

*Review*

# Linezolid for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia: Queries continue

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The latest published Linezolid in the treatment of subjects with nosocomial pneumonia proven to be due to methicillin-resistant *Staphylococcus aureus* (ZEPHYR) trial was a phase IV, randomized, double-blind, multicenter, comparator-controlled study comparing the efficacy of fixed-dose linezolid to dose-optimized vancomycin in hospitalized adults for the treatment of methicillin-resistant *S. aureus* (MRSA) nosocomial pneumonia. They found out that the superiority of linezolid over vancomycin was with regard to both clinical responses and microbiological outcomes but without a survival advantage. However, the study had a number of shortcomings: failing to implement the guideline about vancomycin doing and goal trough level, recruitment of health care-associated pneumonia (HCAP) population, failing to explain mortality rate in different minimal inhibitory concentration (MIC) subgroups and glomerular filtration rates (GFR) subgroups etc. Limitations of the study made us consider routine use of linezolid for the treatment of MRSA pneumonia with prudence.

**Key words:** Nosocomial pneumonia (NP), trough level, ventilator-associated pneumonia (VAP), health care-associated pneumonia (HCAP), methicillin-resistant *S. aureus* (MRSA).

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## INTRODUCTION

This study was a phase IV, randomized, double-blind, multicenter, comparator-controlled study comparing the efficacy of fixed-dose linezolid to dose-optimized vancomycin in hospitalized adults for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia (Wunderink et al., 2012). The primary endpoint of this study was evaluated at the end of study (EOS) in per-protocol (PP) patients, and found superiority of linezolid over vancomycin. The secondary end points included clinical and microbiological outcomes in the modified intent-to-treat (mITT) population at end of

treatment (EOT) and EOS, microbiologic response in the PP population at EOT and EOS, and clinical response in the PP population at EOT. Evaluation of these secondary endpoints also showed superiority of the linezolid arm. Without a doubt, this is the first non-inferior design, with a nested superior randomized controlled trial that exclusively assessed the efficacy, safety and tolerability of linezolid versus vancomycin for the treatment of documented MRSA nosocomial pneumonia.

However, the study has a number of shortcomings besides the ones that the authors have mentioned in the

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article. These additional deficiencies are outlined:

1. The authors wanted to individualize vancomycin dose based on weight, creatinine clearance (Ccr), and trough levels assessed by the pharmacist to validate the previous post hoc analysis (Wunderink et al., 2003; Kollef et al., 2004) (which resulted in outcomes in favor of linezolid), and have been longtime criticized as potentially attributing to a lack of vancomycin dose-optimization in those trials. Additionally, it is unclear whether the dose of vancomycin was optimized in the present trial. The median trough levels were reported as 12.3 µg/ml at day 3 (140 cases), 14.7 µg/ml at day 6 (90 cases), and 16.1 µg/ml at day 9 (33 cases), which implies a great number of patients failed to achieve a trough level of > 15 µg/ml, which is recommended in the latest vancomycin therapeutic and monitoring guidelines (Liu, 2011; Rybak, 2009a, b). Of note, when we focus on day 3 serum vancomycin levels, only 138 (35 + 37 + 33 + 33 = 138) cases (79%) had trough concentrations measures, and only 33/138 (23.9%) achieved trough levels > 17.4 µg/ml. Generally speaking, failing to meet the guidelines' recommendation for vancomycin dosing may jeopardize the interpretation of this excellent trial.

2. Current guidelines (Liu, 2011; Rybak, 2009a, b) recommend an initial vancomycin dose based on body weight and subsequently adjusting the dose according to trough levels. For complicated infections such as bacteremia, infective endocarditis, osteomyelitis, meningitis, severe skin and soft tissue infection (SSTI), and pneumonia, 25 ~ 30 mg/kg vancomycin (based on actual body weight) as a loading dose and then 15 to 20 mg/kg every 8 ~ 12 h should be considered to achieve rapid attainment of the target concentration. However, the authors adopted vancomycin 15 mg/kg every 12 h as an initial dose, which was inconsistent with recommended regimens set forth in the guidelines and likely to fail to achieve the optimal serum concentration (15 to 20 µg/ml).

3. Current guidelines (Liu et al., 2011; Rybak et al., 2009a, b) also suggest how to use vancomycin susceptibility testing to guide clinical therapy. For *S. aureus* with a vancomycin minimum inhibitory concentration (MIC) ≤ 0.5 mg/L, standard vancomycin dosing (1 g every 12 h in patients with normal renal function) can be prescribed; for *S. aureus* with a vancomycin MIC < 1 mg/L, high doses (15 to 20 mg/kg, every 8 to 12 h) are necessary to achieve target concentration; for *S. aureus* with a vancomycin MIC ≥ 2 mg/L, alternative therapies should be considered. A recent article showed that a vancomycin MIC ≥ 2 mg/L was an independent predictor of MRSA-associated mortality, and an early switch to an alternative therapy may improve clinical outcome (Mahajan et al., 2012). Wunderink et al. (2012) did not adopt such regimens.

Furthermore, the trial failed to demonstrate a relationship between vancomycin MIC and clinical success rates (< 1 mg/L, 50%; 1 mg/L, 47.8%; ≥ 2 mg/L, 53.8%, respectively), a finding which is in conflict with a mass of previous reports (Soriano et al., 2008; van Hal et al., 2012).

4. Interestingly, as mentioned, one of the most important objectives of this trial was to validate efficacy of linezolid versus dose-optimized vancomycin for the treatment of proven MRSA nosocomial pneumonia. However, the study failed to demonstrate the relationship between vancomycin trough levels and clinical response (0 to 7.9 µg/ml, 48.6%; 8 to 12.3 µg/ml, 46.0%; 12.4 to 17.4 µg/ml, 45.5%; > 17.4 µg/ml, 45.5%, respectively), which was in contrast to other findings (Albur et al., 2012). Interestingly, clinical success rates were identical in the 2 arms within the subgroup of patients featuring glomerular filtration rates (GFR) < 50 ml/min; however, linezolid demonstrated superiority to vancomycin within the subgroup of patients with GFR ≥ 50 ml/min. A possible explanation for this finding could be that higher serum vancomycin levels were attained in cases with impaired renal function (GFR < 50 ml/min). The authors did not render more detail regarding the trough levels in different GFR subgroups.

5. Health care-associated pneumonia (HCAP) can be defined as pneumonia in a patient with at least one of the following risk factors: (1) Hospitalization in an acute care hospital for two or more days in the last 90 days; (2) residence in a nursing home or long-term care facility in the last 30 days; (3) receiving outpatient intravenous therapy (like antibiotics or chemotherapy) within the past 30 days; (4) receiving home wound care within the past 30 days; (5) attending a hospital clinic or dialysis center in the last 30 days; (6) having a family member with known multi-drug resistant pathogens. Regarding the enrollment of HCAP cases, while these patients accounted for only 15% of the total PP population, we think that this is a detriment to the study design because HCAP cannot be identified as "Nosocomial Pneumonia," from both definition and terminology perspective. Although we recognize that the inclusion of HCAP patients adds heterogeneity to the overall population, we consider that the title of the trial, "Linezolid in Methicillin-Resistant *S. aureus* Nosocomial Pneumonia", is not very precise.

6. While the authors wanted to show all-cause 60-day mortality in the intent-to-treat (ITT) population, 120-day mortality rates were shown in the Kaplan–Meier survival curves in the Appendix Figure 1.

7. With regard to the microbiologic responses, the authors stated that, "MRSA clearance at EOT was 30% greater with linezolid than with vancomycin. A difference of at least 20% persisted until EOS, suggesting that linezolid treatment may result in more complete bacterial

eradication.” However, from the data presented, we observe MRSA clearance at EOT was 21.3% greater with linezolid compared to vancomycin in all PP patients, and 28.5% greater in those with definite respiratory secretion cultures. Furthermore, a difference of only 11 to 11.4% persisted until EOS, which was considerably different with the 20% value claimed in the text of the article.

## CONCLUSION

The significant differences drawn both in clinical and microbiological responses make us reconsider the choice of linezolid or vancomycin in different clinical contexts. While we believe that the study was intended to be well designed and completed with a strict protocol, as we have commented above, several flaws in study design may offset the merits of this study to some extent. Further discussion may be warranted to resolve some of the outstanding contradictions identified in this article.

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## APPENDIX

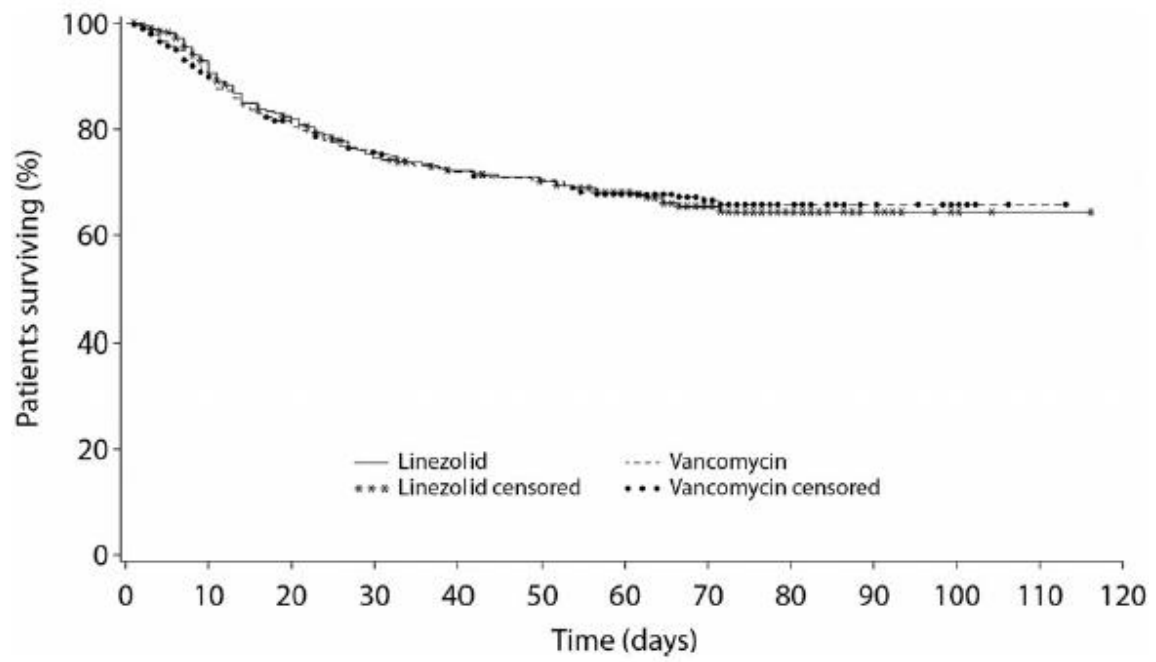


Figure 1. Kaplan–Meier survival curves showing 120-day mortality rates.