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ORIGINAL RESEARCH

Vancomycin-Resistant *Enterococcus* Bacteremia: An Evaluation of Treatment with Linezolid or Daptomycin

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BACKGROUND: Due to high rates of resistance and a limited number of efficacious antimicrobials for vancomycin-resistant *Enterococcus* (VRE), appropriate antibiotic selection is vital to treatment success. The purpose of this study was to assess clinical and microbiologic outcomes associated with the use of linezolid or daptomycin in the treatment of VRE bacteremia.

METHODS: A retrospective analysis of adult patients with VRE bacteremia between January 2004 and July 2009 was conducted at a tertiary care hospital in the United States. Clinical and microbiologic outcomes for both therapies were evaluated using multiple criteria.

RESULTS: Of the 361 patients with VRE bacteremia identified, 201 were included in the study (linezolid group, n = 138; daptomycin group, n = 63). More patients in the daptomycin group had hematologic malignancies (33% vs 14%) or received liver transplants (13% vs 4%). There was no difference in clinical or microbiologic cure between the linezolid and daptomycin groups (74% vs 75% and 94% vs 94%, respectively). Recurrence was documented in 3% of linezolid patients vs 12% of daptomycin patients ($P = 0.0321$). Reinfection was noted in 1% of patients in the linezolid group vs 6% of patients in the daptomycin group (P not significant). The average length of stay (LOS) was 37 days for the linezolid group vs 40 days for the daptomycin group (P not significant). Overall mortality was 20%, occurring in 25/138 linezolid patients vs 15/63 daptomycin patients (P not significant).

CONCLUSIONS: No differences in clinical or microbiologic cure rates, LOS, or mortality were identified between the groups. Various factors may have contributed to the significantly higher recurrence of VRE bacteremia in daptomycin patients. This study suggests that linezolid and daptomycin appear equally efficacious in the treatment of VRE bacteremia. *Journal of Hospital Medicine* 2012;7:243–248. © 2011 Society of Hospital Medicine.

Enterococci have been identified as a causative organism in approximately 10% of all nosocomial bloodstream infections (BSIs).[1,2] In 2006, the Infectious Diseases Society of America identified vancomycin-resistant *Enterococcus faecium* (VRE) as 1 of 6 microbes considered to be among the most dangerous due to high rates of resistance and a limited number of effective antimicrobials.[3] *E. faecium* has exhibited high rates of glycopeptide resistance with as many as 60% of isolates from BSIs being resistant to vancomycin.[2,4] Due to increasing resistance to glycopeptides, vancomycin has become obsolete in the treatment of *E. faecium* infections.[5]

A limited number of antimicrobials are available for the treatment of infections due to VRE. Agents active in vitro are quinupristin-dalfopristin, tigecycline, linezolid, and daptomycin. Quinupristin-dalfopristin was one of the first agents approved for use in VRE infections; however, treatment with this agent has been limited because of mediocre clinical response rates, undesirable adverse effects, high cost, and insufficient *E. faecalis* activity.[6,7] Tigecycline is not an optimal antibiotic for the treatment of VRE bacteremia, because serum concentrations achieved after administration are inadequate to treat BSIs.[7] In contrast, linezolid and daptomycin have evinced efficacy against VRE bacteremia, with reported microbiologic response rates of 85% and 80%, respectively.[7,8] One inherent difference between these antibiotics that may theoretically affect their use in immunocompromised patients is that linezolid is bacteriostatic, whereas daptomycin is bactericidal. It has been postulated that by using a bactericidal antibiotic such as daptomycin in the immunocompromised host, one may achieve superior clinical and microbiologic response rates.[3,7,9,10]

Since the introduction of the oxazolidinone linezolid in 2000, widespread use has led to reports of linezolid-resistant VRE as well as nosocomial transmission of linezolid-resistant VRE in hospitals.[4,11–14] Despite linezolid being a key antibiotic for the treatment of VRE infections over the last 10 years, development of resistance along with potential hematologic and neurologic toxicity during long-term use remains a concern.[7,8] Although daptomycin is active against

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several resistant organisms, including VRE, the evidence supporting use of daptomycin for VRE BSI is limited to case reports or small case series.[7,9] Moreover, daptomycin has not received US Food and Drug Administration approval for the treatment of VRE infections,[15] and emerging data regarding daptomycin-nonsusceptible enterococci (Minimum Inhibitory Concentration, MIC >4 mg/L) highlight a new problem for this multidrug-resistant pathogen.[16,17] Few studies in recent years have compared these 2 antibiotics in the treatment of VRE BSIs.[4,18,19] Due to the high rates of vancomycin resistance reported at our institution and the ubiquitous use of linezolid and daptomycin in the treatment of VRE bacteremia, we chose to evaluate response rates for these antibiotics in an effort to add to previously published literature on this topic.

MATERIALS AND METHODS

Patient Selection

Methodist University Hospital (MUH) in Memphis, Tennessee, is part of a 7-hospital system with 697 licensed beds. MUH is a tertiary teaching hospital with centers of excellence in neuroscience and transplantation. Patients admitted to MUH diagnosed with VRE bacteremia between January 1, 2004, and July 31, 2009, were identified by the microbiology laboratory. All patients who were ≥18 years of age, had ≥1 documented positive VRE blood culture, and received linezolid or daptomycin for ≥5 days were eligible. Patients were excluded if they were treated simultaneously with more than 1 agent active against VRE. This study was approved by the MUH Institutional Review Board. Of note, use of linezolid or daptomycin at MUH is restricted to an infectious disease physician or pulmonologist. Currently, there are no protocols at our institution for treating VRE infections.

Data Collection and Definitions

Cerner Millennium was used to collect all pertinent patient information. Patient records were reviewed to determine demographic data, comorbid illnesses, laboratory data (from admission to discharge), medications, and discharge status (home, long-term care facility, or death). Comorbid illnesses evaluated included: chronic obstructive pulmonary disease, diabetes mellitus, malignancy (solid or hematologic), transplant (liver or kidney), end-stage renal disease (ESRD) (hemodialysis or nonhemodialysis), cirrhosis, and endocarditis. ESRD and endocarditis were defined per chart diagnosis. Laboratory data collected included serum creatinine, creatine phosphokinase, absolute neutrophil count (neutropenia defined as absolute neutrophil count <1000), and number and site (intravenous line or peripheral blood draw) of positive VRE blood cultures. Other data collected were (1) time elapsed to adequate antibiotic coverage, which was defined as microbiologic documentation of an infection that was being effectively treated at the time of its identification, and (2) time to appropriate antibiotic coverage, which was defined as antimicrobial treatment selected for efficacy based on presumptive identification of the causative pathogen, the antimicrobial agent's spectrum of activity, and local microbial resistance patterns.[20] Doses of daptomycin and linezolid used in patients with VRE bacteremia were also documented.

Clinical cure was defined as a resolution of signs and/or symptoms of infection (white blood cell count <10,000/mm^3, bands <5%, heart rate <90 beats per minute, respiratory rate <20 breaths per minute, and maximum oral temperature <38°C) after gram-positive therapy was discontinued. The definition of *microbiologic cure* was lack of positive blood cultures for VRE at least 14 days after cessation of gram-positive therapy. *Microbiologic failure* was defined as positive VRE blood cultures obtained on gram-positive therapy necessitating a change in treatment. *Recurrence* was defined as VRE bacteremia within 30 days after discontinuation of gram-positive therapy. *Reinfection* was defined as VRE bacteremia that appeared 30 days after completion of primary gram-positive therapy.

All isolates were tested for susceptibility to linezolid using the MicroScan system, whereas daptomycin susceptibility patterns were obtained by either the Etest or MicroScan system. Of importance, our laboratory did not routinely report isolate susceptibility for daptomycin until 2008. Clinical Laboratory Standards Institute breakpoint guidelines were used to delineate minimum inhibitory concentrations for linezolid and daptomycin.

Outcomes

The primary objective was to determine the cure rate, both clinical and microbiologic, of VRE bacteremia with the use of linezolid and daptomycin. Secondary outcomes were rates of recurrence and reinfection as well as 30-day mortality. Clinical and microbiologic response rates for subsets of the patient population that were deemed immunocompromised or at an increased risk for VRE infections (neutropenic, transplant, malignancy, and ESRD on hemodialysis) were also evaluated.

Statistical Analysis

Data were analyzed using SAS version 9.2 (SAS Inc, Cary, NC). Patients with categorical characteristics were compared using a chi-square test or Fisher's exact test. Continuous data were analyzed using a Student *t* test and are expressed as the mean ± standard deviation. The mean duration of initial antibiotics, time to appropriate antibiotics, time to adequate antibiotic therapy, and LOS were all calculated for the linezolid and daptomycin group with a Student *t* test used to compare the differences. Multivariate logistic regression was used for the following outcomes:

TABLE 1. Patient Demographics

	Linezolid (n = 138)	Daptomycin (n = 63)	*P* Value
Average age, years, mean ± SD	60 ± 16	53 ± 15	0.0028
Male, No. (%)	59 (43)	36 (57)	0.0682
Race, No. (%)			
Caucasian	34 (25)	23 (37)	0.1043
African American	103 (75)	39 (62)	
Other	1 (1)	1 (2)	
COPD, No. (%)	8 (6)	2 (3)	0.7277
Diabetes mellitus, No. (%)	61 (44)	21 (33)	0.1655
Hemodialysis, No. (%)	35 (25)	17 (27)	0.8627
Malignancy, No. (%)			
Solid organ	26 (19)	16 (25)	0.3499
Hematologic	19 (14)	21 (33)	0.0021
Transplant, No. (%)			
Liver	5 (4)	8 (13)	0.0264
Kidney	3 (2)	0	0.5533
Endocarditis,* No. (%)	4 (3)	3 (5)	0.6801
Species of VRE (%)			
Enterococcus faecalis	33 (24)	10 (16)	0.2658
Enterococcus faecium	105 (76)	53 (84)	0.2658
Time to appropriate abx therapy, hours, mean ± SD	12.4 ± 26.9	8 ± 18.8	0.1851
Time to adequate abx therapy, days, mean ± SD	2.3 ± 1.8	1.8 ± 1.5	0.0554
Duration of initial abx, days, mean ± SD	11.1 ± 6.0	14.1 ± 14.6	0.0401
Abx before initial therapy, No. (%)	85 (62)	34 (54)	0.3541
Average dose, mg/kg, mean ± SD	NA	6.1 ± 1.5	NA
Mortality, No. (%)	25 (18)	15 (24)	0.3481
LOS (days)	37.5 ± 27.7	40.8 ± 27.9	0.4336

Abbreviations: abx, antibiotic; COPD, chronic obstructive pulmonary disease; LOS, length of stay; NA, not applicable; SD, standard deviation; VRE, vancomycin-resistant *Enterococcus*. *Patients developing endocarditis during the course of therapy, defined per chart diagnosis.

clinical cure, microbiologic cure, mortality, reinfection, and recurrence. For the interval variable, LOS, stepwise multiple regression was used to choose significant independent variables. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Of the 361 patients identified with a positive VRE blood culture, 201 were included in the study. The remaining 160 patients were excluded for one of the following reasons: <5 days of therapy (n = 87), no documented gram-positive therapy (n = 49), simultaneous gram-positive therapy (n = 10), or insufficient data to evaluate response rates (n = 14). For the treatment of VRE bacteremia, 138 patients received linezolid and 63 patients received daptomycin. Demographics, comorbid illnesses, and patient characteristics are shown in Table 1. There was a statistically significant difference in the average age, with the linezolid group consisting of older patients. The daptomycin group had more patients with hematologic malignancies than the linezolid group (33% vs 14%; $P = 0.0021$) and more patients who received liver transplants (13% vs 4%; $P = 0.0264$).

TABLE 2. Response Rates

	Linezolid (n = 138)	Daptomycin (n = 63)	*P* Value
Patients with positive culture on G+ therapy	11 (8)	14 (22)	0.0097
Clinical cure	102 (74)	47 (75)	1
Microbiologic cure	130 (94)	59 (94)	1
Recurrence*	3 (3)	6 (12)	0.0321
Reinfection*	1 (1)	3 (6)	0.0992

NOTE: All values are expressed as No. (%). *Calculations based on the number of patients who had follow-up cultures for each patient group (linezolid, n = 107; daptomycin, n = 51).

From the microbiology laboratory report of initial blood cultures, 78.6% of the isolates were noted as being *E. faecium*, with the remainder being *E. faecalis* (21.4%). One patient was classified as having linezolid-resistant *E. faecium* (MIC >4 mg/L) upon repeat blood culture. Daptomycin MICs were obtained for 44 isolates using the Etest or MicroScan system; all isolates were susceptible with MICs ranging from 0.25–4 mg/L. As mentioned previously, our laboratory did not routinely report isolate susceptibility to daptomycin until 2008.

There were no statistically significant differences between the treatment groups with regard to time to appropriate or adequate antibiotic therapy (Table 1). However, there was a statistically significant difference in the mean duration of initial antibiotics between linezolid and daptomycin (11.1 days vs 14.1 days; $P = 0.0401$). Dosing strategies used in these patients were also evaluated. All linezolid patients received a dose of 600 mg every 12 hours by mouth or intravenously. The average dose of daptomycin was 6.1 mg/kg (range, 3.4–10.4 mg/kg; median, 6 mg/kg). The average LOS was 37 days for linezolid vs 40 days for daptomycin, which did not confer statistical significance. Overall mortality was 20%, occurring in 25 linezolid patients versus 15 daptomycin patients ($P = 0.3481$). The stepwise multiple regression analysis did not identify any statistically significant variables in patients treated with linezolid or daptomycin that affected any of the outcomes.

Outcomes and Analysis

As shown in Table 2, there were no statistically significant differences in clinical or microbiologic cure between the linezolid and daptomycin groups (74% vs 75% and 94% vs 94%, respectively). However, the linezolid group compared with the daptomycin group had fewer patients that developed a positive blood culture while on their initial antibiotic therapy (8% vs 22%; $P = 0.0097$). Follow-up cultures were required to determine rates of recurrence and reinfection. Only 107/138 patients in the linezolid group and 51/63 patients in the daptomycin group had follow-up cultures collected. Recurrence was documented in 3% of linezolid patients vs 12% of daptomycin patients ($P = 0.0321$). The odds ratio for developing a recurrent

TABLE 3. Response Rates in Immunocompromised Patients

	Neutropenia (%)		Hematologic Malignancy (%)		ESRD on Hemodialysis (%)		Liver Transplant (%)	
	LZD (n = 16)	Dapto (n = 5)	LZD (n = 19)	Dapto (n = 21)	LZD (n = 35)	Dapto (n = 17)	LZD (n = 5)	Dapto (n = 8)
Clinical cure, No. (%)	12 (75)	5 (100)	18 (95)	17 (81)	24 (69)	12 (71)	4 (80)	3 (38)
Microbiologic cure,* No. (%)	13 (81)	5 (100)	18 (95)	20 (95)	33 (94)	16 (94)	5 (100)	8 (100)
Recurrence,* No. (%)	2 (13)	1 (20)	1 (6)	2 (11)	0	2 (15)	0	1 (14)
Reinfection,* No. (%)	0	0	0	0	1 (4)	2 (15)	0	1 (14)
Mortality, No. (%)	3 (19)	1 (20)	4 (21)	3 (14)	7 (20)	4 (24)	1 (20)	4 (50)
LOS, days, mean ± SD	57.4 ± 22	39.4 ± 12.4	47.6 ± 26.2	41 ± 27.1	38.8 ± 33.8	39.6 ± 40.4	50 ± 34.5	73.3 ± 38.8

Abbreviations: Dapto, daptomycin; ESRD, end-stage renal disease; LOS, length of stay; LZD, linezolid; SD, standard deviation. *Calculations based on the number of patients who had follow-up cultures for each patient group.

infection with daptomycin versus linezolid was 5.51 (95% confidence interval, 1.25–24.28). Out of 6 patients that developed a recurrent VRE infection in the daptomycin group, 2 were prescribed doses <4 mg/kg with no reported MICs, and 2 patients received ≈6 mg/kg with reported MICs of 4 mg/L. No statistically significant difference existed for the rate of reinfection between linezolid and daptomycin (1% vs 6%; $P = 0.0992$).

Table 3 provides information on subsets of the patient population deemed high-risk for VRE infection or immunocompromised. There was no statistically significant difference between the 2 antibiotic groups in clinical or microbiologic cure. In the subsets of immunocompromised patients, there was no difference in recurrence or reinfection between the linezolid and daptomycin patients. Furthermore, all groups had similar LOS regardless of the antibiotic used to treat the VRE BSI. Moreover, there were no statistically significant differences in 30-day mortality in these subsets of the population with regard to initial antibiotic choice. No significant independent variables were found between linezolid or daptomycin that affected any of the outcomes listed in Table 3.

DISCUSSION

Vergis et al[21] reported that infections with VRE compared with vancomycin-sensitive infections were associated with a higher rate of mortality and that the chosen antimicrobial therapy may play a pivotal role in the risk of death. Our retrospective study suggests that linezolid and daptomycin appear to be equally efficacious for the treatment of VRE BSIs. The results from our study for clinical and microbiologic cure rates for linezolid and daptomycin are similar to previously published data.[7,8] In accordance with previous studies,[4] our data demonstrate that there is a higher rate of recurrence in patients treated with daptomycin. This finding may be explained by the fact that the daptomycin group was comprised of more complex patients with a greater disease burden versus the linezolid group; therefore, they were more susceptible to a recurrent VRE infection. In our study, patients who were treated with daptomycin were 5.5 times more likely to have a recurrent infection than linezolid-treated patients. However, this finding must be scrutinized, because over half of the patients with recurrence either received an inappropriate dose or had high MICs to daptomycin.

Despite there being few clinical and microbiologic outcome data with daptomycin, our study proposes that a bactericidal antibiotic and a bacteriostatic antibiotic have comparable efficacy in the treatment of VRE BSIs. Previous literature has mainly comprised case studies or series that have evaluated clinical outcomes with daptomycin in the treatment of VRE BSIs. Gallagher et al[7] reported the results of a retrospective case series of 30 patients with VRE bacteremia who were treated with daptomycin. In this study, microbiologic cure was achieved in 80% of patients, with clinical success in 59% of the patients. In 2009, Mave et al[4] compared clinical outcomes between daptomycin and linezolid in the treatment of VRE bacteremia. Reported results demonstrated a microbiologic cure rate of 90% for daptomycin versus 88% for linezolid.[4] Moreover, there were no differences in mortality between the groups in our study. In 2010, Crank et al[18] reported no differences in mortality (in-hospital) for hospitalized patients with VRE BSIs treated with linezolid or daptomycin. Our results seem to be consistent with what has been published previously concerning clinical outcomes associated with linezolid or daptomycin in the treatment of VRE BSI.

The average daptomycin dose received in our patients was 6.1 mg/kg with doses ranging from 3.4–10.4 mg/kg. The underdosing as well as higher MICs to daptomycin may have contributed to a higher rate of recurrence. Previous reports state that *Enterococcus* species may have higher MICs to daptomycin than *Staphylococcus* or *Streptococcus* species; consequently, higher doses may be needed to adequately treat enterococcal infections.[7] In the aforementioned study by Gallagher et al,[7] doses of daptomycin ≥6 mg/kg were associated with a positive clinical outcome in 81% of patients compared with 31% if the dose used was <6 mg/kg. Linezolid is dosed 600 mg every 12 hours by mouth or intravenously, with no variations. There

have been no studies comparing the uniform dosing of linezolid to the weight-based dosing of daptomycin and their effects on outcomes.

Patients particularly susceptible to VRE infections include those with neutropenia and/or cancer, patients receiving long-term hemodialysis, and liver transplant recipients.[3,22,23] Upon review of this immunocompromised population, we noted no statistically significant differences in overall outcomes. A study by Kraft et al.[24] supports the findings in our study that both drugs appear useful in the treatment of VRE bacteremia in patients with hematologic malignancy. We did identify a difference, albeit nonsignificant, in LOS for daptomycin versus linezolid in patients with a history of liver transplantation. Again, the level of care that these patients needed compared with the general population may explain this difference. As mentioned previously, another pertinent factor would be the dose of daptomycin used in these patients, because the dose can affect clinical success. Because all of the other patients had a similar LOS, we cannot determine that the increased LOS seen in liver transplant patients treated with daptomycin was solely due to daptomycin use. The reason for the increased LOS seems to be multifactorial. In the neutropenic population, a difference in LOS was also recognized, but follow-up complete blood count values were not collected for these patients to determine whether linezolid contributed to further bone marrow suppression leading to an increase in LOS. For both of these patient populations, the number of patients included is very small (n = 21 for neutropenia total, n = 13 for liver transplant total), which can lead to a high degree of variance.

This study has several limitations. This was a retrospective review; therefore, we had no control over the selection of therapy. This may be reflected in an apparent preferential use of daptomycin in immunocompromised patients. Furthermore, 62% of linezolid patients and 54% of daptomycin patients received an antibiotic before initial therapy that could have potentially altered response rates. Due to the paucity of documentation surrounding initial site of infection, some of the positive cultures may represent potential contamination, because VRE may contaminate skin.[25] Contamination seems implausible, however, because patients were seen by an infectious disease physician and had at least $\geq$1 documented positive VRE blood culture. We chose arbitrary definitions for clinical cure, microbiologic cure, microbiologic failure, recurrence, and reinfection. Previous studies have used their own definitions leading to discrepancies in reporting. Another limitation was that follow-up cultures were not obtained on all of the patients, which was needed to determine rates of recurrence, reinfection, and microbiologic cure. MICs to daptomycin were not reported in 30% of our patients, potentially altering the recurrence rate seen in the daptomycin-treated patients. Because clinical cure was not documented in the chart, it was inferred from the laboratory values and vital sign information. One investigator analyzed all of the values and made the determination of clinical cure, allowing for a consistent approach to data review.

In the face of the imposing threat of a highly resistant organism such as VRE with a limited number of efficacious antibiotics, antimicrobial selection becomes increasingly important and is requisite to clinical and microbiological success. To our knowledge, this is one of the largest studies to date comparing the efficacy of linezolid with that of daptomycin in the treatment of VRE bacteremia. Both of these agents are effective for the treatment of VRE BSIs. Nevertheless, specific factors related to the medication (eg, dose, route of administration) as well as the patient (eg, comorbid conditions, acuity of illness) should be taken into consideration when selecting an initial antimicrobial agent. Because the treatment of VRE BSIs continues to be a challenge, larger prospective randomized controlled trials are needed to corroborate our results and determine the optimal therapy for this serious infection.

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