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.

J Infect Dev Ctries 2017; 11(12):926-934. doi:10.3855/jidc.9447

(Received 21 May 2017 – Accepted 03 November 2017)

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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 (Cmin) 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 regimen, 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 (I² > 50%) and a fixed effects model (I² < 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.
(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

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

| Study            | Year | Gender (F/M*) | Median age (or mean ± SD) | Case (linezolid/teicoplanin) | Dosage regimens | Type of infection | Treatment duration (d) | Jadad score |
|------------------|------|---------------|---------------------------|------------------------------|-----------------|-------------------|------------------------|-------------|
| Lopez et al.     | 2003 | 105/98        | 48.4±19.7                 | 97 vs 106                    | Iv 600 mg bid, followed by oral 600 mg bid | Pneumonia SSTI bacteraemia | 7-28           | 2           |
| Cepeda et al.    | 2004 | 67/135        | 59.2±17.2 (L²) / 57.3±17.6 (T) | 100 vs 102                   | Iv 600 mg q12h, followed by oral 400 mg q24h | Gram-positive infections pneumonia bacteraemia | 8-21           | 4           |
| Wilcox et al.    | 2004 | 196/234       | 54±19                     | 215 vs 215                    | Iv 600 mg q12h, followed by oral 600 mg q24h | Pneumonia SSTI bacteraemia | 7-28           | 3           |
| Hayman et al.    | 2007 | N*            | N                         | 21 vs 26                      | Iv 600 mg q12h, followed by oral 600 mg bid | Empirical therapy | 1-7            | 2           |
| Tascini et al.   | 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 bid | Pneumonia SSTI bacteraemia | 3-34           | 3           |
| Tasbakan et al.  | 2010 | 28/13         | 66.0±16.0                 | 19 vs 22                      | Iv 600 mg q12h, followed by Ivgtt 600 mg q24h | Pneumonia SSTI bacteraemia | 7-21           | 2           |
| Bi HY et al.     | 2010 | 3/26          | N                         | 11 vs 18                      | Ivgtt 400 mg q24h | Pneumonia SSTI bacteraemia | 7-14           | 2           |
| Tang J et al.    | 2010 | 25/57         | 58.4±26.3                | 37 vs 45                      | Ivgtt 400 mg q24h | Pneumonia SSTI bacteraemia | 7-15           | 2           |
| Chen JL et al.   | 2012 | 52/82         | 78.5±6.8                 | 27 vs 57                      | Ivgtt 400 mg q24h | Pneumonia SSTI bacteraemia | 7-15           | 3           |
| Zhu AJ et al.    | 2012 | 46/54         | 63±9.63                  | 50 vs 50                      | Ivgtt 400 mg q24h | Pneumonia SSTI bacteraemia | 7-28           | 2           |
| Yao MY et al.    | 2012 | 21/47         | 61.8                      | 33 vs 35                      | Ivgtt 400 mg q24h | MRSA^c | 14-18           | 3           |
| Tong WN et al.   | 2013 | 15/48         | 72.6±5.7 (L) / 74.1±3.8 (T) | 29 vs 34                      | Ivgtt 400 mg q24h | Pneumonia SSTI bacteraemia | 12-15          | 2           |
| Shi Z et al.     | 2015 | 97(M)         | 85.9                      | 42 vs 55                      | Ivgtt 400 mg q24h | MRSA | 7-21           | 2           |
| Liu L et al.     | 2015 | 41/49         | 70.89±4.32               | 45 vs 45                      | Ivgtt 400 mg q24h | Gram-positive infections | 3-21           | 2           |
| Wang MQ et al.   | 2015 | 21/43         | 60.21±15.68 (L) / 58.4±16.3 (T) | 31 vs 33                      | Ivgtt 400 mg q24h | MRSA | 10-21          | 2           |
| Wang Y et al.    | 2016 | 29/51         | 55.4±8.5 (L) / 54.7±7.3 (T) | 40 vs 40                      | Ivgtt 400 mg q24h | Pneumonia | 14            | 2           |
| Du ZL et al.     | 2016 | 55/45         | 56.9±11.1 (L) / 58.1±12.5 (T) | 50 vs 50                      | Ivgtt 400 mg q24h | Pneumonia | 14            | 2           |

*F: female; M: male; MRSA: methicillin-resistant *Staphylococcus aureus*; SSTI: skin and soft tissue infection; N: not mentioned; Ivgtt: intravenously guttae; IV: intravenous injection; L: Linezolid; T: 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, I² = 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, I² = 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, I² = 38%).

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

| Study or subgroup | Linezolid | Teicoplanin | Risk ratio M-H, Fixed, 95% CI |
|-------------------|-----------|-------------|-----------------------------|
| Bi HY 2010 [27]   | 8         | 11          | 2.62 [1.14, 5.99]           |
| Cepeda 2004 [22]  | 15        | 18          | 1.01 [0.77, 1.31]           |
| Du ZL 2016 [37]   | 20        | 50          | 1.67 [0.92, 3.03]           |
| Hayman 2007 [24]  | 18        | 21          | 1.01 [0.80, 1.29]           |
| Liu L 2015 [34]   | 32        | 45          | 1.28 [0.93, 1.76]           |
| Lopez 2003 [21]   | 95        | 97          | 1.05 [0.99, 1.11]           |
| Shi Z 2015 [33]   | 21        | 42          | 1.38 [0.87, 2.18]           |
| Tascini 2009 [25] | 142       | 169         | 1.21 [1.04, 1.41]           |
| Tong WN 2013 [32] | 10        | 29          | 1.30 [0.61, 2.76]           |
| Wang MQ 2015 [35] | 14        | 31          | 0.93 [0.55, 1.57]           |
| Wang YF 2016 [36] | 14        | 40          | 1.27 [0.66, 2.45]           |
| Wilcox 2004 [23]  | 205       | 215         | 1.09 [1.03, 1.16]           |
| Yao MY 2012 [31]  | 22        | 33          | 1.11 [0.77, 1.60]           |
| Zhu AJ 2012 [30]  | 26        | 50          | 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)

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

| Study or subgroup | Linezolid | Teicoplanin | Risk ratio M-H, Fixed, 95% CI |
|-------------------|-----------|-------------|-----------------------------|
| Bi HY 2010 [27]   | 9         | 11          | 2.10 [1.11, 4.00]           |
| Cepeda 2004 [22]  | 10        | 12          | 1.22 [0.83, 1.79]           |
| Du ZL 2016 [37]   | 24        | 50          | 1.60 [0.96, 2.67]           |
| Hayman 2007 [24]  | 31        | 41          | 1.46 [1.06, 1.99]           |
| Liu L 2015 [34]   | 30        | 45          | 1.36 [0.95, 1.96]           |
| Shi Z 2015 [33]   | 25        | 34          | 1.40 [0.97, 2.01]           |
| Tang J 2010 [28]  | 30        | 37          | 1.66 [1.18, 2.32]           |
| Tasbakan 2010 [26]| 19        | 19          | 1.36 [1.04, 1.77]           |
| Tong WN 2013 [32] | 26        | 29          | 1.27 [0.99, 1.63]           |
| Wang MQ 2015 [35] | 26        | 31          | 0.99 [0.80, 1.22]           |
| Wang YF 2016 [36] | 18        | 40          | 1.38 [0.79, 2.43]           |
| Wilcox 2004 [23]  | 77        | 94          | 1.17 [0.99, 1.39]           |
| Yao MY 2012 [31]  | 30        | 34          | 1.02 [0.85, 1.21]           |
| Zhu AJ 2012 [30]  | 40        | 50          | 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 < 0.000001)
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, I² = 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
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.

Acknowledgements

This study was supported by the National Natural Science Fund of China (81173133), the Fund of Excellent Talents in Colleges and Universities of Anhui Province, China (gxbjZD06) and the Fund of Academic leaders of Anhui Province, China (2015D068).

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.

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Conflict of interests: No conflict of interests is declared.