Original Article

Efficacy and safety of linezolid versus teicoplanin for the treatment of MRSA infections: a meta-analysis

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Abstract

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of serious infections. Linezolid and teicoplanin are widely used in the treatment of infections caused by MRSA. However, the efficacy and safety of linezolid compared with teicoplanin remains controversial. The purpose of this study was to systematically review the efficacy and safety of linezolid versus teicoplanin for the treatment of MRSA infections.

Methodology: A meta-analysis was performed on the published studies. Pooled relative risk (RR) and 95% confidence interval (95% CI) were calculated to determine whether there were significant differences between the linezolid group and the teicoplanin group on the efficacy and safety.

Results: Seventeen studies were included, involving 2,040 patients. The results showed that linezolid was associated with better clinical cure rate (RR = 1.14, 95% CI = 1.08-1.21, p < 0.00001) and microbiological eradication rate (RR = 1.28, 95% CI = 1.18-1.39, p < 0.00001) compared with teicoplanin. There were no statistically significant differences between the two groups in the treatment of MRSA infections regarding the adverse events (RR = 1.15, 95% CI = 0.97-1.35, p = 0.10) and the mortality (RR = 0.85, 95% CI = 0.61-1.18, p = 0.33).

Conclusions: The results suggest that linezolid may be a better choice for the treatment of patients with MRSA infections. However, our recommendation is that the decision about treating MRSA infections with linezolid or with teicoplanin should depend on local availability, patient population, dosage regimens, costs and safety, rather than presumed differences in efficacy.

Key words: linezolid; teicoplanin; methicillin-resistant *Staphylococcus aureus;* MRSA; meta-analysis.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) represents a predominant pathogen associated with serious infections, including pneumonia, bacteremia and skin and soft tissue infection. The mortality rate in patients with MRSA pneumonia ranged from 33% to 55% [1]. Therefore, the treatment options against MRSA infections have become an urgent priority. The glycopeptide antibiotic teicoplanin is the first or second line drug in the treatment of MRSA infections [2]. The level of plasma concentrations (C_{min}) of teicoplanin are widely considered as the predominant factor for the positive clinical outcome [3]. However, pharmacokinetic disposition of teicoplanin in patients with MRSA infections is scarce and shows extensive individual variation, while the appropriate dosage

regimens for teicoplanin remain controversial [4,5,6,7]. Furthermore, adverse effect, such as renal toxicity, limits its use in patients with renal dysfunction [8]. Linezolid has also been widely used in the treatment of MRSA infections in recent years [9,10]. It inhibits bacterial protein synthesis by preventing formation of the 70S initiation complex [11], resulting in good efficacy in treating MRSA infections. However, several studies reported that critically ill patients receiving the standard dosing regimen of linezolid still show treatment failure even though the isolated pathogens are sensitive to linezolid [12,13]. Other potential problems of treatment with linezolid include its bacteriostatic rather than bactericidal action and the high incidence of adverse events [11].

Several studies compared the efficacy and safety of linezolid and teicoplanin in the past ten years. However, the results are diverse, and unique conclusion has not been made. For example, a meta-analysis of nine randomized controlled trials (RCTs) did not demonstrate the clinical superiority of linezolid versus glycopeptide antibiotics for the treatment of nosocomial pneumonia [14]. Another meta-analysis of eight RCTs reported similar results [15]. Though, only RCTs published until 2011 were included in that meta-analysis. Recently, a meta-analysis of seven studies reported superior clinical effective rate and microbiological eradication rate of linezolid comparing to teicoplanin [16]. The results were consistent with the findings of other meta-analysis [17,18]. However, only patients with pneumonia were included in these meta-analysis.

In light of this controversy, it is necessary to review the efficacy and safety of linezolid versus teicoplanin in patients with MRSA infections. Therefore, we conducted the meta-analysis to highlight the present evidence for both, the efficacy and safety, of linezolid versus teicoplanin for the treatment of MRSA infections, and thus provide valuable information for clinicians in the clinical practice.

Methodology
Literature search
The literature search was performed on the PubMed, Cochrane Central Register of Controlled Trials, ScienceDirect, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), VIP Database for Chinese Technical Periodicals (VIP) and Wan Fang Digital Periodicals Database (WFDP) from their inception up to May 2017. The following subject headings were employed: "linezolid", "teicoplanin or targocid", "MRSA" or "Methicillin-resistant *Staphylococcus aureus*".

Study selection
The following inclusion criteria were applied: (1) study designed RCTs, including quasi-RCT; (2) study population consisting of patients with MRSA infections and (3) intervention therapies consisting of linezolid and teicoplanin; (4) outcome variables: the primary outcomes provided should include at least one of the following: total clinical cure, microbiological eradication, major drug adverse events and the mortality. Studies were excluded if: (1) they were not written in English or Chinese; (2) the control group did not use teicoplanin; (3) clinical success was not assessed as an end point; (4) the data were either not complete or not available; (5) the focus was pharmacokinetic or pharmacodynamics variables.

Data collection and quality assessment
The following data were extracted from each study: name of first author, publication year, gender, median age, total number of treatment and control group, dosage regimens, a type of infection, treatment duration. In order to maintain uniformity and reduce potential bias, two investigators independently assessed the quality and extracted the data according to the inclusion and exclusion criteria. They examined and recorded the trial characteristics and outcomes, using the Jadad-scale [19] to review the reliability of studies and discussed with each other if there were any disagreement. One point was awarded for each procedure, with a maximum score of 5 scores of 3 or more points were high-quality trials, whereas those with 2 or fewer points were low-quality trials.

Statistical analysis
Meta-analysis was performed according to the Quality of reporting of meta-analyses guidelines and the Cochrane handbook 5.0.1 for Systematic reviews of interventions [20]. The Mantel-Haenszel (MH) RR, 95% CI and p-value were used to assess efficacy and safety endpoints. Heterogeneity was examined by Chi-square test. Chi-square statistics with a p-value < 0.1 was considered to be significant across trials. Treatment effects across trials were combined using a random effects model ($I^2 > 50\%$) and a fixed effects model ($I^2 < 50\%$). The publication bias was assessed using funnel plots with visual inspection of asymmetry and Begg's or Egger's tests, with a $p < 0.05$ indicating potential bias

Figure 1. Flow diagram of the studies for meta-analysis.

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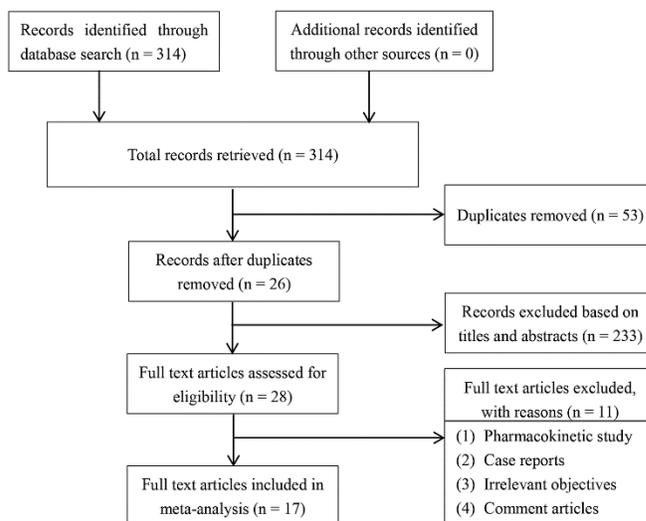
(STATA version 11.0). Forest plots for the relevant comparisons were performed using Review Manager version 5.2 software.

Results

Characteristics of eligible studies

The electronic database search yielded 148 potentially relevant publications with a total sample size of 2,040 patients (1,016 in the treatment group and 1,024 in the control group). Seventeen of these studies

fulfilled the inclusion criteria and were included in the meta-analysis [21-37]. (Figure 1) The main characteristics of these studies are presented in Table 1.

In these seventeen studies, all studies design included a baseline assessment and no significant differences were found between the baseline data.

Clinical cure and microbiological eradication

Comparisons of clinical cure and microbiological eradication between linezolid and teicoplanin are

Table 1. Main characteristics the studies included in the meta-analysis.

Study	Year	Gender (Fª/Mᵇ)	Median age (or mean ± SD)	Case (linezolid/teico planin)	Dosage regimens		Type of infection	Treatment duration (d)	Jadad score
					Linezolid	Teicoplanin			
Lopez *et al.* [21]	2003	105/98	48.4±19.7	97 vs 106	Ivᵍ 600 mg bid, followed by oral 600 mg bid	Dosed per local prescribing guidelines	Pneumonia SSTIᵈ bacteremia	7-28	2
Cepeda *et al.* ˡ[22]	2004	67/135	59.2±17.2(Lʰ) / 57.3±17.6(Tⁱ)	100 vs 102	Iv 600 mg q12h	Iv 3 days 400 mg q12h, followed by oral 400 mg q24h	Gram-positive infections pneumonia bacteremia	8-21	4
Wilcox *et al.* [23]	2004	196/234	54±19	215 vs 215	Iv 600 mg q12h, followed by oral 600 mg q12h	Dosed per local prescribing guidelines	Pneumonia SSTI bacteremia	7-28	3
Hayman *et al.* [24]	2007	Nᵉ	N	21 vs 26	Iv 600 mg q12h	Iv 6 mg/kg q24h	SSTI	1-7	2
Tascini *et al.* [25]	2009	99/161	56.21±18.15(L) / 59.98±20.34(T)	169 vs 91	Iv 600 mg q12h, followed by oral 600 mg q12h	Empirical therapy	Pneumonia SSTI bacteremia	3-34	3
Tasbakan *et al.* [26]	2010	28/13	66.0±16.0	19 vs 22	Iv 600 mg q12h	Iv 600 mg q12h	Pneumonia	7-21	2
Bi HY *et al.* [27]	2010	3/26	N	11 vs 18	Ivgttᶠ 600 mg q12h	Ivgtt 400 mg q24h	Pneumonia	7-14	2
Tang J *et al.* [28]	2010	25/57	58.4±26.3	37 vs 45	Ivgtt 600 mg bid	Ivgtt 400 mg qd	Pneumonia	7-15	2
Chen JL *et al.* [29]	2012	52/82	78.5±6.8	27 vs 57	N	N	Pneumonia	7-15	3
Zhu AJ *et al.* [30]	2012	46/54	63±9.63	50 vs 50	Ivgtt 600 mg q12h	Ivgtt 400 mg q24h	Pneumonia SSTI bacteremia	7-28	2
Yao MY *et al.* [31]	2012	21/47	61.8	33 vs 35	Ivgtt 600 mg q12h	Ivgtt 3 days 400 mg q12h，followed by ivgtt 400 mg q24h	MRSAᶜ	14-18	3
Tong WN *et al.* [32]	2013	15/48	72.6±5.7(L) / 74.1±3.8(T)	29 vs 34	Ivgtt 600 mg q12h	Ivgtt 400 mg q24h	Pneumonia	12-15	2
Shi Z *et al.* [33]	2015	97(M)	85.9	42 vs 55	Ivgtt 600 mg q12h	Ivgtt 400 mg q24h	MRSA	7-21	2
Liu L *et al.* [34]	2015	41/49	70.89±4.32	45 vs 45	Ivgtt 600 mg q12h	Ivgtt 3 days 0.4 g q24h, followed by ivgtt 0.2 g q24h	Gram-positive infections	3-21	2
Wang MQ *et al.* [35]	2015	21/43	60.21±15.68(L) / 58.47±16.34(T)	31 vs 33	Ivgtt 600 mg q12h	Ivgtt 3 days 0.4 g q12h，followed by ivgtt 0.4 g q24h	MRSA	10-21	2
Wang YF *et al.* [36]	2016	29/51	55.4±8.5(L) / 54.7±7.3(T)	40 vs 40	Ivgtt 600 mg q12h	Ivgtt 400 mg q12h	Pneumonia	14	2
Du ZL *et al.* [37]	2016	55/45	56.9±11.1(L) / 58.1±12.5(T)	50 vs 50	Ivgtt 600 mg q12h	Ivgtt 400 mg q12h	Pneumonia	14	2

ªF: female; ᵇM: male; ᶜMRSA: methicillin-resistant *Staphylococcus aureus*; ᵈSSTI: skin and soft tissue infection; ᵉN: not mentioned; ᶠIvgtt: intravenously *guttae*; ᵍIV: intravenous injection; ʰL: Linezolid; ⁱT: Teicoplanin

shown in Figure 2 and Figure 3, respectively. Heterogeneity was considered absent at the sensitivity analyses. A fixed effects model was performed on outcome measurements. The results showed that clinical cure between linezolid and teicoplanin for the treatment of MRSA infections were statistically significant differences (n = 14 studies, 1678 patients; RR = 1.14, 95% CI = 1.08-1.21，p < 0.00001, I^2 =

38%). The results were similar for microbiological eradication (n = 14 studies, 1,100 patients; RR = 1.28, 95% CI = 1.18-1.39, p < 0.00001, I^2 = 37%).

Adverse events and mortality

There were no statistically significant differences in the total adverse events (Figure 4) (n = 12 studies, 1,454 patients; RR = 1.15, 95% CI = 0.97-1.35, p = 0.10, I^2 =

Figure 2. Linezolid versus teicoplanin: meta-analysis of clinical cure for the clinically assessed patients.

Study or subgroup	Linezolid Events	Total	Teicoplanin Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Bi HY 2010 [27]	8	11	5	18	0.7%	2.62 [1.14, 5.99]
Cepeda 2004 [22]	15	18	24	29	3.4%	1.01 [0.77, 1.31]
Du ZL 2016 [37]	20	50	12	50	2.2%	1.67 [0.92, 3.03]
Hayman 2007 [24]	18	21	22	26	3.7%	1.01 [0.80, 1.29]
Liu L 2015 [34]	32	45	25	45	4.6%	1.28 [0.93, 1.76]
Lopez 2003 [21]	95	97	99	106	17.6%	1.05 [0.99, 1.11]
Shi Z 2015 [33]	21	42	20	55	3.2%	1.38 [0.87, 2.18]
Tascini 2009 [25]	142	169	63	91	15.2%	1.21 [1.04, 1.41]
Tong WN 2013 [32]	10	29	9	34	1.5%	1.30 [0.61, 2.76]
Wang MQ 2015 [35]	14	31	16	33	2.9%	0.93 [0.55, 1.57]
Wang YF 2016 [36]	14	40	11	40	2.0%	1.27 [0.66, 2.45]
Wilcox 2004 [23]	205	215	188	215	35.0%	1.09 [1.03, 1.16]
Yao MY 2012 [31]	22	33	21	35	3.8%	1.11 [0.77, 1.60]
Zhu AJ 2012 [30]	26	50	22	50	4.1%	1.18 [0.78, 1.78]
Total (95% CI)		851		827	100.0%	1.14 [1.08, 1.21]
Total events	642		537			

Heterogeneity: Chi² = 21.07, df = 13 (p = 0.07); I² = 38%
Test for overall effect: Z = 4.78 (p < 0.00001)

Risk ratio M-H, Fixed, 95% CI
0.1 0.2   0.5   1   2   5   10
Favours Teicoplanin   Favours Linezolid

Figure 3. Linezolid versus teicoplanin: meta-analysis of microbiological eradication for the clinically assessed patients.

Study or subgroup	Linezolid Events	Total	Teicoplanin Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Bi HY 2010 [27]	9	11	7	18	1.7%	2.10 [1.11, 4.00]
Cepeda 2004 [22]	10	12	15	22	3.3%	1.22 [0.83, 1.79]
Du ZL 2016 [37]	24	50	15	50	4.7%	1.60 [0.96, 2.67]
Hayman 2007 [24]	31	41	27	52	7.4%	1.46 [1.06, 1.99]
Liu L 2015 [34]	30	45	22	45	6.9%	1.36 [0.95, 1.96]
Shi Z 2015 [33]	25	34	20	38	5.9%	1.40 [0.97, 2.01]
Tang J 2010 [28]	30	37	22	45	6.2%	1.66 [1.18, 2.32]
Tasbakan 2010 [26]	19	19	16	22	4.8%	1.36 [1.04, 1.77]
Tong WN 2013 [32]	26	29	24	34	6.9%	1.27 [0.99, 1.63]
Wang MQ 2015 [35]	26	31	28	33	8.5%	0.99 [0.80, 1.22]
Wang YF 2016 [36]	18	40	13	40	4.1%	1.38 [0.79, 2.43]
Wilcox 2004 [23]	77	94	60	86	19.5%	1.17 [0.99, 1.39]
Yao MY 2012 [31]	30	34	33	38	9.7%	1.02 [0.85, 1.21]
Zhu AJ 2012 [30]	40	50	34	50	10.6%	1.18 [0.93, 1.49]
Total (95% CI)		527		573	100.0%	1.28 [1.18, 1.39]
Total events	395		336			

Heterogeneity: Chi² = 20.69, df = 13 (p = 0.08); I² = 37%
Test for overall effect: Z = 6.05 (p < 0.00001)

Risk ratio M-H, Fixed, 95% CI
0.1 0.2   0.5   1   2   5   10
Favours Teicoplanin   Favours Linezolid

0%). The results were similar for mortality (Figure 5) (n = 6 studies, 1,100 patients; RR = 0.85， 95% CI = 0.61-1.18, p = 0.33, I^2 = 22%).

Publication bias analysis

Begg's funnel plot and Egger's test were performed to assess the publication bias of the seventeen studies. The results of Begg's funnel plot are shown in Figure 6. No publication bias was detected in this meta-analysis with either Begg's test (p > 0.05) or Egger's test (p > 0.05).

Sensitivity analyses

The trial by Cepeda *et al* was the only study adopted double-blind [22]. Its removal from all analyses did not change our results for the meta-analysis. For clinical

cure, there was no change on our results (RR = 1.15， 95% CI = 1.09-1.22, p < 0.00001). The results were similar for microbiological eradication (RR = 1.28, 95% CI = 1.18-1.39, p < 0.00001). For adverse events and mortality, the data were not used for sensitivity analysis due to lower heterogeneity.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Discussion

In the present meta-analysis, we collected and analyzed the clinical data from seventeen studies. The results showed that linezolid was associated with better clinical cure and microbiological eradication compared

Figure 4. Linezolid versus teicoplanin: meta-analysis of adverse events for the clinically assessed patients.

Study or subgroup	Linezolid Events	Total	Teicoplanin Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Bi HY 2010 [27]	1	11	2	18	0.9%	0.82 [0.08, 8.00]
Chen JL 2012 [29]	1	27	3	57	1.2%	0.70 [0.08, 6.46]
Du ZL 2016 [37]	9	50	10	50	6.1%	0.90 [0.40, 2.02]
Shi Z 2015 [33]	4	42	7	55	3.7%	0.75 [0.23, 2.39]
Tang J 2010 [28]	10	37	7	45	3.9%	1.74 [0.73, 4.12]
Tascini 2009 [25]	12	169	0	91	0.4%	13.53 [0.81, 225.92]
Tong WN 2013 [32]	10	29	12	34	6.8%	0.98 [0.50, 1.92]
Wang MQ 2015 [35]	3	31	2	33	1.2%	1.60 [0.29, 8.92]
Wang YF 2016 [36]	5	40	4	40	2.5%	1.25 [0.36, 4.32]
Wilcox 2004 [23]	121	215	110	215	67.4%	1.10 [0.92, 1.31]
Yao MY 2012 [31]	3	30	4	35	2.3%	0.88 [0.21, 3.60]
Zhu AJ 2012 [30]	8	50	6	50	3.7%	1.33 [0.50, 3.56]
Total (95% CI)		**731**		**723**	**100.0%**	**1.15 [0.97, 1.35]**
Total events	187		167			

Heterogeneity: Chi^2 = 5.79, df = 11 (P = 0.89); I^2 = 0%
Test for overall effect: Z = 1.65 (P = 0.10)

Favours Teicoplanin   Favours Linezolid

Figure 5. Linezolid versus teicoplanin: meta-analysis of mortality for the clinically assessed patients.

Study or subgroup	Linezolid Events	Total	Teicoplanin Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
Chen JL 2012 [29]	6	27	15	57	14.6%	0.84 [0.37, 1.93]
Lopez 2003 [21]	2	97	10	106	14.5%	0.22 [0.05, 0.97]
Tang J 2010 [28]	3	37	3	45	4.1%	1.22 [0.26, 5.67]
Tasbakan 2010 [26]	8	19	14	22	19.7%	0.66 [0.36, 1.22]
Tascini 2009 [25]	27	169	10	91	19.7%	1.45 [0.74, 2.87]
Wilcox 2004 [23]	15	215	18	215	27.3%	0.83 [0.43, 1.61]
Total (95% CI)		**564**		**536**	**100.0%**	**0.85 [0.61, 1.18]**
Total events	61		70			

Heterogeneity: Chi^2 = 6.43, df = 5 (P = 0.27); I^2 = 22%
Test for overall effect: Z = 0.98 (P = 0.33)

Favours Teicoplanin   Favours Linezolid

with teicoplanin. It is possible that efficacy differences between linezolid and teicoplanin might be related to excellent tissue penetration and 100% oral bioavailability of linezolid [38,39]. On the other hand, the reported good penetration of linezolid into skin was an important factor shown in several studies that may partly explain the higher efficacy of skin and soft tissue infection (SSTI). Meanwhile, the availability of an oral formulation can improve the patient's quality of life [40]. In the present meta-analysis, several studies focused on elderly patients with nosocomial pneumonia and reported linezolid was associated with better efficacy compared with teicoplanin in elderly patients [27,29,32-34]. We believe that higher clinical cure rate may contribute to better outcomes in elderly patients with nosocomial pneumonia because the immune system and organ function are often affected by aging and underlying diseases [41]. In contrast, teicoplanin have significant drawbacks which compromise their clinical usefulness for the treatment of serious MRSA

infections. For example, clinical efficacy is relatively slow following initiation of therapy [42], and continued administration invariably results in the need for monitoring of serum levels and prolonged hospital stay. Consequently, some clinicians recommend that loading doses of teicoplanin should be used for critically ill patients. Data on whether or not loading doses of teicoplanin were used are not available for patients in this study. In brief, we recommend that linezolid may be a better choice for the treatment of skin and soft tissue infections and nosocomial pneumonia. Notably, our findings argue against widespread routine use of linezolid for MRSA infection based on the presumption of superior efficacy. Targeted use of linezolid may be of greater importance given the outbreak of linezolid-resistant *Staphylococcus aureus* [43].

There were no statistically significant differences in the total adverse events. Falagas *et al*. demonstrated that the increased thrombocytopenia was associated with linezolid [44]. Similar results were found in our study.

Figure 6. Estimate of each of the publication bias. Funnel plots of the studies comparing the efficacy and safety of linezolid and teicoplanin (A: clinical cure; B: microbiological eradication; C: adverse events; D: Mortality)**.**
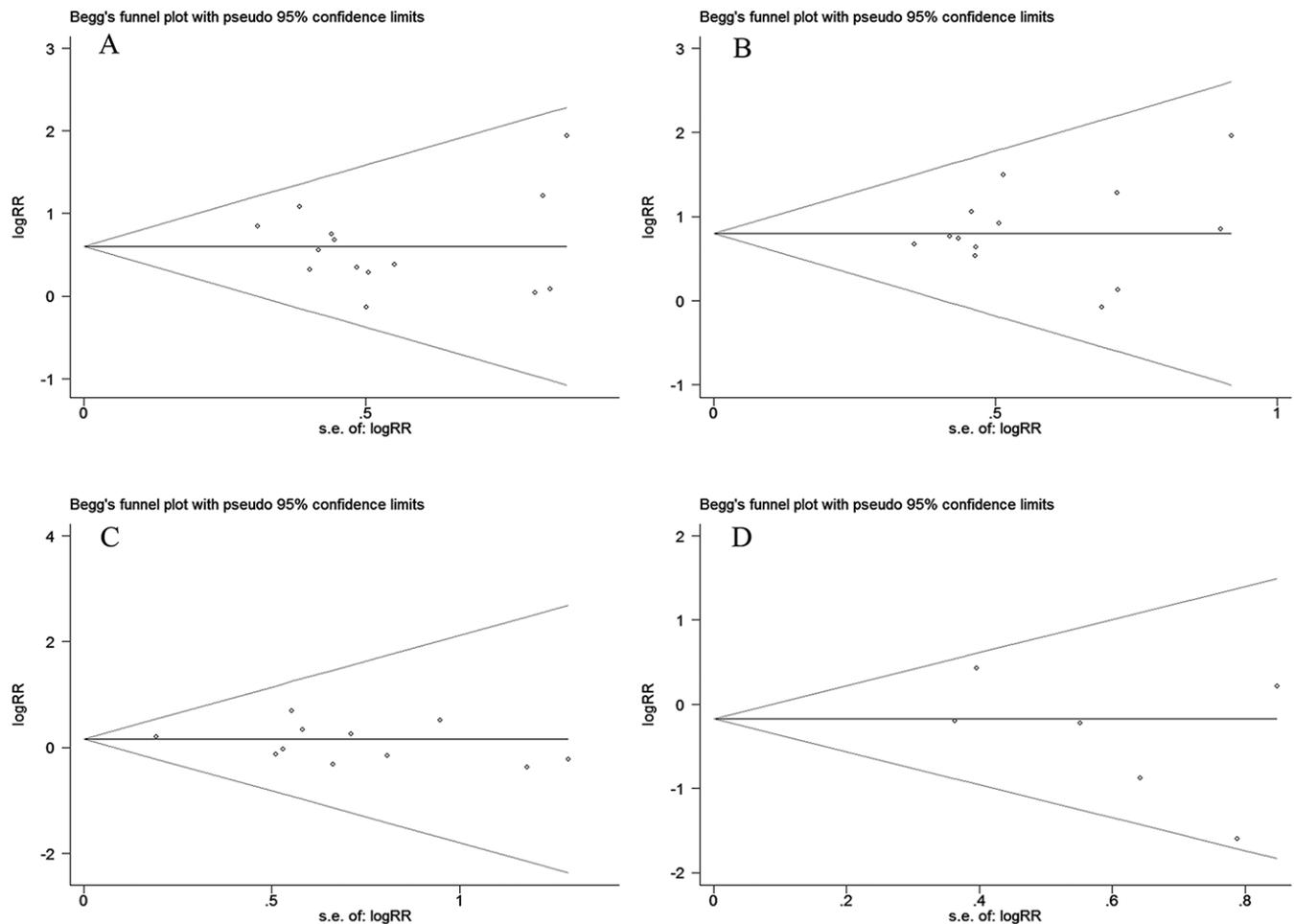
Besides, adverse events such as diarrhea, nausea, headache and fever were associated with linezolid. Given these potential adverse events, the safety of linezolid should be monitored during treatment. Clinicians should be aware of the symptoms and sign of toxicity so that linezolid can be immediately discontinued if these occur. In contrast, the most common adverse event of teicoplanin is renal toxicity, which may limit its use in patients with renal dysfunction [8]. Therefore, linezolid may be safer than teicoplanin for treating patients with renal dysfunction caused by MRSA. Clinicians should pay careful attention to the safety of antibiotics for treating specific patient population with MRSA infections. In addition, no difference in mortality was noticed in the pooled trials. This could be attributed to the patients with more serious infections were enrolled in the linezolid group.

Previous economic studies have demonstrated that linezolid was more cost-effective than teicoplanin in treating MRSA infections [45,46]. This may be due to linezolid's higher efficacy and fewer days of hospital stay, leading to a reduction in the total duration of hospital stay, treatment and costs.

The funnel plot is asymmetric, which reveal a potential publication bias may be caused by a language bias, inflated estimates by a flawed methodological design in small and low quality studies. Therefore, publication bias was assessed using Begg's and Egger's test. The results showed that no publication biases were detected, and the included studies could be thought no affect the outcomes assessment.

There are several limitations that should be considered in the present meta-analysis: (1) some studies were not double-blind and the lack of blinding could affect the outcomes assessment; (2) only English and Chinese studies were included in this analysis, which may cause language bias and finally (3) the most important limitation was publication bias. In the present analysis, although the assessment of publication bias was not significant, the possibility of publication bias may exist in any research, because the negative studies and studies with small sample sizes may be less likely to be published.

Conclusion

In conclusion, based on currently available data from seventeen studies, the findings suggest that linezolid has superior clinical efficacy and similar safety for the treatment of MRSA infections compared to teicoplanin. It may provide valuable information for clinicians to decide and optimize dosage regimens of linezolid and teicoplanin for treating MRSA infections in clinical practice. The conclusions still need to be further validated by more well-designed RCTs with large samples.

Authors' contributions

H Chen, XH Huang, ML Wang and JB Li conceived the idea, designed the study and wrote the manuscript. All authors contributed to the qualitative and quantitative synthesis of the included trials. L Li, YY Liu, MM Wu and SL Xu revised the manuscript. All authors read and approved the final version of the manuscript.

References

1. DeRyke CA, Lodise TP Jr, Rybak MJ, McKinnon PS (2005) Epidemiology, treatment, and outcomes of nosocomial bacteremic *Staphylococcus aureus* pneumonia. Chest 128: 1414-1422.
2. Zhao W, Zhang D, Storme T, Baruchel A, Decleves X, Jacqz-Aigrain E (2015) Population pharmacokinetics and dosing optimization of teicoplanin in children malignant haematological disease. Br J Clin Pharmacol 80: 1197-1207.
3. Pea F, Viale P, Candoni A, Pavan F, Pagani L, Damiani D, Casini M, Furlanut M (2004) Teicoplanin in patients with acute leukaemia and febrile neutropenia: a special population benefiting from higher dosages. Clin Pharmacokinet 43: 405-415.
4. Pea F, Brollo L, Viale P, Pavan F, Furlanut M (2003) Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. Chemother 51: 971-975.
5. Niwa T, Imanishi Y, Ohmori T, Matsuura K, Murakami N, Itoh Y (2010) Significance of individual adjustment of initial loading dosage of teicoplanin based on population pharmacokinetics. Int J Antimicrob Agents 35: 507-510.
6. Kanazawa N, Matsumoto K, Ikawa K, Fukamizu T, Shigemi A, Yaji K, Shimodozono Y, Morikawa N, Takeda Y, Yamada K (2011) An initial dosing method for teicoplanin based on the area under the serum concentration time curve required for MRSA eradication. J Infect Chemother 17: 297-300.
7. Ogawa R, Kobayashi S, Sasaki Y, Makimura M, Echizen H (2013) Population pharmacokinetic and pharmacodynamic analyses of teicoplanin in Japanese patients with systemic MRSA infection. Int J Clin Pharmacol Ther 51: 357-366,
8. Li N, Zhu L, Xu G, Ge T, Qi F,Li M (2017) Optimal teicoplanin dosage regimens for methicillin-resistant *Staphylococcus aureus* infections in endocarditis patients and renal failure patients. J Chemother 6: 1-7.
9. Li J, Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, Pan F, Huang WX (2017) Linezolid vs vancomycin in treatment of methicillin-resistant *Staphylococcus aureus* infections: a meta-analysis. Eur Rev Med Pharmacol Sci 21: 3974-3979.

10. Alvarez-Lerma F, Munoz-Bermudez R, Samper-Sanchez MA, Gracia Arnilla MP, Grau S, Luque S (2017) Successful treatment of Panton-Valentine leukocidin-positive methicillin-resistant *Staphylococcus aureus* pneumonia with high doses of linezolid administered in continuous infusion. Med Intensiva 41: 56-59.

11. Ager S, Gould K (2012) Clinical update on linezolid in the treatment of Gram-positive bacterial infections. Infect Drug Resist 5: 87-102.

12. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ (2003) Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 42: 1411-1423.

13. Smith PF, Birmingham MC, Noskin GA, Meagher AK, Forrest A, Rayner CR, Schentag JJ (2003) Safety, efficacy and pharmacokinetics of linezolid for treatment of resistant Gram-positive infections in cancer patients with neutropenia. Ann Oncol 14: 795-801.

14. Kalil AC, Murthy MH, Hermsen ED, Neto FK, Sun J, Rupp ME (2011) Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: a systematic review and meta-analysis. Crit Care Med 38: 1802-1808.

15. Walkey AJ, O'Donnell MR, Wiener RS (2011) Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a meta-analysis of randomized controlled trials. Chest 139: 1148-1155.

16. Peng Y, Chen XF, Bi JQ, Yao ZJ (2013) Linezolid versus teicoplanin for the treatment of methicillin-resistant *Staphylococcus aureus* pneumonia: a meta-analysis. Chin J Evid-based Med 20: 1340-1346.

17. Jiang H, Tang RN, Wang J (2013) Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: meta-analysis of randomised controlled trials. Eur J Clin Microbiol Infect Dis 32: 1121-1128.

18. Fu J, Ye X, Chen C, Chen S (2013) The efficacy and safety of linezolid and glycopeptides in the treatment of *Staphylococcus aureus* infections. PLoS One 8: e58240.

19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1-12.

20. Higgins JPT, Green S (2008) Cochrane handbook for systematic reviews of interventions version 5.0.1. The Cochrane Collaboration. Available:http://www.handbook.cochrane.org. Accessed 20 November 2017.

21. Lopez H, Li JZ, Balan DA, Willke RJ, Rittenhouse BE, Mozaffari E, Vidal G, Zitto T, Tang T (2003) Hospital resource use and cost of treatment with linezolid versus teicoplanin for treatment of serious Gram-positive bacterial infections among hospitalized patients from South America and Mexico: results from a multicenter trial. Clin Ther 25: 1846-1871.

22. Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, Taylor L, Hayman S, Shaw S, Kibbler C, Shulman R, Singer M, Wilson AP (2004) Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. J Antimicrob Chemother 53: 345-355.

23. Wilcox M, Nathwani D, Dryden M (2004) Linezolid compared with teicoplanin for the treatment of suspected or proven Gram-positive infections. J Antimicrob Chemother 53: 335-344.

24. Hayman S, Wilson AP, Singer M, Bellingan G (2007) Effect of linezolid and teicoplanin on skin staphylococci. J Antimicrob Chemother 59: 1281-1282.

25. Tascini C, Gemignani G, Doria R, Biancofiore G, Urbani L, Mosca C, Malacarne P, Papineschi F, Passaglia C, Dal Canto L, Procaccini M, Furneri G, Didoni G, Filipponi F, Menichetti F (2009) Linezolid treatment for Gram-positive infections: a retrospective comparison with teicoplanin. J Chemother 21: 311-316.

26. Tasbakan MS, Korkmaz Ekren P, Pullukcu H, Basarik B, Susur A, Aydemir S, Basoglu OK, Bacakoglu F (2010) Comparison of teicoplanin and linezolid therapies in patients with methicillin-resistant *Staphylococcus aureus* pneumonia acquired from respiratory intensive care unit. Mikrobiyol Bul 44: 357-366.

27. Bi HY, Yang HJ, Tian F (2010) Curative-effect observation of linezolid and teicoplanin for gerontal patients with MRSA pneumonia. MMJC 12: 14-16.

28. Tang J, Zhu ZH (2010) Curative-effect observation of linezolid, vancomycin and teicoplanin for methicillin-resistant *Staphylococcus aureus* related severe pneumonia. Clin Med 23: 58-59.

29. Chen JL, Xie CJ (2012) Clinical research on methicillin-resistant *Staphylococcus aureus* pneumonia in aged patients. Chin J Nosocomiol 22: 4136-4138.

30. Zhu AJ, Xu L (2012) Comparison of clinical efficacy of linezolid and teicoplanin in the treatment of Gram-positive cocci infection. China Pharmacy 23: 914-916.

31. Yao MY, Xing LH, Zhang QX, Xu AG, Zhang WH (2012) Clinical efficacy of teicoplanin and linezolid for MRSA infections: a comparative study. Chin J Nosocomiol 22: 2183-2185.

32. Tong WN, Zhuo AS, Cao YS, Xu SL (2013) Clinical comparison of several common anti-MRSA antibiotics in elderly patients with lung infection. Clin J Med Offic 41: 124-127.

33. Shi Z, Kang JQ (2015) Restrospective analysis of linezolid and teicoplanin in the treatment of elderly patients with severe MRSA infection. China Pharmacy 26: 4140-4142.

34. Liu L (2015) The efficacy of linezolid in the treatment of elderly patients with Gram-positive infection. Jilin Med J 36: 3289-3290.

35. Wang MQ, Zhang SS, Liu XJ, Qi SY, Xu YL (2015) Efficacies of teicoplanin, vancomycin, and linezolid in treatment of patients with MRSA infections. Chin J Nosocomiol 25: 3923-3927.

36. Wang YF, Zhong W, Chen DL (2016) Clinical observation of linezolid , teicoplanin and vancomycin in the treatment of hospital- acquired MRSA pneumonia. China Pharmacy 27: 3708-3710.

37. Du ZL, Jiao YK, Cheng ZT, Niu YK (2016) Clinical observation of linezolid combined with teicoplanin in the treatment of severe methicillin-resistant *Staphylococcus aureus* pneumonia. China Pharmacy 27: 4541-4543.

38. Boselli E, Breilh D, Rimmelé T, Djabarouti S, Toutain J, ChassardD, Saux MC, Allaouchiche B (2005) Pharmacokinetics andintrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. Crit Care Med 33: 1529–1533.

39. Boselli E, Breilh D, Caillault-Sergent A, Djabarouti S, Guillaume C, Xuereb F, Bouvet L, Rimmelé T, Saux MC, Allaouchiche B (2012) Alveolar diffusion and pharmacokinetics of linezolid administered incontinuous

infusion to critically ill patients with ventilator-associated pneumonia. J Antimicrob Chemother 67: 1207–1210.

40. Grau S, Mateu-de Antonio J, Soto J, Marin-Casino M, Salas E (2005) Pharmacoeconomic evaluation of linezolid versus teicoplanin in bacteremia by Gram-positive microorganisms. Pharm World Sci 27: 459-464.

41. Mizokami F, Shibasaki M, Yoshizue Y, Noro T, Mizuno T, Furuta K (2013) Pharmacodynamics of vancomycin in elderly patients aged 75 years or older with methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia. Clin Interv Aging 8: 1015-1021.

42. Ferrara AM (2007) Treatment of hospital-acquired pneumonia caused by methicillin-resistant Staphylococcus aureus. Int J Antimicrob Agents 30: 19-24.

43. Sanchez Garcia M, De la Torre MA, Morales G, Pelaez B, Tolon MJ, Domingo S, Candel FJ, Andrade R, Arribi A, Garcia N, Martinez Sagasti F, Fereres J, Picazo J (2010) Clinical outbreak of linezolid-resistant *Staphylococcus aureus* in an intensive care unit. JAMA 303: 2260-2264.

44. Falagas ME , Siempos II , Vardakas KZ (2008) Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials . Lancet Infect Dis 8: 53-66.

45. Grau S, Aguado JM, Mateu-de Antonio J, Gonzalez P, Del Castillo A (2007) Economic evaluation of linezolid versus teicoplanin for the treatment of infections caused by gram-positive microorganisms in Spain. J Chemother 19: 398-409.

46. Nathwani D, Li JZ, Balan DA, Willke RJ, Rittenhouse BE, Mozaffari E, Tavakoli M, Tang T (2004) An economic evaluation of a European cohort from a multinational trial of linezolid versus teicoplanin in serious Gram-positive bacterial infections: the importance of treatment setting in evaluating treatment effects. Int J Antimicrob Agents 23: 315-324.

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