Patterns of Early and Late Ventilator-Associated Pneumonia Due to Methicillin-Resistant *Staphylococcus aureus* in a Trauma Population

Jeffry L. Kashuk, MD, Ernest E. Moore, MD, Connie S. Price, MD, Christopher Zaw-Mon, MD, Theresa Nino, RN, James Haenel, RRT, Walter L. Biffl, MD, C. Cothren Burlew, MD, and Jeffrey L. Johnson, MD

Background: Community-acquired methicillin-resistant *Staphylococcal aureus* (CA-MRSA) infection is approaching endemic proportions nationally, and it is a potential cause for early ventilator-associated pneumonia (VAP) in the acutely injured patient. We sought to determine the prevalence of early (≤4 days) and late (>4 days) MRSA pneumonia in ventilated multisystem trauma patients and to correlate findings with admission nasal swabs.

Methods: We performed a review of our prospective trauma and infectious disease data bases for all patients admitted to our surgical intensive care unit with early (≤4 days) and late (>4 days) VAP during a 4-year period. The diagnosis of pneumonia was established by clinical pulmonary infection score >6, bronchoalveolar lavage, and quantitative cultures showing $>10^4$ organisms. Nasal swabs for early identification of MRSA carriers were performed routinely at admission.

Results: One hundred seventy-six patients were identified with *S. aureus* VAP. Patients with MRSA were compared with those with methicillin-susceptible *S. aureus* (MSSA). There were 47 (27%) early MSSA VAP and only 4 (2.2%) with early MRSA VAP. One hundred twenty-five patients were diagnosed with late VAP. Forty patients (23%) had MRSA VAP and 85 patients (64%) had MSSA VAP. None of the four patients with an early MRSA VAP had positive nasal swabs at admission.

Conclusion: Despite an increase of MRSA nationally, we found a low incidence of early and late MRSA VAP in trauma patients, which was not identified by nasal swab screening. On the basis of our results, we question the efficacy of empiric vancomycin therapy in early (≤4 days) *S. aureus* VAP. Furthermore, nasal swabs were not helpful in identifying patients at risk for MRSA VAP.

Key Words: Ventilator-associated pneumonia, *Staphylococcus aureus*, Methicillin resistant, Trauma.

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From the Department of Surgery (J.L.K.), Division of Acute Care Surgery, Penn State Hershey Medical Center and College of Medicine, Hershey, PA; Departments of Surgery (E.E.M., C.Z.-M., J.H., W.L.B., C.C.B., J.L.J.), Medicine (Infectious Diseases) (C.S.P.), and Nursing (T.N.), Rocky Mountain Regional Trauma Center, Denver Health Medical Center, University of Colorado, Denver School of Medicine, Denver, Colorado.
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Address for reprints: Jeffry L. Kashuk, MD, Department of Surgery, Division of Trauma, Acute Care, and Acute Care Surgery, Penn State Hershey Medical Center and College of Medicine, 500 University Dr, MC H075, Hershey, PA 17033; email: jkashuk@hmc.psu.edu.

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Recent reports of escalating methicillin-resistant *Staphylococcal aureus* (MRSA) infection are of significant concern to critically ill trauma patients.[1–4] With greater bacterial resistance, there is a need for broader empiric antibiotic coverage of these resistant organisms. Based on these trends, current recommendations for treatment of community-acquired infections, including certain pneumonias, advocate the use of antibiotics that cover MRSA when *Staphylococcus aureus* is suspected.[5,6]

S. aureus is commonly found as a part of human skin flora in specific locations such as axilla, groin, anterior nares, and the perirectal area. Up to 31% of healthy individuals are colonized with *S. aureus*. Methicillin-resistant *S. aureus* in the community is believed to add to the burden of *S. aureus* colonization and its prevalence is increasing.[7] Furthermore, it has long been known that *S. aureus* nasal carriers are at higher risk for wound infections,[8] and MRSA carriers have been shown to have similar risk for acquiring MRSA infection compared with noncarriers.[9] It is unknown how these data can be applied to a critically ill trauma population and whether MRSA colonization status should play a role in perioperative antibiotic selection and empiric treatment regimens.

S. aureus is the most important cause of serious infection at our institution, and we have noted an increasing incidence of MRSA infection and colonization in critically ill patients admitted to our surgical-trauma ICU. We queried whether this trend would be reflected in our trauma surgical intensive care unit (SICU) population diagnosed with early *S. aureus* ventilator-associated pneumonia (VAP). Thus, our primary objective was to determine the proportion of early and late VAP (defined as VAP per 1,000 ventilator days) due to MRSA among our critically ill trauma patient. As a secondary objective, we examined trends in nasal colonization rates with MRSA at admission to our trauma ICU in at attempt to correlate these results with the prevalence of early MRSA VAP.

METHODS

Setting and Population

This study involved only patients admitted for trauma to our 20-bed SICU. Nontrauma, general surgical (elective and emergent) were not included in the study. Denver Health Medical Center–Rocky Mountain Trauma Center is the only

academic Level I trauma center in Colorado and serves as a five-state referral system for multisystem trauma.

After appropriate Institutional Review Board approval, the medical records of 176 trauma patients diagnosed with *S. aureus* VAP during a 4-year period (July 2004–July 2007) were reviewed with additional data from the trauma and infectious disease databases. Patients with early and late MRSA VAP were compared with patients with early and late methicillin-susceptible *S. aureus* (MSSA) VAP. The mean age, gender, and Injury Severity Score were then calculated. Patients having onset of symptoms and positive bronchoalveolar culture obtained within 4 days of hospital admission were considered to be early community-acquired VAP cases. Any positive bronchial cultures obtained from patients with onset of symptoms after 4 days were considered to be late hospital-acquired VAP cases.

VAP was diagnosed using quantitative cultures obtained by either bronchoscopic-guided bronchoalveolar lavage (BAL) or mini-BAL. The sample area for obtaining bronchoscopic specimens was based on both the chest radiography and/or the segment with the most copious secretions visualized on bronchoscopy. In brief, the bronchoscope was wedged into the identified airway lumen, and 80 mL to 120 mL of saline was infused in aliquots of 30 mL each. All mini-BAL specimens were performed by trained critical care Registered Respiratory Therapists. Before the mini-BAL, patients were positioned with the head of bed up; if contraindicated, they were placed in reverse Trendelenburg's position preceding infusion of 20 mL saline aliquots. Mini-BAL specimens were rejected by the respiratory therapist if the volume of aliquot return was <3 mL or if it was determined that the specimen was potentially contaminated by upper airway secretions. Indications for obtaining a BAL were determined on daily SICU rounds with the surgical attending based on the combination of clinical, radiographic, and laboratory assessment of the patients at risk for a VAP. For consistency, we used the modified Clinical Pulmonary Infection Score (CPIS) as a trigger for obtaining an invasive quantitative culture. The CPIS score is based on the following criteria: (a) purulent respiratory secretions; (b) new pulmonary infiltrates on chest radiograph; (c) body temperature >38.5°C or <36.5°C; (d) white blood cell count $>10^4/mm^3$ or $<4{,}000$ K/μL; and (e) P_{AO_2}/FIO_2 ratio <240. Patients with a CPIS score >6 had a bronchial sampling performed either blind (mini-BAL) or under fiberoptic examination (BAL). Once the lower respiratory tract culture was obtained, empiric antibiotics were initiated. For early suspected VAP, our practice is to start a single agent (usually a third generation cephalosporin) appropriate for community-acquired organisms. For late suspected VAP, broad spectrum antibiotic therapy is typically initiated with vancomycin and a carbapenem or antipseudomonal penicillin. Once culture data are available, antibiotics are de-escalated or discontinued based on the results and sensitivities. BAL cultures with colony counts $\geq 10^5$ colony forming units/mL are required to confirm VAP in patients who had been continuously ventilated for at least 48 hours before the onset of infection.[10]

Nasal swabs from the bilateral anterior nares of patients admitted to the trauma ICU were obtained within 24 hours of admission per institution infection control policy.[11] *S. aureus* was cultured and resistance to methicillin was characterized using standard methods. The nasal swab was plated onto mannitol salt agar (BD, Franklin Lakes, NJ) and incubated overnight at 35°C to 37°C in a non-CO_2 incubator. After overnight incubation, plates were interpreted. Any yellow colonies were subcultured onto a blood agar plate. Gram-positive cocci in clusters from the blood agar plate were subjected to catalase and coagulase tests after 24 hours incubation. Isolates that were both catalase and coagulase-positive were inoculated onto selective agar containing 6 μg/mL of oxacillin. Isolates that showed no growth after 24 hours on the oxacillin plate were reported as methicillin-sensitive *S. aureus* (MSSA) and isolates that showed growth after 24 hours were reported as MRSA.[12] The prevalence of *S. aureus* nasal colonization was defined as a number of patients who grew *S. aureus* from their admission nasal swab divided by the total number of patients screened per month.

RESULTS

During the 4-year period ending in July 2007, 5,082 patients were admitted to the SICU. Of this group, 176 patients were determined to have *S. aureus* VAP. There were 146 men (83%) and 30 women (17%) with a mean age of 41.75 years (range, 14–93 years). Of note, >80% of injuries were caused by blunt trauma mechanisms.

A summary of the results of MRSA versus MSSA VAP in our trauma population is shown in Figure 1. One hundred seventy-six patients were determined to have *S. aureus* pneumonia by quantitative culture. Only four patients had early MRSA VAP. Forty patients (22%) manifested a late (>4 days) MRSA VAP. One hundred thirty-two patients (75%) with *S. aureus* VAP were found to be methicillin sensitive. There was no notable difference between the mean calculated age and Injury Severity Score in early or late MSSA and MRSA VAP.

During the 4-year period, emergence of community-acquired (CA)-MRSA from outpatient settings was well documented in our community. *S. aureus* resistant to methicillin from outpatient settings ranged from ~40% at beginning of study period to just >60% by the end of study period. In

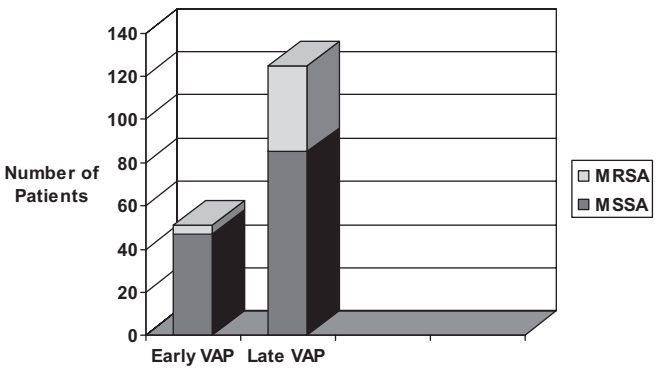

Figure 1. MRSA vs. MSSA VAP in our trauma population.

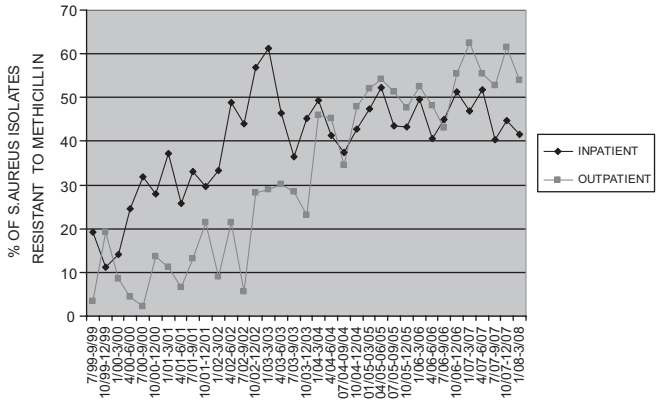

Figure 2. Percentage of nasal swabs positive for MRSA over time.

contrast, *S. aureus* resistant to methicillin from inpatient settings remained stable between 40% and 50%. During the last 1 year of the study, rates of methicillin resistance in our outpatient population exceed that of our inpatient population.

Furthermore, there had been an increase in positive nasal swabs for MRSA colonization from 0% to 6% from 2003 to 2006 (Fig. 2). None of the four patients with early CA-MRSA had positive nasal swabs on admission; positive nasal swabs were noted in three of the late MRSA VAP patients and two MSSA VAP patients.

DISCUSSION

The results of this study demonstrate that the prevalence of early MRSA ventilated-associated pneumonia in this group of trauma patients during a 4-year period ending July 2007 was very low (2.2%), while MRSA as a cause of late VAP was much higher (22%). None of the four patients with an early MRSA VAP had positive nasal swabs on admission, while only a minority of those with late MRSA VAP had positive nasal swabs (7.5%), suggesting that MRSA nasal swab status may not accurately predict those at risk for MRSA VAP in a trauma ICU population. In addition, we could not identify a known risk factor for the early appearance of MRSA infections in the four patients with early MRSA pneumonias, after reviewing potential factors, such as prior hospitalization, exposure to antibiotics, chronic medical conditions, or prior institutionalization.

Earlier reports from our institution demonstrated an increase in the percentage of outpatient *S. aureus* isolates resistant to methicillin increased from 6% to 45% from 2002 to 2004, which were primarily skin and soft tissue infections.[11] The trend has continued to increase, and in 2008, nearly 60% of *S. aureus* isolated in our outpatient setting have been methicillin resistant. This increase in the prevalence of MRSA in skin and soft tissue infections has been reported by other investigators.[13,14]

The discrepancy between the MRSA prevalence in Skin and Soft Tissue Infections (SSTI) and early VAP confirms what we know to date about the pathogenesis of pneumonia. Early VAP is essentially a community-acquired pneumonia. The organisms most commonly implicated in as causing community-acquired pneumonia are *S. pneumonia*, *H. influenza*, and less commonly (in patients with chronic obstructive pulmonary disease) *M. catarrhalis*, which colonize the throat and nasopharynx. In this population of trauma patients who are emergently incubated in the field or Emergency Department, these are organisms that patients likely aspirate with contamination starting in the initial days of hospitalization. Before the increased incidence of MRSA, true MSSA pneumonia was rarely a cause of early VAP, although it was frequently identified on cultures as low numbers due to colonization. As MRSA colonization at admission was not found to be frequent in our trauma population during the time period of this study, it is also not surprising that this was not found to be a common etiology of early VAP as well.

The discrepancy between the MRSA prevalence in SSTI and early VAP also confirms what we know to date about the emergence of CA-MRSA. Most CA-MRSA have pulsed field gel electrophoresis patterns distinct from the endemic strain transmitted in hospitals, and we have previously demonstrated the same findings in our population.[11] The emergence of this distinct clone in the community is associated with well-described differences between clinical syndromes caused by CA-MRSA and healthcare-associated MRSA (HA-MRSA). Among 1,100 MRSA infections evaluated in a large epidemiologic study, skin and soft tissue infections were highly significantly associated with a CA-MRSA etiology versus HA-MRSA (75% vs. 37%, respectively; $p < 0.001$), whereas respiratory infections were highly significantly associated with a HA-MRSA etiology versus CA-MRSA (22% vs. 6% respectively, $p < 0.001$).[15] This may be a result of the differences in pathogenesis due to exotoxin genes contained in CA-MRSA strains. Both the Panton-Valentine leudocidin (PVL) and the SCCmec type IV allele are common among CA-MRSA strains (>75%) and rarely found in HA-MRSA (<5%) and most (93%) furunculosis cases are caused by PVL-containing *S. aureus*.[16] Only 2% of infections due to CA-MRSA strain have been associated with pneumonia, and when it occurs, it manifests as a severe necrotizing disease, likely due to the presence of PVL.[17] Thus, it is not surprising that MRSA was not a common pathogenesis of VAP in our trauma population.

The utility of nares swabs in documenting colonization with CA-MRSA has been questioned, and indeed, we were unable to predict MRSA infection in early VAP with anterior nasal swabs, although previous reports suggest that patients with positive nasal culture for MRSA are at a higher risk for developing MRSA infections during their stay in the ICU.[13] This may be due to the fact that, although nasal swabs have accurately detected MRSA colonization in >70% of HA-MRSA, they may not be as accurate in documenting colonization status in CA-MRSA strains. This may be due to higher predilection of CA-MRSA strains to the skin versus the anterior nares.

We think that the findings of our study are important for clinical management of suspected VAP. The risks associated with the inappropriate treatment of MRSA include the development of increasingly resistant *S. aureus* and the selection of other resistant organisms such as vancomycin-resistant en-

terococci. Interestingly, there is conflicting evidence that methicillin resistance in *S. aureus* ventilated-associated pneumonia has a worse prognosis compared with MSSA ventilated-associated pneumonia.[14,18] Treatment of early VAP in the trauma ICU population with vancomycin has the potential to increase the risk of resistant organisms and may be suboptimal therapy for MSSA VAP when used without an anti-staphylococcal beta lactam. In this study, we noted that the prevalence of early MRSA VAP in our trauma population was only 2.2%. This low incidence of methicillin resistance in early VAP does not warrant the empiric widespread use of vancomycin within the first 3 days of admission.

Certain risk factors in patients have been identified for developing HA-MRSA infections in the ICU, but these risks are different from CA-MRSA. Prolonged hospitalization in the ICU, the presence of patients colonized with MRSA in the same ICU at the same time, previous antibiotic use, and central venous catheter insertion are independent risk factors for ICU-acquired HA-MRSA infections.[13] Although the results of this study suggest that community-acquired VAP does not require antibiotic coverage for MRSA, patients who have increased risk factors for MRSA pneumonia such as previously hospitalized patients in institutions of high MRSA prevalence may require empiric antibiotic treatment that covers this organism. In addition, presentation of a necrotizing pneumonia, particularly after a viral infection, such as influenza, with findings of gram-positive cocci on Gram's stain should be considered for vancomycin therapy until cultures can rule out MRSA as an etiology.[19]

There are certain limitations to our study. As a retrospective review of medical records in the trauma critical care population, there are known limitations of a retrospective study. In addition, although not all patients had nasal swab tests performed, all who developed an early MRSA VAP did have the procedure, and this group failed to exhibit MRSA nasal colonization on admission.

SUMMARY

This study shows a low incidence of early MRSA causing VAP in a trauma population. This is in stark contrast to the high incidence of community-acquired MRSA found in skin and soft tissue infection. The use of vancomycin in this setting may contribute to the ever increasing bacterial resistance that has been observed in our ICUs. Further studies are needed to test the efficacy of nasal swabs for MRSA colonization and its potential to predict early MRSA pneumonia in the current era of escalating CA-MRSA. Furthermore, as the epidemiology of MRSA continues to evolve, further studies will be required to monitor the efficacy and untoward affects of empiric therapy in critically ill trauma patients.

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