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ORIGINAL ARTICLE

Methicillin-resistant *Staphylococcus aureus* in diabetic and non-diabetic foot infections

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Abstract

To identify the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, reinfection and clinical outcomes. Four hundred forty-six patients that were admitted to the hospital with moderate or severe foot infections were retrospectively reviewed. Tissue and bone cultures were obtained from the index hospital admission. Conversion was defined as methicillin susceptible *Staphylococcus aureus* in the first culture and subsequently MRSA when there was a reinfection. The incidence of MRSA was 7.8% ($n = 35$), with no significant difference between soft tissue infections (7.7%) and osteomyelitis (8.0%). MRSA incidence was 9.4 times higher in non-diabetics (23.8% vs. 3.2%, $p = <0.01$). The incidence of reinfection was 40.8% ($n = 182$). Conversion to MRSA was seen in 2.2% ($n = 4$) total, occurring in 5.4%. Non-diabetics were 20.1 times more likely to have MRSA reinfection than people with diabetes (28.6% vs. 1.9%, $p < 0.001$). MRSA patients had a higher proportion of healed wounds (82.4% vs. 69.3%, $p = 0.02$). There were no differences in other clinical outcomes in MRSA vs. other infections in reinfection (28.6% vs. 24.3%, $p = 0.11$), amputation (48.6% vs. 52.0%, $p = 0.69$) or hospitalization (28.6% vs. 42.6%, $p = 0.11$). The incidence of MRSA for the first infection (7.8%), reinfection (6.0%) and conversion to MRSA (2.2%) was low. MRSA was 9.4 times more common in people without diabetes.

KEYWORDS

amputation, diabetes, infection, osteomyelitis, ulcer

Key Messages

- The rise of resistant bacterial pathogens continues to be a concern in patients with diabetic foot infections because poor outcomes have been previously associated.
- Our objective was to evaluate the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and reinfection with clinical outcomes. We reviewed 446 patients with 12-month follow-up.

- The incidence of MRSA was 7.8%, and the incidence of reinfection was 40.8%. MRSA incidence was higher in non-diabetics, and non-diabetics were more likely to have MRSA reinfection.

1 | INTRODUCTION

Diabetic neuropathic foot ulcers, infections and peripheral arterial disease are part of the triad of diabetes related complications that often lead to foot and leg amputations.¹ Foot ulcers and PAD can exist for prolonged periods without amputation. Infection is often the sentinel event in the disease process that drives surgery, hospitalization and amputation. Infection is the most common underlying disease processes that leads to foot and leg amputation.

The incidence of bacterial pathogens that are resistant to antibiotics is a growing concern in patients with diabetic foot infections because bacterial resistance has been associated with poor clinical outcomes in skin and soft tissue infections (STIs).^{2–4} The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) varies from country to country and even from hospital to hospital within the same region. Incidence has been reported as high as 61% and as low as 1%.^{5–10} To reduce the spread of bacterial resistant organisms' antibiotic stewardship is encouraged, patients' nares are often cultured at the time of admission,¹¹ and various levels of quarantine are implemented in clinics and hospitals.¹²

There are several common beliefs concerning MRSA that we planned to evaluate. Many physicians believe that patients that have a history of MRSA infection will have repeated MRSA if there is a reinfection, and patients that are exposed to repetitive and prolonged antibiotics are likely to develop resistant pathogens.^{13,14} Several studies suggest that diabetes is a risk factor for developing MRSA infection.¹⁵ However, we have not identified any reports that compare the incidence of MRSA or clinical outcomes in people with and without diabetes. Therefore, we proposed a retrospective cohort study to identify the incidence of MRSA infection, reinfection and clinical outcomes.

2 | METHODS

This is a retrospective cohort study of 446 people admitted to hospital with moderate and severe foot infections (Table 1). After obtaining approval for the study from the hospital's institutional review board, we reviewed electronic medical records including demographics data, medical history, social history, lab results, radiographs,

vascular lab studies clinical outcomes, and surgical and/or vascular interventions. Medical history included peripheral neuropathy, foot ulceration, peripheral vascular disease and amputation. We used the American Diabetes Association criteria to define the diagnosis of diabetes mellitus.¹⁶ We defined sensory neuropathy as abnormal vibration sensation with a 128 Hz tuning fork or if any site was not accurately identified with the 10-g Semmes-Weinstein monofilament. We used arterial Doppler studies to evaluate peripheral arterial disease and included ankle brachial indices for the posterior tibial and the dorsalis pedis arteries, systolic toe pressures and toe brachial indices for the involved foot.¹⁷

We used the International Working Group on the Diabetic Foot infection classification to define infection and infection severity.¹⁸ Systemic inflammatory response syndrome criteria was used to define severe infections.¹⁹ We used either positive bone culture or bone histopathology to confirm the diagnosis of osteomyelitis (OM). A negative MRI, single-photon emission computed tomography/computed tomography or bone biopsy were used to rule out bone infection, as false negatives are low.^{20–22} Reinfection was defined as a soft tissue or bone infection on the same foot during a 1-year evaluation period.

We used SPSS version 27 for statistical analysis. Dichotomous variables were presented as frequency (percentage), and continuous variables are reported as means $\pm$ standard deviation. Proportional comparisons were made using the Chi-squared (χ^2) test, and continuous variable comparisons were made using the Mann-Whitney *U*-test. The measure of association between outcomes and covariates was determined with odds ratios with their 95% confidence intervals and are presented as odds ratios (confidence interval). We used an alpha of 0.05 for all tests.

3 | RESULTS

We included 446 total patients, 345 with diabetes and 101 without diabetes. The incidence of MRSA was 7.8% ($n = 35$), with no significant difference between STI (7.7%) and OM (8.0%). During the index hospitalization, MRSA incidence was 9.4 times higher in non-diabetics (23.8% vs. 3.2%, $p = <0.01$). The incidence of reinfection was 40.8% ($n = 182$). Reinfection occurred significantly

TABLE 1 Risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) infection in patients with foot infections.

	+ MRSA <i>n</i> = 35	No MRSA <i>n</i> = 411	OR (CI 95%)	<i>p</i> -Value
Age	48.4 (14.7)	52.9 (11.9)	−9.6 to 0.6	0.08
Male	28 (80.0)	304 (74.0)	1.4 (0.6–3.3)	0.43
BMI (kg/m ²)	29.3 (6.7)	31.4 (9.2)	−5.3 to 0.9	0.18
Medical history				
Anaemia	21 (60.0)	296 (72.0)	0.6 (0.3–1.2)	0.13
No diabetes	24 (68.6)	77 (18.7)	9.5 (4.4–20.1)	0.001
Acute kidney injury	6 (17.1)	160 (39.5)	0.3 (0.1–0.8)	0.01
CKD I–IV	7 (20.0)	131 (32.3)	0.5 (0.2–1.2)	0.13
ESRD	1 (2.9)	38 (9.4)	0.3 (0.03–2.1)	0.19
PAD	11 (31.4)	273 (66.4)	0.2 (0.1–0.5)	0.001
Sensory neuropathy	20 (57.1)	347 (84.4)	0.3 (0.1–0.5)	0.001
History of ulceration	18 (51.4)	243 (59.1)	0.7 (0.4–1.5)	0.37
Retinopathy	3 (8.6)	95 (23.1)	0.3 (0.1–1.0)	0.05
History of amputation	8 (22.9)	132 (32.1)	0.6 (0.3–1.4)	0.26
Medications				
Steroids (oral or inhaled)	1 (2.9)	18 (4.4)	0.6 (0.1–4.9)	0.66
Calcium channel blockers	8 (22.9)	112 (27.7)	0.8 (0.4–1.8)	0.54
Beta-blockers	9 (25.7)	147 (36.3)	0.6 (0.3–1.4)	0.21
ACE inhibitors	7 (20.0)	163 (40.2)	0.4 (0.2–0.9)	0.02
Statins	9 (25.7)	179 (44.2)	0.4 (0.1–0.9)	0.03
Insulin	10 (28.6)	267 (65.9)	0.2 (0.1–0.5)	0.001
Anti-depressants	5 (14.3)	29 (7.2)	2.2 (0.8–6.1)	0.13
Admission characteristics				
SIRS criteria	15 (42.9)	143 (35.5)	1.3 (0.6–2.7)	0.38
Osteomyelitis diagnosis	18 (51.4)	208 (50.4)	1.0 (0.5–2.1)	0.92
Admission labs				
WBC	11.7 (4.2)	10.3 (4.2)	−0.03 to 2.9	0.05
CRP	6.7 (7.9)	6.9 (8.4)	−3.1 to 2.6	0.88
ESR	57.7 (41.8)	66.1 (37.1)	−21.3 to 4.5	0.20
Glycated haemoglobin	6.4 (2.2)	8.5 (2.7)	−2.9 to 1.2	0.001
eGFR	53.9 (14.1)	50.4 (17.5)	−2.5 to 9.4	0.26

Note: Mean and standard deviation (SD) and median (IQR) are presented for continuous variables. Categorical variables presented as *N* (%). Length of stay, duration of antibiotics and time to heal are expressed in days.

Abbreviations: CI, confidence intervals; OR, odds ratios; SIRS, systemic inflammatory response syndrome.

more in OM (49.1% vs. 32.3% in STI, $p = <0.01$) and people with diabetes (45.3% vs. 28.3%, $p < 0.001$). The incidence of MRSA reinfection was 6.0% with no difference between STI and OM (Table 2). People without diabetes were 20.1 times more likely to have MRSA isolated during reinfection than people with diabetes (28.6% vs. 1.9%, 4.9–82.2, $p < 0.001$). Conversion to MRSA was seen in 2.2% ($n = 4$) total, occurring in 5.4% of the reinfections in patients with OM. During the index hospitalization, patients with MRSA infection had longer median

antibiotic duration (42.0, 18.5–46.0 vs. 21.0, 14.0–46.0, $p = 0.03$).

During the 12-month follow-up, MRSA infection was not associated with higher reinfection (28.6% vs. 24.3%, $p = 0.11$), amputations (48.6% vs. 52.0%, $p = 0.69$), median time to wound healing (91.0, 45.8–220.0 vs. 102.0, 50.0–227.0, $p = 0.55$) and the median duration of hospitalization (12.0, 8.0 vs. 20.0 vs. 15.0, 8.0–29.0 $p = 0.22$). MRSA patients had a higher proportion of healed wounds (82.4% vs. 69.3%, $p = 0.02$) and a longer median

TABLE 2 Clinical outcomes in patients with and without methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

	+ MRSA (n = 35)	No MRSA (n = 411)	OR (CI 95%)	p-Value
Index hospital admission				
Length of stay (days)	9.0 (6.0–12.5)	8.0 (5.0–14.0)		0.97
Median (IQR)				
Antibiotic duration (days)	42.0 (18.5–46.0)	21.0 (14.0–46.0)		0.03
Median (IQR)				
12-Month follow-up period				
Healed	28 (82.4)	244 (69.3)	2.7 (1.2–6.4)	0.02
Time to heal (days)	91.0 (45.8–220.0)	102.0 (50.0–227.0)		0.55
Median (IQR)				
Reinfection	10 (28.6)	172 (42.6)	0.5 (0.3–1.2)	0.11
MRSA reinfection	7 (20.0)	4 (1.0)	25.4 (7.0–92.1)	0.001
Hospitalization—Same foot	10 (28.6)	172 (42.6)	0.5 (0.3–1.2)	0.11
Amputation—Total	17 (48.6)	211 (52.0)	0.8 (0.4–1.7)	0.69
Length of stay (days)	12.0 (8.0–20.0)	15.0 (8.0–29.0)		0.22
Median (IQR)				
Antibiotic duration (days)	49.0 (20.5–77.5)	28.0 (15.0–60.0)		0.03
Median (IQR)				
Death	0 (0.0)	13 (3.2)	0.4 (0.0–7.1)	0.54

Note: Mean and standard deviation (SD) and median (IQR) are presented for continuous variables. Categorical variables presented as N (%). Length of stay, duration of antibiotics and time to heal are expressed in days.

Abbreviations: CI, confidence intervals; OR, odds ratios.

1-Year Outcomes

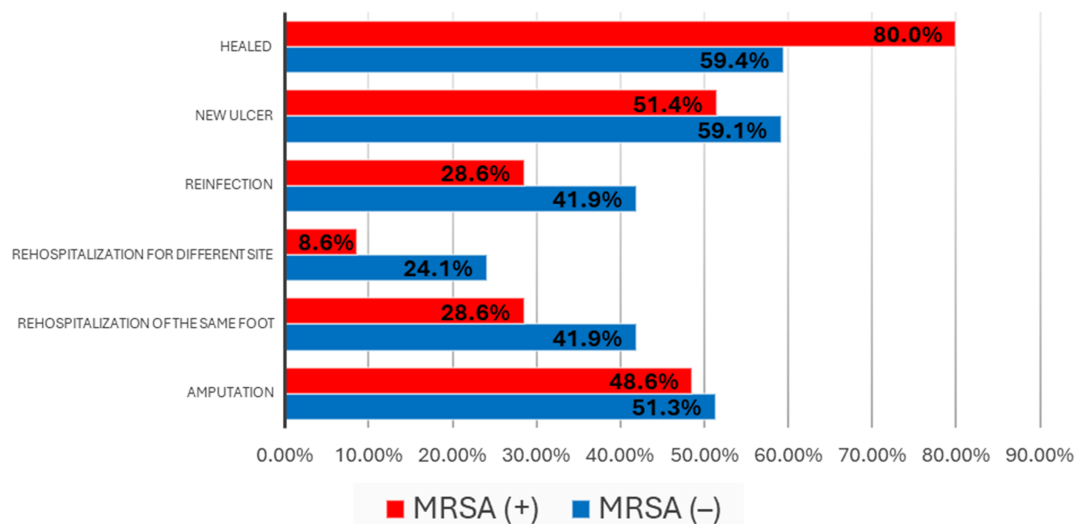
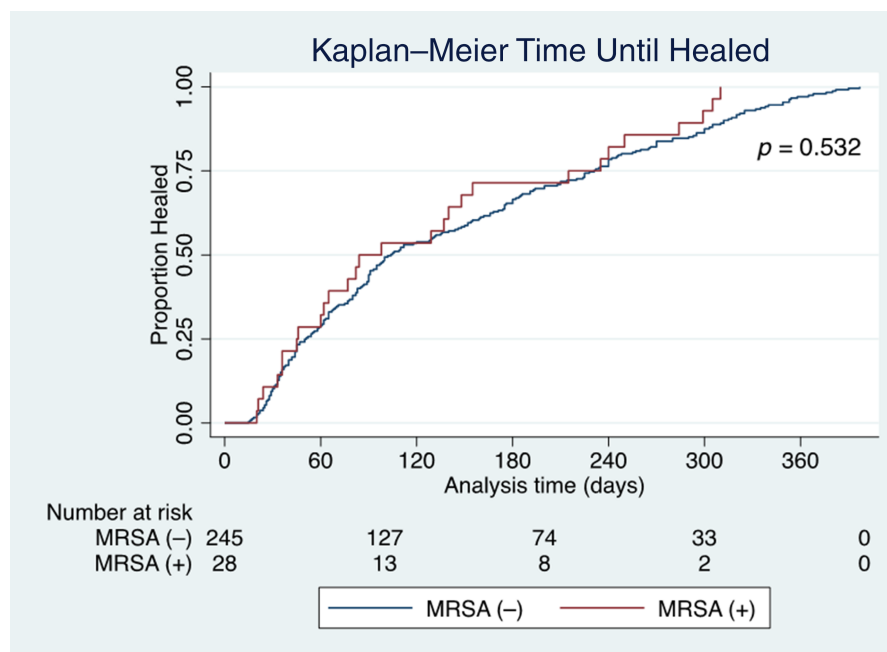


FIGURE 1 12-month outcomes comparison of patients with and without methicillin-resistant *Staphylococcus aureus* (MRSA) infection. This bar chart compares the 12-month clinical outcomes in patients with and without MRSA infection. MRSA infection did not have a detrimental effect on healing as patients with MRSA were 2.7× more likely to have healed (82.4% vs. 69.3%, $p = 0.02$). There were no other differences in clinical outcomes after hospital discharge.

duration of antibiotic treatment (49.0, 20.5–77.5 vs. 28.0, 15.0–60, $p = 0.02$) (Figure 1). The Kaplan–Meier survival analysis shows the time to healing in patients with and

without MRSA infections (Figure 2). The plot presents the proportion of patients that healed. There was no difference in the average time until healing for patients with

FIGURE 2 Kaplan–Meier survival plot comparing the time to heal in patients with and without methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Kaplan–Meier time until wound healing by MRSA. The plot presents the proportion of patients who had wound healing. The red line represents MRSA (+), and the blue line represents MRSA (–). The average time until healing for patients with MRSA (+) 129.9 ± 98.1 days and without MRSA (–) 143.1 ± 106.9 days, $p = 0.53$. No significant associations were observed between these two groups.



MRSA (129.9 ± 98.1 days) and without MRSA (143.1 ± 106.9 days, $p = 0.53$).

4 | DISCUSSION

This is the first study that has compared the incidence of MRSA in people with foot infections with and without diabetes. The results of this paper suggest that the incidence of MRSA in foot infections in our hospital was low; however, the incidence of MRSA was 9.4 times higher in non-diabetic foot infections compared to people with diabetes, and non-diabetics were 9.8 times more likely to be reinfected with MRSA compared with diabetics. Other authors have reported similar results. For instance, van Asten et al.¹³ reported the results of 143 people with diabetic foot OM and reported a higher rate of resistant pathogens when there was reinfection among people that had resistant pathogens for their index foot infection (52.6% vs. 25.8%, $p = 0.02$). Suludere evaluated 219 people with diabetic foot infections (DFI) with 28.3% experiencing reinfection in the following 12 months. Suludere reported that patients with reinfections were 2.2 times more likely to have MRSA compared with the index infection.²³ Lavery et al.⁵ also reported that people with a history of MRSA foot infection in the past 12 months increased the risk MRSA infection in subsequent infections.

There was no difference in most clinical outcomes in people with and without MRSA in our study. Most DFI studies report few differences in clinical outcomes.^{23,24} For instance, Alvaro-Afonso et al.²⁵ reported that patients

with MRSA took about twice as long to heal compared to people with methicillin-sensitive *Staphylococcus aureus*, and MRSA patients required more surgeries (41.7% vs. 33.3%, $p = 0.46$). Chen et al.²⁶ reported MRSA patients had longer hospitalizations, but there were no differences in surgical procedures or amputations. Suludere et al. reported that patients with DFI due to MRSA were twice as likely to have reinfection and required longer antibiotic treatment. However, there were no differences in wound closure, time to closure, amputation, reulceration and rehospitalization.²³ Lavery et al.⁵ found no difference in amputations or length of hospitalization in diabetic patients with and without MRSA. We have not been able to identify any studies that report outcomes of MRSA foot infections in people without diabetes.

There are several limitations and strengths of this study. This was a retrospective study, so the operational definitions used for co-morbidities may have been inconsistent across providers and across hospital services. However, all of the people with foot infections were treated by the podiatry service. Our clinical evaluation, operating room procedures, culture protocols and outcome evaluations were standardized.

5 | CONCLUSION

People without diabetes were more likely to have MRSA than people with diabetes. People that had MRSA for their index infection were significantly more likely to have MRSA when there was reinfection of the foot. Patients with MRSA were treated with antibiotics longer.

However, there were no differences in reinfection, amputations and length of hospitalization when people had MRSA.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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