Time to Clinical Stability in Patients with Ventilator-Associated Pneumonia due to Methicillin-Resistant *Staphylococcus aureus* Treated with Linezolid versus Vancomycin: Results from the IMPACT-HAP Study

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ABSTRACT

Background: Time to clinical stability (TCS) is a well-defined early clinical outcome in hospitalized patients with community-acquired pneumonia, but it has not been evaluated in patients with VAP. The objective of this study was to compare TCS in patients with MRSA VAP treated with linezolid (Lin) versus vancomycin (Van).

Methods: This was a multicenter, retrospective, observational study of patients with MRSA VAP treated with Lin or Van. Non-consecutive patients requiring intensive care were enrolled from five academic institutions in the USA. VAP was defined according to CDC criteria. MRSA VAP was considered when MRSA was isolated from a tracheal aspirate or bronchoalveolar lavage. A patient was considered to reach clinical stability the day that the following four criteria were met: 1) Afebrile for 24 hours, 2) Decrease in WBC >10%, 3) Improving of PaO_2/FIO_2 ratio of >20%, and 4) Systolic blood pressure >90 mmHg. TCS for linezolid and vancomycin were compared using the Chi-Squared and Student's t-tests.

Results: A total 50 patients treated with Lin and 50 patients treated with Van were evaluated. From the population of Lin treated patients, 64% reached clinical stability, compared to 70% of the population of Van treated patients (P=0.671). Mean number of days to reach clinical stability was 5.8 days (SD 3.0) for patients treated with Lin, versus 7.2 days (SD 3.7) for patients treated with Van (P=0.040).

Conclusions: In patients with MRSA VAP, early TCS is achieved for patients treated with Lin when compared to Van. The number of days for patients to reach clinical stability can be used as an early clinical outcome in patients with VAP.

INTRODUCTION

- Time to clinical stability (TCS) is a well-defined early clinical outcome in hospitalized patients with community-acquired pneumonia (CAP). Several guidelines for the management of patients with CAP have established criteria to define when a patient reaches clinical stability.[1,2] White blood cell count (WBC), temperature, and respiratory symptoms are within the criteria commonly used.
- On the contrary, few studies have been published evaluating TCS in patients with ventilator-associated pneumonia (VAP).[3-7] Clinical resolution has been described to be between 3 and 10 days depending on the cohort of patients being evaluated. Patients with VAP due to methicillin-resistant *Staphylococcus aureus* (MRSA) have a longer time to resolution when compared with patients with VAP due to methicillin-susceptible *Staphylococcus* aureus (MSSA) or *Haemophilus influenza*.[4] The presence of ARDS (Acute respiratory distress syndrome) also delays clinical resolution.[5]
- In the field of clinical research on CAP, TCS has been used as a clinical outcome to compare effectiveness of initial intravenous antibiotics.[8] It can be hypothesized that those antibiotics with better activity against the etiologic organism will produce a faster clinical response and early time to clinical stability. None of the published data on VAP has evaluated the impact of antibiotic treatment in TCS.
- The objective of this study was to compare TCS in patients with VAP due to MRSA treated with linezolid versus vancomycin.

MATERIALS AND METHODS

Study Design

The Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) was a multicenter, retrospective, observational study of intensive care unit (ICU) patients with VAP due to MRSA treated with linezolid or vancomycin. Non-consecutive patients requiring intensive care were enrolled from 5 sites in the United States: the University of Louisville Medical Center (Louisville, KY); the Henry Ford Health System (Detroit, MI); the University of Miami/Jackson Memorial Hospital (Miami, FL); the Summa Health System (Akron, OH); and Michigan State University (East Lansing, MI). Data were collected from November 2008 through October 2012. The study was approved by each institutional review board.

Study Definitions

Inclusion Criteria

- VAP was defined according to the Centers for Disease Control and Prevention National Healthcare Safety Network surveillance definitions.[9] VAP was considered to be due to MRSA when MRSA was isolated from tracheal aspirates, bronchoalveolar lavage (BAL) obtained by bronchoscopy, or blinded BAL.

Exclusion criteria

- Comfort care or a do not resuscitate order
- Clinical failure during the initial 48 hours of antibiotic therapy

Predictor variable: Study Groups

Patients were included in the linezolid group if they received linezolid within 48 hours of diagnosis and received at least 5 consecutive days of linezolid therapy. Patients were included in the vancomycin group if they received vancomycin within 48 hours of diagnosis and received at least 5 consecutive days of vancomycin therapy.

Outcome variable: TCS

Variables were collected daily from day 0 to day 14. A patient was considered to reach clinical stability the first day that the following four criteria were cumulatively met: 1) Afebrile for 24 hours, 2) Decrease in WBC >10% (or WBC within normal range), 3) Improving of PaO2/FIO2 ratio of >20% (or PaO2/FIO2 ratio >250) and 4) Systolic blood pressure >90 mmHg.
For those patients who reached clinical stability, the percentage of patients who met the study definition for clinical stability for each criterion were documented.

Confounding variables

At the time of clinical diagnosis of pneumonia (day 0), data on patients' demographic and baseline characteristics, severity of illness including the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Clinical Pulmonary Infection Score (CPIS), diagnostic procedures, and treatment were collected. Vital signs and laboratory values were collected during the first 14 days of hospitalization. Identification of MRSA isolates and in vitro susceptibilities were determined using clinical microbiology tests with automated susceptibility testing methods at each participating center. Vancomycin serum trough levels were collected throughout the study period.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages and were compared between the two treatment groups using Chi-square or Fisher's Exact tests. Continuous variables were expressed as medians and interquartile ranges and were compared between the two groups using the Mann-Whitney U-test. P-values of ≤0.05 were considered statistically significant in all analyses unless otherwise specified. To compare the TCS between those who reached clinical stability and were treated with linezolid or vancomycin, Kaplan-Meier survival curves were created. The Log-Rank test was use to compare the two survival curves.

RESULTS

- A total of 50 patients treated with linezolid and 50 patients treated with vancomycin were evaluated.
- Baseline characteristics of the study population are shown in **Table 1.**
- The study flow is shown in **Figure 1**.
- Kaplan Meier curves for TCS is shown in **Figure 2.** For those patients who reached clinical stability, the mean number of days to reach clinical stability was 5.8 days (SD 3.0) for patients treated with linezolid, versus 7.2 days (SD 3.7) for patients treated with vancomycin (P=0.040).
- The percentage of patients who met the study definition for clinical stability for each criterion is shown in **Figure 3.**

Table 1: Baseline characteristics of the study population

	Linezolid	Vancomycin	P value
Age, median (IQR)	61 (16.2)	57.5 (23.2)	0.332
Male gender, n (%)	36 (72)	27 (54)	0.097
BMI, mean (IQR)	27.9 (11.9)	28.3 (8.3)	0.931
Severity of Disease			
APACHE II score, median (IQR)	20 (10)	18 (9.5)	0.177
CPIS on Day 0, Median (IQR)	7 (3)	6 (2)	0.174
Severe Sepsis, n (%)	39 (78)	35 (70)	0.495
Multilobar Infiltrates, n (%)	22 (44)	18 (36)	0.541
Comorbidities			
Renal Disease, n (%)	3 (6)	5 (10)	0.715
Respiratory Disease, n (%)	16 (32)	14 (28)	0.828
Active Cancer, n (%)	4 (8)	4 (8)	1
COPD, n (%)	11 (22)	6 (12)	0.287
Diabetes, n (%)	15 (30)	11 (22)	0.495
End-Stage Liver Disease, n (%)	1 (2)	0 (0)	1
Cardiac Disease, n (%)	18 (36)	18 (36)	1
Vascular Disease, n (%)	14 (28)	18 (36)	0.521
Colonization with MDRO, n (%)	20 (40)	21 (42)	1
Empiric therapy			
Appropriate, n (%)	49 (98)	50 (100)	1

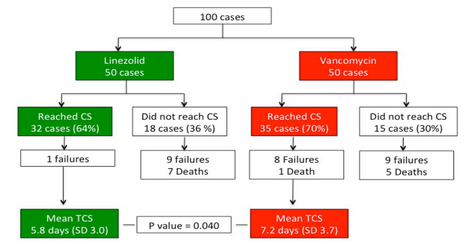

Figure 1: Study flow

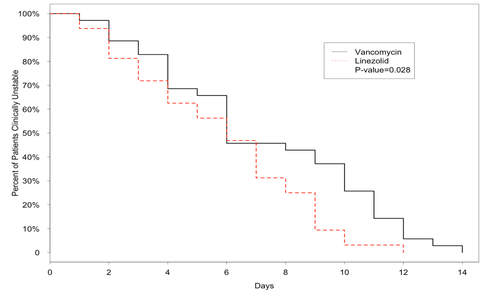

Figure 2: Kaplan-Meier curves for TCS for both study groups

RESULTS (cont'd)

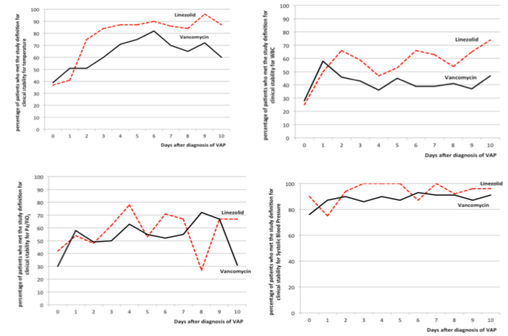

Figure 3: Percentage of patients who met the study definition for clinical stability for each criterion

CONCLUSIONS

- This study shows that in patients with VAP due to MRSA, earlier TCS is achieved for patients treated with linezolid when compared to vancomycin.
- The TCS for both study groups is within the range reported in the literature. The number of days for patients to reach clinical stability can be used as an early clinical outcome when comparing different antibiotics for therapy of VAP.
- Prior studies evaluating the clinical course of patients with VAP have used similar parameters such as temperature, WBC, PaO2/FiO2 ratio, CPIS, microbiology.[3-7] In these studies, a fix predetermined value was selected to define improvement. For example temperature ≤ 38° C, WBC ≤ 10,000, PaO2/FiO2 ratio ≥ 250, or negative micro results. Meeting these criteria practically defines the time when the patient is almost back to baseline. This is a difference with our study where some of the criteria used define an improvement (and not resolution) from the prior day.
- The number of days for patients to reach clinical stability can be used as an early clinical outcome in patients with VAP.

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