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

Methods: This was a secondary analysis of the IMPACT-HAP study database. 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% or WBC within normal range, 3) Improving of PaO\textsubscript{2}/FiO\textsubscript{2} ratio of >20%, or PaO\textsubscript{2}/FiO\textsubscript{2} ratio >250, or extubation, or FiO\textsubscript{2} ≤ 30% if extubated, and 4) Systolic blood pressure >90 mmHg. Time to clinical stability for linezolid and vancomycin were compared using the Chi-Squared and Student’s t-tests.

Results: A total of 89 patients treated with linezolid and 75 patients treated with vancomycin met study criteria. From the population of linezolid treated patients, 79% reached clinical stability, compared to 75% of the population of vancomycin treated patients ($P=0.463$). Median time to clinical stability was 6 days (IQR 8) for patients treated with linezolid, versus 7 days (IQR 12) for patients treated with vancomycin ($P=0.490$).

Conclusions: This study failed to demonstrate a statistically significant difference in time to clinical stability in patients with MRSA VAP treated with linezolid or vancomycin. The number of days for patients to reach clinical stability can be used as an early clinical outcome in patients with VAP.
which in turn could reflect in an early improvement of signs and symptoms. The late evaluation of outcomes may not be able to detect differences between antibiotics and time to clinical stability over the first week of the infection could be the endpoint that more closely relates to this activity.

Time to clinical stability is a well-defined early clinical outcome in hospitalized patients with CAP and a well-defined early efficacy endpoint to be used in clinical trials for CAP. Several guidelines for the management of patients with CAP have established criteria to define when a patient reaches clinical stability. White blood cell count (WBC), temperature, and respiratory symptoms are within the criteria commonly used.

On the contrary, fewer studies have been published evaluating patients with VAP and these studies all utilized absolute resolution of the criteria used to define clinical stability. 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 MRSA have a longer time to resolution when compared with patients with VAP due to MSSA or H influenza. The presence of ARDS (Acute respiratory distress syndrome) also delays clinical resolution.

In the field of clinical research on CAP, time to clinical stability has been used as a clinical outcome to compare effectiveness of initial intravenous antibiotics. During the initial 7 days of antimicrobial therapy, a number of patients will reach clinical stability. It can be hypothesized that those antibiotics with better activity against the etiologic organism may produce an early time to clinical stability and therefore increase the number of patients reaching clinical stability by day 7. None of the published data on VAP has evaluated the impact of antibiotic treatment in time to clinical stability.

The primary objective of this study was to compare time to clinical stability in patients with MRSA VAP treated with linezolid versus vancomycin. Secondary objectives were: 1) to compare the number of patients reaching time to clinical stability, 2) to compare the mortality within 30 days of diagnosis for those who reached clinical stability.

2 Methods

2.1 Study Design

This was a secondary analysis of The Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP), a multicenter, retrospective, observational study of intensive care unit (ICU) patients with VAP due to MRSA treated with linezolid or vancomycin. Patients were enrolled from 5 sites in the United States: the University of Louisville Medical Center (Louisville, KY); the Henry Ford Health System (Detroit, MD); 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. Patient data were collected on a case report form, entered into a web-based database, and transferred electronically to the University of Louisville Clinical and Translational Research Support Center for data validation and quality. The study was approved by the institutional review board at each participating institution (University of Louisville Human Subjects Protection Program Office; Summa Health System Institutional Review Board; Michigan State University Human Research Protection Program; Henry Ford Health System Institutional Review Board; University of Miami Human Subjects Research Office), all of which waived the requirement for informed consent since this was a retrospective observational study.

2.2 Study Definitions

2.2.1 Inclusion Criteria

- VAP was defined according to the Centers for Disease Control and Prevention National Healthcare Safety Network surveillance definitions. VAP was considered to be due to MRSA when MRSA was isolated from tracheal aspirates, bronchoalveolar lavage (BAL) obtained by bronchoscopy, or blinded BAL. Patients must have received more than 48 hours of either vancomycin or linezolid. Vancomycin was dosed based on blood levels according to standard of care.

2.2.2 Exclusion Criteria

- Data used to define clinical stability criteria missing for more than 2 consecutive days
- Comfort care or a do not resuscitate order
- Clinical failure during the initial 48 hours of antibiotic therapy
- In clinical practice, ICU physicians change antibiotics due to their own preferences without the evidence of patients’ clinical deterioration. Patients were also excluded if there was a switch from vancomycin to linezolid or vice versa after 48 hours in a patient without evidence of clinical failure.

2.2.3 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.

2.2.4 Clinical Stability Criteria

The following four criteria were used to evaluate clinical stability:

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), or extubation, or FiO2 ≤ 30% if extubated
4. Systolic blood pressure >90 mmHg.

Variables were collected daily from day 0 (day of diagnosis of VAP) to day 14 if available. If a value was missing on one day,
Table 1 Baseline characteristics in adult intensive care unit patients with ventilator-associated pneumonia due to methicillin-resistant Staphylococcus aureus

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Median (IQR)</td>
<td>60 (20)</td>
<td>55 (27.5)</td>
<td>0.205</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>28 (31)</td>
<td>24 (32)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Body Mass Index, Median (IQR)</td>
<td>28.9 (12)</td>
<td>27.5 (10.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>APACHE II Score, Median (IQR)</td>
<td>21 (10)</td>
<td>19 (9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis, n (%)</td>
<td>7 (8)</td>
<td>1 (1)</td>
<td>0.072</td>
</tr>
<tr>
<td>Cardiac Disease, n (%)</td>
<td>26 (29)</td>
<td>13 (17)</td>
<td>0.097</td>
</tr>
<tr>
<td>Respiratory Disease, n (%)</td>
<td>7 (8)</td>
<td>6 (8)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Active Cancer, n (%)</td>
<td>8 (9)</td>
<td>5 (7)</td>
<td>0.773</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>15 (17)</td>
<td>6 (8)</td>
<td>0.515</td>
</tr>
<tr>
<td>Vascular Disease, n (%)</td>
<td>4 (4)</td>
<td>6 (8)</td>
<td>0.515</td>
</tr>
<tr>
<td>Severity of Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II Score, Median (IQR)</td>
<td>21 (10)</td>
<td>19 (9)</td>
<td>0.014</td>
</tr>
<tr>
<td>CPIS on Day 3, Median (IQR)</td>
<td>7 (3)</td>
<td>6 (2)</td>
<td>0.041</td>
</tr>
<tr>
<td>CPIS on Day 5, Median (IQR)</td>
<td>7 (3)</td>
<td>7 (3)</td>
<td>0.060</td>
</tr>
<tr>
<td>Severe Sepsis, n (%)</td>
<td>60 (78)</td>
<td>48 (64)</td>
<td>0.06</td>
</tr>
<tr>
<td>Multilobar Infiltrates, n (%)</td>
<td>37 (42)</td>
<td>24 (32)</td>
<td>0.257</td>
</tr>
<tr>
<td>Empiric Therapy based on Guidelines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate Empiric Therapy, n (%)</td>
<td>88 (99)</td>
<td>72 (97)</td>
<td>0.593</td>
</tr>
</tbody>
</table>

APACHE: Acute Physiology and Chronic Health Evaluation; COPD: Chronic Obstructive Pulmonary Disease; CPIS: Clinical Pulmonary Infection Score; ESLD: End-Stage Liver Disease; ESRD: End-Stage Renal Disease; MDRO: multidrug-resistant organism

the last observation was carried forward. If a second value was missing, the next observation was carried backward. Values that have been carried forward or backwards were not considered to meet clinical stability unless they were within normal ranges.

A patient was considered to have reached clinical stability on the day that all four criteria for clinical stability were met. Patients who died during the first 2 weeks after the diagnosis of VAP were classified as not reaching clinical stability and assigned the worse outcome (day 14).

2.2.5 Outcome variables

1. Primary Outcome: Time to clinical stability
2. Secondary Outcomes:
   (a) Population of patients reaching time to clinical stability
      The number of patients who reached clinical stability between day 1 and 14 after the diagnosis of VAP was calculated for both study groups.
   (b) Mortality
      All-cause mortality within 30 days after VAP diagnosis was assessed for the linezolid and the vancomycin groups including those who reached clinical stability.

2.2.6 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. While hospitalized, patients were followed until discharge, death, or 28 days after VAP diagnosis, whichever occurred first. Vital signs and laboratory values were collected during hospitalization. Identification of MRSA isolates and in vitro susceptibility were performed at each participating center. Vancomycin serum trough levels were collected throughout the study period.

2.2.7 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 or means and standard deviations and were compared between the two groups using the Mann-Whitney U-test or Student’s t-test.

2.2.8 Multivariate analysis for time to clinical stability

To compare the adjusted effect of therapy on the time to clinical stability, Accelerated Failure Time models were used. Since these models require a pre-specified distribution, we evaluated eight possible models and reported the results of the model with the lowest Akaike Information Criterion (log normal model). Clinically significant confounding variables, as deemed by the research team, were selected for adjustment in the multivariable models. This model was adjusted for the following variables: age, sex, BMI, risk factors for multidrug resistant organisms, bronchiectasis, COPD, vascular disease, diabetes, multilobar infiltrates on chest image, severity of disease on day 0 (CPIS, severe sepsis, and APACHE II score), and appropriate empiric therapy based on na-
Adjusted survival curves were created to compare the two groups. R v3.2.2 was used for all analysis. P-values of \( \leq 0.05 \) were considered statistically significant in all analyses unless otherwise specified.

3 Results

A total of 89 patients treated with linezolid and 75 patients treated with vancomycin met study criteria and are included in the analysis. Baseline characteristics of the study population are shown in Table 1.

3.1 Time to clinical stability

The median time to clinical stability was 6 days (IQR 8) for patients treated with linezolid, versus 7 days (IQR 12) for patients treated with vancomycin \((P=0.490)\). The adjusted effect of therapy on time to clinical stability is shown in Fig. 1.

3.2 Proportion of patients who reached clinical stability

From the population of linezolid treated patients, 79\% (70 patients) reached clinical stability within 14 days of VAP diagnosis, compared to 75\% (56 patients) of the population of vancomycin treated patients \((P=0.463)\).

3.3 Mortality

All cause-mortality within 30 days for the total study was 18\% (16 patients) for the linezolid group versus 17\% (13 patients) for the vancomycin group \((P>0.959)\). Of the patients who reached clinical stability, the mortality within 30 days of diagnosis was 6\% (5 patients) for the linezolid group versus 7\% (4 patients) for the vancomycin group \((P>0.999)\).

4 Discussion

This study failed to demonstrate a statistically significant difference in time to clinical stability in patients with MRSA VAP treated with linezolid or vancomycin. The median time to clinical stability was 6 days (IQR 8) for patients treated with linezolid, versus 7 days (IQR 12) for patients treated with vancomycin \((P=0.490)\). This time to clinical stability occurred in patients who received appropriate empiric therapy. A longer time to clinical stability is expected in the event of inappropriate empiric. If this 1-day difference in reaching clinical stability happens to be accurate, 2,178 patients will be needed in order to assure enough power to detect a statistically significant difference.

No prior studies in VAP have defined criteria for clinical stability. Considering well-established criteria in the field of CAP, we selected lack of fever and improvement in WBC as part of the criteria for clinical stability. Prior studies evaluating the clinical course of patients with VAP have used PaO\(_2\)/FiO\(_2\) ratio, CPIS, and microbiology. In these studies, a fix predetermined value was selected to define resolution, such as PaO\(_2\)/FiO\(_2\) ratio \(\geq\) 250, or negative micro results.\(^{10-14}\) Meeting these criteria practically defines the time when the particular abnormality is back to normal but fails to define when it is improving. In an attempt to define improvement, we compared WBC count and oxygenation with the values of the prior day and define a level of change that will be considered as improvement.

The number of days to reach clinical stability for both study groups is within the range reported in the literature for time to resolution of symptom,\(^ {10-14}\) and is close to the already well-established time to clinical stability of CAP. Early clinical improvement at day 3 to 5 has been used as the primary efficacy endpoint in CAP clinical trials based on recommendations from the Food and Drug Administration.\(^ 4\) However, primary endpoint for hospital-acquired and ventilator-associated pneumonia remains to be evaluated at 14 to 28 days and clinical stability considered a secondary endpoint.\(^ 7\)

Several CAP studies evaluating the safety of switch therapy showed that reaching clinical stability is associated with resolution of infection and good clinical outcomes.\(^ {17,18}\) However, reach-
ing clinical stability in VAP is still associated with higher mortality rates likely due to underlying diseases\textsuperscript{19,20} Our data emphasizes the challenge of selecting mortality as an outcome in patients with VAP, since the mortality at 30 days still occurred in 5-10% of the patients reaching clinical stability. The number of days for patients to reach clinical stability could be an early clinical outcome used when comparing different antibiotics for therapy of VAP.

The primary limitation of this study is that in an attempt to evaluate antibiotic effectiveness against MRSA VAP, patients with clinical failure during the initial 48 hours of diagnosis of VAP were excluded from study. By excluding this sicker population, the number of patients reaching clinical stability and the time to clinical stability was likely biased. There are several other limitations in this study that are due to the retrospective, observational nature of the study. Furthermore, patients included in the database were randomly selected and did not represent consecutive cases of hospitalized patients with VAP. Being a secondary analysis with a small number of patients and no sample size calculation, this study may have not been powered to detect statistically significant differences.

In conclusion, our data suggest that time to clinical stability may be used as an early clinical outcome in patients with VAP, better reflecting antibiotic activity. Late outcomes, such as mortality, may represent a combination of antibiotic activity as well as severity of underlying conditions that predispose the patient to develop VAP.

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