CLINICAL RESEARCH ARTICLE

Risk factors for methicillin-resistant *Staphylococcus aureus* in diabetic foot infections

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Objective: The purpose of this study was to evaluate risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) in patients hospitalized for diabetic foot infections.
Methods: We reviewed hospital admissions for foot infections in patients with diabetes which had nasal swabs, and anaerobic and aerobic tissue cultures at the time of admission. Data collected included patient characteristics and medical history to determine risk factors for developing an MRSA infection in the foot.
Results: The prevalence of MRSA in these infections was 29.8%. Risk factors for MRSA diabetic foot infections were history of MRSA foot infection, MRSA nasal colonization, and multidrug-resistant organisms ($p < 0.05$). Positive predictive value (PPV) and negative predictive value (NPV) of nasal colonization with MRSA to identify MRSA diabetic foot infections were 66.7% and 80.0% (sensitivity 41%, specificity 90%). Admission from a nursing home was not a significant risk factor.
Conclusion: Positive nasal swabs are not predictive of the infecting agent; however, a negative nasal swab rules out MRSA as the infecting agent in foot wounds with 90% accuracy.

Keywords: *MRSA*; *infection*; *diabetic foot*; *ulcer*

Approximately one-in-four people with diabetes will develop an ulcer during their lifetime and as many as half of these ulcerations will develop an infection (1, 2). Early diagnosis is key to adequate treatment and appropriate precautions to prevent the spread of infection, especially with resistant bacterial strains and immunocompromized individuals. *Staphylococcus aureus* is the most common infecting organism in diabetic foot infections. As many as 46% of *Staphylococcus aureus* isolates are methicillin-resistant *Staphylococcus aureus* (MRSA) (3). Identifying risk factors for MRSA infections could improve prevention and treatment in diabetic foot infections, reduce resistance patterns, and reduce healthcare costs. Current literature involving MRSA and diabetic foot ulcers primarily involves studies that evaluate wound colonization and not clinically infected wounds. The objective of this study was to evaluate risk factors for MRSA in patients with diabetic foot infections requiring hospital admission.

Research design and methods
This is a retrospective cohort study of 57 consecutive patients hospitalized for diabetic foot infections. Institutional Review Board approval was obtained prior to data collection. Data were abstracted to evaluate potential risk factors for diabetic foot infections. Patients included in the analysis had both nasal swabs at the time of admission, and anaerobic and aerobic wound cultures from deep tissue specimens collected in the operating room. Briefly, once the patient arrived to the operating room, the affected foot was prepared with aseptic technique. Once the infected area was addressed surgically, infected tissue was acquired and sent in their respective container to microbiology. The diagnosis of infection was based on criteria from the Infectious Disease Society of America

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and the International Working Group on the Diabetic Foot (4, 5). We evaluated age, gender, diabetes type, glycated hemoglobin, amputation, neurovascular status, tobacco use, previous hospitalization, nursing home residence, and antibiotic therapy in the 12 months prior to admission. Peripheral arterial disease was defined as a nonpalpable foot pulse or an ankle brachial index <0.70. Neuropathy was defined as inability to detect a 10 g Semmes-Weinstein monofilament at one location out of 10 sites, or absent vibratory sensation with a 128 Hz tuning fork at the hallux. We evaluated the positive predictive value (PPV) and negative predictive value (NPV) and sensitivity and specificity of nasal swabs, history of MRSA diabetic foot infections, and multidrug-resistant organisms to diagnose MRSA foot infection. Due to the small sample size, univariate analysis was conducted. Chi-squared test was used to evaluate factors contributing to MRSA diabetic foot infections using a 95% confidence interval and an alpha of 0.05.

Results

Demographics are provided in Table 1. The prevalence of *Staphylococcus aureus* in diabetic foot infections was 42.1%; 70% of these isolates were methicillin resistant. Overall, the prevalence of MRSA in diabetic foot infections was 29.8%.

There was no difference in the length of hospitalization, bone infection or amputation in patients with MRSA compared to non-MRSA diabetic foot infections (Table 1). We identified three risk factors associated with MRSA infection: the presence of multidrug-resistant organisms, history of an MRSA diabetic foot infection, and a positive MRSA nasal culture ($p < 0.05$). There was a trend that previous hospitalization in the last 12 months was associated with MRSA ($p = 0.07$). Several traditional risk factors for MRSA were not associated with diabetic foot infections, such as previous antibiotic treatment ($p = 0.40$). None of the patients with MRSA were nursing home residents, and 17.5% of the patients with other bacterial pathogens were from nursing homes ($p = 0.07$).

PPV and NPV of nasal colonization with MRSA to identify MRSA diabetic foot infections were 66.7% and 80.0% (sensitivity 41%, specificity 90%). Patients with MRSA nasal cultures were eight times more likely to have an MRSA diabetic foot infection (OR 8.0 CI 2.05–31.02). The PPV and NPV for a previous MRSA foot infection were 100% and 75.5% (sensitivity 23.5%, specificity 100%). PPV and NPV for multidrug-resistant organisms were 40% and 86.4% (sensitivity 82.4%, specificity 47.5%). The positive likelihood ratios were as follows: positive nasal swab was 4.11; previous history of MRSA infection was 0.23, and multidrug resistance 1.73. The negative likelihood ratios were as follows: positive nasal swab was

Table 1. Risk factors and outcomes associated with methicillin-resistant *Staphylococcus aureus* (MRSA) in diabetic foot infections

	MRSA negative $n = 40$	MRSA positive $n = 17$	p
Age	60.1 (15.38)	59.0 (14.25)	0.78
Gender (%, male)	65.0%	70.6%	0.68
Type 2 diabetes (%)	75.0%	88.2%	0.26
HgA1C	9.57 (3.28)	9.80 (2.34)	0.80
Current tobacco use	32.50%	47.00%	0.30
Peripheral vascular disease ABI < 0.9	58.10%	52.60%	0.69
Ankle brachial index	1.06 (0.59)	1.22 (0.51)	0.50
Peripheral neuropathy	90.0%	88.2%	0.84
Previous hospitalization <12 months	82.5%	100%	0.07
Nursing home resident	17.5%	0	0.07
Previous MRSA antibiotics <12 months	45.0%	58.8%	0.34
Previous antibiotics <12 months	52.5%	64.7%	0.40
Positive nasal swab	7.5% (4)	41.2% (7)	0.002
History + MRSA foot infection <12 months	0	23.5% (4)	0.001
Multidrug-resistant organism (≥2 pathogens)	47.5% (19)	82.4% (14)	0.02
Outcomes			
Length of stay days (SD)	6.02 (4.16)	4.95 (3.46)	0.36
Amputation during hospitalization			0.69
°None	32.5%	41.2%	0.75
°Foot	65.0%	58.8%	0.89
°Leg	2.5%	0	1.00
Osteomyelitis	1.5%	17.6%	0.80

0.65, previous history of MRSA infection was 0.76, and multidrug resistance was 0.33.

Discussion

MRSA is an increasing problem in industrialized countries. It is commonly believed to be an important cause of poor outcomes, increased length of hospital stay, increased cost and increased mortality (6, 7). However, in patients with diabetic foot infections, MRSA has not been demonstrated to be associated with longer hospitalization or more amputations (8–11). In our study, we identified three risk factors associated with MRSA infection: the presence of multidrug-resistant organisms, history of an MRSA diabetic foot infection, and a positive MRSA nasal culture. There was no difference in amputations, amputation level, length of hospital stay, or bone infections in patients with MRSA diabetic foot infections. However, being a nursing home resident was not a risk factor for MRSA.

Modalities to diagnose and prevent MRSA infections are expensive. To address concerns about MRSA infections, some hospitals have adopted protocols to isolate patients transferred from nursing homes or with existing wounds. In addition, some institutions collect nasal swabs of all patients admitted to the hospital in order to identify MRSA carriers. Antibiotic coverage with vancomycin for MRSA is often standard protocol for diabetic foot infections, even when there are no risk factors for MRSA.

Treating every diabetic foot infection for MRSA is likely to lead to an increase in resistance as well as raise the healthcare cost burden. Conventional risk factors for hospital and community acquired MRSA infections may not apply to diabetic foot infections. For MRSA infections that involve other sites, previous hospitalizations, nursing home residence, immunocompromised patients, previous antibiotic therapy, history of MRSA, and open wounds have all been risk factors for MRSA infections (6, 12, 13). Current literature suggests that only a few of the traditional MRSA risk factors apply in diabetic foot infections.

Most studies discuss risk factors for diabetic foot ulcer colonization with MRSA and not clinical infection. These studies have identified that a history of MRSA infection, chronic wounds, previous hospitalization, and nasal swabs are associated with the colonization of diabetic foot ulcers with MRSA (9, 10, 14). We identified only one study that evaluated patients admitted to the hospital with diabetic foot infections and their associated risk factors (15). Yates identified previous hospitalization for the same ulceration, chronic wounds, and inpatient treatment as risk factors. However, he did not evaluate nasal swabs, history of MRSA infection, previous antibiotic use, nursing home residence, peripheral arterial disease, or multidrug-resistant organisms. A recent study by Taha looked at 222 *S. aureus* isolation (16). Seventy one (30.87%) of the

patients was *S. aureus* infection diabetic foot with nasal carriage. Among diabetic foot infection and nasal carriage patients, 40.85% of *S. aureus* were considered as MRSA. However, the author does not specify the severity of the infection. We evaluated a population of high-risk patients with severe diabetic foot infections that required hospitalization, whose care is costly and have poor outcomes. In addition, we relied on tissue specimens rather than swab cultures to isolate bacterial pathogens.

This study shares many of the same limitations present in any retrospective study. The most important limitation is the accuracy of the data and consistency of operational definitions for clinical criteria. In addition, our sample size may not have been large enough to identify all of the contributing risk factors for MRSA infections. For instance, there was a trend for previous hospitalizations in the last 12 months being a risk factor for MRSA infection ($p = 0.07$). However, a positive likelihood ratio of 4.11 indicates that a positive MRSA nasal swab is four times more likely to occur in patients with diabetic foot infection involving MRSA. Thus, nasal swab may be an easy test to identify those patients with diabetic foot infection that MRSA may be involved, allowing immediate intravenous antibiotics. The study is probably underpowered to identify factors such as previous hospitalizations that may help physicians develop better guidelines for MRSA therapy for patients admitted to the hospital for diabetic foot infections. However, this preliminary work will help develop an adequate sample size justification to plan prospective studies. Even though the number of study subjects was small, there were several risk factors associated with MRSA from deep tissue cultures, which may suggest that the associations are robust and clinically relevant.

To address MRSA infections more effectively, we may need to consider a paradigm shift in the rationale to culture diabetic foot ulcers. The standard of care advocated by the Infectious Disease Society of America guidelines is to culture wounds only when clinical signs of infection are present (2). Nasal colonization for MRSA is associated with clinical infections; however, for diabetic foot infections it seems more logical to culture existing wounds, since they are more likely to be the direct source of bacterial pathogens. Tissue cultures of non-infected diabetic foot ulcers could identify MRSA carriers and direct antibiotic selection to high-risk patients in the outpatient and inpatient setting if they develop clinical infections. This could prevent an increase in drug resistance and reduce hospital costs. Also, we hope the data presented on this article helps clinicians in identifying those patients at risk of developing MRSA infection once the patient develops an ulcer.

Conflict of interest and funding

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