

Diabetic Foot Infections: Local Prevalence of and Case–Control Study of Risk Factors for Methicillin-Resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*

Justin J. Kim,¹ Alison Lydecker,² Rohini Davé,³ Jacqueline T. Bork,^{4,5} and Mary-Claire Roghmann^{2,6}

¹Division of Infectious Diseases, University of Maryland Medical Center, Baltimore, Maryland, USA, ²Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, USA, ³Department of Pharmacy, VA Maryland Health Care System, Baltimore, Maryland, USA, ⁴Division of Infectious Diseases, University of Maryland School of Medicine, Baltimore, Maryland, USA, ⁵Department of Medicine, VA Maryland Health Care System, Baltimore, Maryland, USA, and ⁶Geriatrics Research Education and Clinical Center, VA Maryland Health Care System, Baltimore, Maryland, USA

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Diabetic foot infections (DFIs) are a feared complication of diabetic foot ulcers. DFIs range from superficial cellulitis to deep necrotizing infections, abscesses, and osteomyelitis. Appropriate antimicrobial therapy is a cornerstone of successful DFI treatment, in addition to wound care, surgical debridement, amputation, revascularization, and glycemic control. Antibiotic regimens are most influenced by the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* (PsA) on deep culture or—if culture-negative—by the clinician's index of suspicion for these pathogens based on local prevalence and patient risk factors. In this study, we characterize the microbiology of DFIs in our institution and examine potential risk factors for DFIs with MRSA and PsA.

METHODS

Study Design

We conducted a single-center, population-based case–control study to identify potential risk factors for DFI with MRSA or PsA. We also determined the local prevalence of MRSA, PsA, and other bacteria cultured from DFIs. Our protocol was approved by the Research and Development Committee of the VA Maryland Health Care System (VAMHCS) and the Institutional Review Board of the University of Maryland Baltimore.

Study Location and Population

The VAMHCS outpatient podiatry clinics serve about 6000 patients, 75% of whom are diabetic. We used the TheraDoc Clinical Surveillance System (Premier, Inc., Charlotte, NC, USA) to identify patients with foot cultures between January 1, 2017, and December 31, 2019. The culture source was confirmed by chart review using the Computerized Patient Record System. By definition, our study populations included only moderate and severe DFIs [1], the majority of which are cultured at this institution. We included unique positive and negative cultures from bone, soft tissue, or abscess drainage involving the feet, associated with at least 2 diagnosis codes of diabetes at primary care encounters within the year before a patient's first foot culture of the study period and excluding cultures unrelated to diabetes (eg, tumor excision, hardware removal). We determined pathogen prevalence using this complete study population (n = 158). For the case–control study, we used a selective study population (n = 149), excluding cultures from patients with foot cultures obtained within 3 months before the study period to account for persistent or recurrent infections (Supplementary Figure 1).

Data Collection

Using the complete study population (n = 158), we determined the local prevalence of MRSA, PsA, and other bacteria using first isolates per patient to minimize the influence of repeat isolates [2]. From the selective study population (n = 149), we conducted case–control studies for both MRSA and PsA, defining cases as the patients whose first diabetic foot culture from the study period grew MRSA or PsA; the remainder were controls. The date of the first diabetic foot culture was the reference for collecting the patient characteristics (Supplementary Table 1).

Correspondence: Justin J. Kim, MD, University of Maryland Medical Center, 725 West Lombard Street, Baltimore, MD 21201 (justin.kim@som.umaryland.edu).

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Data Analysis

We measured the association between having MRSA or PsA DFIs and the various patient characteristics using the Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables. All statistical tests were 2-tailed, and *P* values <.05 were considered statistically significant.

RESULTS

A list of pathogens with their relative prevalence rates is provided in Table 1; gram-positive and gram-negative antibiograms are provided in Supplementary Table 2. MRSA accounted for 6% of isolates, while PsA accounted for 23%. The case-control studies identifying risk factors for MRSA (*n* = 6) and PsA (*n* = 25) DFIs are summarized in Table 2. This largely male study population—two-thirds Black and one-third White—was

Table 1. Pathogens from Diabetic Foot Infections at the VAMHCS^a

Pathogens	No. ^b (%) ^c
Gram-positive cocci	
<i>Staphylococcus aureus</i>	40 (25)
MSSA	30 (19)
MRSA	10 (6)
<i>Staphylococcus lugdunensis</i>	17 (11)
CoNS ^d	58 (37)
<i>Streptococcus agalactiae</i>	21 (13)
VGS	22 (14)
<i>Enterococcus faecalis</i>	62 (39)
Gram-positive rods	
<i>Corynebacterium</i> species	36 (23)
<i>Dermabacter hominis</i>	9 (6)
Gram-negative rods	
<i>Escherichia coli</i>	20 (13)
<i>Klebsiella pneumoniae</i>	17 (11)
<i>Proteus mirabilis</i>	25 (16)
<i>Enterobacter cloacae</i>	22 (14)
<i>Morganella morganii</i>	14 (9)
<i>Pseudomonas aeruginosa</i>	37 (23)
Gram-positive anaerobes	
<i>Peptostreptococcus</i> species ^e	28 (18)
<i>Clostridium</i> species ^f	13 (8)
<i>Anaerococcus</i> species	9 (6)
Gram-negative anaerobes	
<i>Prevotella</i> species	20 (13)
<i>Bacteroides</i> species ^g	18 (11)

Abbreviations: CoNS, coagulase-negative *Staphylococcus*; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; VAMHCS, VA Maryland Health Care System; VGS, viridans group *Streptococcus*.

^aIsolates with prevalence ≥5%.

^bFirst isolates (eg, *S. aureus* was isolated from 40 patients).

^c*N* = 158, 15 patients with no growth.

^dNot *Staphylococcus lugdunensis*, including *Staphylococcus epidermidis* (*n* = 34), *Staphylococcus capitis*, *Staphylococcus cohnii*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus intermedius*, *Staphylococcus kloosii*, *Staphylococcus pasteurii*, *Staphylococcus pettenkoferi*, *Staphylococcus schleiferi*, *Staphylococcus simulans*, *Staphylococcus warneri*.

^e*Peptostreptococcus magnus* (*Fingoldia magna*; *n* = 20).

^f*Clostridium perfringens* (*n* = 1).

^g*Bacteroides fragilis* (*n* = 12).

elderly with poor glycemic control, reduced renal function, and minimal recent antibacterial or health care system exposures. Almost all had a diabetic foot ulcer, though fewer had a history of foot surgery, severe infection, gangrene, or clinical or histological evidence of osteomyelitis. A history of MRSA and the presence of gangrene were the only significant risk factors for MRSA and PsA, respectively.

DISCUSSION

In this survey of DFI cultures, MRSA was less prevalent than literature values (10%–20%) [3, 4], whereas PsA was more prevalent (5%–10%) [5–7]. In the case-control study, a history of MRSA was associated with MRSA DFIs, and the presence of gangrene was associated with PsA DFIs.

The lower prevalence of MRSA DFIs was surprising, as the institution-wide MRSA prevalence was higher (31%), and 24% of the study population had a history of MRSA. However, this population had low exposure to the health care setting and antibacterials: 17% were recently hospitalized, 10% were on hemodialysis, and 12% had recently received an antistaphylococcal antibiotic. Additionally, only 8% of those assessed for nasal colonization (*n* = 112) were MRSA positive within a year of their DFI. Our study design excluded mild infections (eg, superficial cellulitis), which are usually treated empirically and rarely cultured. This might have resulted in underestimation of the prevalence of MRSA DFI, though it seems less plausible for MRSA to cause disproportionately more mild than moderate to severe infections. We did exclude superficial swabs (*n* = 5), though none of these grew MRSA.

A history of MRSA was the only risk factor significantly associated with MRSA DFIs, though MRSA nasal colonization approached significance (*P* = .07); both risk factors have been reported previously [3, 5]. Notably, MRSA nasal colonization has been characterized as an insensitive but specific predictor of MRSA in DFIs [8, 9]. It is intuitive that the microbiological risk factors would have the strongest association with MRSA DFIs. The literature assessing other risk factors for MRSA DFIs is heterogeneous across disparate study populations. The Infectious Diseases Society of America (IDSA) recommends empiric MRSA coverage in patients with a history of MRSA infection or colonization, severe infection (IDSA infection severity >3), or if the local prevalence is high (ie, 30%–50% of *S. aureus* isolates) [1]. Other reported risk factors for MRSA DFI include chronic ulcers, recent prolonged antibiotics, prior hospitalization, osteomyelitis, and chronic kidney disease [3–5].

The higher prevalence of PsA DFIs—the highest among gram-negatives—was also surprising, as the institution-wide PsA prevalence was lower (11%). This increased prevalence is likely not attributable to weather, given the relatively temperate climate of the mid-Atlantic region. Recent exposure to antipseudomonal antibiotics was low (11%). The exposure of feet to water was not explicitly explored, though the frequency

Table 2. Case–Control Study for Diabetic Foot Infections From MRSA and PsA at the VAMHCS

Characteristics	Total ^a (n = 149)	MRSA			PsA		P
		Cases ^a (n = 6)	Controls ^a (n = 143)	P	Cases ^a (n = 25)	Controls ^a (n = 124)	
Age, y	65 (58–70)	72 (61–74)	65 (58–70)	.19	68 (61–70)	64 (58–70)	.28
Hemoglobin A1c, %	7.9 (7–9.3)	7.2 (6.8–7.7)	8.1 (7.0–9.4)	.38	7.7 (6.8–8.7)	8.1 (7.0–9.5)	.11
eGFR, mL/min/1.73 m ²	68 (41–91)	70 (35–90)	68 (47–92)	.93	62 (43–83)	69 (47–98)	.27
ESR, mm/h	74 (47–107)	100 (96–112)	68 (45–105)	.08	70 (53–118)	75 (45–105)	.38
CRP, mg/L	58 (20–123)	66 (53–90)	57 (20–104)	.98	64 (23–142)	55 (16–120)	.47
Male	143/149 (96)	5/6 (83)	138/143 (97)	.22	25/25 (100)	118/124 (95)	.59
Race				1.00			.58
White	53/149 (36)	2/6 (33)	51/143 (36)		7/25 (28)	46/124 (37)	
Black	95/149 (64)	4/6 (67)	91/143 (64)		18/25 (72)	77/124 (62)	
Other	1/149 (1)	0/6 (0)	1/143 (1)		0/25 (0)	1/124 (1)	
Severe infection	39/149 (26)	1/6 (17)	38/143 (27)	1.00	6/25 (24)	33/124 (27)	1.00
Current diabetic foot ulcer	140/149 (94)	6/6 (100)	143/143 (94)	1.00	24/25 (96)	116/124 (94)	1.00
Probe to bone	39/149 (26)	3/6 (50)	36/143 (25)	.18	7/25 (28)	32/124 (26)	.81
Osteomyelitis	56/84 (67)	3/3 (100)	53/81 (65)	.55	14/18 (78)	42/66 (64)	.40
Gangrene	42/149 (28)	2/6 (33)	40/143 (28)	.68	14/25 (56)	28/124 (23)	<.01
History of foot surgery	36/149 (24)	1/6 (17)	35/143 (24)	1.00	7/25 (28)	29/124 (23)	.62
BKA or AKA	5/149 (3)	0/1 (0)	23/35 (66)	1.00	1/7 (14)	4/29 (14)	1.00
Partial amputation	24/149 (16)	1/1 (100)	5/35 (14)		5/7 (71)	19/29 (66)	
I&D	7/149 (5)	0/1 (0)	7/35 (20)		1/7 (14)	6/29 (21)	
Dialysis	15/149 (10)	1/6 (17)	14/143 (10)	.48	4/25 (16)	11/124 (9)	.28
Recent hospitalization	25/149 (17)	2/6 (33)	23/143 (16)	.26	2/25 (8)	24/124 (19)	.25
History of MRSA ^b	36/149 (24)	4/6 (67)	32/143 (22)	.03	6/25 (24)	30/124 (24)	1.00
History of PsA ^c	21/149 (14)	2/6 (33)	19/143 (13)	.20	6/25 (24)	15/124 (12)	.12
MRSA nasal colonization	9/112 (8)	2/6 (33)	7/106 (7)	.07	2/20 (10)	7/92 (8)	.66
Recent antibiotics against MRSA	18/149 (12)	2/6 (33)	16/143 (11)	.15	2/25 (8)	17/124 (14)	.74
Recent antibiotics against PsA	17/149 (11)	2/6 (33)	15/143 (10)	.14	3/25 (12)	14/124 (11)	1.00
Infection during summer ^d	38/149 (26)	2/6 (33)	36/143 (25)	.65	3/25 (12)	35/124 (28)	.13

Abbreviations: AKA, above knee amputation; BKA, below knee amputation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; I&D, incision and drainage; MRSA, methicillin-resistant *Staphylococcus aureus*; PsA, *Pseudomonas aeruginosa*; VAMHCS, VA Maryland Health Care System.

^aMedian (interquartile range) for continuous variables, fraction (percentage) for categorical variables.

^bFrom skin and soft tissue (n = 21), nares (n = 9), blood (n = 2), urine (n = 2), and bone (n = 1), median 3.44 years ago (interquartile range, 0.54–7.64).

^cFrom skin and soft tissue (n = 15), bone (n = 3), respiratory (n = 2), urine (n = 2), median 1.63 years ago (interquartile range, 0.83–3.73).

^dDuring the months of June, July, or August.

of a current diabetic foot ulcer (94%) implies poor self-foot care and that feet were not being kept clean and dry; this may be a distinguishing feature of this study population.

The case–control study only identified gangrene as a risk factor for PsA DFI, as has been previously described [5]. PsA is classically associated with other gangrenous infections such as ecthyma gangrenosum, and it is intuitive that the presence of gangrene—a surrogate for the presence of PsA—would have the strongest association with PsA DFIs. There were no other significant risk factors including a history of PsA and infection during the summer. This is one of the few studies specifically examining risk factors for PsA DFI, and even fewer studies have assessed the veteran population. The IDSA recommends empirically covering PsA in cases of high local prevalence (undefined in the guidance), warm climate, and frequent exposure of the feet to water [1]. Other reported risk factors include a history of amputation, wound dressings, and chronic kidney disease [5, 10].

Our study has several strengths. We included a variety of specimen types and performed intensive chart review to capture accurate information and increase internal validity. Our facility was not a site for research that would have influenced the frequency of deep foot cultures over time [11]. Data were collected according to physiologic plausibility (eg, inflammatory markers were only recorded if collected before the culture date, as a bone culture itself can cause an acute rise in inflammatory markers). There are several weaknesses in this single-center retrospective study. The veteran population is not representative of the general population, though our study may be generalizable to other facilities caring for veterans. Our analysis was limited to the clinical data in medical records. While our risk factor analysis is probably generalizable to moderate and severe DFIs, which are usually cultured at our institution, this may not be generalizable to patients with recurrent or mild DFIs, as we did not include patients with foot cultures within 3 months before inclusion or DFIs that were

not cultured. Finally, the risk factors were difficult to interpret because of the small number of cases.

Our findings have important clinical implications. While it is well known that the local prevalence of pathogens is highly variable, our work demonstrates that the syndrome-specific prevalence of pathogens can be unpredictable and should be investigated by each institution. Here, the prevalence of PsA DFIs would probably be sufficient to warrant antipseudomonal coverage for a patient with DFI who is acutely ill. However, antipseudomonal coverage should also be considered for the empiric treatment of culture-negative moderate to severe DFI, and the presence of a gangrenous infection on presentation could further guide this decision. Our MRSA prevalence was relatively low, though the prevalence of coagulase-negative *Staphylococcus*, *Enterococcus*, and *Corynebacterium* would still warrant MRSA-active coverage, particularly because of the degree of methicillin resistance found in coagulase-negative *Staphylococcus*. Historical microbiology and pathogen-specific findings were the most significant risk factors for MRSA and PsA DFIs, though larger prospective studies are needed to increase our understanding of the relative contribution of other potential risk factors.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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