Evaluation of the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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Abstract: *Background:* Bloodstream infections are a leading cause of death in the United States. Methicillin-resistant *Staphylococcus aureus* (MRSA) encompasses >50% of all *S aureus* strains in infected hospitalized patients and increases mortality, length of stay and healthcare costs. The objective of this study was to evaluate the treatment of MRSA bacteremia with daptomycin, linezolid and vancomycin. *Methods:* Patients with MRSA bacteremia between June 2008 and November 2010 were reviewed retrospectively. A microbiology laboratory report identified patients with ≥1 positive MRSA blood culture. Patients ≥18 years receiving daptomycin, linezolid or vancomycin for ≥7 consecutive days were included. Polymicrobial blood cultures and patients treated concomitantly with >1 anti-MRSA agent were excluded. *Results:* Of 122 patients included, 53 received daptomycin, 15 received linezolid and 54 received vancomycin. Clinical and microbiologic cure rates were similar between daptomycin, linezolid and vancomycin (58.5% versus 60% versus 61.1%; 93.6% versus 100% versus 90%, respectively). Thirteen patients (daptomycin 4/24 versus linezolid 1/9 versus vancomycin 8/49, $P = 0.5960$) had recurrence while 12 patients had re-infection (daptomycin 5/42 versus linezolid 0/9 versus vancomycin 7/49, $P = 0.4755$). Treatment failure occurred in 11 patients treated with daptomycin, 4 with linezolid and 9 with vancomycin ($P = 0.662$). Compared with daptomycin and vancomycin, linezolid-treated patients had higher mortality ($P = 0.0186$). *Conclusions:* No difference in clinical or microbiologic cure rates was observed between groups. Daptomycin and vancomycin appear equally efficacious for MRSA bacteremia, whereas linezolid therapy was associated with higher mortality.

Key Indexing Terms: Methicillin-resistant *Staphylococcus aureus*; Bacteremia; Daptomycin; Linezolid; Vancomycin. **[Am J Med Sci 2015;349(1):36–41.]**

Bloodstream infections (BSIs) are a leading cause of death in the United States, with approximately 250,000 cases occurring annually. *Staphylococcus aureus* (SA) is responsible for 20% of all nosocomial BSI.[1] Methicillin-resistant *S aureus* (MRSA) accounts for more than 50% of all *S aureus* strains causing clinical disease in hospitalized patients, and infection with this organism leads to increased morbidity and mortality, length of stay (LOS) and healthcare costs.[2,3] Delays in appropriate antibiotic therapy have been associated with increases in mortality and hospital LOS, and in a cohort of 562 patients with MRSA BSI, Lodise et al[4–7] determined that only half of all patients received appropriate antibiotic therapy.

Practice guidelines recommend daptomycin or vancomycin for the treatment of both complicated and uncomplicated MRSA bacteremia, with daptomycin receiving a higher recommendation grade.[8] Vancomycin has long been the standard therapy for MRSA infections, although questions exist over its continued clinical utility. Vancomycin demonstrates slow bactericidal activity against MRSA, and a consensus review recommends use of an alternative agent for MRSA strains when the minimum inhibitory concentration (MIC) is ≥2 μ/mL because of observed increases in mortality, longer treatment durations, lower likelihood of organism eradication and higher median days to organism eradication.[9–12] Linezolid is not approved by the Food and Drug Administration for the treatment of MRSA bacteremia, although utilization is appealing because the drug possesses 100% oral bioavailability and does not require renal dose adjustments.[8,13]

Cost presents an ongoing therapeutic problem, as newer agents have significant drug acquisition costs, yet data suggest newer agents may be overall more cost-effective. In a comparison between daptomycin and the combination of vancomycin and gentamicin for MRSA bacteremia and endocarditis, both therapies were similar in cost-effectiveness, even when considering the cost of vancomycin as $0.[14]

Although different options are available for treatment of MRSA bacteremia, antimicrobial resistance and treatment failure are growing concerns. In 2009, 70% of *S aureus* isolates at our institution were methicillin resistant. Less than 1% of isolates were resistant to vancomycin according to Clinical and Laboratory Standards Institute breakpoints, but approximately 35% of strains had a reported MIC of 2 μg/mL. On account of the high rate of MRSA isolates and various antimicrobials used in our institution, this study was conducted to evaluate patients treated for MRSA bacteremia with daptomycin, linezolid or vancomycin.

MATERIALS AND METHODS

Study Design

A retrospective analysis was performed of patients diagnosed with MRSA bacteremia between June 2008 and November 2010 at Methodist University Hospital, an academic, tertiary care center in Memphis, TN. The protocol was approved by the University of Tennessee institutional review board before study initiation. A microbiology laboratory report identified patients with at least 1 positive blood culture for MRSA, and patients were then screened for inclusion into the study. Eligible patients were adults aged 18 years or older who received at least 7 consecutive days of daptomycin, linezolid or vancomycin. Patients with a polymicrobial blood culture and those who were treated concomitantly with more than 1 agent active against MRSA were excluded. Susceptibility testing for each antimicrobial was performed by MicroScan (Prompt

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method) on all isolates, with 2 isolates requiring Etest for susceptibility confirmation (1 linezolid and 1 daptomycin).

The primary objective was to determine clinical cure rates in patients treated for MRSA bacteremia with daptomycin, linezolid and vancomycin. Secondary objectives included rates of microbiologic cure, recurrence, re-infection and treatment failure. MICs used in relation to treatment were assessed, along with LOS and healthcare costs.

Data Collection

Electronic medical records were reviewed for patient demographics, comorbid illnesses, concurrent infections, vital signs and laboratory data, treatment information, LOS and discharge disposition. Pneumonia, endocarditis and osteomyelitis were documented based on results from cultures or diagnostic tests, and data were collected on the presence of intravenous catheters and prosthetic devices. Vital signs and laboratory data were recorded at baseline and at the end of therapy, day of discharge or death. Results of blood cultures were collected, including specimen location and organism susceptibility to daptomycin, linezolid and vancomycin. Treatment information included the antimicrobial used, initial dosing regimens, therapeutic drug monitoring and changes in MRSA therapy. Other drug therapy recorded was use of rifampin, systemic corticosteroids and immunosuppressants. Cost information was obtained by an institution CostFlex report. Patients admitted to the Methodist University extended-care hospital were not included in the financial analysis because financial data were not available.

Definitions

Primary bacteremia was defined as MRSA bacteremia in the absence of an identified source of infection, and complicated bacteremia was defined as catheter-related bacteremia or bacteremia secondary to an identified source of infection. Clinical cure was based on resolution of signs and/or symptoms of infection, including white blood cell count $<10{,}000/mm^3$, bands $<5\%$, heart rate <90 beats per minute, respiratory rate <20 breaths per minute and oral temperature max $<38°C$ after therapy was discontinued. Microbiologic cure was defined as lack of repeat positive blood cultures for MRSA at least 14 days after cessation of therapy. Only patients with repeat blood cultures were evaluated for microbiologic cure. Patients surviving hospitalization were included in the analysis for recurrence and re-infection. Recurrence was defined as MRSA bacteremia within 30 days after discontinuation of therapy, and re-infection was documented if patients had positive blood cultures for MRSA ≥ 30 days after completion of primary therapy. Patients were classified as treatment failures if therapy was changed to an alternative intravenous agent or another MRSA agent was added.

Statistical Analysis

Categorical variables were compared using χ^2 test or Fisher's exact test. Continuous variables were compared using analysis of variance, followed by Tukey's multiple comparison and are expressed as mean $\pm$ standard deviation. Statistical significance was declared at a 0.05 level. All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics and Treatment

Of 267 patients identified with a positive blood culture for MRSA, 122 were included in the study. The majority of patients were excluded because of receiving less than 7 days of therapy in the hospital setting (n = 77), followed by having polymicrobial blood cultures (n = 38) and being treated concurrently with more than 1 agent active against MRSA (n = 30). In the 30 patients treated simultaneously with more than 1 MRSA agent, the most common regimens were daptomycin plus linezolid and vancomycin plus linezolid. The study population included 53 patients treated with daptomycin, 15 with linezolid and 54 with vancomycin. Of the 122 patients included, 84 had an infectious disease consult (29/54 vancomycin, 51/53 daptomycin and 4/15 linezolid). In the daptomycin group, 49 patients had previous antibiotic exposure (44 included vancomycin). Twelve patients in the linezolid group had previous antibiotic exposure (all included vancomycin), and in the vancomycin group, 6 patients had previous antibiotic exposure (3 included vancomycin). Enrollment of patients with follow-up blood cultures, to allow for evaluation of microbiologic cure, are displayed in Figure 1.

Patient demographics and characteristics are displayed in Table 1. Body mass index (BMI) was significantly different between all treatment groups ($P = 0.0097$). Total patients classified according to BMI ranges were as follows: BMI <25 (46 patients), BMI = 25 to 29.9 (36 patients), BMI = 30 to 34.9 (23 patients) and BMI ≥ 35 (17 patients). Patients with end-stage renal disease were more likely to be treated with daptomycin or vancomycin compared with linezolid ($P = 0.0206$), and patients with pneumonia were more likely to receive linezolid or vancomycin compared with daptomycin ($P = 0.0142$). Patients with endocarditis confirmed by a transesophageal echocardiogram were treated with daptomycin (n = 11) or vancomycin (n = 11), and no patients with endocarditis received linezolid.

Patients treated with daptomycin received an average of 6.7 ± 1.8 mg·kg^{-1}·d^{-1} as an initial dose and patients treated with vancomycin received an average of 13.6 ± 4 mg·kg^{-1}·dose^{-1}. Eighteen patients received daptomycin doses <6 mg·kg^{-1}·d^{-1}, with each patient having an infectious disease consult. Fifteen of these patients received ≥ 5.2 mg·kg^{-1}·d^{-1} of daptomycin with only 3 patients receiving <5 mg/kg. All patients treated with linezolid received 600 mg every 12 hours. Serum vancomycin levels were obtained in 46 of 54 patients. Of all levels drawn, 35.3% (65/184) were below 15 μg/mL. For the 46 patients with vancomycin levels drawn, 26 patients had all levels >15 μg/mL, 15 patients with ≥ 1 level <15 μg/mL and 5 patients with no levels >15 μg/mL. Mean duration of inpatient therapy was 16.4 ± 9.6 days in the daptomycin group, 10.1 ± 3.2 days in the linezolid group and 13.6 ± 7.1 days in the vancomycin group.

Clinical Outcomes

Outcomes are displayed in Table 2. Clinical cure was achieved in 59% of patients treated with daptomycin, 60% with linezolid and 61% with vancomycin ($P = 0.9624$). Overall clinical cure for all treatment groups was 60%. Of the 49 patients not achieving the definition of clinical cure, 41 had persistent leukocytosis, 7 were febrile and 1 was tachypneic. No differences were noted between any of the 3 treatment groups. Microbiologic cure was achieved in 94% of patients treated with daptomycin, 100% with linezolid and 90% with vancomycin ($P = 0.6777$). Recurrence and re-infection were evaluated in 42 patients receiving daptomycin, 9 receiving linezolid and 49 receiving vancomycin, with no statistically significant differences being observed. Treatment failure occurred in 11 patients treated with daptomycin, 4 treated with linezolid and 9 treated with vancomycin. Overall, all-cause mortality was 17.2%, with