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Original Article

Methicillin-Resistant *Staphylococcus aureus* in Foot Osteomyelitis

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Abstract

Background: Conflicting studies exist regarding the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) on increased time to wound healing, future need for surgical procedures, and likelihood of treatment failure in patients with diabetic foot osteomyelitis. The purpose of this study is to determine the overall significance of MRSA in predicting treatment failure in bone infections of the foot and to determine an appropriate pre-operative and empiric post-operative antibiotic regimen.

Patients and Methods: Patients presenting with an initial episode of ''probable'' or ''definite'' foot osteomyelitis were included for review and analysis if the following criteria were met: (1) Osteomyelitis occurred in the foot (i.e., distal to the malleoli of the ankle); episodes occurring above the ankle were excluded. (2) Patients received either no antibiotics or only oral antibiotics for long-term treatment; episodes managed with long-term parenteral antibiotics were excluded. (3) The infection was managed initially with medical therapy or conservative surgical therapy; episodes managed with major (above-ankle) amputation as the initial treatment were excluded. The primary objective of this study was to assess whether episodes of foot osteomyelitis associated with MRSA resulted in treatment failure more frequently than not.

Results: Of 178 episodes included in the study, 50 (28.1%) episodes had treatment failure. Median time-to-treatment failure was 60 days (range 7–598 days). In 28.1% (9/32 episodes) in which treatment failure occurred and 39.0% (41/105) episodes in which no treatment failure occurred, MRSA was present. The presence of MRSA was not significantly associated with treatment failure ($p = 0.99$).

Conclusions: The presence of MRSA in bone culture and whether antibiotic use had anti-MRSA activity was not associated with increased treatment failure of diabetic foot osteomyelitis in our institution. Empiric antibiotic coverage of MRSA may not be necessary for many patients presenting with foot osteomyelitis.

Keywords: diabetes; MRSA; MSSA; osteomyelitis; staphylococcal infections

Diabetic foot ulcerations are an important cause of hospitalizations occurring in approximately 6% of patients with diabetes mellitus [1]. Development of a diabetic foot ulcer has been associated with excess morbidity and mortality including excess care costs of approximately $28,000 for two years after initial diagnosis [1]. Diabetic foot infections (DFI) are defined by the Infectious Diseases Society of America (IDSA) as the presence of more than two findings of inflammation (e.g., redness, warmth, swelling or induration, tenderness and pain, and purulent secretions) at any foot wound and may occur because of spread of various pathogens to a wound site such as a foot ulcer. [2]

Osteomyelitis has been shown to occur in 20%–29% of DFI and can lead to multiple complications including future limb amputation [3,4]. The need for surgical intervention in DFI can be prolonged with appropriate intravenous or oral antimicrobial agents; however, adequate treatment with antimicrobial agents in patients with diabetes mellitus who have bone and joint infections can be difficult because of poor vascularization at the site of infection. To maximize efficacy of antimicrobial therapy, antibiotic selection is often focused on targeting known pathogens from intra-operative procedures. If a pathogen is not isolated or identified, empiric antibiotic therapy is focused on pathogens most likely to be present [5].

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DFIs of the bone are poly-microbial with greater prevalence of gram-positive aerobe pathogens (55%–78%)—specifically, *Staphylococcus aureus*—compared with gram-negative aerobes and anaerobes [6,7]. Conflicting studies exist regarding the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) on increased time to wound healing, future need for surgical procedures, and likelihood of treatment failure [8–10].

Current literature, including the IDSA diabetic foot osteomyelitis guidelines, suggest MRSA nares colonization as a risk factor for an MRSA isolate being found at the site of infection [2,11,12]. MRSA nasal surveillance could be an effective method to determine when MRSA treatment should be included as part of an intravenous or oral medication regimen for an inpatient or at discharge. Because of conflicting data and possible concern for poor outcomes when MRSA is present in culture, patients treated for bone infections of the foot empirically receive MRSA antibiotics before surgical intervention while an inpatient and often at discharge. The purpose of this study is to determine the overall significance of MRSA in predicting treatment failure in bone infections of the foot and to determine an appropriate pre-operative and empiric post-operative antibiotic regimen.

Patients and Methods

Study objectives

The primary objective of this study was to assess whether episodes of foot osteomyelitis associated with MRSA more often result in treatment failure. Treatment failure was defined as either (1) an unanticipated surgical resection of additional bone; or (2) above-ankle amputation. The secondary objective included evaluating the role of nasal swab testing for MRSA colonization in identifying episodes of osteomyelitis associated with MRSA.

Study design

A single-center, retrospective review was conducted of all patients presenting to the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) between January 1, 2011 and May 31, 2015 with an initial episode of ''probable'' or ''definite'' foot osteomyelitis as assessed by the surgical service [13]. These initial episodes were included for review and analysis if the following criteria were met:

1. Osteomyelitis occurred in the foot (i.e., distal to the malleoli of the ankle); episodes occurring above the ankle were excluded.
2. Patients received either no antibiotics or only oral antibiotics for definitive treatment; episodes of patients treated with long-term parenteral antibiotics as definitive therapy were excluded.
3. Infections were managed initially with medical therapy or conservative surgical therapy; episodes managed with major (above-ankle) amputation as the initial treatment were excluded.

During this study period, the treatment of patients with foot osteomyelitis was under the direction of a single surgical service and consisted predominately (although not exclusively) of surgical resection of bone to grossly negative margins. The operating room logs and a clinical registry from this service served to identify patients meeting inclusion criteria. Surgical incision and drainage were performed within 48 hours of admission for all patients with either (1) local findings suggesting abscess, fasciitis, joint space infection or (2) foot ulcer or gangrene with systemic signs of infection.

The unit of analysis was a new episode of osteomyelitis; therefore, more than one episode of osteomyelitis from a single patient was included if present in non-contiguous areas. For example, a person presenting with left foot osteomyelitis that had right foot osteomyelitis develop subsequently would be included as having two separate episodes if the above-described inclusion criteria were met. Similarly, a person with osteomyelitis in the left first toe in whom osteomyelitis of the left fifth toe developed subsequently could be considered as having two separate episodes. In contrast, a patient who underwent left first toe amputation for osteomyelitis and osteomyelitis developed subsequently at the distal portion of the remaining metatarsal or in the second toe/metatarsal would be considered as having a treatment failure (see above).

Clinical protocols

During the study period, diagnosis and management of foot osteomyelitis generally adhered to our hospital's guidelines for management of foot osteomyelitis (the Addendum is available online at www.liebertpub.com/sur). These guidelines were based largely on recommendations from the IDSA with consideration of the hospital antibiogram and antimicrobial formulary. Diagnostic evaluation by surgical service categorized patients suspected of having osteomyelitis into the ''probable,'' ''definite,'' or ''other'' categories based most often on history, physical examination, laboratory results, and plain radiograph; magnetic resonance imaging was used selectively for cases in which the categorization was otherwise unclear or equivocal. Nasal swabs to screen for nares colonization of MRSA were performed at the time of admission to the hospital.

Patients often received empiric vancomycin and either ertapenem or piperacillin/tazobactam in the peri-operative period. Decisions for long-term antibiotic treatment were determined by the patient's primary surgeon based on results of bone margin pathology and microbiology. The surgical service made antibiotic decisions in conjunction with the infectious diseases physician and pharmacist. Our hospital preferentially prescribed oral antibiotic agents for the definitive treatment of patients with foot osteomyelitis unless organisms identified on bone culture were only susceptible to parenteral agents.

Data analysis

Electronic medical records were reviewed retrospectively using the Veterans Health Administration Computerized Patient Record System to collect all data, including baseline characteristics (demographics and co-morbidities) and laboratory values (including hemoglobin A1c, serum creatinine/estimated glomerular filtration rate, and serum albumin up to 90 days before presentation); vital signs and laboratory values (including white blood cell count and carbon dioxide level) within the 72 hours before initiating treatment; microbiologic results from any bone specimens obtained (including pathogen species and antimicrobial sensitivities) and MRSA nasal swabs; lesion characteristics (location, instigating foot ulcer,

presence/extent/type of soft tissue infection); treatment characteristics (including surgical vs. medical).

Toe pressures and ankle pressures were measured using plethysmography in an Intersocietal Accreditation Commission approved non-invasive vascular laboratory. Measurements were obtained via pneumoplethysmography by vascular laboratory technologists with Registered Vascular Technician certification using Parks Flow-Lab Model 2100 SX2 machines and SonovaE software (Parks Medical Electronics, Inc., Beaverton, OR). Toe pressure results were used preferentially to assess severity of peripheral artery disease in cases where there appeared to be a discrepancy between toe pressures and ankle pressures. Patients who had severe peripheral artery disease were considered generally for revascularization.

The presence of MRSA was determined based on positive identification by the MEDVAMC microbiology laboratory based on culture speciation and sensitivity obtained from intra-operative specimens obtained during bone resection or from percutaneous, image-guided bone biopsies using 11 gauge needles. All samples were analyzed using the Vitek® 2 microbial identification system (bioMerieux, Inc., Durham, NC) and classified as sensitive, intermediate, or resistant according to reference points established by the Clinical & Laboratory Standards Institute guidelines at the time. The following antibiotic agents were considered to have MRSA activity: Trimethoprim/sulfamethoxazole (TMP/SMX), clindamycin, doxycycline, minocycline, vancomycin, daptomycin, and linezolid. All other antibiotic agents were considered non-MRSA antibiotic agents.

Proportions and medians were used for categorical/binary variables, and medians were used for continuous variables. Chi-square and Fisher exact tests were used to identify differences in proportions. The non-parametric Mann-Whitney rank-sum test was used to compare median values between groups. Multivariate Cox regression was used to determine whether the presence of MRSA in bone specimens had a significant association with time to treatment failure. Multivariate logistic regression was used to identify variables with a significant association with presence of MRSA in bone culture results. Statistical analyses were performed using Intercooled Stata version 8.2 (StataCorp, College Station, TX). The standard p value threshold of <0.05 was considered to be statistically significant. The study was approved by the Institutional Review Board at the Baylor College of Medicine and the Office of Research and Development at the MEDVAMC.

Results

A total of 184 episodes of foot osteomyelitis met the inclusion criteria for this study. Six episodes were excluded because of treatment with long-term parenteral antibiotic therapy, leaving 178 unique episodes occurring among 131 patients. A description of baseline characteristics is shown in Table 1. The majority of patients in the study were elderly (MRSA group 64.4 years, non-MRSA group 64.6 years, $p=0.78$) and had diabetes mellitus (MRSA group 97.9%, non-MRSA group 87%, $p=0.13$). Significantly more patients in the MRSA group were receiving insulin therapy (68.8% vs. 61.6%, $p=0.02$) and had presence of MRSA nares colonization (56.3% vs. 14%, $p<0.001$) compared with the non-MRSA group.

Bone cultures were obtained in 135 episodes. The MRSA, MSSA, and other staphylococcal species were isolated in 31 (23%), 27 (20%), and 14 (10.4%) episodes, respectively. Tetracycline and TMP/SMX demonstrated greater than 90%

Table 1. Baseline Characteristics

Variable	*Overall (n=178)*	*MRSA+ (n=32)*	*MRSA- (n=146)*	p
Median age (range)	65 (58– 69)	64 (57–71)	65 (58–69)	0.78
Diabetes mellitus, n (%)	158 (88.8)	31 (97.9)	127 (87.0)	0.13
Median hemoglobin A1c, (range)	7.9 (6.7– 9.7)	7.8 (6.9– 9.4)	8.0 (6.7– 9.8)	0.73
Insulin therapy, n (%)	112 (62.9)	22 (68.8)	90 (61.6)	0.02
Median serum glucose (range)	199	203	194	0.58
Coronary artery disease, n (%)	51 (28.7)	12 (37.5)	39 (26.7)	0.22
Congestive heart failure, n (%)	27 (15.2)	3 (9.4)	24 (16.4)	0.31
Median estimated glomerular filtration rate, mL/min (range)	68 (40– 95)	73 (47– 100)	68 (38–95)	0.65
Median body mass index (BMI), kg/m^2 (range)	28.6 (16.9–56.3)	29.6 (19.8–40.4)	28.4 (16.9–56.3)	0.38
Active tobacco use, n (%)	61 (34.5)	9 (28.1)	52 (35.9)	0.41
Arterial insufficiency, n (%)[20]				0.69
None	135 (75.8)	26 (81.3)	109 (74.7)	
Mild	16 (9.0)	1 (3.1)	15 (10.3)	
Moderate	9 (5.1)	2 (6.3)	7 (4.8)	
Severe	18 (10.1)	3 (9.4)	15 (10.3)	
Previous revascularization of index limb, n (%)	52 (29.2)	6 (18.8)	46 (31.5)	0.20
Homeless, n (%)	8 (4.5)	0 (0.0)	8 (5.5)	0.35
Fever (temp >100.5°F), n (%)	12 (6.7)	3 (9.4)	9 (6.2)	0.44
Leukocytosis (>12 K/cm^2), n (%)	49 (27.5)	8 (25.0)	41 (28.1)	0.82
Tachycardia (>90 bpm), n (%)	30 (16.9)	7 (21.9)	23 (16.8)	0.35
MRSA nares colonization, n (%)	38 (21.7)	18 (56.3)	20 (14.0)	<0.001
Mean albumin, g/dL (range)	3.1 (1.3– 4.5)	3.0 (1.3– 4.0)	3.1 (1.5– 4.5)	0.74

MRSA = methicillin-resistant *Staphylococcus aureus*; bpm = beats per minute.

sensitivity against MRSA species. Low rates of sensitivity were observed for clindamycin (29%) and levofloxacin (19.4%) against MRSA species.

Treatment failure occurred in 50 of 178 (28.1%) episodes. Median time-to-treatment failure was 60 days (7–598 days). MRSA was present in 9 of 32 (28.1%) episodes in which treatment failure occurred and 41 of 105 (39.0%) episodes in which no treatment failure occurred ($p = 0.26$, chi-square analysis). Cox multivariate analysis demonstrated that the presence of *Pseudomonas aeruginosa*, *Eschericia coli*, serum albumin <2.8 g/dL, 60+ pack-year history of cigarette smoking, positive bone margin with fewer than seven days isolate-specific antibiotic therapy, and first toe or metatarsal location of osteomyelitis all significantly increased treatment failure risk (hazard ratios 2.3–21, all $p < 0.05$).

Delayed primary closure was associated with a significantly decreased risk of treatment failure (hazard ratio 0.4, $p = 0.01$). The presence of any staphylococcal species or of MRSA in particular was not significantly associated with treatment failure ($p = 0.99$). The presence of any staphylococcal species or of MRSA in particular was not significantly associated with treatment failure ($p = 0.99$).

The proportion of microbial species with sensitivity to tested antimicrobial agents is shown in Table 2. In a total of 123 episodes, patients received at least one oral antibiotic agent at discharge. Twenty-four (77%) of MRSA-positive foot osteomyelitis patients received at least one antibiotic agent that provided coverage for MRSA. No significant difference in treatment failure rates were observed among patients with MRSA bone isolates at discharge with antibiotics that provided coverage against MRSA compared with those who received either no antibiotic agents or antibiotic agents that did not provide coverage against MRSA ($p = 0.6$, Fisher exact test).

A nasal swab was performed in 175 of the 178 (98.3%) episodes of foot osteomyelitis. Of those, patients in 39 episodes (22.3% of episodes) had MRSA isolated from their nasal passage (nares colonization). The MRSA nares colonization was associated with the presence of MRSA isolates on bone specimens ($p < 0.001$, chi-square analysis). There was a positive association between MRSA bone isolates and MRSA nares colonization determined by logistic regression (odds ratio 8.1, $p < 0.001$). Also, a trend toward significance was noted between MRSA bone isolates and presence of soft tissue abscess at admission (odds ratio 2.4, $p = 0.09$). MRSA was found in bone isolates of only two of 39 (5.1%) episodes when no abscess was present and nares testing was negative; 16 of 70 (22.9%) cases when either an abscess or nares colonization was present; and 14 of 24 (58.3%) episodes when both an abscess was present and nares testing was positive.

Discussion

The IDSA recommendations for the use of MRSA therapy for the treatment of patients with diabetic foot osteomyelitis are based on the premise that MRSA could promote an increased risk of treatment failure. Recommendations for inclusion of MRSA therapy are dependent on the presence on one of the following risk factors: History of previous MRSA infection or colonization in the past year, high local prevalence of MRSA (>10%) or an ''unacceptable risk of treatment failure and severe infection.'' Vardakas et al [8] performed a meta-analysis comparing different antibiotic regimens for the treatment of patients with DFI, rates of treatment failure, and factors potentially associated with such treatment failure. The results from this study are in support of the recommendations given by the IDSA. Although the presence of MRSA was associated with treatment failure in the 18 randomized controlled trials included for analysis ($p = 0.02$), a multivariable analysis was not performed to identify whether presence of MRSA was an independent risk factor for treatment failure.

In the current study, MRSA bone isolates were not associated with a greater risk of treatment failure for episodes of foot osteomyelitis. This finding corroborates the work from Aragón-Sánchez et al. [9]. In this previous study, there were no statistically significant differences in surgical outcomes such as need for minor or major amputation among patients with MRSA compared with those without MRSA. Zenelai et al. [10] performed a literature search evaluating how outcomes of diabetic foot infections (soft tissue and bone infection) related to their specific microbiology. Four publications assessed in their review reported a worse outcome in patients with MRSA, but these differences did not reach statistical significance. As a result, the authors concluded that diabetic foot infections caused by MRSA do not require any special treatment.

Similar to studies performed by Senneville et al. [14,15], the current study showed the *Staphylococcocus* spp. to be most prevalent in diabetic foot osteomyelitis. Although type of antimicrobial agent received was not shown to be

Table 2. Percentage of Common Microbial Species with Sensitivity to Tested Antimicrobial Agents

Antimicrobial agent	*Methicillin-sensitive* S. aureus *(n = 27)*	*Methicillin-resistant* S. aureus *(n = 31)*	*Other staphylococcal species (n = 14)*
Intravenous			
Vancomycin	26 (96.3%)	31 (100%)	13 (92.9%)
Oral			
Clindamycin	23 (85.1%)	9 (29%)	7 (50%)
Levofloxacin	23 (85.1%)	6 (19.4%)	10 (71.4%)
Oxacillin	23 (85.1%)	–	8 (57.1%)
Tetracycline	23 (85.1%)	28 (90.3%)	–
Sulfamethoxazole-trimethoprim	26 (96.3%)	28 (90.3%)	10 (71.4%)

Numbers in the table represent the percentage with sensitivity to the antimicrobial agent listed.
S. aureus = Staphylococcus aureus.

statistically significant, our results may demonstrate clinical significance. On the basis of susceptibility results of isolates identified during surgical interventions, clindamycin was not the most appropriate oral antimicrobial agent to be used empirically at our institution because it provided improper empiric coverage of gram-positive organisms.

Although vancomycin provided appropriate gram-positive coverage, the results of our study failed to show a correlation between presence of MRSA after initial intervention and risk for future treatment failure. Empiric use of antibiotic agents for suspected infections is appropriate until pathogens are known, but improper use of antibiotic agents is known to promote antimicrobial resistance [16]. In addition, antimicrobial resistance is believed to be associated with more than 23,000 deaths annually and an estimated $20 billion a year in excess healthcare costs according to the Centers for Disease Control and Prevention [17,18]. Limiting the use of empiric antimicrobial agents would help to decrease improper use, resistance, and costs.

As in many centers, our current empiric antibiotic regimen for patients presenting with foot infections—including osteomyelitis—includes vancomycin for MRSA coverage. Given the moderate overall prevalence (24% in our series) and the lack of association with treatment failure, selective coverage for MRSA may be worth considering. In our series, MRSA nares colonization had a strong correlation with MRSA bone isolates and some association with the presence of an abscess. If other series corroborate these findings, vancomycin or other MRSA coverage may not be needed for empiric treatment in patients who do not demonstrate nares colonization and do not have clinical findings suggestive of an abscess.

This study had some limitations that are important to note. Vancomycin has been part of our empiric treatment algorithm at our institution during the study period. As such, most patients received 24–72 hours of intravenous vancomycin before surgery or bone biopsy. While clinicians would not expect a brief duration of vancomycin to eradicate MRSA in bone (treatment is often 6–8 weeks or more), this relatively brief period of MRSA antimicrobial coverage may have affected the results of our study. In addition, our study sample comprised predominately elderly males; this may limit external validity and applicability to other institutions. Finally, our assessment of MRSA colonization did not factor in the presence of MRSA in sites besides the nasal passages, such as the axillary and inguinal regions.

Presence of MRSA in bone culture and whether antibiotic coverage that did not cover for MRSA was not associated with increased treatment failure of diabetic foot osteomyelitis at our institution. Empiric antibiotic coverage of MRSA may not be necessary for many patients presenting with foot osteomyelitis when MRSA nares colonization testing has negative results, especially if no abscess is present. For those presenting with an abscess and/or nares colonization with MRSA, TMP/SMX and doxycycline (>90% susceptibility, respectively) appear to be the best empiric oral agents to use until isolate-specific results are available, although these susceptibility results are site-specific.

On the basis of the results of this study, vascular surgery physicians at our facility will begin using MRSA nasal swab results to guide empiric therapy and limit vancomycin to populations who display signs and symptoms of severe infection as defined per IDSA definition [2]. The results of this study may be useful to clinicians and those who participate in antimicrobial stewardship practices at other facilities.

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Author Disclosure Statement

No competing financial interests exist.

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