Open Forum Infectious Diseases

MAJOR ARTICLE

Prevalence and Predictors of *Pseudomonas aeruginosa* Among Hospitalized Patients With Diabetic Foot Infections

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Background. Diabetic foot infections (DFIs) are commonly associated with antibiotic overuse. Empiric DFI treatment often includes coverage for *Pseudomonas aeruginosa* (PsA), but the frequency of PsA DFIs is poorly understood. The study objectives were to quantify the prevalence of and determine predictors for PsA DFIs.

Methods. This multicenter, retrospective cohort included hospitalized patients with DFI from 2013 through 2020 who were age ≥18 years; diabetes mellitus diagnosis; and DFI based on *International Classification of Diseases, Tenth Revision* coding, antibiotic treatment, and DFI culture with organism growth. Osteomyelitis was excluded. Patient characteristics were described and compared; the primary outcome was presence of PsA on DFI culture. Predictors of PsA DFI were identified using multivariable logistic regression.

Results. Two hundred ninety-two patients were included. The median age was 61 (interquartile range [IQR], 53–69) years; the majority were men (201 [69%]) and White (163 [56%]). The most commonly isolated organisms were methicillin-susceptible *Staphylococcus aureus* (35%) and streptococci (32%); 147 (54%) cultures were polymicrobial. Two hundred fifty-seven (88%) patients received empiric antibiotics active against PsA, but only 27 (9%) patients had PsA DFI. Immunocompromised status (adjusted odds ratio [aOR], 4.6 [95% confidence interval {CI}, 1.3–16.7]) and previous outpatient DFI antibiotic treatment failure (aOR, 4.8 [95% CI, 1.9–11.9]) were associated with PsA DFI.

Conclusions. PsA DFI is uncommon, but most patients receive empiric antipseudomonal antibiotics. Empiric broad-spectrum antibiotics are warranted given the frequency of mixed infections, but patient-specific risk factors should be considered before adding antipseudomonal coverage.

Keywords. diabetic foot infection; *Pseudomonas aeruginosa*; antimicrobial stewardship.

Diabetic foot infections (DFIs) are an increasingly common complication from diabetes mellitus that present a significant clinical and economic burden to the healthcare system [1, 2]. Each year, >3 million adults experience a DFI [1], and the corresponding annual cost exceeds $13 billion dollars [2, 3]. DFIs are estimated to be the most common cause of diabetes-related hospital admissions, and infection-related readmission rates are reported to be as high as 40% [1, 4]. Within current literature, there are several obstacles in determining the appropriate management and long-term outcomes of patients experiencing DFIs. These include discrepancies in optimal DFI antibiotic regimens, treatment durations, intensity of wound care/source control, and impact of infectious diseases (ID) consultation.

A broad range of pathogens have been implicated in DFIs, and many infections are polymicrobial [5–7]. This creates a complexity in selection of appropriate antibiotic therapy decision making, and as a result, several antibiotics are recommended to mitigate DFIs [2, 5, 7]. To further complicate DFI treatment, multidrug-resistant organisms (MDROs) are of increasing concern in this population [1, 2, 7]. Some of these MDROs include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* species, and extended-spectrum β-lactamase–producing gram-negative bacilli [2, 7]. The true distribution of these organisms among patients with DFIs is not well characterized and has likely led to the ubiquitous overprescribing of broad-spectrum antibiotics. Many clinicians focus on antibiotic coverage targeting

Received 24 March 2022; editorial decision 10 June 2022; accepted 14 June 2022; published online 17 June 2022

Presented in part: 31st European Congress of Clinical Microbiology and Infectious Diseases, Virtual, 9–12 July 2021.

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https://doi.org/10.1093/ofid/ofac297

Pseudomonas aeruginosa (PsA) despite limited evidence to support this practice in the United States [2]. Antibiotics with activity against anaerobes and enteric gram-negative bacilli are recommended empiric therapies in select moderate to severe DFIs [5, 6], while the use of antipseudomonal agents is suggested only in patients with general MDRO risk factors [2, 5, 6]. To prevent the potential overuse of broad-spectrum antibiotics and antibiotic-related adverse effects, a better understanding of the pathogen distribution among patients with DFIs is needed. Additionally, there is a need to delineate the clinical and demographic characteristics of the small proportion of DFI patients actually at risk for PsA compared to those who can use alternative antibiotics that target the pathogens most likely encountered in DFIs. This could be advantageous because it may also expedite transition to oral antibiotics and potentially facilitate earlier discharge from the hospital.

The purpose of this study was to improve understanding of the management of patients with DFIs, with a focus on identifying patients who are suitable candidates for targeted empiric antibiotic therapy. The objectives of this study were to (1) characterize the pathogen distribution observed in patients with DFIs, (2) identify the clinical/demographic features of patients most likely to be infected with PsA, and (3) describe empiric DFI antibiotic therapy treatment practices. The study hypothesis was that PsA DFIs are uncommon, but most patients receive empiric antipseudomonal therapy.

Table 1. Diabetic Foot Infection Severity Classification System

Infection Severity	Criteria
Mild soft tissue infection	Infections limited to skin or superficial subcutaneous tissues, without local complication or systemic illness. Additionally, ≥2 manifestations of the following:
	• Local swelling or induration
	• Erythema (any extending ≤2 cm around the ulceration)
	• Local tenderness or pain
	• Local warmth
	• Purulent discharge
Moderate/severe soft tissue infection[a]	Either systemically stable or unstable patient with ≥1 of the following:
	• Erythema extending >2 cm from the ulceration, lymphangitis, spread beneath fascia, deep tissue abscess, or gangrene
	• Temperature >38°C (>100.4°F)
	• Heart rate >90 beats/min
	• Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg
	• WBC count >12 000 or <4000 cells/μL or ≥10% immature bands

Source: Modified Infectious Diseases Society of America and International Working Group on the Diabetic Foot Infection scoring system [5, 9, 10].

Abbreviations: $PaCO_2$, partial pressure of carbon dioxide; WBC, white blood cell.

[a]Can involve muscle, tendon, and joints. Excludes bone involvement.

METHODS

Study Population

This was a multicenter, retrospective cohort performed at five geographically distinct urban acute care centers located throughout the United States: University of Tennessee Medical Center (Knoxville, Tennessee), University of California, San Diego Health (San Diego, California), Loyola University Medical Center (Chicago, Illinois), Beth Israel Deaconess Medical Center (Boston, Massachusetts), and Bon Secours St Francis Hospital (Greenville, South Carolina). This study received institutional review board approval from all sites with waiver of consent.

The patient cohort consisted of hospitalized patients with DFI from January 2013 to December 2020. Patients were included if they (1) were aged ≥18 years; (2) were hospitalized for ≥24 hours; (3) had DFI as defined by *International Classification of Diseases, Ninth* and *Tenth Revision* (*ICD-9/ICD-10*) codes for diabetes mellitus and skin and soft tissue infection as described by Fincke et al [8] (*ICD-9*: 249, 250, 680–686, 707, 785; *ICD-10*: E11.621); (4) had documented signs/symptoms of infection as described in Table 1; (5) had available DFI cultures with speciated organisms; and (6) received treatment with an antibiotic. Patients with uninfected ulcers or DFIs with bone involvement were excluded. Individual subjects were included once, and if a subject was eligible over multiple admissions, the first admission meeting either group definition was identified as the index admission or infection.

Data Sources

Data were manually reviewed and extracted from the patients' electronic medical records. Patient demographics, comorbidities, prior antimicrobial and healthcare exposures, pertinent laboratory markers (ie, C-reactive protein), healthcare utilization, hospital and intensive care unit admission, severity of illness markers (ie, vasopressor use, Acute Physiology and Chronic Health Evaluation II [APACHE-II] score), length of stay, and patient disposition at discharge were collected. Characteristics of DFI included type (ie, abscess, ulcer), severity, and location. Characteristics associated with diabetes control were also collected, including glycosylated hemoglobin A1c (HbA1c) at time of DFI assessment, wound care utilization, and use of and type of outpatient antidiabetic medications. DFI management characteristics collected included surgical intervention, specialist consultation, antimicrobial therapy selection, and microbiology data including organism, culture type, and susceptibilities of isolated organisms per Clinical and Laboratory Standards Institute breakpoints where available [11]. Other specific isolates of interest included gram-negative organisms with laboratory-confirmed extended-spectrum β-lactamase–producing Enterobacterales or that were carbapenem-resistant. All data were collected with a standardized electronic case report form created through REDCap

(Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee) and hosted on secure internal servers at each participating site.

Key Definitions

The primary outcome of interest was the prevalence of PsA isolated from a microbiologic DFI culture. Identification of bacterial isolates were determined by conventional methods and performed by each institution's local microbiology laboratory standards of care. Secondary objectives were to describe DFI antibiotic prescribing patterns and to assess the proportion of patients who receive empiric anti-PsA therapy, as well as describe antibiotic-related adverse drug events while on therapy.

DFI cultures were categorized into quality and nonquality types. Quality DFI cultures included deep wound, surgical wound, abscess drainage, or tissue biopsy; nonquality cultures included superficial swabs or if the culture location or technique was not described. Patients with positive blood cultures were considered to be DFI related if they were documented to be associated with DFI from medical record notes. DFIs were classified as mild or moderate/severe severity in accordance to a modified Infectious Diseases Society of America and International Working Group on the Diabetic Foot Infection scoring system (Table 1) [5, 9, 10].

Immunocompromised status was defined as any of the following: history of solid organ transplant, AIDS diagnosis, splenectomy, bone marrow transplant, receipt of chemotherapy or transplant immunosuppressant in the prior 90 days, receipt of chronic steroids, or neutropenia at time of care. DFI treatment was categorized as empiric and definitive therapy: Empiric antibiotic therapy was defined as antibiotics given prior to organism identification from microbiologic cultures, and definitive therapy was defined as any antimicrobials given after DFI cultures were finalized and targeted toward the cultured organism. Antimicrobial spectrum was categorized to enteric gram-negative coverage, antipseudomonal coverage, anti-MRSA coverage, or combination therapy including any of the aforementioned groups as determined by 2 infectious diseases pharmacists (M. P. V. and N. P.). Antimicrobial-related adverse events while on therapy included *Clostridioides difficile* infection, defined as unexplained and new onset of >3 unformed stools in past 24 hours or ileus with a positive *C difficile* stool sample [12].

Statistical Analyses

This study was designed to identify the incidence of and risk factors for PsA DFI. Assuming a type I error frequency of 5% and power of 0.8, a minimum of 300 patients were needed to detect a 15% difference in frequency of outcome between any 2 levels of exposure variables.

In bivariate analyses, categorical variables were compared by the Pearson χ^2 or Fisher exact test; continuous variables were compared by the Mann-Whitney *U* test. Stratified analyses were performed to assess the presence/absence of effect modification. To determine the patients who have the greatest likelihood of PsA DFI, variables associated with the outcome ($P < .25$) in bivariate analyses were entered into a multivariable model using a backwards-stepwise approach. Variables were retained in the model as a potential confounder if their presence/absence changes the point estimate for antimicrobial therapy by >10%. Model fit was assessed using the Hosmer-Lemeshow test. All statistical analyses were performed using SPSS Software for Macintosh version 26.0 (IBM Corporation, Armonk, New York).

RESULTS

A total of 292 patients were included in this study: 27 (9%) patients with PsA DFI, and 265 (91%) with non-PsA DFI. Baseline patient demographics and clinical characteristics of the total population and between those with and without a PSA DFI are listed in Table 2. Of those who received outpatient antidiabetic medications at time of DFI admission, they most commonly included insulin (160 [56%]), metformin (108 [37%]), and sulfonylureas (40 [14%]). Inflammatory markers were generally elevated among the group, as median erythrocyte sedimentation rate and median C-reactive protein at time of DFI assessment were 67 (interquartile range [IQR], 33–100.5) mm/hour and 11.6 (IQR, 3.4–30.2) mg/L, respectively.

The median age-adjusted Charlson Comorbidity Index was higher in patients with PsA compared to non-PsA DFI groups (6 [IQR, 5–8] vs 5 [IQR, 4–7], $P = .04$). Among the 257 (88%) patients with HbA1c values, the overall median HbA1C value prior to hospitalization was 8.3% (IQR, 7.1%–10.0%). HbA1c was higher in patients with PsA DFI compared to non-PsA DFI groups (8.5 [IQR, 7.1–10.4] vs 7.3 [IQR, 6.5–8.0], $P = .004$). Patients with PsA DFI were also more likely to be smokers than those without PsA DFI (37% vs 19%, $P = .04$) and have an immunocompromised condition (67% vs 30%, $P < .001$). Other healthcare exposures, such as prior intravenous or oral antibiotic use within 90 days (56% vs 40%, $P = .11$), previous hospitalization within 180 days (41% vs 25%, $P = .08$), or PsA isolation within the past year from index DFI admission (4% vs 1%, $P = .25$), were not different between PsA and non-PsA DFI groups, respectively. Antipseudomonal agent use within the past 90 days was also not found to be different between PsA and non-PSA groups (15% vs 13%, $P = .77$). The median hospital length of stay was 8 (IQR, 5–13) days and was not different between PsA and non-PsA DFI groups (9 [IQR, 6–13] vs 8 [IQR, 5–13] days, $P = .46$).

Patients with PsA DFI more commonly had an "other" DFI location (37% vs 11%, $P < .001$) (Table 2), which was primarily an infection that extended into the ankle (12 [30%]). Patients with PsA DFI were also more likely to have failed outpatient

Table 2. Baseline and Infection Characteristics of Patients With Diabetic Foot Infections

Characteristic	Total Population (N = 292)	PsA DFI (n = 27)	Non-PsA DFI (n = 265)	*P* Value[a]
Demographics				
Sex, male	201 (69)	16 (63)	185 (69)	.25
Age, y, median (IQR)	61 (53–69)	64 (62–71)	60 (52–68)	.02
Race, White	163 (56)	9 (33)	154 (58)	.014
Active smoker	59 (20)	10 (37)	49 (19)	.022
Active insurance coverage	272 (93)	25 (93)	247 (93)	1.0
Home aid/assisted living	29 (10)	4 (15)	25 (10)	.32
Comorbidities				
Type 2 DM	282 (97)	25 (93)	257 (97)	.23
Peripheral artery disease	91 (32)	11 (41)	80 (30)	.26
Active outpatient DM medications	242 (83)	21 (78)	221 (84)	.42
Age-adjusted CCI, median (IQR)	5 (4–7)	6 (5–8)	5 (4–7)	.04
Hospitalization, prior 180 d	78 (27)	11 (41)	67 (25)	.084
Prior antibiotic use, 90 d	120 (41)	15 (56)	105 (40)	.11
Nursing home resident	9 (3)	2 (7)	7 (3)	.2
Immunocompromised condition[b]	19 (7)	4 (15)	15 (6)	.09
Failed outpatient DFI antibiotics, preceding 90 d	63 (22)	11 (41)	52 (20)	.01
Infection characteristics				
Moderate/severe DFI	157 (54)	12 (44)	145 (55)	.31
DFI location				
Toe	128 (44)	8 (30)	120 (45)	.12
Lateral/under foot	85 (29)	6 (22)	79 (30)	.41
Heel	48 (16)	5 (19)	43 (16)	.79
Other	40 (14)	10 (37)	30 (11)	.001
Not listed	25 (9)	1 (4)	24 (9)	.49
Type of DFI				
Ulcer	203 (70)	22 (82)	181 (68)	.16
Abscess	61 (21)	3 (11)	58 (22)	.19
Ulcer and abscess	28 (10)	2 (7)	26 (10)	1.0
ICU stay	17 (6)	0	17 (6)	.38
APACHE II score, median (IQR)	7 (5–12)	8 (5–11.5)	7 (5–12)	.92
Treatment characteristics				
Infectious diseases consultation	124 (43)	15 (56)	109 (41)	.15
Empiric antibiotic therapy, inpatient				
Anti-MRSA	280 (96)	26 (96)	254 (96)	1.0
Anti-PsA	257 (89)	24 (89)	233 (89)	1.0
Antianaerobic	224 (77)	23 (85)	201 (76)	.27
Days of total antibiotic therapy, median (IQR)	16 (12–22)	18 (13–29)	16 (12–22)	.51

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; DFI, diabetic foot infection; DM, diabetes mellitus; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; PsA, *Pseudomonas aeruginosa*.

[a]Comparisons reflective of PsA DFI to non-PsA DFI.

[b]Immunocompromised conditions include history of solid organ transplant, AIDS diagnosis, splenectomy, bone marrow transplant, receipt of chemotherapy or transplant immunosuppressant in the prior 90 days, receipt of chronic steroids, or neutropenia at time of care.

antibiotic treatment for a DFI within the prior 90 days (41% vs 22%, $P = .011$). Of these patients (63 [22%]), the most common antibiotics included cephalexin (11 [17%]), doxycycline (11 [17%]), ciprofloxacin (10 [16%]), and trimethoprim-sulfamethoxazole (8 [13%]); the majority (84%) did not receive antibiotic therapy with antipseudomonal coverage.

Five hundred sixty-eight organisms were isolated; 147 (54%) patients had polymicrobial cultures and the median number of organisms per patient was 2 (IQR, 1–2). The majority (70%) of patients had at least 1 quality DFI culture, which were most commonly surgical drainage (24%), deep wound culture (17%), abscess drainage (16%), and tissue biopsy (14%). Eighty-one (28%) patients had at least 1 nonquality DFI culture obtained (superficial swabs [18%] and unknown culture type [10%]). Fifty (17%) patients had a bloodstream infection secondary to DFI, and the median duration of bacteremia was 3 (IQR, 2–5) days. All patients cleared blood cultures, except 1 patient never had repeat blood cultures obtained. Of the 27 patients with a PsA DFI, 19 (70%) had a documented quality culture obtained, and 1 patient had a PsA bloodstream

infection due to a DFI. Of the 586 organisms cultured, gram-positives were predominant (61%), followed by gram-negatives (30%), and anaerobes or fungi (7%) (Table 3); 75 of 292 (26%) patients had mixed gram-positive and gram-negative DFI. The most commonly isolated organisms were methicillin-susceptible *S aureus* (102 [35%]), *Streptococcus* spp (93 [32%]), MRSA (58 [20%]), coagulase-negative *Staphylococcus* spp (40 [14%]), *Enterococcus faecalis* (32 [11%]), *Klebsiella* spp (30 [10%]), and PsA (27 [9%]). Only 11 (4%) patients were infected with an extended-spectrum β-lactamase–producing or carbapenem-resistant gram-negative organism.

Podiatry was consulted in 104 (36%) patients (30% PsA DFI vs 36% non-PsA DFI, $P = .50$); there were also no differences in the proportion of patients where infectious diseases (56% PsA DFI vs 41% non-PsA DFI, $P = .50$) or surgical (70% PsA DFI vs 55 non-PsA DFI, $P = .13$) consultants were involved in patient care. A similar proportion of PsA and non-PsA DFI patients had surgical interventions performed as a part of their treatment (59% vs 62%, $P = .77$). The most common surgical interventions included wound debridement (69 [24%]), amputation (55 [19%]), operating room incision & drainage (I&D) (43 [15%]), and bedside I&D (29 [10%]). The median time to surgical intervention was not different between PsA and non-PsA DFI groups (4.5 [IQR, 2.3–6.5] vs 3 [IQR, 2–5] days, $P = .18$). Sixty-one (34%) patients required an additional surgical procedure while hospitalized, which was not different between PsA DFI and non-PsA DFI groups (19% vs 36%, $P = .18$). Twenty-two (32%) patients underwent a below-the-knee amputation, which was also not different between PsA DFI and non-PsA DFI groups (14% vs 34%, $P = .41$).

Regarding antimicrobial therapy, most patients received empiric treatment with an anti-MRSA agent (280 [96%]), an anti-PsA agent (257 [88%]), and antianaerobic agent (224 [77%]). The proportion of antipseudomonal agents used was piperacillin-tazobactam (165 [57%]), antipseudomonal fluoroquinolones (42 [14%]), cefepime (39 [13%]), ceftazidime (31 [11%]), meropenem (14 [5%]), aztreonam (13 [5%]), and aminoglycosides (4 [1%]). Twenty-one of 292 (7%) patients received empiric enteric gram-negative therapy only; 14 (5%) patients did not receive any empiric gram-negative coverage. The total median duration of therapy was 16 (IQR, 12–22) days; this did not differ between PsA and non-PsA DFIs (18 [IQR, 13–29] days vs 16 [IQR, 12–22] days, $P = .51$). The total median duration of antipseudomonal therapy was 5 (IQR, 3–9) days. Three (1%) patients developed *C difficile*–associated diarrhea while on DFI antibiotic therapy; all of these patients had non-PsA DFIs.

Results of the bivariate analyses and clinical rationale dictated the variables selected for inclusion into the multivariate regression model: immunosuppressive status and failed outpatient DFI antibiotics within the prior 90 days (Table 4). Other variables were excluded from the model because of unmet clinical or statistical criteria, to preserve the *n*:k ratio or to prevent inclusion of variables that may covary. In the final parsimonious model, both immunosuppressive status and failed outpatient DFI antibiotics within the prior 90 days were independently associated with an increased odds of PsA DFI.

Table 3. Microbiology of 292 Patients With Diabetic Foot Infections

Organisms	Organisms per 292 Patients, No. (%)
Gram-positive organisms (n = 349)	
MSSA	102 (35)
Streptococcus spp	93 (32)
MRSA	58 (20)
Coagulase-negative staphylococci	40 (14)
Enterococcus faecalis	32 (11)
Enterococcus spp, vancomycin susceptible	5 (2)
Enterococcus spp, vancomycin resistant	4 (1)
Enterococcus faecium	2 (1)
Other gram-positive organisms	13 (4)
Gram-negative organisms (n = 186)	
Klebsiella spp	30 (10)
Pseudomonas aeruginosa	27 (9)
Proteus spp	27 (9)
Escherichia coli	26 (9)
Enterobacter spp	23 (8)
Morganella spp	13 (4)
Bacteroides spp	9 (3)
Citrobacter spp	8 (3)
Serratia spp	7 (2)
Providencia spp	7 (2)
Other gram-negative organisms	5 (2)
Acinetobacter baumannii	4 (1)
Other organisms (n = 33)	
Candida spp	8 (3)
Other anaerobes	25 (9)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

DISCUSSION

This study found that the prevalence of PsA from DFI without bone involvement to be 9%. This is paradoxical to the proportion (88%) of patients receiving empiric antipseudomonal coverage for a median duration of 5 (IQR, 3–9) days. The most commonly isolated bacteria were gram-positive, and 26% of the cohort had mixed gram-positive and gram-negative DFIs. Additionally, there were low proportions of patients infected with resistant-phenotype gram-negative organisms or anaerobes, although broad-spectrum gram-negative and anaerobic therapy was used frequently. Immunocompromised patients and those who recently failed outpatient DFI antibiotic therapy were populations identified to be at an increased risk of PsA DFI. Overall, these findings are consistent with other literature

Table 4. Variables Associated With *Pseudomonas aeruginosa* Diabetic Foot Infection

Characteristic	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Any immunosuppression[a]	2.9 (.89–9.5)	.09	4.6 (1.3–16.7)	.019
Failed outpatient DFI antibiotics, prior 90 d	2.8 (1.2–6.4)	.011	4.8 (1.9–11.9)	.001
Recent surgery, 30 d	4.7 (1.8–11.8)	.003	Not tested	
Active smoker or history of smoking	2.6 (1.1–6.0)	.022	Not tested	
History of MI	2.2 (.6–8.4)	.19	Not tested	
Recent hospitalization, 90 d	2.1 (.9–4.8)	.076	Not tested	
Congestive heart failure	1.9 (.76–4.8)	.17	Not tested	
DFI abscess	0.45 (.13–1.5)	.19	Not tested	
Outpatient insulin use	0.21 (.08–5.3)	<.001	Not tested	

Abbreviations: CI, confidence interval; DFI, diabetic foot infection; MI, myocardial infarction; OR, odds ratio.

[a]Immunosuppression: history of solid organ transplant, AIDS diagnosis, splenectomy, bone marrow transplant, receipt of chemotherapy or transplant immunosuppressant in the prior 90 days, receipt of chronic steroids, or neutropenia at time of care.

describing DFI microbiology and expand upon limited previous literature identifying patient-specific factors associated with PsA DFI. These data also suggest that real-world treatment of DFI is not congruent with guideline-driven recommendations to avoid empiric use of antipseudomonal agents in most scenarios, and represent an important implementation gap and target for antimicrobial stewardship programs [6, 7, 13].

The incidence of and predictors for PsA in DFI has been widely debated, but existing evidence remains limited and/or conflicting. Epidemiologically, PsA DFI have been more commonly isolated in locations with warmer or tropical climates; however, these populations may not be reflective of patients who reside in other locales [5]. The 2012 Infectious Diseases Society of America guideline for the diagnosis and treatment of DFIs, among other medical society guideline consensus, recommends against the empiric use of antipseudomonal agents in DFIs, except for patients with risk factors (strong recommendation, low-quality evidence), but few studies have examined PsA risk factors among patients with DFI in the context of local climate [5–7]. A study from the Detroit Medical Center assessed the prevalence of MDROs from DFI, and identified broad risk factors for MDRO and DFI pathogens resistant to guideline-recommended treatments [14]. *Staphylococcus aureus* was the commonly isolated (55%), and PsA was isolated in 131 of 963 (13.6%) organisms, both which reflect similar distribution to the current article. In a stratified analysis, the investigators found only that a history of PSA DFI was independently predictive of PSA DFI. Lebowitz and colleagues found a higher proportion of PsA DFI in subsequent or recurrent DFI cases, which is similar to the findings of the current study in that patients who failed outpatient DFI treatment had higher odds of PsA DFI compared to those who did not [15].

There have been several larger studies assessing DFI microbiology without pathogen-directed risk factor analyses. Macdonald and colleagues performed a meta-analysis of patients with diabetic foot ulcers that encompassed 112 studies from several different countries and included >16 000 patients [16]. Similar to the current study, *S aureus* was the predominant organism cultured (21%–26%), whereas PsA was isolated in 10%–11% based on culturing technique (ie, anaerobic or aerobic). These conclusions, although representative of predominantly countries with tropical locale, support against the routine use of empiric antipseudomonal therapy. Additional studies have identified the prevalence of PsA to be within 7.8%–16.4% [14, 15, 17]. Ultimately, limited studies have evaluated empiric antibiotic decision making in regards to spectrum of antibiotic activity for DFI treatment and in concordance with national guidelines [7, 13, 18–20].

Identification and application of patient-specific risk factors is a foundational concept for individualized therapies in infectious diseases and antimicrobial stewardship. This study determined that DFI patients, regardless of severity, are frequently prescribed empiric antipseudomonal therapy even though this is not a recommended practice for most patients. Additionally, >40% of patients with DFI had recent antibiotic exposures. Many of these patients will also likely require antibiotics in the future for retreatment or new infections due to the pathophysiology of nonhealing wounds and ulcers [5]. Repeated exposures to a given antibiotic class significantly increases the risk of subsequent resistance in PsA. This is problematic, as the available agents with activity against PsA are limited, particularly for oral therapies. In a case-control study, Gasink et al examined risk of fluoroquinolone resistance in PsA among 872 isolates; prior fluoroquinolone exposure (adjusted odds ratio, 3.4 [95% confidence interval, 2.4–5.0]) was the only risk factor independently associated with resistance [21]. In a multicenter cohort of >7000 patients with sepsis, each day of anti-PsA β-lactam conferred an additional 4% risk for development of new resistance to the anti-PsA [22]. While our objective was not to determine risk associated with

resistance, those with prior treatment failures and immunosuppression were more likely to have PsA DFI. Furthermore, the initial screening period of this study suggested that >50% of DFI patients either did not have microbiology cultures or cultures that had no organism growth; these data suggest that most DFI patients represent a population likely to receive unnecessary courses of anti-PsA therapy. Future directions of patient-centered DFI care could include selective use of emerging advanced diagnostics (ie, point-of-care polymerase chain reaction) to improve diagnostic yield in a subset of patients thought to be at risk for PsA [23]. These collective findings suggest that DFIs should be an educational and interventional target (ie, clinical pathways) for antimicrobial stewardship programs given their propensity for recurrence, resistance, and rehospitalization [18, 24].

For clinically stable patients with minimal risk of PsA and serious complications, targeted therapies against PsA should be deferred. Instead, our data suggest that the majority of DFI patients should receive empiric antibiotic coverage targeted toward *S aureus*, streptococci, enteric gram-negative organisms, and gram-negative anaerobes. In conjunction with local antibiogram data, clinicians should consider oral treatment in nonsevere cases with agents like trimethoprim-sulfamethoxazole (with or without metronidazole after debridement), tetracyclines, or amoxicillin-clavulanate in areas with low MRSA prevalence. Intravenous agents could include ampicillin-sulbactam or ceftriaxone (with or without metronidazole after debridement), or in combination with vancomycin when MRSA is frequent. These recommendations are in line with recent DFI guideline updates [6].

While our study provides useful information for the treatment of DFIs, there are several limitations that should be noted when interpreting the results. The retrospective design has inherent limitations, but is appropriate given the research question. The multicenter design and large number of patients included in our study provide for significant heterogeneity that is well representative of the general population. These findings do not represent DFI patients complicated by osteomyelitis, as this population likely represents more severe and chronic infections that may have worse outcomes. However, it is reasonable to conclude there is a low prevalence of PsA infections within this population due to the pathophysiology of DFIs with bone involvement and contiguous spread. Frequent exposure to the healthcare system is known to be associated with PsA infections and inclusion of these individuals could have upwardly biased the PsA prevalence point estimates [10]. Last, this study did not capture full antibiotic susceptibility data to assess treatment-pathogen mismatches but remains an important area for subsequent study, particularly for Enterobacterales.

The results of this study provide evidence to suggest that *P aeruginosa* is an infrequent cause of DFI. This reinforces existing guideline recommendations to avoid empiric anti-PsA agents in patients with DFIs. As DFI are often chronic recurrent infections, patients are at increased risk for antimicrobial-associated adverse effects. Antimicrobial stewardship programs should prioritize interventions tailored to improve antimicrobial use in DFIs, with a focus on avoiding antipseudomonal agent use when not warranted.

Notes

Patient consent. Given the retrospective nature of the study design, all participating study sites received institutional review board approval with waiver of patient consent.

Financial support. This work was supported by an investigator-initiated research grant from Paratek Pharmaceuticals, Inc.

Potential conflicts of interest. M. P. V. reports receipt of funding from Paratek Pharmaceuticals. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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