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Perspective

MRSA Pneumonia: Linezolid versus Vancomycin; A Factual Treatment Choice is Emerging

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Abstract

Currently, in the medical community, there is debate concerning the most effective antibiotic treatment for pneumonia secondary to Methicillin-resistant *Staphylococcus aureus* (MRSA). There is evidence of emerging resistant strains of gram-positive bacteria associated with vancomycin resistance, such as Vancomycin-resistant *Enterococcus* (VRE). It has been suggested that the minimum inhibitory concentrations (MICs) of vancomycin are increasing, necessitating a higher dose of vancomycin to be effective. This suggests that strains of MRSA are becoming resistant or evolving [1]. Another relatively new antibiotic, linezolid (Zyvox), has been introduced into the market with the labelled use for treating MRSA pneumonia. Many clinicians have posited that linezolid is superior to vancomycin in enhanced lung tissue penetration and decreased difficulties in achieving appropriate drug levels as linezolid levels do not need to be monitored [2]. The debate continues as studies conclude that neither drug is superior to the other regarding mortality; however, linezolid is associated with fewer morbidities, higher clinical cure rates, and better microbiological cure rates. These ancillary findings and other considerations could position linezolid as the treatment of choice in many MRSA pneumonia clinical scenarios.

Keywords: Linezolid; Nephrotoxicity; Pneumonia; Trough level; Vancomycin, Ventilator-associated pneumonia; MRSA; Zyvox

Abbreviations

BAL	:	Bronchoalveolar Lavage
CINAHL	:	Cumulative Index to Nursing & Allied Health Literature
COI	:	Conflict of Interest
ICD-9	:	International Classification of Diseases, Ninth Revision
ICU	:	Intensive Care Unit
IV	:	Intravenous
MIC	:	Minimum Inhibitory Concentration
MRSA	:	Methicillin-resistant *Staphylococcus aureus*
MSOF	:	Multisystem Organ Failures
PICOT	:	Patient, Intervention, Comparison, Outcome, Time
PO	:	Per Oral (Oral)
VAP	:	Ventilator-Associated Pneumonia
VRE	:	Vancomycin-Resistant Enterococci

Introduction

In patients diagnosed with MRSA pneumonia, which drug-linezolid or vancomycin-is superior to the other in reducing mortality? In this PICOT-formatted question, the "P" stands for the Patient Population; this includes patients diagnosed with MRSA pneumonia. The "I" stands for Intervention; this refers to the antimicrobial medications in question. The "C" stands for Comparison; which represents the comparison between linezolid and vancomycin. The "O" stands for the outcome; which is to reduce mortality. The "T" stands for Time; the time it takes for the intervention to achieve an outcome or how long the participants are observed.

In January 2014, twenty studies were reviewed for relevance. Search engines utilized included Google Scholar, PubMed, Medline, and CINAHL (Cumulative Index to Nursing & Allied Health

Literature). Keywords included "MRSA", "MRSA pneumonia", "vancomycin", "linezolid", and "Zyvox". Search phrases included "MRSA and pneumonia", "vancomycin versus linezolid and MRSA and pneumonia", "vancomycin and linezolid and MRSA and pneumonia", "vancomycin and MRSA and pneumonia", and "linezolid and MRSA and pneumonia". From the initial twenty studies, the search was narrowed resulting in the selection of three articles that were recent and relevant and included a comparison of linezolid and vancomycin for MRSA pneumonia.

The studies chosen had designs that observed the outcomes of linezolid and vancomycin in subjects with proven MRSA infection by culture or inoculation of a known pathogen, and were published five or fewer years ago. Research was excluded if the free full-text versions were not available. Papers were omitted if they were published more than five years ago. (Note: The study by Wunderink et al. (2008) [3] was published in December 2008; the initial search was done in early January 2014 which dates the publication at precisely five years.) The research needed to include human subjects. Investigations were excluded if they did not include human subjects or if linezolid or vancomycin were not statistically compared. Papers were rejected if their "limitations of research" proved problematic or if any "Conflict of Interest" (COI) statement seemed suspect in influencing the results; and in the case of one dismissed article, the COI statement was absent from the publication.

Discussion

The three peer-reviewed articles chosen are cited below for easy reference.

Caffrey AR, Quilliam BJ, LaPlante K L, (2010) Comparative effectiveness of Linezolid and vancomycin among a cohort of patients infected with methicillin-resistant *Staphylococcus aureus*. Antimicrobial Agents and Chemotherapy 54: 4394-4400 [4].

Wunderink RG, Mendelson MH, Somero MS, Fabian TC, May AK, et al. (2008). Early microbiological response to linezolid vs. vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*. Chest 134: 1200-1207 [3].

Wunderink RG, Neiderman MS, Kollef MH, Shorr A F, Kunkel M J, et al. (2012). Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: A randomized, controlled study. Clinical Infectious Disease 54: 621-629 [2].

The discussion that follows is formatted into two sections: "Description and Findings" of each study and "Critical Analysis and Comparison" for each study; followed by a Summary and Conclusion.

The Caffrey, Quilliam, and LaPlante (2010) [4] Study-Description and Findings.

The Caffrey et al. (2010) [4] research examined retrospectively the efficacy of linezolid versus vancomycin in 20,107 patients with MRSA infections, with the exclusion of VRE and endocarditis [4]. Patients were included based on medical records review and ICD-9 codes. The evaluation was based on clinical outcomes with the two antibiotics and then compared statistically. Parameters examined included length of time to discharge, time to discontinuation of therapy, survival time, and 90-day readmission. The results revealed linezolid was associated with less time to discharge than vancomycin (6 days versus 9 days, $p < 0.001$), longer time to discontinuation of therapy with linezolid than vancomycin (16 days versus 13 days, $p < 0.001$), and average survival time and 90-day readmission were not significantly different between the two groups [4].

The Wunderink et al. (2008) [3] Study-Description and Findings.

The Wunderink et al. (2008) [3] research evaluated 100 patients with culture-proven MRSA ventilator-associated pneumonia (VAP) obtained from bronchoalveolar lavage (BAL) from November 2002 to January 2005 [3]. Patients received vancomycin or linezolid (both optimally dosed based on trough levels).

If the culture from BAL confirmed MRSA, patients were analyzed and compared in both groups. Patients who died were analyzed as a separate group. The study found that, although the differences in the parameters were not significant, linezolid was associated with increased microbiological cure rates, clinical cure rates, survival rates, and time spent alive not on a ventilator; and decreased mean duration of ventilation, hospitalization, and days of ICU stay. A notable finding was none of the patients treated with linezolid died, but five of the patients treated with vancomycin died ($p = 0.03$). Although the difference in deaths was suggestive, the researchers determined at the time that non-inferiority between linezolid and vancomycin could not be established because the power (N=10 for each group) was inadequate [3].

The Wunderink et al. (2012) [2] Study-Description and Findings.

The Wunderink et al. (2012) [2] research included 1,225 patients with culture-positive MRSA pneumonia and significant clinical signs and symptoms; examined internationally from October 2004 to January 2010 [2]. Patients were randomly assigned to receive optimally-dosed vancomycin or optimally-dosed linezolid and were evaluated by researchers every 72 hours for clinical signs and symptoms, chest x-ray findings, and sputum culture results. The two groups were analyzed and compared. Results showed that, by the end of the study, linezolid was associated with a higher clinical cure rate than vancomycin ($p = .042$). Vancomycin was linked to a higher incidence of nephrotoxicity than linezolid (18.2% versus 8.4%). Mortality at 60 days was similar between the two groups (15.7% linezolid, 17% vancomycin) [2].

The Caffrey et al. (2010) [4] Study-Critical Analysis and Comparison.

The research by Caffrey et al. (2010) [4] included a considerable number of human subjects (20,107) which is a strength of this study. Moreover, no variables were manipulated; it was pure observation. For these reasons, this study was chosen. However, a recognized weakness in the investigation was the use of ICD-9 codes for inclusion criteria. ICD-9 codes, alone, do not prove that a subject had MRSA as cultures may have been negative or not taken. Also, although it was stated that VRE and endocarditis were excluded, it was not reported what percentage of the patients had MRSA pneumonia versus other MRSA infections. In contrast, the other two studies reported herein take into account culture-proven MRSA in patients with high clinical suspicion.

The results appear straightforward, except for certain findings. It makes sense that time to discontinuation of therapy was longer with linezolid than with vancomycin since linezolid had an oral (PO) formulation for MRSA infections while vancomycin did not. Thus, linezolid subjects could continue with oral linezolid as outpatients while intravenous (IV) vancomycin patients, when discharged, had no non-extemporaneous PO vancomycin available to them, and treatment would have ended. Linezolid having had a PO formulation and vancomycin having none may have also contributed to the difference in discharge time as patients receiving linezolid may have been discharged with a PO formulation but those patients receiving vancomycin may have remained admitted with an IV formulation [4].

It is abstruse, however, that in some matched groups examined with "infections not specified", the readmission rates for linezolid were higher. Had the researchers been able to delineate which specific infections were included in this "infections not specified" group, this characterization may have ascribed more meaning to this finding and provided more relevant information. One consideration that this study did not account for was vancomycin trough levels [4]. In contrast, the other two studies monitored vancomycin trough levels, and optimized its dose. In MRSA infections, excluding VRE and endocarditis, it can be inferred from this study that vancomycin (trough levels unknown) and linezolid (trough levels not tested) were similar regarding mortality, given that differences in survival were not statistically significant.

The Wunderink et al. (2008) [3] Study-Critical Analysis and Comparison.

The research by Wunderink et al. (2008) [3] has several strengths including its design. In contrast to the research done by Caffrey et al. (2010) [4], this study allowed its variables to be accounted for and manipulated. Due to the strength of a clinical trial, this report and the Wonderink et al. (2012) [2] report were chosen. Another apparent strength of this study is that MRSA was proven on cultures obtained by BAL. BAL-derived cultures tend to be more accurate than standard sputum cultures since the specimen in BAL is obtained directly from the affected lung tissue [3].

In contrast, sputum cultures–such as those obtained in Wunderink et al. (2012) [2]–tend to be less accurate as they may be colonized with multiple organisms not necessarily involved in the infectious process. On the other hand, BAL is invasive and expensive and requires a trained clinician to perform the procedure; the authors attributed these factors for why relatively few patients were included in the 2008 study [3]. The low number of participants, a total of 100 (with 50 being culture-positive for MRSA), is a weakness in this study; the authors of the study acknowledged this fact [3].

Nonetheless, linezolid outperformed vancomycin on the parameters mentioned above even when vancomycin was optimally-dosed based on trough levels. Interpretation of the results was consistent with the study population and findings, except for one finding that the authors considered statistically significant rather than suggestive–the number of deaths in each group (as previously pointed out). The authors of the study described this as a 50% increased risk of death if the patient was treated with vancomycin. While this description is technically correct, from this small study group it cannot be applied to the general population in the way the authors proposed. Their assumption is also in doubt due to conflicting results reported by other researchers.

Furthermore, the authors attributed death to microbiological response failure which infers that the MRSA was resistant to vancomycin; this is still a rare occurrence [1]. While this scenario is possible, it is unlikely that all five patients died due to vancomycin resistance. Death in patients with MRSA pneumonia is more likely to be caused by inflammation, such as myocardial infarction or multisystem organ failure (MSOF).

The Wunderink et al. (2012) [2] Study-Critical Analysis and Comparison.

The research by Wunderink et al. (2012) [2] investigated non-ventilated patients with MRSA pneumonia rather than ventilated patients with MRSA pneumonia as in the Wunderink et al. (2008) [3] research. The methods were similar, with the difference that sputum cultures were obtained rather than cultures by BAL. The sputum cultures were collected by a variety of researchers which, theoretically, could have impacted the results of the cultures. While this Wunderink et al. (2012) [2] study did not include as many subjects as the study by Caffrey et al. (2010) [4], it did have a larger population than the Wunderink et al. (2008) [3] study and is, therefore, stronger in that regard.

The results of the Wunderink et al. (2012) [2] study are compatible with the other two studies. Linezolid tended to outperform vancomycin regarding clinical cure rates. The mortality rates were

slightly different between the two groups, but not statistically significant [2]. The results, interpreted by the authors, seem consistent with the findings. The authors went on to state that the differences in the results may have been due to the increasing MICs of vancomycin. While vancomycin may still prove useful, the MICs for linezolid, at the time, were lower and resulted in enhanced clinical and microbiological cure rates [2].

Summary of the Selected Studies

The findings of the three selected studies contribute to answering the PICOT question posed in the Introduction. In patients diagnosed with MRSA pneumonia, which drug–linezolid or vancomycin–is superior to the other in reducing mortality? All three studies, although factorially distinct, demonstrated consistency in their results. Neither antibiotic was superior to the other regarding mortality in treating patients with MRSA pneumonia (as non-inferiority between the two drugs could not be established). However, trends showed that linezolid was associated with better rates of microbiological cure, among other parameters. It is appreciable that none of the three studies showed vancomycin associated with a higher microbiological cure rate than linezolid; linezolid outperformed vancomycin in that regard.

Docobo-Perez et al. (2012) [1] concluded that clinical differences in vancomycin and linezolid were due to the changing MICs of vancomycin over time. This conclusion seems to explain the results of the studies reviewed herein. Wunderink et al. (2012) [2] referred to a similar conclusion. Also, as discussed above, vancomycin tends to be associated with a higher incidence of renal failure than linezolid.

Among the three studies, the beneficial findings regarding linezolid were shorter hospital stay with $p < 0.001$ (Caffrey et al., 2010) [4], higher clinical cure rate with $p = 0.042$ (Wunderink et al., 2012) [2], and no deaths occurred with linezolid in patients with VAP with $p = 0.03$ [3]. Despite these findings, again, there was no mortality advantage noted with linezolid versus vancomycin that was statistically significant.

Linezolid performed better than vancomycin in microbiological cure rates (56.5% vs. 47.4% $p = 0.757$), clinical cure rates (66.7% vs. 52.9%), survival rates (86.7% vs. 70%), mean duration of ventilation (10.4 vs. 14.3 days), hospitalization (18.8 vs. 20.1 days), days in ICU (12.2 vs. 16.2 days), and time spent alive while not receiving ventilation (15.5 vs. 11.1 days) [3].

In Wunderink et al. (2012) [2], linezolid was associated with lower rates of nephrotoxicity (18.2% with vancomycin and 8.4% with linezolid) and lower mortality at 60 days (17% with vancomycin and 15.7% with linezolid). Wunderink et al. (2012) [2] stated the clinical cure rate as significant ($p = 0.042$) while Wunderink et al. (2008) [3] reported it was not.

Conclusion

If MICs are increasing for vancomycin (and recent studies are suggesting such), this antibiotic could be reserved for patients who are clinically stable. It takes time to achieve effective trough levels, and patients, critically ill with MRSA pneumonia, can decompensate quickly. Clinically stable patients show fewer tendencies in developing renal failure; thus, vancomycin could be prescribed for this population. Vancomycin could be considered for noncritical cases with no renal compromise.

In patients with overt renal failure, vancomycin should be avoided as the incidence of renal failure is dramatically increased with vancomycin. If vancomycin is dosed all of the time appropriately, it can be inferred that microbiological cure rates may stabilize with vancomycin over time. However, concerning trough levels, vancomycin is problematic to dose and requires thorough monitoring. These characteristics are exacting and may result in the rejection of the usage of vancomycin in the future.

Given that mortality rates appear similar between the two drugs; linezolid is indicated over vancomycin for critically ill patients with suspected MRSA. Linezolid levels do not require detailed monitoring. More effective dosing will likely occur with linezolid than vancomycin; this may add to better outcomes with linezolid.

Based on the evidence presented from the three selected papers and a review of numerous external articles and studies, clinicians are best advised that–although neither of the two antibiotics was superior to the other regarding mortality–linezolid outperformed vancomycin even when the latter drug wass optimally-dosed. Linezolid was associated with enhanced outcomes, such as fewer side effects, easier dosing, higher clinical and microbiological cure rates, and shorter ICU stays.

Further research is needed to more accurately access why mortality rates of linezolid and vancomycin were similar while microbiological cure rates among other outcomes were superior with linezolid. MIC trends should be studied and compared in these two antibiotics for different strains of MRSA in different geographical regions. Studies evaluating MICs of linezolid and vancomycin in animal models have found that MICs tended to be lower with linezolid due to heightened lung tissue perfusion. Nonetheless, these results should be replicated in human subjects, preferably in clinical trials, so that mortality can be assessed based on MICs; in addition to clinical outcomes and microbiological cure rates.

This paper focuses on treatment considerations between linezolid and vancomycin in the confirmed presence of MRSA pneumonia. By design, it does not discuss the procedures or protocol to diagnose MRSA pneumonia which is, deservedly, a distinct review. However, it seems appurtenant to note that MRSA pneumonia can

only be diagnosed in the presence of pneumonia. Obtaining cultures when pneumonia is not likely may lead to ambiguous results. MRSA can colonize multiple sites, including the upper airways, in normal, healthy patients without disease. MRSA coverage remains a clinical decision that may take into account multiple factors.

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None.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Docobo-Perez F, Lopez-Rojas R, Dominguez-Herrera J, Jimenez-Mejias ME, Pichardo C, et al. (2012) Efficacy of Linezolid versus a pharmacodynamically optimized therapy in an experimental pneumonia model caused by methicillin-resistant *Staphylococcus aureus*. Journal of Antimicrobial Chemotherapy 67: 1961-1967.

2. Wunderink RG, Neiderman MS, Kollef MH, Shorr A F, Kunkel M J, et al. (2012) Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: A randomized, controlled study. Clinical Infectious Disease 54: 621-629.

3. Wunderink RG, Mendelson MH, Somero MS, Fabian TC, May AK, et al. (2008) Early microbiological response to linezolid vs. vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*. Chest 134: 1200-1207.

4. Caffrey AR, Quilliam BJ, LaPlante K L, (2010) Comparative effectiveness of Linezolid and vancomycin among a cohort of patients infected with methicillin-resistant *Staphylococcus aureus*. Antimicrobial Agents and Chemotherapy 54: 4394-4400.