



ORIGINAL RESEARCH

Sepsis in Patients with Ventilator Associated Pneumonia due to Methicillin-Resistant *Staphylococcus aureus*: Incidence and Impact on Clinical Outcomes

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Abstract

Background: Sepsis is a clinical syndrome associated with organ dysfunction due to a dysregulated host response to infection. Methicillin-resistant *Staphylococcus aureus* (MRSA) ventilator-associated pneumonia (VAP) is a serious infection frequently associated with sepsis. The objectives of this study were to define the incidence of sepsis and clinical failure in patients with MRSA VAP.

Methods: This was a secondary analysis of the Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (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. We used the 3rd International Consensus Definitions for sepsis. The presence of clinical failure was evaluated at the 14 day follow-up and defined as: 1) progression of baseline signs and symptoms of pneumonia, or 2) death. The Chi-Square Trend Test was utilized to determine the association between the level of organ dysfunction and clinical failure.

Results: MRSA VAP was diagnosed in 205 patients with 138 (67%) presenting with sepsis. Clinical failure occurred in 14% (8/57) of patients without sepsis. Clinical failure occurred in 18% (13/73) of patients with sepsis and 1 organ dysfunction, in 28% (12/43) of patients with sepsis and 2 organ dysfunction, in 28% (5/18) of patients with sepsis and 3 organ dysfunction, and in 100% (4/4) of patients with sepsis and 4 organ dysfunction ($p=0.01$).

Conclusions: Sepsis is a frequent complication of MRSA VAP and the number of organ dysfunction correlates with clinical failure in these patients. Effective prevention and treatment of sepsis and associated organ dysfunction is essential to avoid cumulative burden of disease in MRSA VAP.

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1 Introduction

Ventilator-associated pneumonia (VAP) can occur in up to 8-28% of intubated patients in the Intensive Care Unit (ICU).¹ This infectious complication of mechanical ventilation has been associated with significant morbidity and mortality and linked to several risk factors in the literature: severity of underlying comorbidities, inappropriate initial antibiotic regimen and multidrug resistant or-

ganisms (MDRO).² Amongst MDRO, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a significant etiologic agent in nosocomial infections worldwide.³ MRSA has been reported as a common cause of VAP, along with Enterobacteriaceae (usually the most common cause) and *Pseudomonas aeruginosa* in several series.³⁻⁵ In this context, it is important to better understand the determinants of clinical failure in VAP. Septic shock has been linked to VAP clinical failure, as measured by a mortality predictive score, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) Score.^{1,6,7} The magnitude of organ dysfunction related to clinical failure, however, has not been clearly defined. The objectives of this study were to determine if there is an association between the number of organ dysfunction

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and clinical failure in patients with MRSA VAP and to better characterize the type and frequency of organ dysfunction with MRSA VAP and sepsis.

2 Materials and 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) database, a multicenter, retrospective, observational study of 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, 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. 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.⁸ 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

- 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.

Sepsis in patients with MRSA VAP was defined as the presence of dysfunction of at least one organ system that was not attributable to other causes at the time of VAP diagnosis.⁹

Organ dysfunction was defined according to specific organ systems, as follows:^{10,11}

- **Cardiovascular system:** shock defined as arterial systolic blood pressure <90 mmHg (shock for at least 1 hour, despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in an attempt to maintain a systolic blood pressure > 90 mmHg or a mean arterial pressure of > 70 mmHg)
- **Respiratory system:** PaO₂/FiO₂ ratio < 250 (< 200 if the lung was the only dysfunctional organ).
- **Hematological system:** thrombocytopenia (platelets <100,000/mm³) or coagulation abnormality (INR > 1.5; PTT 60 seconds)
- **Renal system:** increased creatinine >50% from baseline or acute oliguria (< 0.5 ml/kg/h for >2 hours) or creatinine increase > 0.5 mg/ dl.

2.3 Study Outcomes

The presence of clinical failure was evaluated at a 14-day follow-up and was defined as: 1) progression of baseline signs and symptoms of pneumonia, or 2) death.

2.4 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 means and standard deviations and were compared between the two groups using the Mann-Whitney U-test or Student's t test. The Chi-square trend test was utilized to determine the association between the magnitude of organ dysfunction and clinical failure in MRSA VAP patients. *P*-values of ≤0.05 were considered statistically significant in all analyses unless otherwise specified.

3 Results

A total of 205 patients diagnosed with MRSA VAP were included in this analysis. Sepsis was identified in 138 (67%) patients. Patients with organ system dysfunction presented with higher mean APACHE II scores (*p* < 0.001) and had a higher rate of diabetes mellitus (*p* 0.027) when compared to the patients without organ dysfunction. Baseline characteristics of the study population are further outlined in **Table 1**.

The percentage of patients with MRSA VAP clinical failure increased along with the magnitude of organ dysfunction (**Figure 1**). Fourteen percent (8/57) of patients in the group without organ dysfunction failed to respond to treatment, when compared to 18% (13/73) in patients with single organ system dysfunction; 28% (12/43) in patients with dysfunction of two organ systems; 28% (5/18) with dysfunction of three organ systems and 100% (4/4) in patients with dysfunction of four organ systems (*p* = 0.01).

The frequency of organ dysfunction is shown in **Table 2**.

Table 1 Baseline characteristics of the study population

	MRSA VAP Sepsis: No	MRSA VAP Sepsis: Yes	p-value
Total	57	138	
Age, mean (SD)	58 (16)	56 (16)	0.428
Males, n (%)	34 (60)	85 (62)	0.800
Cancer, n (%)	3 (5)	10 (7)	0.881
COPD, n (%)	4 (7)	20 (15)	0.148
ESLD, n (%)	1 (2)	10 (7)	0.222
ESRD, n (%)	2 (4)	5 (4)	0.999
Cardiac disease, n (%)	12 (23)	44 (32)	0.205
Vascular disease, n (%)	17 (30)	12 (9)	0.389
Diabetes mellitus, n (%)	8 (14)	40 (29)	0.027
Lung disease, n (%)	8 (14)	36 (26)	0.067
CPIS day 0, mean (SD)	6 (2)	6 (2)	1.000
APACHE II score, mean (SD)	17 (5)	21 (7)	< 0.001

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

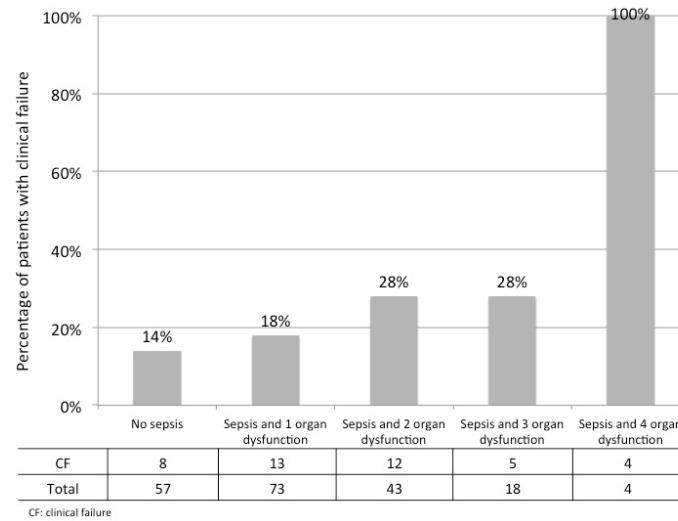


Fig. 1 Percentage of patients with clinical failure according to the number of failing organ systems

4 Discussion

This study analyzed the correlation between MRSA VAP clinical failure and specific organ system dysfunction.

The true impact of VAP on mortality and the role of MDRO in outcomes of this disease process remain poorly defined. Attributable mortality rates for VAP are still debatable and described as being between 33-50% in some series.^{12,13} Melsen *et al*, however, did not find evidence of attributable mortality due to VAP in patients with trauma or acute respiratory distress syndrome (ARDS).¹⁴ There was such evidence in other patient groups, although unable to be quantified due to heterogeneity of study results and pooled analysis. Conflicting results have also been found regarding the role of MDRO on VAP mortality and outcomes, largely due to overlap of confounding factors, such as associated comorbidities and organ failure in severe and advanced presentations of VAP.

Several studies have explored early predictors of infection recurrence and death in patients with VAP. Female sex, age over 70, disease severity at onset of VAP and persistent fever have been identified as indicators of poor outcomes.² Age over 70, higher

APACHE II scores, and associated comorbidities have been described as risk factors for VAP clinical failure in some series.¹ Scores to predict 30-day mortality in hospitalized patients, such as the APACHE II score, have been noted to be early and independent indicators of mortality and clinical failure in VAP patients.^{1,6,7,15} In our study, patients with higher APACHE II scores were more likely to experience MRSA VAP clinical failure.

The presence of generalized, multi-organ failure has been linked to 30-day all-cause mortality in MRSA pneumonia.³ In terms of the impact of specific organ system failure on VAP outcomes, Gursel *et al* described a 38% incidence of acute renal failure (ARF) in this patient population.¹⁶ High APACHE scores, MDRO and sepsis were independent risk factors for development of ARF during VAP episodes in that series. The renal system was found to be the second most affected organ system in our study.

In face of the significant morbidity associated with MRSA VAP, identifying and defining modifiable risk factors and patients at a potential risk for poor outcomes becomes essential. This strategy would allow for early and aggressive intervention and treatment of organ dysfunction in VAP.

Table 2 Type of organ system dysfunction

Organ failure	Patients: 138
Cardiovascular	20 (14%)
Pulmonary	123 (89%)
Hematology	22 (16%)
Renal	40 (29%)
Metabolic	24 (17%)

5 Conclusions

Sepsis and increasing magnitude of organ dysfunction were observed in 67% of our patients with MRSA VAP. The most common organ systems to fail were pulmonary, renal, metabolic, hematologic and cardiovascular, respectively. It is uncertain if this distribution is seen mainly in sepsis subsequent to VAP or is similar in sepsis due to other infections. The cumulative burden of organ dysfunction leading to clinical failure makes effective prevention and treatment of these conditions essential in the context of MRSA VAP.

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