Comparison of Nephrotoxicity between Vancomycin and Comparator Anti-MRSA Antibiotics among Patients with Methicillin-Resistant *Staphylococcus aureus* Pneumonia: a Systematic Review and Meta-Analysis

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Introduction

- Vancomycin is the antibiotic of choice in treatment of invasive methicillin-resistant *staphylococcus aureus* (MRSA) infections such as pneumonia[1]
- Vancomycin monitoring guidelines recommend targeting trough concentrations of 15-20 mg/L for MRSA pneumonia although this exposure range is associated with increased risk of nephrotoxicity[1,2]
- Several variables contribute to acute kidney injury periodically coexist with vancomycin exposure, precluding the ability to conclude accurate estimation of the magnitude of potential increased toxicity[2]
- Alternative anti-MRSA therapy are generally less nephrotoxic but the majority of the data supporting this are from observational studies[3]
- This systematic review and meta-analysis will assess the association of nephrotoxicity in vancomycin and alternative anti-MRSA therapy in treatment of MRSA pneumonia

Methods

- The primary outcome was nephrotoxicity
- Systematic literature search was performed using keywords: “randomized controlled trial,” “vancomycin,” and “pneumonia”
- Relevant studies were searched through Embase and Pubmed (MEDLINE)
- Each study was individually screened by two independent reviewers and duplicates were removed through the use of structured data form
- Inclusion criteria: adults ≥ 18 years old with pneumonia, randomized controlled trial, IV vancomycin treatment group, and studies in English language
- Exclusion criteria: other known nephrotoxic antibiotics that were part of the study therapy in any treatment group: aminoglycosides, telavancin, and polymyxins, and did not report numbers or percentages of renal toxicity in both vancomycin and comparator group
- Risk of bias in included studies were assessed using the Revised Cochrane Risk-of-Bias tool
- Heterogeneity was assessed using I^2 statistic
- Meta-analysis was performed using a Mantel-Haenszel random effects model
- Statistical analysis was performed through RevMan 5.3
- *P* values ≤ 0.05 were considered statistically significant

References

1. Huang, D. B., File, T. M., Torres, A., Shorr, A. F., Wilcox, M. H., Hadvary, P., … Corey, G. R. (2017). *A Phase II Randomized, Double-blind, Multicenter Study to Evaluate Efficacy and Safety of Intravenous Iclaprim Versus Vancomycin for the Treatment of Nosocomial Pneumonia Suspected or Confirmed to be Due to Gram-positive Pathogens. Clinical Therapeutics, 39(8), 1706–1718.* doi:10.1016/j.clinthera.2017.07.007
2. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clinical Therapeutics. 2003;25(3):980-992. doi:10.1016/S0149-2918(03)80118-2
3. Wunderink, R. G., Niederman, M. S., Kollef, M. H., Shorr, A. F., Kunkel, M. J., Baruch, A., … Chastre, J. (2012). *Linezolid in Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Randomized, Controlled Study. Clinical Infectious Diseases, 54(5), 621–629.* doi:10.1093/cid/cir895

Results

Author (Publication Year)	Comparator	Toxicity definition	Duration of tx in vancomycin group	Duration of tx in comparator group	Average trough/trough goal	Empiric coverage
Wunderink R.G., et al. (2003)	Linezolid	Acute kidney failure	9.4 (4.5)	9.5(4.5)	n/a	Yes, Aztreonam
Huang D.B., et al. (2017)	Iclaprim	Increased serum creatinine	7	7	n/a	Yes, Aztreonam
Wunderink R.G., et al. (2012)	Linezolid	0.5 mg/dL or 50% increase from baseline	10	10	12.3 (9.45)/ n/a	Yes, Per protocol

Table 1: Main characteristics of studies included in meta-analysis

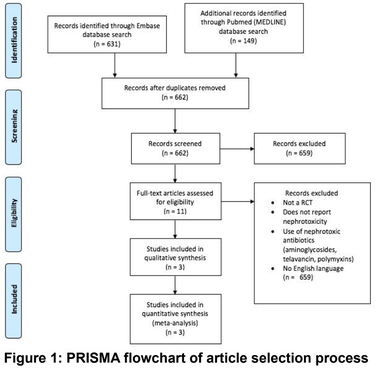

Figure 1: PRISMA flowchart of article selection process

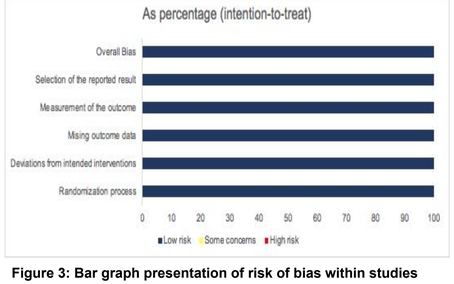

Figure 3: Bar graph presentation of risk of bias within studies

Study (Publication Year)	Study quality/bias	Randomization process	Deviations from intended Interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias	Comments
Wunderink R.G., et al. (2012)	Low	Low	Low	Low	Low	Low	**Low**	Toxicity definition was not well defined
Wunderink R.G., et al. (2003)	Low	Low	Low	Low	Low	Low	**Low**	N/A
Huang D.B., et al. (2017)	Low	Low	Low	Low	Low	Low	**Low**	Toxicity definition was not well defined

Table 2: Rob2 Assessment tool in risk of bias within studies

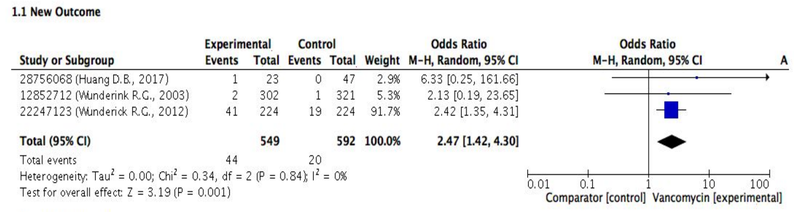

Figure 2: Forest plot of studies included in meta-analysis

Discussion

- Literature search found 780 results. 118 were removed as duplicates. 659 were removed due to exclusion criteria
- The meta-analysis included three randomized controlled trial studies with a total of 1,141 patients.
- Huang D.B, et al., compared vancomycin and iclaprim, while the two other studies, Wunderink R.G., et al. 2003 and 2012, compared vancomycin and linezolid in treatment of MRSA nosocomial pneumonia
- Huang D.B., et al., study results indicated that vancomycin treatment group was associated with increased risk of nephrotoxicity when compared to iclaprim treatment group (OR= 6.33; 95% CI, 0.25-161.66)
- The results from two studies, Wunderink R.G., et al. 2003 and 2012, comparing vancomycin to linezolid also presented with increased risk of nephrotoxicity was similarly shown in vancomycin treatment group (OR=2.13; 95% CI, [0.19-23.65] and OR, 2.42; 95% CI, [1.35-4.31] respectively)
- Overall, the meta-analysis of the three studies showed that nephrotoxicity was significantly more common in vancomycin-treated patients. (OR=2.47; 95% CI, [1.42-4.30]; P=0.001)

Conclusions

- The odds of nephrotoxicity were more than 2-fold greater among patients with MRSA pneumonia randomized to receive vancomycin[3]
- The meta-analysis had few limitations which included limited number of randomized controlled trials, relatively small sample sizes, and variable toxicity definitions[2]
- Despite these limitations, data strongly supports that nephrotoxicity occurs more frequently with vancomycin compared with other anti-MRSA treatment for pneumonia[1,2,3]
- These findings indicate that vancomycin therapy is an independent risk factor for nephrotoxicity and supports the need of additional studies to assess the current recommendation of vancomycin dosing in treatment of MRSA pneumonia[3]