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Daptomycin *vs*. vancomycin for osteoarticular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA): A nested case-control study

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Abstract

Purpose—Vancomycin is the standard antibiotic for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. While daptomycin is approved for MRSA bacteremia, its effectiveness in osteoarticular infections (OAI) has not been established.

Methods—1:2 nested case-control study of adult patients with MRSA OAI admitted to an academic center from 2005–2010. Clinical outcomes and drug toxicity in patients treated with daptomycin *vs.* vancomycin were compared.

Results—20 patients with MRSA OAI treated with daptomycin were matched to 40 patients treated with vancomycin. Median age was 52 years (range, 25–90), and 40 (67%) were male. Most patients had osteomyelitis (82%), predominantly from a contiguous source (87%). Forty percent were diabetics. Diabetic patients were more likely to receive vancomycin than daptomycin [20

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Authors' Contributions

SYL participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. HNK participated in acquisition of data and critical revision of the manuscript. JRM participated in critical revision of the manuscript. HMB participated in the conception and design of the study and critical revision of the manuscript. JM participated in the conception and design of the study, analysis and interpretation of data, and drafting of the manuscript. All authors read and approved the final manuscript

Competing Interests

None of the following authors has a conflict of interest (S. Liang: no conflict, H. Khair: no conflict, J. McDonald: no conflict, J. Marschall: no conflict). H. Babcock has received honoraria from Sanofi Pasteur.

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(50%) *vs.* 4 (20%); p=0.03]. Vancomycin was more often combined with other antibiotics than daptomycin [22 (55%) *vs.* 5 (25%); p=0.03]. Median total antibiotic treatment duration was 48 (daptomycin) *vs.* 46 days (vancomycin) (p=0.5). 90% of daptomycin-treated patients had previously received vancomycin for a median 14.5 days (range, 2–36). Clinical success rates were similar between daptomycin and vancomycin at 3 months [15 (75%) *vs.* 27 (68%); p=0.8] and 6 months [14 (70%) *vs.* 23 (58%); p=0.5], even after propensity score-based adjustment for antibiotic assignment. Frequency of adverse events was similar between treatment groups [1 (5%) *vs.* 7 (18%); p=0.2].

Conclusions—Daptomycin and vancomycin achieved similar rates of clinical success and drug tolerability. Daptomycin is a reasonable alternative for treating MRSA OAIs, particularly in patients where therapy with vancomycin has not been well-tolerated.

Keywords

Staphylococcus aureus; osteomyelitis; septic arthritis; daptomycin; vancomycin

Background

Staphylococcus aureus is the most common cause of osteoarticular infections (OAIs) [1]. Appropriate antibiotic therapy is tailored to the antibiotic resistance profile of the individual *S. aureus* isolate. Methicillin-resistant *S. aureus* (MRSA) is typically treated with vancomycin, a glycopeptide antibiotic. Vancomycin, however, has the potential to cause significant nephrotoxicity [2]. The emergence of vancomycin-intermediate *S. aureus* (VISA) has further limited its use in many settings [3].

Daptomycin is the first of a new class of antibiotics, the cyclic lipopeptides, and has a mechanism of action unlike any other currently marketed antibiotic [4]. It is bactericidal and active against otherwise drug-resistant Gram-positive bacteria. Daptomycin is also well-tolerated and convenient to administer, making it a desirable option for outpatient parenteral antibiotic therapy [5]. It is currently approved in the United States for the treatment of skin and soft tissue infections, bloodstream infections, and right-sided endocarditis. Since its initial introduction in 2003, daptomycin has been increasingly used in the management of OAIs [6]. Common reasons for using daptomycin in MRSA OAIs include intolerance to or failure of the standard antibiotic treatment. Vancomycin failures have been attributed to poor bone penetration, increasing minimum inhibitory concentrations (MIC), and difficult-to-titrate dosing requiring frequent monitoring of drug levels [7].

A number of case series and analyses of registries have demonstrated that daptomycin can achieve high cure rates in osteoarticular infections [6, 8–10]. Gonzalez-Ruiz and colleagues reported findings from 64 cases of osteomyelitis seen in Europe where success was achieved in 80% [11]. Few studies have compared daptomycin *vs.* vancomycin for treatment of OAIs. Moenster *et al.* published a case-control study of 51 patients with osteomyelitis but did not exclusively focus on MRSA infections; patients treated with daptomycin had significantly fewer recurrent infections six months after completing intravenous antibiotics [12]. Lalani *et al.* performed a *post hoc* subanalysis of OAIs identified in a randomized controlled trial of

patients with staphylococcal bloodstream infection and right-heart endocarditis, and found higher success rates in the daptomycin group [13].

Our objective was to analyze data from a retrospective cohort of OAIs and compare patient characteristics, clinical manifestations, and outcomes of MRSA OAIs treated with either daptomycin or vancomycin.

Methods

Study design, setting, and inclusion/exclusion criteria

This was a 1:2 nested case-control study performed at Barnes-Jewish Hospital (BJH), a 1250-bed tertiary care hospital. We included adult patients admitted to BJH between August 1, 2005 and July 31, 2010 who were diagnosed with methicillin-resistant *Staphylococcus aureus* (MRSA) osteomyelitis or septic arthritis per tissue or fluid culture (with documentation of the infection in their medical records). Cases and controls were selected based on antibiotic assignment. All patients with MRSA osteomyelitis or septic arthritis treated with daptomycin during the specified time frame were included as cases, regardless of the duration of treatment. We matched controls treated with vancomycin to cases by month and year of hospital admission. No further matching was performed in order to allow analysis of potential factors influencing antibiotic selection. We excluded patients with: 1) polymicrobial infections, 2) persistent bacteremia (>72 hours), and 3) concurrent endocarditis. Eligible patients were identified using the hospital's outpatient intravenous antibiotic registry. The diagnosis of MRSA osteomyelitis or septic arthritis was confirmed by microbiology records for all patients in the study.

Data collection, outcomes, and statistical analysis

We collected demographic characteristics, comorbidities, clinical presentation, diagnostic work-up including laboratory values, microbiology (including MICs for daptomycin and vancomycin when available), and imaging studies, as well as type and duration of antibiotic treatment from hospital electronic medical records. The presence of orthopedic hardware at the site of infection including prosthesis and internal or external fixation was identified. Follow-up laboratory values and imaging studies as well as outcomes, including adverse events, were identified through review of outpatient electronic medical records from the infectious disease clinic. Mean serum vancomycin trough concentrations encompassing the entire treatment period and averaged over all measurements were calculated for all patients receiving vancomycin as well as for those pre-treated with vancomycin prior to starting daptomycin. For daptomycin, creatine phosphokinase (CPK) levels obtained during therapy were reviewed to determine a peak level. Reasons for changing antibiotic therapy (*e.g.*, clinical failure, microbiological failure including discovery of VISA, toxicity-related discontinuation, or problems stemming from convenience or insurance-related issues) were documented. At our institution, a *S. aureus* strain with an elevated vancomycin MIC of 4 to 8 mcg/mL is considered VISA.

We compared drug toxicity, medical/surgical management, and clinical outcomes in patients treated with daptomycin *vs.* vancomycin. This comparison was based on the following

endpoints: 1) ***Treatment success***, which was defined as resolution of signs and symptoms *and* improvement of function *and* normalization of inflammatory markers (when available) *and* no repeat surgery for osteomyelitis after discharge *and* no readmission related to the osteomyelitis within 8 weeks (of starting antibiotics); and 2) ***Tolerability of antibiotic treatment*** including occurrence of and readmission for adverse events and early discontinuation of prescribed antibiotic if associated with adverse events. Treatment success rates were calculated both with inclusion of those lost to follow-up as failures and excluding those lost to follow-up altogether. Clinical outcomes were compared, adjusting for propensity to antibiotic assignment using propensity score methods. For this purpose, we created a regression model predicting assignment to either study antibiotic. A weighted score was assigned to patients in the daptomycin (1/probability) and vancomycin groups [1/(1−probability)]. Then, in a logistic regression to elicit predictors of clinical success at six months, we included variables that had a $p<0.1$ in univariate analysis along with the weighted propensity score. Adverse events included *C. difficile* infection, bloodstream infection attributed to a central venous catheter, elevated liver function tests, elevated CPK, nephrotoxicity (serum creatinine ≥1.5 mg/dL), leukopenia (white blood cell count ≤3.5 cells per μL), and a rash and/or allergic reaction.

Statistical analysis was conducted using SPSS version 18 (SPSS Inc., Chicago IL). This study was approved by the Washington University Human Research Protection Office.

Results

We identified 20 patients with MRSA OAIs treated with daptomycin and 237 treated with vancomycin during the study period. Of the patients treated with vancomycin, forty were matched as controls to the twenty daptomycin cases by month and year of hospital admission. Overall, the patients' median age was 52 years (range, 25–90 years), 40 (67%) out of 60 were male, and 40 (67%) were white (Table 1). Most patients had osteomyelitis (82%) and a contiguous source of infection (87%). Eleven patients (18%) had isolated septic arthritis, whereas an overlapping diagnosis between septic arthritis and osteomyelitis was encountered in 10/60 (17%). Forty percent of the total study population was diabetic. Eight of sixty (13%) patients had renal insufficiency (serum creatinine >1.5 mg/dL) on admission. Seven (12%) had peripheral vascular disease.

The mean daptomycin dose encountered in the cases was 6.0 mg/kg (±0.6 mg/kg), in accordance with standard dosing of the drug for bloodstream infection. The mean serum vancomycin trough concentration achieved in controls receiving only vancomycin was 17.8 μg/mL, in accordance with recommended target concentrations of 15–20 μg/mL for MRSA OAI [3]. In the vancomycin group, there were more diabetic patients compared to the daptomycin group [20/40 (50%) *vs.* 4/20 (20%); p=0.03]. Conversely, in the vancomycin group there were fewer patients with preexisting hardware at the site of the infection compared to the other group [18/40 (45%) *vs.* 16/20 (80%); p=0.01]. Approximately half of the patients in the daptomycin and vancomycin groups had a prior history of osteoarticular infection at the same site [10/20 (50%) *vs.* 19/40 (48%); p=0.9] suggesting that the current infection was either chronic or relapsing; the remainder were acute. Vancomycin was more

often part of an antibiotic combination regimen than daptomycin [22 (55%) *vs.* 5 (25%); p=0.03].

The median treatment duration was 39 days for daptomycin (range 3–112) *vs.* 46 days for vancomycin (range 21–135) (p=0.01). However, most patients in the daptomycin group had initially been treated with vancomycin (18/20; 90%), receiving a median 14.5 days (range 2–36) of vancomycin prior to switching to daptomycin. Out of twenty patients in the daptomycin group, fourteen (70%) received ≥4 weeks of treatment with daptomycin and only two (10%) received ≤1 week. Taking into account pre-treatment with vancomycin, median total antibiotic treatment duration was 48 days for the daptomycin group (range 26–118) *vs.* 46 days for the vancomycin group (range 21–135) (p=0.5). Patients receiving daptomycin underwent more surgeries during the initial hospital admission than patients on vancomycin (1.8±0.8 *vs.* 1.4±0.6; p=0.04).

Treatment success was achieved in 70% (42/60) of all patients at 3 months and in 62% (37/60) at 6 months after completing intravenous antibiotics when loss to follow-up was considered equivalent to failure. Documented success rates were similar between daptomycin and vancomycin at 3 months [15/20 (75%) *vs.* 27/40 (68%); p=0.8] and 6 months [14/20 (70%) *vs.* 23/40 (58%); p=0.5]. When those lost to follow-up were excluded from analysis, treatment success in all patients improved to 84% (42/50) at 3 months and 82% (37/45) at 6 months. Success rates likewise improved for both daptomycin and vancomycin at 3 months [15/18 (83%) *vs.* 27/32 (84%); p=1.0] and 6 months [14/16 (87%) *vs.* 23/29 (79%); p=0.7].

As indicated before, diabetes mellitus predicted assignment to vancomycin in univariate analysis. In contrast, the presence of orthopedic hardware predicted assignment to daptomycin. Both variables were included in the propensity score for antibiotic assignment. Even after adjustment for propensity scores, antibiotic assignment to receive daptomycin or vancomycin was not predictive of clinical outcomes at six months [OR 0.55 (95% CI 0.08–3.74)]. However, the absence of an antibiotic allergy was associated with more favorable outcomes when compared to those with a history of antibiotic allergy [21/32 (92%) *vs.* 8/13 (62%); p=0.03]; this association persisted in a multivariate model [OR 0.2 (95% CI 0.03–0.85)].

The frequency of adverse events did not differ significantly between treatment groups [1 (5%) with daptomycin *vs.* 7 (18%) with vancomycin; p=0.2], although patients in the daptomycin group experienced three-fold fewer adverse events than those receiving vancomycin. The single patient with an adverse event reported in the daptomycin group experienced a CPK elevation meeting criteria for discontinuation of the drug (CPK >5 times the upper limit of normal in the presence of signs of myopathy or CPK ≥10 times the upper limit of normal in the absence of symptoms). Six out of seven patients with adverse events in the vancomycin group had nephrotoxicity attributed to that antibiotic.

Of the 20 patients in the daptomycin group, 18 (90%) were pre-treated with vancomycin. The reasons for replacing vancomycin with daptomycin were rash (including red man's syndrome) (5/20; 25%), failure to achieve therapeutic vancomycin levels (5/20; 25%),

detection of a vancomycin-intermediate isolate (4/20; 20%), nephrotoxicity (3/20; 15%), leukopenia (2/20; 10%), and clinical failure (2/20; 10%). Patients could have more than one reason warranting discontinuation of vancomycin.

Discussion

Daptomycin first became available in 2003 as an option to treat Gram-positive bacteria such as *Staphylococcus aureus* but is not currently FDA-approved for osteoarticular infections. Yet, it has been increasingly used to treat OAIs, particularly in the setting of methicillin-resistant *Staphylococcus aureus*, and is frequently used as an alternative to vancomycin. Little evidence exists to support this practice. In this small nested case-control study with comparison of outcomes of patients with MRSA bone and joint infections adjusted for propensity to antibiotic assignment, we found that daptomycin and vancomycin achieved similar rates of clinical success and drug tolerability. Based on these data, daptomycin is a reasonable alternative to vancomycin for treating MRSA bone and joint infections.

Head-to-head clinical trials of different antibiotics for osteoarticular infections are scarce [14]. Current practices are therefore driven by lower-quality comparisons or expert opinion. For a subset of osteoarticular infections, prosthetic joint infections, the Infectious Diseases Society of America (IDSA) has recently issued the first national management guidelines [15]. There, daptomycin is mentioned as an alternative treatment option for staphylococcal and enterococcal infections. In a separate IDSA guideline on MRSA infections, both vancomycin and daptomycin are named as possible agents for treating bone and joint infections. While daptomycin has been shown to be equivalent to vancomycin and other comparators in a landmark randomized-controlled trial on staphylococcal bloodstream infections and endocarditis [16], no such data exist for orthopedic infections. Lalani and colleagues used the data from the study mentioned above to conduct a *post hoc* analysis of patients who subsequently developed osteoarticular infections. Their report was limited by small numbers (*i.e.*, a total of 11 patients with MRSA osteoarticular infections) [13]. Another more recent study by Moenster and colleagues performed at a Veterans Affairs hospital compared daptomycin and vancomycin for osteoarticular infections but included only a subset of 23 patients with infections caused by MRSA [12]. The authors noted fewer recurrences of infection in the daptomycin group, although these findings may have limited generalizability to more heterogeneous, non-veteran populations. As in our study, the majority of patients eventually treated with daptomycin had initially started on vancomycin; reasons leading to changes in antibiotics were not reported. In contrast, our study focused on MRSA infections, which in our experience represent the primary indication for using daptomycin, and included a larger sample size and a more diverse population than previous studies. We also believe that our findings are among the first to demonstrate the wide range of reasons for switching from vancomycin to daptomycin in clinical practice. In our relatively small study, outcomes were similar across the groups, even after antibiotic assignment was adjusted for propensity scores. This is particularly interesting given that patients in the daptomycin group were often pre-treated with vancomycin and more complex (they were more likely to have hardware-associated infection and required more surgeries). While the propensity for assignment to daptomycin *vs.* vancomycin treatment was not found to predict clinical outcomes, a history of antibiotic allergy was predictive of poorer

outcomes. A history of antibiotic allergy may be a marker for treatment with second-line agents, resulting in a greater likelihood of refractory disease. In fact, some evidence indicates that a history of antibiotic allergy impacts patient outcomes [17]. Lastly, more diabetic patients were seen in the vancomycin group than those on daptomycin; this may be a reflection of the general acceptance of vancomycin as part of a combination regimen for diabetic osteoarticular infections. No robust evidence argues against the use of daptomycin in diabetic patients [18].

Future studies of comparative effectiveness of daptomycin *vs.* other antimicrobial agents will likely be compromised by the fact that, in our experience, daptomycin is rarely initiated as first-line therapy for osteoarticular MRSA infections, supporting the need for randomized controlled trials. One major reason for deferring the use of daptomycin is the anticipated cost of treatment, which is also influenced by the prolonged treatment duration required to achieve cure in bone and joint infections. In the U.S., the average cost of therapy associated with daptomycin is more than thirty times that of vancomycin [19]. Among the limitations of our study are the relatively small number of cases, which reflects the still relatively uncommon use of daptomycin at our institution, and the single-center and retrospective design. Follow-up was limited to 6 months after intravenous treatment completion; however, some data suggest that most infection recurrences are identified in the first few months after treatment, and more extended observation for endpoints may not be necessary [20].

Conclusions

Our findings support daptomycin as a useful and well-tolerated option for treating methicillin-resistant *Staphylococcus aureus*, one of the most common pathogens associated with osteoarticular infections. Outcomes of daptomycin-treated infections were similar to those treated with vancomycin, even for pre-treated and complex patients and for those who had experienced toxicities related to the prior antibiotic.

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Table 1

Comparison of 60 patients with osteoarticular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), by treatment group

	Total n=60	Daptomycin n=20	Vancomycin n=40	p-value
Age (mean ± SD, years)	51.7 (±16.5)	51.5 (±15.9)	51.9 (±16.9)	0.9
Male	40 (67%)	12 (60%)	28 (70%)	0.4
White race	40 (67%)	14 (70%)	26 (65%)	0.3
Body mass index (mean ± SD, kg/cm^2)	30.0 (±7.9)	32.2 (±7.4)	29.1 (±8.0)	0.2
Antibiotic allergy (any)	17 (28%)	6 (30%)	11 (27.5%)	0.8
Penicillin allergy	7 (12%)	1 (5%)	6 (15%)	0.4
Prior osteoarticular infection	29 (48%)	10 (50%)	19 (48%)	0.9
Prior MRSA infection	27 (45%)	10 (50%)	17 (43%)	0.6
Diabetes mellitus	24 (40%)	4 (20%)	20 (50%)	0.03
Rheumatoid arthritis	2 (3%)	1 (5%)	1 (3%)	1.0
Peripheral vascular disease	7 (12%)	0 (0%)	7 (18%)	0.08
Degenerative joint disease	2 (3%)	0 (0%)	2 (5%)	0.5
Renal insufficiency	8 (13%)	1 (5%)	7 (18%)	0.2
Human immunodeficiency virus infection	1 (2%)	0 (0%)	1 (3%)	1.0
Current cancer	2 (3%)	1 (5%)	1 (3%)	1.0
Immunosuppression (steroids, immune-modulators, chemotherapy)	3 (5%)	0 (0%)	3 (8%)	0.5
Current or former smoker	34 (57%)	12 (60%)	22 (55%)	0.7
Orthopedic hardware present on admission	34 (57%)	16 (80%)	18 (45%)	0.01
Osteomyelitis	49 (82%)	16 (80%)	33 (83%)	1.0
Septic arthritis	11 (18%)	4 (20%)	7 (18%)	1.0
Fever on admission (>38.3° Celsius)	9 (15%)	3 (15%)	6 (15%)	1.0
Diagnostics on admission				
Blood cultures drawn on admission	31 (52%)	11 (55%)	20 (50%)	0.7
≥1 positive blood culture (any organism)	7/31 (23%)	3/11 (27%)	4/20 (20%)	0.7
Radiography consistent with bone or joint infection	27/43 (63%)	10/17 (59%)	17/26 (65%)	0.7
CT scan consistent with bone or joint infection	9/9 (100%)	5/5 (100%)	4/4 (100%)	1.0
MRI consistent with bone	7/7 (100%)	N/A	7/7 (100%)	N/A
White blood cell count (mean ± SD, cells per μL)	10.6 (±4.5)	9.5 (±4.9)	11.1 (±4.2)	0.2
Serum creatinine (median, range, mg/dL)	0.9 (0.4–5.5)	0.8 (0.4–5.5)	0.9 (0.5–2.2)	0.5
ESR (median, range, mm/h)	63 (1–119)	55 (1–106)	67 (4–119)	0.8
CRP (median, range, mg/dL)	68 (1–352)	90 (2–338)	48 (1–352)	0.2
Study antibiotic given as part of combination antibiotic therapy	27 (45%)	5 (25%)	22 (55%)	0.03
Any surgical treatment	51 (85%)	19 (95%)	32 (80%)	0.2
Outcomes				
Evidence of improvement on initial follow-up	57 (95%)	19 (95%)	38 (95%)	1.0
Treatment successful at 3 month follow-up	42/60 (70%)	15/20 (75%)	27/40 (68%)	0.8

	Total n=60	Daptomycin n=20	Vancomycin n=40	p-value
Treatment successful at 6 months follow-up	37/60 (62%)	14/20 (70%)	23/40 (58%)	0.5

NOTE. All values expressed as n (%), unless otherwise noted. SD = standard deviation, CT = computed tomography, MRI = magnetic resonance imaging, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein.