Treatment of methicillin-resistant *Staphylococcus aureus* ventilator-associated pneumonia with high-dose vancomycin or linezolid

Leslie A. Hamilton, PharmD, G. Christopher Wood, PharmD, Louis J. Magnotti, MD, Martin A. Croce, MD, Julie B. Martin, PharmD, Joseph M. Swanson, PharmD, Bradley A. Boucher, PharmD, *and* **Timothy C. Fabian, MD,** *Auburn, Alabama*

AAST Continuing Medical Education Article

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the American College of Surgeons and the American Association for the Surgery of Trauma. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this Journal-based CME activity for a maximum of *1 AMA PRA Category 1 Credit*™ for each article. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Credits can only be claimed online at this point.

AMERICAN COLLEGE OF SURGEONS
Inspiring Quality:
Highest Standards, Better Outcomes

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

System Requirements

The system requirements are as follows: Adobe® Reader 7.0 or above installed; Internet Explorer® 7 and above; Firefox® 3.0 and above, Chrome® 8.0 and above, or Safari™ 4.0 and above.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons, as the accredited provider of this journal activity, must ensure that anyone in a position to control the content of *J Trauma* articles selected for CME credit has disclosed all relevant financial relationships with any commercial interest. Disclosure forms are completed by the editorial staff, associate editors, reviewers, and all authors. The ACCME defines a 'commercial interest' as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." "Relevant" financial relationships are those (in any amount) that may create a conflict of interest and occur within the 12 months preceding and during the time that the individual is engaged in writing the article. All reported conflicts are thoroughly managed in order to ensure any potential bias within the content is eliminated. However, if you perceive a bias within the article, please report the circumstances on the evaluation form.

Please note we have advised the authors that it is their responsibility to disclose within the article if they are describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

Disclosures of Significant Relationships with Relevant Commercial Companies/Organizations by the Editorial Staff:

Ernest E. Moore, MD, Editor, received research support from Haemonetics. David B. Hoyt, MD, Associate Editor/CME Editor, Ronald Maier, MD, Associate Editor, and Steven Shackford, MD, Associate Editor have nothing to disclose. Jennifer Crebs, Managing Editor, received consulting fees from Golden Helix, Expression Analysis, Illumina, and Lineagan. Jo Fields, Editorial Assistant, and Angela Sauaia, MD, Biostatistician, have nothing to disclose.

Author Disclosures:

G. Christopher Ward, MD is a consultant for Bayer and Ortho, and has received honoraria/speaking fees from Forest (antibiotic-related consulting and speaking).

Cost

For AAST members and *Journal of Trauma and Acute Care Surgery* subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $50.

Submitted: June 16, 2011, Revised: January 23, 2012, Accepted: February 6, 2012.
From the Department of Pharmacy Practice (L.A.H.), Auburn University Harrison School of Pharmacy, Auburn, Alabama; Department of Clinical Pharmacy (G.C.W., J.B.M., J.M.S., B.A.B.), University of Tennessee Health Science Center, Memphis, Tennessee; and Department of Surgery (L.J.M., M.A.C., T.C.F.), University of Tennessee Health Science Center, Memphis, Tennessee.

Address for reprints: Leslie Hamilton, PharmD, BCPS, Auburn University Harrison School of Pharmacy, 1321 Walker Building, Auburn, AL 36849; email: lah0010@auburn.edu.

DOI: 10.1097/TA.0b013e318250911b

BACKGROUND: The purpose of this study was to determine the clinical cure rate of high-dose vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) ventilator-associated pneumonia (VAP) in critically ill trauma patients. Recent trials suggest that a traditional dose of 1 g q12 hours results in unacceptable cure rates for MRSA VAP. Thus, more aggressive vancomycin dosing has the potential to improve efficacy. Based on pharmacokinetic principles, the goal initial dose at the study center has been 20 mg/kg q12 hours or q8 hours since the 1990s.

METHODS: All patients admitted to the trauma intensive care unit from 1997 to 2008 diagnosed with MRSA VAP were retrospectively reviewed. Diagnosis required bacterial growth ≥100,000 colony forming units/mL from a bronchoscopic bronchoalveolar lavage, new or changing infiltrate, plus at least two of the following: fever, leukocytosis or leukopenia, or purulent sputum.

RESULTS: Overall, 125 patients with 141 episodes of MRSA VAP were identified. Mean age was 47 years ± 21 years, median Injury Severity Score was 29 (22–43), 70% of patients were male, and the mean length of intensive care unit stay was 38 days ± 35 days. The mean initial vancomycin dose was 18.1 mg/kg/dose with a mean duration of therapy of 11 days. Clinical success was achieved in 88% (125 of 131) of episodes, with microbiological success in 89% (66 of 74) of episodes with a follow-up bronchoscopic bronchoalveolar lavage. Overall mortality was 20% (25 of 125), with death due to VAP in 12 of 25 deaths. Mean initial vancomycin trough concentrations were 10.6 mg/L in the clinical success group and 13.3 mg/L in the clinical failure group (p = not significant).

CONCLUSIONS: High-dose vancomycin provided an acceptable cure rate for MRSA VAP in critically ill trauma patients. (*J Trauma Acute Care Surg*. 2012;72:1478–1483. Copyright © 2012 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level III.

KEY WORDS: Methicillin-resistant *Staphylococcus aureus*; ventilator-associated pneumonia; vancomycin; linezolid.

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are common complications of critical illness that are associated with increased morbidity and mortality.[1] In particular, methicillin-resistant *Staphylococcus* aureus (MRSA) HAP/VAP has an attributable mortality rate of 22% and its prevalence is increasing in many centers.[2,3] This is noteworthy because MRSA is associated with higher mortality than less resistant organisms and has far fewer treatment options.[4] Traditionally, treatment of MRSA HAP/VAP used vancomycin starting at 1 g intravenous (IV) q12 hours with subsequent monitoring that largely focused on avoiding toxicity rather than achieving aggressive serum concentrations.

Starting in 1999, the first outcome data on using vancomycin for treating MRSA HAP/VAP started to emerge. These studies included comparisons to quinupristin/dalfopristin or linezolid.[5–7] However, clinical response rates for vancomycin were poor (<50%) with traditional dosing. It is unclear why vancomycin failed; however, the drug does have relatively poor lung penetration and slow bacterial killing.[8] Recent data also suggest that poor outcomes are related to a vancomycin minimum inhibitory concentration (MIC) >1 mg/L.[9,10] It was commonly assumed that low vancomycin dosing may have been an important factor in these poor response rates. Nonetheless, these results made some clinicians question the utility of vancomycin for treating MRSA VAP.

Subsequently, recent guidelines recommended increased starting doses of 15 mg/kg to 20 mg/kg q8 hours to 12 hours and higher goal trough levels of 15 mg/L to 20 mg/L for VAP.[1,11,12] However, there are few outcome data to support this trough recommendation. In addition, there are no good outcome data in critically ill trauma patients who are a unique intensive care unit (ICU) population in terms of demographics, pharmacokinetics, and susceptibility to VAP.[13]

Based on pharmacokinetic data and our clinical experience, vancomycin has been dosed aggressively at our center since the 1990s. As part of a well-defined VAP pathway, we used 20 mg/kg IV q12 hours with a trough goal of 5 mg/L to 15 mg/L (10-15 mg/L preferred) until 2005.[14] After the publication of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) VAP guidelines in 2005, we became more aggressive, with goal troughs of 15 mg/L to 20 mg/L and more q8 hours and q6 hours dosing intervals.[1] With uncertainty in the literature over the efficacy of vancomycin for MRSA VAP and a lack of data in trauma patients, the purpose of this study was to evaluate the efficacy of high-dose vancomycin for treating MRSA VAP in critically ill trauma patients.

PATIENTS AND METHODS

Patients

Patients admitted from January 1997 through December 2008 to the Presley Memorial Trauma Center trauma ICU within the Regional Medical Center in Memphis, TN, were eligible for inclusion in this retrospective observational study. This study was approved by the University of Tennessee Health Science Center Institutional Review Board. The need for informed consent was waived. Patients were available for inclusion if they developed a VAP due to MRSA after ≥48 hours of mechanical ventilation. Exclusion criteria were malignancy, pregnancy, immunocompromised state, and those without available medical records.

Diagnosis

Diagnosis of VAP was made as part of routine clinical care using a previously published clinical pathway.[14–20] Diagnosis required bacterial growth $\geq 10^5$ colony forming units (cfu)/mL from a bronchoscopic bronchoalveolar lavage (BAL) in addition to a new or changing infiltrate on chest radiograph. In addition, at least two of the following conditions had to be met: abnormal temperature (>38°C or <36°C), abnormal white blood cell count (>10,000 cells/mm^3 or <4,000 cells/mm^3, or >10% immature neutrophils), or macroscopically purulent sputum. Although some centers use a diagnostic threshold for BAL of 10^4 cfu/mL, the use of 10^5 cfu/mL has been validated in trauma patients by our group and others and is one of the recommended thresholds in the ATS/IDSA guidelines.[1,14–21]

Empiric therapy was immediately begun after each diagnostic BAL and was selected based on the annual analyses of organisms and susceptibility patterns in the study ICU. If

the BAL was performed ≤7 days into hospitalization, ampicillin-sulbactam 3 g IV q6 hours was initiated.[14] If the BAL was performed >7 days into the hospital stay, cefepime 2 g IV q8 hours and vancomycin 20 mg/kg IV q12 hours were started.[14] Starting in 2005, some patients received vancomycin 20 mg/kg IV q8 hours if they were expected to have particularly rapid clearance (e.g., younger patients with normal renal function). For patients with significant beta-lactam allergies, moxifloxacin and ciprofloxacin were substituted for ampicillin-sulbactam and cefepime, respectively.[17–20]

Vancomycin dosing was managed by clinical pharmacists, and peak and trough levels were obtained in all patients once it was expected that a steady state was achieved (i.e., at least the third dose). Peaks were drawn at least 1 hour after the end of infusion to allow for drug distribution. Before the publication of the 2005 VAP guidelines, goal troughs were 5 mg/L to 15 mg/L, with 10 mg/L to 15 mg/L preferred. Afterward, goal troughs were 15 mg/L to 20 mg/L.[1]

Definitions

Patient outcomes were defined as either "treatment failure" or "treatment success" using a set of criteria that have evolved over a number of studies.[17,18,22] The primary outcome of the study was the percentage of patients with treatment success. Treatment success was further delineated as either "clinical success" or "microbiological success." Clinical success was defined as an improvement in the signs and symptoms of the VAP and thus allowed for the discontinuation of antimicrobial therapy without a relapse within 10 days of discontinuing therapy (defined as original VAP pathogen(s) with growth of $\geq 10^5$ cfu/mL on BAL culture). Those patients who initially achieved clinical success but later died of an unrelated event were still considered to have clinical success. Microbiological success was defined by the eradication or inhibition of VAP organism ($<10^4$ cfu/mL) on repeat BAL after >3 days of appropriate therapy, in addition to the criteria for clinical success.[17,18,20] Patients were considered to have an inconclusive microbiological outcome if repeat BAL showed $>10^4$ cfu/mL but $<10^5$ cfu/mL of the original VAP organism or if no follow-up BAL was performed.[18]

Treatment failure was additionally defined as either "clinical failure" or "microbiological failure." Clinical failure was classified as (1) death that was likely caused by VAP (also identified as VAP-related mortality), (2) persistence of clinical signs and symptoms of VAP for >10 days that warranted a change in therapy, or (3) relapse of VAP as defined above. Microbiological failure was defined by persistence of VAP pathogen (at counts of $\geq 10^5$ cfu/mL) on a follow-up culture of a BAL specimen completed >3 days after starting therapy, or counts of $>10^4$ cfu/mL within 10 days after stopping therapy, in addition to above criteria for clinical failure.

Discordant outcomes were defined as either (1) VAP-related death despite eradication or inhibition of VAP organism ($<10^4$ cfu/mL) on repeat BAL after >3 days of appropriate therapy or (2) survival despite failure to clear or inhibit VAP organism on repeat BAL. Inadequate empiric antibiotic therapy was defined as empiric antibiotic therapy that did not have in vitro activity against the organism that was cultured from BAL. Initial vancomycin troughs were defined as the first trough obtained on vancomycin therapy. Optimized vancomycin troughs were defined as the subsequent troughs optimized for patient-specific variables and pharmacokinetic data.

Statistics

The treatment success rates of patients were compared between vancomycin MIC subgroups and vancomycin trough subgroups using the χ^2 test or Fisher's exact test as appropriate (SPSS 16.0, Chicago, IL). A p value of <0.05 was considered statistically significant.

RESULTS

Overall, 125 patients with 141 episodes of VAP met inclusion criteria for this study. The baseline demographics are reported in Table 1. Clinical characteristics of VAP are reported in Table 2. Of the 141 VAP episodes, 76 (54%) were treated with vancomycin, 10 (7%) with linezolid, and 55 (39%) were switched from vancomycin to linezolid. The reasons for switching to linezolid or choosing linezolid as first-line therapy are reported in Table 2.

The initial and optimized vancomycin trough concentrations and MRSA vancomycin MICs were similar in patients with treatment success and failure (Tables 3 and 4). There were six episodes of discordant clinical and microbiological outcomes. In three of these episodes, the patients died with clinical failure, despite microbiological success on repeat BAL. In the other three episodes, the patients survived and achieved clinical success despite microbiological failure on repeat BAL.

Before the publication of the VAP guidelines in 2005, the median initial dose was 1,000 mg q12 hours, with an optimized dose of 1,500 mg q12 hours. After the publication of these guidelines, the median initial dose increased to 1,500 mg q12 hours, with an optimized dose of 1,500 mg q8 hours.

The VAP outcomes are reported in Table 5. The study's primary outcome, treatment success, was 88% (115 of 131). The success rates were statistically similar for the three antibiotic groups. The VAP-related mortality rate was 10% (12 of 125). There were no apparent adverse effects in patients receiving high-dose vancomycin, including acute renal failure leading to hemodialysis following vancomycin therapy.

DISCUSSION

The primary outcome of this study was that treatment success was achieved in 88% of episodes of MRSA VAP in critically ill trauma patients treated with vancomycin or vancomycin switched to linezolid. This success rate was confirmed microbiologically in a large percentage of patients. These data are important for several reasons. First, this is the largest set of MRSA VAP outcomes reported to date. Second, there is continuing uncertainty about the efficacy of vancomycin for treating MRSA VAP, the effect of dosing and trough concentrations on outcomes, and the utility of vancomycin against isolates with an MIC of 2 mg/L. Third, these are the first treatment success data for a large series of trauma patients

TABLE 1. Baseline Demographics

Characteristic	Patients (n = 126)
Age (yr), mean ± SD	47 ± 21
Male, n (%)	88 (70)
Caucasian, n (%)	85 (67)
Weight (kg), mean ± SD	82 ± 21
APACHE II, median (IQR)*	18 (14–22)
ISS, median (IQR)	29 (22–43)
Mechanism of injury, n (%)	
Blunt	112 (89)
Penetrating	14 (11)
Type of injury, n (%)	
TBI	56 (44)
Spinal cord injury	26 (21)
Abdominal organ trauma	21 (17)
Chest trauma†	14 (11)
Pelvic or long bone fracture	9 (7)

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; ISS, Injury Severity Score; TBI, traumatic brain injury.

* Score obtained on admission.

† Includes any of the following: multiple rib fractures, pulmonary contusion, hemothorax, pneumothorax.

with MRSA VAP. Previous studies had focused solely or primarily on medical ICU or general (medical/surgical) ICU populations, who tend to have lower cure rates.[14–20]

Vancomycin Efficacy

Despite the use of vancomycin for decades, the first MRSA HAP/VAP outcome data were not reported until 1999.[23] In that small observational study, the mortality rate of patients with bacteremic MRSA HAP treated with vancomycin was 50% (11 of 22). The following year, a prospective randomized trial of vancomycin versus quinupristin/dalfopristin for Gram-positive HAP/VAP reported an overall clinical success rate of 45% (67 of 148) with vancomycin.[5] Other recent studies of MRSA HAP/VAP showed vancomycin success rates of 31% to 46% in a total of 106 patients.[23]

However, the study that had the biggest impact in making clinicians question the efficacy of vancomycin in MRSA VAP was a post hoc subgroup analysis of two prospective randomized trials of vancomycin versus linezolid.[6] In that study, the clinical cure rate for MRSA VAP was higher with linezolid than vancomycin (62% vs. 21%, $p = 0.001$, n = 70). However, the study had several weaknesses including what appeared to be a more severely ill vancomycin group and no difference in outcomes in patients with high-quality cultures. Moreover, in none of these studies was vancomycin dosed aggressively based on body weight (e.g., 15–20 mg/kg/dose) or optimized to a target trough value. Nonetheless, vancomycin at traditional doses performed rather poorly in these studies of HAP/VAP.

However, other recent data cast vancomycin in a better light. A recent meta-analyses of eight studies reported that vancomycin and linezolid are equivalent for treating HAP/VAP.[24] In particular, a good success rate (69%) was reported in one study that used quantitative BAL cultures for VAP diagnosis and dosed vancomycin somewhat aggressively (15 mg/kg

TABLE 2. VAP Characteristics

Variable	Episodes (n = 141)
Length of mechanical ventilation (d), mean ± SD	33 ± 35
Length of stay ICU (d), mean ± SD	38 ± 35
Length of stay hospital (d), mean ± SD	47 ± 37
Time to initial VAP (d), mean ± SD	17 ± 23
Episodes of polymicrobial VAP, n (%)	73 (52)
Episodes of IEAT, n (%)	39/141 (28)
Clinical success	36/39
Clinical failure	3/39
Length of antibiotic therapy (d), treatment success, mean ± SD	11.6 ± 4.3
Length of antibiotic therapy (d), clinical failure, mean ± SD	5.2 ± 3.6
Length of antibiotic therapy (d), VAP-related death, mean ± SD	4.3 ± 2.7
Episodes, n (%)	
Vancomycin only	76/141 (54)
Combination of vancomycin and linezolid, n (%)	55/141 (39)
Reasons for switching to linezolid	
Vancomycin MIC 2.0	21/55
Physician preference	18/55
Incomplete recovery on follow-up BAL	7/55
Worsening colony count on follow-up BAL	6/55
HD prior to start of antibiotics	3/55
Linezolid only, n (%)	10/141 (7)
Reasons for using linezolid	
Vancomycin MIC	7/10
HD prior to start of antibiotics	1/10
Physician preference	2/10

IEAT, Inadequate empiric antibiotic therapy; HD, hemodialysis.

TABLE 3. Vancomycin Characteristics

Vancomycin MIC, n (%)	
0.5	37/131 (28)
1.0	51/131 (39)
2.0	41/131 (31)
Not available	2/131 (2)
Vancomycin MIC of patients with clinical failure, n	
0.5	5/16
1.0	7/16
2.0	4/16
Initial vancomycin dose (mg/kg/dose), mean ± SD	18.1 ± 4
q6 h	0/131
q8 h	7/131
q12 h	109/131
q24 h	15/141
Optimized vancomycin dose (mg/kg/dose), mean ± SD	20.7 ± 5.1
q6 h	4/81
q8 h	29/81
q12 h	33/81
q24 h	15/81

TABLE 4. Clinical Outcomes

	Vancomycin Trough Concentration*		
	Clinical Success	Clinical Failure	*p*
1997 to 2004			
Initial	10 ± 5.1	11.3 ± 2.3	0.62
Optimized	14.3 ± 5.8	15.1 ± 5.5	0.79
2005 to 2008			
Initial	11.2 ± 7.8	14.4 ± 5.1	0.30
Optimized	16.2 ± 9.3	15.6 ± 5.9	0.87

*Data are reported as mean concentration (mg/L) ± SD.

TABLE 5. VAP Outcomes

Variable	n (%)	Vancomycin Only	Vancomycin and Linezolid	*p*
Treatment success,	115/131 (88)	68/76	47/55	0.591
Evaluable microbiological success	66/74 (89)			—
Discordant clinical and microbiological outcomes	6/131 (5)			—
VAP relapse	4/131 (3)			—
Mortality				
All-cause	25/125 (20)	18/76	7/55	0.176
VAP-related	12/125 (10)	6/76	6/55	0.558

q12 hours).[25] This study is most similar to the current study in terms of dosing and use of a high-quality diagnosis.

Effect of Troughs on Outcomes

Finding a relationship between vancomycin trough concentrations and clinical outcomes has been elusive. In the current study, there was no difference in the mean trough concentrations in patients with treatment success and failure (Tables 3 and 4). Likewise, the aforementioned study by Jeffres et al.[25] found that the trough concentrations were similar in patients with treatment success or failure. Another observational study did not find a difference in outcome between patients who reached the target trough range and those who did not.[12] A recent review of vancomycin pharmacodynamics concluded that there are no good data supporting a relationship between trough concentrations and outcomes.[26]

However, there are some data suggesting that aggressive dosing may improve outcomes. The best treatment success rates to date were seen in the studies where vancomycin was dosed most aggressively: in the current study and the study conducted by Jeffres et al.[25] In addition, pharmacodynamic data suggest that an AUC/MIC ratio >400 is related to better outcomes.[26]

Even with a lack of clinical data, the vancomycin guidelines and the VAP guidelines both recommend a trough of 15 mg/L to 20 mg/L for VAP treatment.[1,11] This recommendation was made in an attempt to maximize pulmonary penetration, to avoid low concentrations that may foster resistance, and to avoid the poor outcomes seen with traditional dosing. Pharmacodynamic data suggest that at least 40 mg/kg/d is needed to meet treatment thresholds in general ICU patients.[26]

Some trauma ICU patients will require even higher dosing because they tend to have faster clearance and a larger volume of distribution than general ICU patients.[13] In the current study, the mean optimized trough was barely above 15 mg/L (Table 3) despite a mean optimized dose of 20.7 mg/kg and q8 hours dosing in 36% of patients. The need for aggressive dosing was confirmed in a recent study that reported that 0% of trauma ICU patients on 1 g q12 hours achieved a trough of 15 mg/L to 20 mg/L.[27] Overall, there does not seem to be a relationship between trough concentrations and outcomes; however, there are some suggestions that aggressive dosing is important in trauma patients due to their different pharmacodynamic properties.

Effect of MIC on Outcomes

Several recent studies reported that vancomycin was less effective against MRSA isolates with an MIC of 2 mg/L.[9,10,12] Based on these data, the 2009 vancomycin guidelines recommend against using vancomycin to treat MRSA isolates with an MIC of 2 mg/L.[11] However, in the current study there was no relationship between MIC and treatment success. It is unknown if this was because of the aggressive vancomycin dosing, to differences in trauma patients compared with medical patients reported in other studies, or some other factor. The current results suggest that vancomycin remains an effective option in trauma ICU patients for treating MRSA isolates with an MIC of 2 mg/L.

Strengths and Weaknesses

The strengths of this study are the large size, the use of an optimal diagnostic technique in all patients (bronchoscopic BAL), a large percentage of patients with follow-up BALs to evaluate microbiologic success, and aggressive vancomycin dosing compared with most other studies. Using a high-quality diagnostic technique is key because most patients in previous studies were diagnosed with lower quality techniques, making it uncertain if they truly had pneumonia.

Weaknesses of the study include the retrospective design and that the data are from a single center. The fact that the study only included trauma patients is a strength and a weakness. Trauma-specific VAP outcome data are needed because those patients are different from general ICU patients in many respects (e.g., demographics, pharmacokinetics and VAP susceptibility). However, this may limit applicability to other ICU populations.

CONCLUSIONS

High-dose vancomycin resulted in a good treatment success rate for MRSA VAP in critically ill trauma patients. Success was not related to trough concentrations or the vancomycin MIC. This suggests that vancomycin can continue to be used against isolates with a vancomycin MIC of 2 mg/L in this patient population. High doses of vancomycin are required in trauma ICU patients to achieve trough concentrations of 15 mg/L to 20 mg/L.

AUTHORSHIP

L.J.M., M.A.C., and T.C.F. designed this study. L.A.H., G.C.W., J.M.S., and B.A.B. conducted the literature search. L.A.H., G.C.W., L.J.M., and J.B.M. collected the data, which L.A.H. and G.C.W. analyzed. L.A.H., G.C.W., J.M.S., and B.A.B. interpreted the data. L.A.H. and J.M.S. performed statistical analyses. L.A.H., G.C.W., J.M.S., and B.A.B. wrote the manuscript; L.A.H. and J.M.S. designed figures.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388–416.
2. DeRyke CA, Lodise TP, Rybak MJ, et al. Epidemiology, treatment, and outcomes of nosocomial bacteremic *Staphylococcus aureus* pneumonia. *Chest*. 2005;128:1414–1422.
3. Rello J, Sole-Violan J, Sa-Borges M, et al. Pneumonia caused by oxacillin-resistant *Staphylococcus aureus* treated with glycopeptides. *Crit Care Med*. 2005;33:1983–1987.
4. Melzer M, Eykyn SJ, Gransden WR, et al. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus?* A comparative cohort study of British patients with nosocomial infection and bacteremia. *Clin Infect Dis*. 2003;37:1453–1460.
5. Fagon J-Y, Patrick H, Haas DW. Treatment of Gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. *Am J Respir Crit Care Med*. 2000;161:753–762.
6. Kollef MH, Rello J, Cammarata SK, et al. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med*. 2004;30:388–394.
7. Rubinstein E, Cammarata SK, Oliphant T, et al; Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402–412.
8. Cruciani M, Gatti G, Lazzarini L, et al. Penetration of vancomycin into human lung tissue. *J Antimicrob Chemother*. 1996;38:865–869.
9. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2008;46:193–200.
10. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother*. 2008;52:3315–3320.
11. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
12. Hidayat LK, Hsu DI, Quist R, et al. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections. *Arch Intern Med*. 2006;166:2138–2144.
13. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. *Crit Care Clin*. 2006;22:255–271.
14. Wood GC, Mueller EW, Croce MA, et al. Evaluation of a clinical pathway for ventilator-associated pneumonia: changes in bacterial flora and the adequacy of empiric antibiotics over a three-year period. *Surg Infect*. 2005;6:203–213.
15. Croce MA, Fabian TC, Waddle-Smith L, et al. Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. *Ann Surg*. 1998;227:743–755.
16. Croce MA, Fabian TC, Mueller EW, et al. The appropriate diagnostic threshold for ventilator-associated pneumonia using quantitative cultures. *J Trauma*. 2004;56:931–934.
17. Mueller EW, Hanes SD, Croce MA, et al. Effect from multiple episodes of inadequate empiric antibiotic therapy for ventilator-associated pneumonia on morbidity and mortality among critically ill trauma patients. *J Trauma*. 2005;58:94–101.
18. Mueller EW, Croce MA, Boucher BA, et al. Repeat bronchoalveolar lavage to guide antibiotic duration for ventilator-associated pneumonia. *J Trauma*. 2007;63:1329–1337.
19. Swanson JM, Wood GC, Croce MA, et al. Utility of preliminary bronchoalveolar lavage results in suspected ventilator-associated pneumonia. *J Trauma*. 2008;65:1271–1277.
20. Magnotti LJ, Schroeppel TJ, Fabian TC, et al. Reduction in inadequate empiric antibiotic therapy for ventilator-associated pneumonia: impact of a unit-specific treatment pathway. *Am Surg*. 2008;74:516–522.
21. Miller PR, Meredith JW, Chang MC. Optimal threshold for diagnosis of ventilator-associated pneumonia using bronchoalveolar lavage. *J Trauma*. 2003;55:263–268.
22. Wood GC, Hanes SD, Croce MA, et al. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of acinetobacter ventilator-associated pneumonia. *Clin Infect Dis*. 2002;34:1425–1430.
23. González C, Rubio M, Romero-Vivas J, et al. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis*. 1999;29:1171–1177.
24. Walkey AJ, O'Donnell MR, Wiener RS. Linezolid versus glycopeptide antibiotics for the treatment of suspected methicillin-resistant *Staphylococcus Aureus* nosocomial pneumonia: a meta-analysis of randomized controlled trials. *Chest*. 2011;139:1148–1155.
25. Jeffres MN, Isakow W, Doherty JA, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associate pneumonia. *Chest*. 2006;130:947–955.
26. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42:S35–S39.
27. Patanwala AE, Norris CJ, Nix DE, et al. Vancomycin dosing for pneumonia in critically ill patients. *J Trauma*. 2009;67:802–804.

