netilmicin. Staphylococci (12% Staphylococcus aureus) were isolated from 50 episodes and viridans streptococci from 2. Clinical cure occurred in 29/31 (93.5%) teicoplanin-treated and 18/21 (85.7%) vancomycin-treated episodes. All teicoplanin and vancomycin treated episodes showed microbiological response. Mild renal insufficiency appeared in 5 vancomycin-treated patients that was corrected without drug discontinuation. While both glycopeptides exhibit equal clinical and microbiological efficacy, teicoplanin is less likely to induce allergic reactions or nephrotoxicity in children. (17)

In the clinical trial from Clin. Drug Invest. published by Liu C et al. forty patients with methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia were selected to receive either teicoplanin or vancomycin therapy to compare the clinical efficacy and safety of these glycopeptides. All MRSA pathogens isolated were susceptible to both glycopeptides by the disc diffusion test. Treatment was successful in 17 (85%) of 20 patients from the teicoplanin group; and in 15 (75%) of 20 patients from the vancomycin group. The microbiological eradication rate was 85% (17 of20 isolates) for teicoplanin and 75% (15 of 20 isolates) for vancomycin. Adverse reactions occurred in 19% of patients treated with teicoplanin and 60% of patients treated with vancomycin. There was no significant difference in the occurrence of skin rash or in elevation of aminotransferase (p = 0.18). However, nephrotoxicity was significantly greater in the vancomycin group than in the teicoplanin group. In conclusion, the results of this study showed that teicoplanin seems to be a valuable alternative to vancomycin because it is as efficacious as vancomycin, but has fewer adverse reactions, and is conveniently administered. (26)

Fortún J. et al published a prospective, randomized clinical trial among drug abusers in the CID journal. They wanted to assess the efficacy and safety of a short-course of a combination of a glycopeptide (vancomycin or teicoplanin) and gentamicin compared with a combination of cloxacillin and gentamicin for treatment of right-side endocarditis caused by Staphylococcus aureus. Therapeutic success was significantly more frequent with cloxacillin than with a glycopeptide. They concluded that a course of vancomycin or teicoplanin plus gentamicin is ineffective in this instance because it is associated with a high rate of clinical and microbiological failure. (24)

Auperin A. et al. published in Med. Mal Infect. journal a study to compare teicoplanin versus vancomycin for the treatment of febrile granulocitopenic children during their post-chemotherapy period. They performed an intention-to-treat analysis that included a total of 65 children evaluable. Thirty two of them received teicoplanin and thirty three received vancomycin. The conclusion of their study was that because of cost reasons, treatment with vancomycin was preferable to teicoplanin, but in terms of clinical and microbiological cure they found no differences. (15)

Akan et al. reported a multicenter, prospective and randomized study. It's a 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. Both adults and paedriatric subjects were included. Each group received ceftazidime and amikacin, in addition to Teicoplanin (97 subjects) or Vancomycin (93 patients) with treatment duration between 5 or 21 days. Therapeutic success was 54/97 for teicoplanin and 48/90 for vancomycin. The conclusion is that both glycopeptides can be used as a valid treatment for febrile neutropenic with high risk for gram positive infection. (36)

The rest of the studies were published by Gerard M. et al in the ICAAC journal; by Herdstrom SA. et al. in the 7th ECCMID (23); Klaus G in the Advances Perit-Disease (16); 37. Gerard, M et al. in the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy (37); and Choi JY. et at. in the J Korean Soc. Chemother (19). We did not have access to these studies but we extracted

relevant data from previous meta-analyses. We have no further information about them, except that they included hematologic/oncologic patients with Staphylococcal infection; Gram-positive infection suspected or confirmed; peritoneal dialysis related infection; and febrile neutropenic patients respectively.

DISCUSSION.

In this systematic review and meta-analysis, we found a similar effect of teicoplanin compared to vancomycin on our pre-defined main outcome of clinical cure. This result is in agreement with, and provides further support, to, those of previous meta- analyses.

In 1996 MJ Wood published a first systematic review with a basic meta- analysis which included 11 RCTs published until that date. By that time, neither the PRISMA statement for reporting this type of studies nor the CONSORT statement for reporting clinical trials had been released, so that the quality of both the RCTs analyzed, and Wood´s report itself, were rather low. However, Wood found that both the clinical response and the bacteriological response were very similar in patients treated with vancomycin and those treated with teicoplanin. (8)

As mentioned earlier, there are two meta- analyses published by Chinese authors. The first one, published in 2013 by Peng et al. (10), included only Chinese patients. Twelve articles met entry criteria. There was no statistically significant difference between the two groups regarding the clinical cure rate (risk ratio [RR], teicoplanin vs vancomycin, 0.94; 95% CI, 0.74~1.19; P=0.60), microbiological cure rate (risk ratio [RR], teicoplanin vs vancomycin, 0.99; 95% CI, 0.91~1.07; P=0.74) and adverse event rate (risk ratio [RR], teicoplanin vs vancomycin, 0.86; 95% CI, 0.40~1.84; P=0.70). The second one dates from 2014 and was published by Bao et al in a Chinese journal (in Chinese) (9). In the abstract, accessible at the Cochrane Library, it is stated that twenty RCTs were finally included, involving 1555 patients with severe gram-positive bacterial infection. The results of meta-analysis showed that there was no significant difference between teicoplanin and vancomycin with regards to all-cause mortality (OR=1.67, 95%CI 0.86 to 3.23, P=0.13), clinical cure rates (OR=1.24, 95%CI 0.95 to 1.60, P=0.11), effective rates (OR=1.03, 95%CI 0.75 to 1.41, P=0.87), and bacterial clearance rates (OR=0.96, 95%CI 0.66 to 1.39, P=0.83). However, the incidence of adverse reaction was lower in the teicoplanin group than in the vancomycin with a significant difference (OR=0.50, 95%CI 0.34 to 0.72, P=0.0002).

Finally, two meta-analyses have been published in English in the PRISMA era, although one was done so in a local journal in Sao Paulo (Br) (12), not indexed in MedLine. The first one was published by Svetitsky et al in 2009 (11), authors who chose mortality as their main outcome, although they report a summary result on clinical efficacy. Twenty-four trials were included. All-cause mortality was similar overall (RR, 0.95; 95% CI, 0.74 to 1.21), and there was no significant heterogeneity. In trials that used adequate allocation concealment, the results favored teicoplanin (RR, 0.82; 95% CI, 0.63 to 1.06), while in trials with unknown methods or inadequate concealment, the results favored vancomycin (RR, 3.61;

95% CI, 1.27 to 10.30). There were no significant differences between teicoplanin and vancomycin with regard to clinical failure (RR, 0.92; 95% CI, 0.81 to 1.05), microbiological failure (RR, 1.24; 95% CI, 0.93 to 1.65), and other efficacy outcomes. The Brazilian report dates from 2013 and focused on safety issues, with particular mention to nephrotoxicity but, again, it reports also summary results on efficacy. 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).

Therefore, our more detailed analysis on the comparative efficacy of teicoplanin and vancomycin provides additional evidence supporting the use of teicoplanin for the treatment of infections, proven or suspected, by gram-positive bacteria, when safety and convenience issues are a consideration; and in any case, confidently of its efficacy as compared with the standard of treatment for these infections.

As reported in these meta-analyses previously mentioned, we found little heterogeneity between the RCTs included in ours, although it must also be acknowledged that the quality overall (as evaluated by the risk of bias) tended to be low. However, the best quality RCTs analyzed (those double-blind with specification of the randomization methods used) are major drivers of the results, but all trials point to the same direction. Our sensitivity analyses found the same trend, in support of the general conclusion.

A funnel plot is a graph designed to check for the existence of publication bias; funnel plots are commonly used in systematic reviews and meta-analyses. In the absence of publication bias, it assumes that studies with high precision will be plotted near the average, and studies with low precision will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias. Our funnel-plot reveals a very well distributed scatter-plot, reinforcing our confidence in the validity of our analyses and results. (Figure 9.)
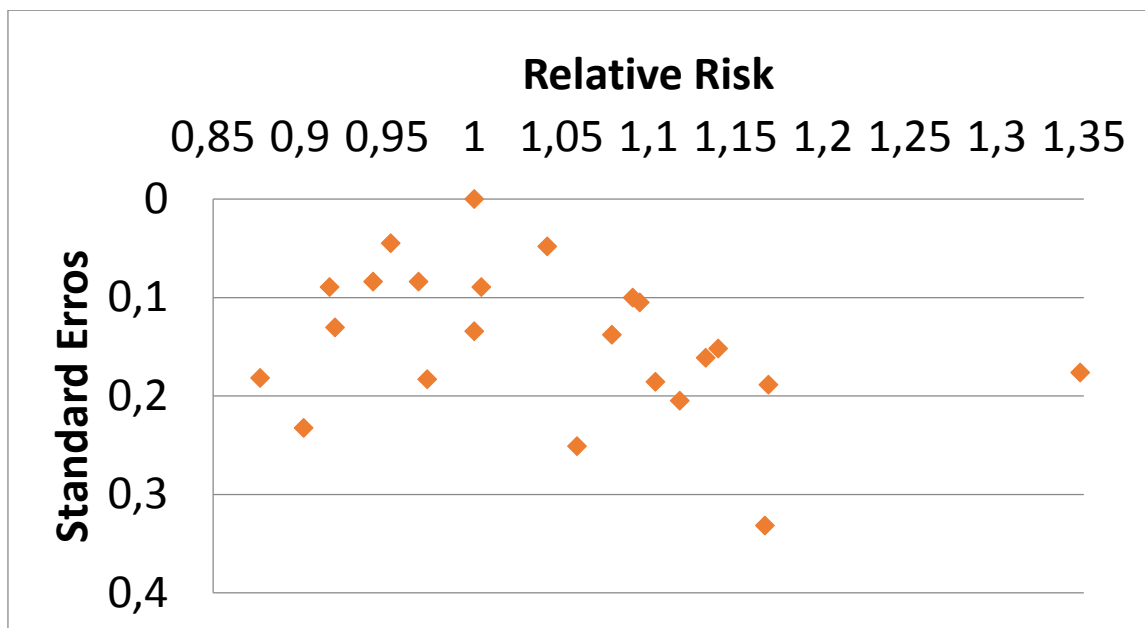
Figure 9. Funnel plot. RRs are plotted against standard errors, as a measure of the study's precision.

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.

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 (19, 38, 40). 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 (I2 = 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.

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.

Limitations in this review include the lack of a uniform definition of "clinical cure" or "clinical efficacy" in the original studies. In fact, we have reclassified a small but not dismissible proportion of cases to approach the current standard definition of "treatment failure" under the intention-to-treat principle.

Other limitation regards the uncertainty of the optimal dosing of teicoplanin along the years of its use, particularly in severe infections or critically ill patients. Initial studies with teicoplanin used a much lower dose, generally half of that currently used. 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.

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.

Teicoplanin is as efficacious as vancomycin regarding clinical and microbiological cure, although it is associated with a lower risk of nephrotoxicity and skin rash, as reported in other meta- analyses. There is no consistent evidence of efficacy of teicoplanin compared to vancomycin for treating endocarditis. Therefore, teicoplanin cannot be currently recommended for this condition.

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