Improved outcome of ventilator-associated pneumonia caused by methicillin-resistant *Staphylococcus aureus* in a trauma population

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**KEYWORDS:** Ventilator-associated pneumonia; Trauma; Methicillin-resistant *Staphylococcus aureus*; Vancomycin; Linezolid

Abstract

**BACKGROUND:** The treatment of ventilator-associated pneumonia (VAP) secondary to methicillin-resistant *Staphylococcus aureus* (MRSA) remains controversial.

**METHODS:** We performed a review of all blunt trauma patients diagnosed with MRSA VAP from June 2005 to June 2011. VAP for the first 3 years was diagnosed by sputum aspiration and treated with vancomycin. For the last 3 years of the study period, VAP was diagnosed with bronchoalveolar lavage and treated with linezolid.

**RESULTS:** MRSA VAP patients treated with vancomycin had an average hospital length of stay (LOS) of 49 days (range 9–99 days), an average intensive care unit (ICU) LOS of 43 days (range 6–98 days), and average ventilator days of 34.4 (range 3–76 days). Seventeen MRSA VAP patients treated with linezolid had an average hospital LOS of 27 days (range 11–61), an average ICU LOS of 22 days (range 10–42) days, and average ventilator days of 16.6 (range 2–42).

**CONCLUSIONS:** Trauma patients who develop MRSA VAP appear to have fewer ventilator days and shorter ICU and hospital LOS when treated with linezolid.

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development, new therapies have been developed with particular effectiveness for eradicating MRSA.

Vancomycin, a glycopeptide antibiotic, has long been the standard treatment for MRSA pneumonia; however, the American Thoracic Society and Infectious Disease Society of America guidelines suggest that linezolid, an oxazolidinone antibiotic, may be preferred over vancomycin for the treatment of MRSA pneumonia.  

The recommendation by these societies and others is based on a post hoc analysis of data from a randomized controlled trial of antibiotic treatment with linezolid versus vancomycin that showed a survival advantage with linezolid for the treatment of MRSA nosocomial pneumonia.  

Authors have questioned the superiority of linezolid versus vancomycin for the treatment of nosocomial pneumonia.  

The purpose of this study was to investigate and compare the efficacy of vancomycin and linezolid for the treatment of MRSA VAP in the trauma population.

**Results**

Twenty-eight patients were treated for MRSA VAP during the entire 6-year study period. Eleven patients were diagnosed with MRSA VAP during the first 3 years of the study period and were treated with vancomycin. Five (45%) of the patients treated with vancomycin were diagnosed with polymicrobial VAP. During the second 3-year period of the study, 17 patients were diagnosed with MRSA VAP and were treated with linezolid. Six (35%) of the patients treated with linezolid were diagnosed with polymicrobial VAP. Baseline demographics of both study groups are reported in Table 1. Clinical characteristics of VAP patients (n = 11) were excluded for pregnancy, the unavailability of medical records, an immunocompromised state, and the presence of malignancy.

During the first 3 years of the study, VAP was routinely diagnosed by endotracheal aspirate with pneumonia diagnosed by moderate or large growth on culture media. In addition to positive cultures and abnormal infiltrate on a chest radiograph, at least 2 of the following criteria had to be met: an abnormal temperature (>38°C or <36°C), an abnormal white blood cell count (>10,000 cells/mm³ or <4,000 cells/mm³ or >10% immature neutrophils), or macroscopically purulent sputum. If MRSA pneumonia was identified from the sputum culture, the patient was started on vancomycin (1 g intravenously every 12 hours for a 14-day course). During the second 3-year period, similar clinical criteria were applied for the diagnosis of pneumonia; however, sputum culture was obtained with bronchoalveolar lavage, and pneumonia was diagnosed with ≥10⁴ colony-forming units/mL. When >10⁴ colony-forming unit/mL MRSA were identified, the patient was started on linezolid (600 mg intravenously every 12 hours for a 14-day course). Identical vent-weaning protocols and daily sedation withholding protocols were used in each group. Several patients underwent tracheostomy insertion in each group; however, no standard protocol was used for the timing of tracheostomy insertion. Hospital survival analyses were conducted for all MRSA VAP patients.

**Methods**

This study was performed through a retrospective chart review of all blunt trauma patients diagnosed with MRSA VAP during a 6-year period (ie, June 1, 2005–June 30, 2011). All patients entered were treated in the surgical-trauma intensive care unit (ICU) of the University of South Alabama Medical Center, Mobile, AL. This study was approved by the University of South Alabama Medical Center Institutional Review Board. Patients were included in the study if they were greater than 14 years of age and developed VAP caused by MRSA more than 48 hours after the commencement of mechanical ventilation. Patients

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<th>Table 1 Patient demographics</th>
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<td>Vancomycin-treated patients (n = 11)</td>
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<td>Mean age (y)</td>
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<td>Male, n (%)</td>
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<td>Mean weight (lb)</td>
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<td>Mean ISS</td>
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Values in parentheses are ranges unless otherwise indicated. ISS = injury severity score.

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<th>Table 2 VAP characteristics</th>
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<tr>
<td>Vancomycin-treated patients (n = 11)</td>
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<tr>
<td>Mean length of mechanical ventilation (d)</td>
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<td>Mean length of ICU stay (d)</td>
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<td>Mean length of hospital stay (d)</td>
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<td>Mean time to MRSA VAP (d)</td>
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<td>Mean time of antibiotic duration (d)</td>
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<td>Mortality (%)</td>
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Values in parentheses are ranges unless otherwise indicated.

ICU = intensive care unit; MRSA = methicillin-resistant Staphylococcus aureus; VAP = ventilator-associated pneumonia.
a severe closed-head injury. On postadmission day 26, his family elected to withdraw care. Three (18%) patients died in the linezolid-treated group. Two of these patients had severe closed-head injuries, one of whom succumbed to multiple organ failure. That patient developed acinetobacter pneumonia after treatment for MRSA pneumonia. The family of the other severe closed-head injury patient elected to withdraw care on day 4 of linezolid therapy. The third patient who died in the linezolid-treated group was an 88-year-old man who suffered a flail chest with severe pulmonary contusions. The patient had do not resuscitate orders and died on hospital day 16 because of pulmonary failure during his 5th day of linezolid therapy.

Comments

It is widely accepted that initial treatment with appropriate antimicrobial therapy is important for the successful management of VAP. Although appropriate antimicrobial therapy may be instituted in a timely and appropriate manner, decreased mortality and clinical cure rates may not be realized. An explanation for this may be that antibiotics are ineffective despite achieving adequate minimum inhibitory concentration.

MRSA VAP has consistently shown poor outcomes including an increased ICU length of stay despite appropriate antibiotic therapy. The American Thoracic Society and Infectious disease Society of America guidelines suggest that linezolid is preferred over vancomycin for the treatment of MRSA VAP. This recommendation is based on a retrospective analysis of a prospective randomized controlled trial of MRSA VAP patients who were treated with linezolid or vancomycin. Because of the nature of this analysis, many investigators believe further analysis comparing the efficacy of these antibiotics for the treatment of MRSA VAP is warranted.

Until the development of the oxazolidinone antibiotic linezolid, few treatment options were available for the treatment of MRSA infections. Vancomycin was considered the standard of care, and today many still consider it the standard of care for the treatment of MRSA VAP. However, vancomycin has poor lung penetration as documented in pharmacokinetic studies and high rates of clinical failures. Reports have suggested linezolid as a superior alternative to vancomycin for the treatment of MRSA pneumonia because of the higher drug concentration in the lung. The primary hypothesis is that greater pulmonary parenchymal levels would result in more rapid resolution of the pneumonia. This difference in the diagnostic method may have contributed to the differences in outcome. Based on our findings, trauma patients who develop MRSA VAP may have an improved clinical outcome with linezolid antibiotic therapy as opposed to standard dosing of vancomycin (1 g every 12 hours).

References


Discussion

**Roxie Albrecht, M.D.** (Oklahoma City, OK): I noticed on your presentation that you treated for somewhere around 12 days. Did you have a standard time of therapy that was your goal? Did you have any recurrence of MRSA pneumonia in those patients who had a shorter time course? Did you include only patients with MRSA pneumonia, or did some of these patients have prior or subsequent non-MRSA pneumonia? Given your small sample size, did you compare ventilator-free days or days that they were alive and off the mechanical ventilator or look at hospital discharge data to see the numbers going to rehabilitation centers, long-term acute care, or home?

**Richard P. Gonzalez, M.D.** (Mobile, AL): We intended to treat the patients for 14 days. Depending on mortality, some patients were treated less. The average time that they were treated was 12 days, but we actually tried to treat the patients for a total of 14 days. It was difficult to find if there were any recurrences, but one thing that we could say was that it was not necessary to treat patients in either group for a recurrence of MRSA. As far as hospital stay, hospital days were longer in the vancomycin group, but that correlated with the increased number of ventilator days. So the rest of the hospital days in the hospital really were actually very similar, whether it was vancomycin or linezolid after extubation. We did not evaluate disposition.

**Donald Fry, M.D.** (Chicago, IL): Should an endotracheal aspirate in an intubated patient be compared with patients who had bronchoalveolar lavage, as with endotracheal aspirates you may culture an assortment of microbes that may not be related to the infection at all. Secondly, all MRSA are not created equal. Community-acquired MRSA in the lung are devastating. Were the pathogens in the 2 groups of patients actually the same? I have been very interested in using length of stay as a measure of outcome of our patients but with historic controls that can be very problematic, so do you have a reference group of what has been the changing pattern of all patients with all pneumonias in your ICU over this period of time? Finally, is the reluctance to use linezolid totally an economic one, and is this a harbinger of health reform?

**Dr. Gonzalez:** I agree with you about endotracheal aspirates, which is why we went to bronchoalveolar lavage. I think there is still controversy over the magnitude, whether you use 10 to the 2nd, 10 to the 3rd, 10 to the 4th, or 10 to the 5th, and, in so doing, the lower the concentration that you use, the more patients you are going to treat. As far as Panton-Valentine leukocidin goes, I agree with you that in the community acquired they are more virulent. Because this is strictly a trauma population, most of the MRSA is not community acquired so Panton-Valentine leukocidin should be rare. As far as the economics of linezolid versus vancomycin, strikingly, a 14-day course of 1 g vancomycin costs $75. A 14-day course of linezolid is around $2,000.

**Jeffrey Claridge, M.D.** (Cleveland, OH): Was the dosing adequate in the vancomycin-treated group? What were your rates of pneumonia between the 2 periods using 1,000 ventilator days? Your diagnosis changed significantly.

**Dr. Gonzalez:** I agree with you. This is why the trend now is to go to weight-based dosing to achieve higher levels in the endothelium of the lung.

**Anna Ledgerwood, M.D.** (Detroit, MI): I hate to be so skeptical, but I just find it hard to believe that a different antibiotic makes this significant difference in ventilator days. Did you change the frequency of bronchoscopy, cleaning the airway out, or time to tracheostomy?

**Dr. Gonzalez:** I think we can say there is an association, but to actually say the antibiotics were the direct cause of the decrease would be a stretch, and I admit that as well.