Systematic Review and Meta-Analysis Comparing Nephrotoxicity between vancomycin and linezolid

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Introduction

- Vancomycin has been the historical treatment of choice for MRSA pneumonia and soft skin tissue infections (SSTI) requiring intravenous therapy.
- However, there are concerns regarding vancomycin-associated nephrotoxicity in patients at high risk for acute kidney injury.
- Linezolid is a potential less nephrotoxic vancomycin alternative for MRSA pneumonia and SSTI but, current data is conflicting on whether vancomycin is truly more nephrotoxic relative to linezolid and much of the evidence suggesting vancomycin is nephrotoxic is observational in nature.
- This limits the ability to conclude that vancomycin causes more nephrotoxicity and prevents an accurate estimation of the magnitude of the potential increased toxicity.
- To address this, we conducted a systematic review and meta-analysis of randomized controlled trials comparing vancomycin and linezolid in patients with MRSA pneumonia or SSTI.

Methods

- This is a systematic review and meta-analysis of randomized controlled trials comparing the relative incidences of nephrotoxicity in patients with MRSA pneumonia or soft-skin tissue infection treated with intravenous vancomycin or the comparator linezolid.
- Studies were found through searching PubMed (MEDLINE) and Embase with the following search terms: “Vancomycin” and “Linezolid” and “Randomized.”

Table 1: Inclusion and Exclusion Criteria Utilized in Systematic Review

Inclusion Criteria	• Randomized controlled trials • Adults ≥ 18 years of age • Linezolid treatment group • IV Vancomycin treatment group • Reports number or percentage of patients in each group who experience renal toxicity • Studies published in the English language
Exclusion Criteria	• Patients receiving aminoglycosides as combination antibiotic therapy • Studies that are not published.

- The primary outcome is nephrotoxicity or as defined within the individual studies.
- Risk of bias in included studies was assessed using the Revised Cochrane risk-of-bias tool for randomized trials. Meta-analysis was performed via random-effects Mantel-Haenszel model. Heterogeneity between included studies was assess via the chi-squared statistical test. Subgroup analyses were performed to evaluate the potential role of vancomycin dosing strategy. Statistical analysis was performed using RevMan5.3. P values ≤0.05 were considered statistically significant.

References

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Results

Figure 1: PRISMA Flow Diagram[1]

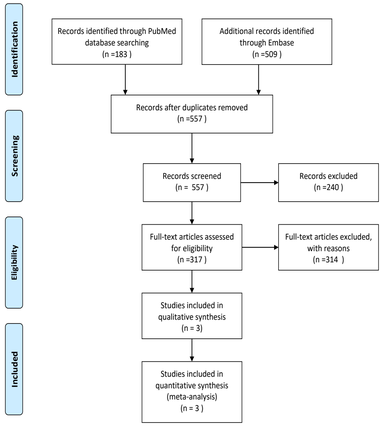
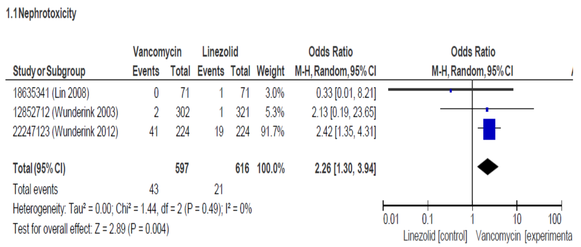


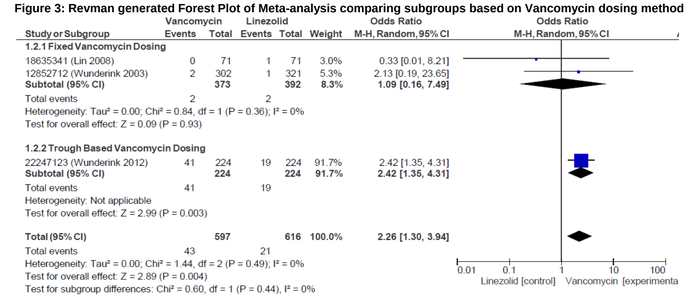
Figure 2: Revman generated Forest Plot of Meta-analysis of all included studies



- A total of three randomized controlled trials were included in this review involving a total of 1,213 participants who were either administered vancomycin or linezolid with gram negative coverage for the treatment of MRSA pneumonia or soft-skin tissue infections (Figure 1)
- The relative incidence of nephrotoxicity within each study was identified as the reported number of participants that had nephrotoxicity as defined within the study or as the number of participants who had acute renal failure.

As vancomycin induced nephrotoxicity is commonly associated to relative vancomycin exposure, subgroups that included the: specific dosing regimens used were analyzed for the relative effect on the incidence of nephrotoxicity

Figure 3: Revman generated Forest Plot of Meta-analysis comparing subgroups based on Vancomycin dosing method



- Only trough-based vancomycin dosing subgroup exhibited positive association of vancomycin and nephrotoxicity

Risk of Bias Assessment

Table 2: Risk of Bias Assessment Utilizing Rob2 Assessment Tool [4]

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Lin2008	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk	Some Concerns
Wunderink 2003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Wunderink 2012	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Figure 4: Graphical Presentation of Percentage of Bias in the included studies

- Two of the three randomized controlled trials exhibited low risk of bias
- Wunderink 2012 considered low risk but with comments to the lack of definition for ‘acute kidney failure’
- Some concerns of overall risk of bias in Lin 2008 was due to the lack of explanation to how or why the acute renal failure that occurred 1-week post treatment was specifically caused by linezolid treatment

Conclusions

- Patients receiving vancomycin had more than 2-fold greater odds of nephrotoxicity compared with those receiving linezolid
- The increased toxicity with vancomycin was seen in a single study of patients with pneumonia with vancomycin dosed to achieve trough concentrations between 15 and 20 mg/L suggesting a dose-specific effect.
- Although these results suggest vancomycin is more nephrotoxic than linezolid at currently recommended doses, this was based on a single study and it is unclear whether the results are reproducible or apply to other patient populations.
- Additional randomized studies involving contemporary vancomycin dosing practices are needed to draw definitive conclusion.