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Pseudomonal Diabetic Foot Infections: Vive la Différence?

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Abstract

Objective: To assess the outcomes of diabetic foot infections (DFIs) due to *Pseudomonas aeruginosa*.

Patients and Methods: From April 24, 2013 to July 31, 2016, we analyzed data from patients prospectively enrolled in our clinical pathway of DFIs, comparing those with infection due to *Pseudomonas* with those without infection due to *Pseudomonas*.

Results: Overall, we assessed 1018 cases of DFIs: 392 with osteomyelitis and 626 with only soft tissue infections. The prevalence of *P aeruginosa* in deep wound cultures was 10% (104/1018); of the 1018 cultures, 22 were monomicrobial, 82 were polymicrobial, and 46 were with osteomyelitis. Overall, the patients were treated with a median of 1 surgical debridement and a total of 20 days of antibiotic therapy. In a comparison of crude groups, the proportion of clinical failures was significantly higher with *Pseudomonas* than with other pathogens (36/104 [35%] vs 218/914 [24%], respectively; $P=.02$). A multivariate analysis showed that pseudomonal DFIs did not recur more often than nonpseudomonal DFIs (hazard ratio, 1.0; 95% confidence interval, 0.6-1.7). Among the 104 cases of pseudomonal DFIs, there was no association between failure of treatment and the total duration of antibiotic therapy, duration of intravenous therapy, duration of combined antibiotic therapy with more than 1 agent, or duration of oral (fluoroquinolone) therapy. Among 15 cases of pseudomonal recurrence, 2 (13%) developed resistance to the antibiotic agent used for the index episode.

Conclusion: For DFIs caused by *P aeruginosa*, other than choosing an antibiotic agent that is active against the organism, it does not appear necessary to treat with a different therapeutic regimen compared with the treatment of nonpseudomonal DFIs. There is no difference!

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Diabetic foot infections (DFIs) and diabetic foot osteomyelitis (DFO) are associated with substantial morbidity, the failure of treatment, and financial costs even when treated with prolonged antibiotic therapy, professional wound care, and appropriate surgical debridement.[1-3] There are multiple reasons for the poor outcomes, including limb ischemia, inadequate pressure offloading of the foot, poor glycemic control, and the lack of patient adherence.[1] In contrast, the specific causative pathogen of the infection is generally not a decisive factor for the outcome of therapy[3-8] unless it is resistant to multiple antibiotic agents.[9] For example, in almost all published reports, the clinical or microbiological outcomes are no worse for patients infected with health care-associated methicillin-resistant *Staphylococcus aureus*[10] or obligately anaerobic bacteria than for those infected with other pathogens.[11] Even in randomized, controlled trials of the treatment of DFIs, the role of the causative pathogen(s) in the failure of treatment is negligible compared with that of other parameters.[4-6]

Nevertheless, 1 pathogen seems to have an exceptional role in the clinical management decisions of many clinicians: *Pseudomonas aeruginosa*. On the basis of many published microbiological surveys, this organism is significantly less frequent as a pathogen in DFIs in temperate geographic areas than in DFIs in subtropical regions such as South-(Eastern) Asia[12-14] or the Middle East.[1,15,16] Moreover, *P aeruginosa* is naturally resistant to many standard antibiotics commonly used for mild and moderate DFIs,[17,18] such as aminopenicillins[7] or first- and second-generation

cephalosporins. This fact usually leaves quinolone agents as the only oral antibiotics available for the treatment of pseudomonal DFIs. In addition to its natural resistance, *P aeruginosa* is also well known for its propensity to develop antibiotic resistance,[14,16,19,20] especially during therapy.[21-24] This observation motivates many experts to recommend a regimen comprising an initial combination antibiotic in most (or even all) severe pseudomonal infections,[9,22] especially for those with a substantial risk of recurrence.

However, it is noteworthy that the guidelines for treating DFIs by neither the Infectious Diseases Society of America (IDSA)[17] nor the International Working Group on the Diabetic Foot (IWGDF)[18] provide specific guidance for antibiotic therapy for patients with pseudomonal DFIs. The IDSA guidelines state that empiric therapy directed at *P aeruginosa* is usually unnecessary, except for patients with risk factors for true infection with this organism. Infection due to these organisms requires specifically targeted antibiotic therapy, but empiric coverage in all cases is not prudent.[17] The newer IWGDF guidelines suggest that empiric treatment aimed at *P aeruginosa* is not usually necessary in temperate climates, but should be considered if *P aeruginosa* has been isolated from cultures of the affected site in the previous few weeks, or in tropical or subtropical climates.[18] Using a single-center database with more than 1000 cases of DFIs and to evaluate strategies for antibiotic stewardship in patients with DFIs and DFO,[2] we intended to answer some of these clinically important questions.

METHODS

At Geneva University Hospitals, we developed a clinical pathway for defining and managing DFIs on the basis of the IDSA guidelines,[17] which ran from April 24, 2013, to July 31, 2016.

Our microbiological samples were obtained from pus or intraoperative tissue specimens and were processed in our hospital's laboratory using standard (not molecular) culture methods and criteria.[3] We defined the clinical remission of DFIs as the resolution of all clinical, and any available laboratory and imaging, evidence of infection.

This clinical pathway aimed to streamline the management of all suspected and confirmed cases of DFIs among adult patients, including cases of DFO, who were hospitalized or were referred to the Services of Orthopedic Surgery, Infectious Diseases, or the Diabetic Foot Policlinic. During the aforementioned period, at least 1 of the authors of the current study saw (and possibly treated) corresponding patients within the frame of the clinical pathway. Additionally, 1 author (B.K.) noted all cases of DFIs in the associated EXCEL database and actively searched for patients regularly hospitalized in other wards for concomitant diabetic foot problems. Hence, the associated database collected all cases of DFIs but excluded cases of uninfected diabetic foot ulcers. Moreover, we regularly restituted key elements of the global management of DFIs—as medical, scientific presentations to other medical and surgical disciplines—and made all recommendations available on the hospital's intranet (in the French language).[1] Medical direction supported the pathway with a total of 50,000 Swiss Francs (at that time equaling $50,000) and dedicated work time for B.K. The database served as the basis for several publications by our research group.[3,7,25,26] Our clinical pathway was approved as a part of a hospital-wide quality program, for which patients were not required to provide consent. However, many of the patients participated in various randomized DFI trials (Ethical Committee 13-178),[4,5] for which they were required to sign approved consent forms.

Study Design and Statistical Analyses

This was a stratified, retrospective, case-control study and survival analysis on the basis of a prospective cohort (which was the clinical pathway). The following authors controlled and corrected the database before the analysis: K.G., D.L., B.K., E.v.D., and I.U. The primary aim was to attempt to define the role of pseudomonal (co)infection in the likelihood of the clinical remission of DFIs. The secondary outcomes concerned stratified analyses specifically targeting the antibiotic treatment modalities of pseudomonal DFIs: the effect of combination antibiotic therapy, role of oral quinolone therapy, and risk of the development of antibiotic resistance in

patients with the recurrence of DFIs due to *P aeruginosa*. We compared the groups using the Pearson χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. On the basis of our previous published experiences with our database,[3,7,25,26] we knew that the values in most strata analyzed were nonparametrically distributed. Hence, we did not perform parametric analysis methods. Regarding the success of our therapies for DFIs over time, we used a Cox regression analysis with cluster control (random effect at the patient level) to separately determine its associations with the outcome "failure." We ran the same Cox model twice: first for the entire study population and again for the subgroup of cases of pseudomonal DFIs separately. For both multivariate models, we individually introduced independent variables that attained a *P* value of $\leq$.05 in the univariate analysis into a multivariate analysis, except for surgical interventions and antibiotic treatment, which we automatically included in the final model. We checked for collinearity and effect modification with interaction terms and Mantel-Haenszel covariates. All the analyses were performed by I.U. and K.G. using the STATA software (version 15.0). We considered *P* values $\leq$.05 (two-tailed) as statistically significant.

RESULTS

Study Population

We assessed 1018 cases of DFIs occurring in 482 individual patients (279 [27%] women) in our clinical pathway and followed up with them for a median of 3.3 years (interquartile range [IQR], 0.8-9.0 years). Among the cases of DFIs, we diagnosed DFO in 392 patients (39%; 82 in the calcaneum, 276 in the forefoot, and 34 in the midfoot), which we confirmed using bone histology in 275 (70%) of these cases. Overall, 335 cases (33%) were complicated by local necrosis, 246 (24%) by an abscess, and 322 (32%) by cellulitis. The most frequent pathogen was *S aureus* (n=389; 38%). The median glycosylated hemoglobin level was 7.3%, and the median C-reactive protein level was 81 mg/L. In the included cases, the median duration of diabetes mellitus at the time of enrollment was 15 years, and the type of diabetes was type 1 in 86 cases (8.4%) and type 2 in 932 cases (91.6%).

Therapies and General Outcomes

Overall, 824 (81%) cases of DFIs required surgical debridement in the operating theater, whereas 598 cases (59%) also required partial amputation (of necrotic or shattered bone). The median number of surgical interventions per case of DFI was 1 (range, 0-7). All the patients also underwent bedside wound debridement, which was performed by experienced nurses or podiatrists as required. At admission, all the patients began receiving systemic antibiotic therapy and were treated for a median duration of 20 days (IQR, 11-35 days), with a median duration of 5 days of the therapy via the intravenous route (IQR, 0-12 days). In 313 cases (31%), the patients underwent a revascularization procedure of the lower extremity. We provided all the patients with instructions about, and appropriate devices for, the pressure offloading of the site of DFIs. Overall, the treatment failed to resolve DFIs in 251 cases (25%) after a median delay of 7.5 months. However, in only 142 (57%) of these failures was a pathogen isolated that was congruent with the index pathogen(s). Hence, at least 43% of the clinical failures appeared to have been caused by a new microbiological episode of DFI.

P aeruginosa DFIs

P aeruginosa was isolated from tissue specimens or pus in 104 of the 1018 cases of DFIs, with a prevalence of 10%. Among these, 22 were monomicrobial, 82 were polymicrobial, 46 were cases of DFO, and 58 were cases of soft tissue DFIs. The *Pseudomonas*-specific antibiotic agents were piperacillin or tazobactam (n=25), piperacillin (n=2), imipenem (n=11), cefepime (n=10), ceftazidime (n=3), levofloxacin (n=17), ciprofloxacin (n=33), gentamicin (n=3), amikacin (n=1), and ceftobiprole (n=1). Overall, we treated 50 of the 104 cases (48%) with oral quinolones for a median duration of 18 days (IQR, 0-105 days). Further, we used combined antibiotic therapy for *P aeruginosa* in 64 cases, which was successive in 23 cases (with a few temporal overlaps over the course in <50%) or simultaneous (concomitant) in 41 cases (substantial temporal overlap). The median

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TABLE 1. Comparison of Selected Factors in Patients With Pseudomonal Infection vs Those With Non-pseudomonal Diabetic Foot Infections

Factor (n=1018)	Nonpseudomonal infection n=914	*P* value	Pseudomonal infection n=104
Female sex	248 (27%)	.56	31 (30%)
Median age (y)	69	.12	73
First episode of diabetic foot infection in life	436 (48%)	.16	42 (40%)
Empirical antibiotic therapy before admission	150 (16%)	.44	14 (13%)
Presence of an abscess	211 (23%)	.02[a]	35 (34%)
Osteomyelitis (any foot bone)	346 (38%)	.21	46 (44%)
Calcaneal involvement	58 (6%)	.01[a]	24 (23%)
Cellulitis	281 (31%)	.07	41 (39%)
Important concomitant necrosis	296 (32%)	.29	39 (38%)
Bacteremia associated with diabetic foot infection	70 (8%)	.48	10 (10%)
Median C-reactive protein level at admission	81 mg/L	.59	80 mg/L
Diabetes mellitus type I	74 (8%)	.23	12 (12%)
Median duration of diabetes mellitus	18 y	.02[a]	15 y
Median glycosylated hemoglobin level	7.4 mmol/L	.23	7.0 mmol/L
Symptomatic peripheral arterial disease	543 (59%)	.32	67 (64%)
Median ankle-brachial index	1.02	.47	0.97
Median number of surgical debridements	1	.61	1
(Partial) foot amputation	539 (59%)	.66	59 (57%)
Median duration of antibiotic treatment	20 d	.21	21 d
Median duration of parenteral therapy	5 d	.01[a]	8.5 d
Negative-pressure vacuum therapy	205 (8%)	.81	22 (13%)
Hyperbaric oxygen therapy	83 (9%)	.08	15 (14%)
Overall treatment failures (after end of therapy)	218 (24%)	.02[a]	36 (35%)
Microbiological recurrence (same pathogen as initially)	100 (11%)	.22	15 (14%)

[a]Significant *P* values ≤.05 (two-tailed).

duration of initial combined antibiotic therapy was 7 days (IQR, 0-42 days). Table 1 displays the group comparisons between the cases of DFIs and the involvement of *P aeruginosa* vs without the involvement of *P aeruginosa*.

Overall, the infections caused by *P aeruginosa* were not more severe than those caused by other pathogens, but these were associated with significantly higher rates of abscesses and calcaneal involvement (Table 1). The proportion of the overall clinical failure of treatment was higher in the pseudomonal group (36/104 [35%] vs 218/914 [24%]; *P*=.02), but the risk of pseudomonal recurrence was not (15/104 [14%] vs 100/914 [11%]; *P*=.22). Among the 15 cases of pseudomonal recurrence, 2 cases (13%) developed resistance to the antibiotic agents used for the index episode. In the multivariate results (Table 2, left side), only partial foot amputation was protective (hazard ratio [HR], 0.4; 95% confidence interval [CI], 0.3-0.5). Specifically, the number of debridements, the performance of angioplasty, the duration of the use of antibiotics, and infection with *P aeruginosa* (HR, 1.0; 95% CI, 0.6-1.7) were not associated with failure.

Combined Therapy and Oral Quinolones

We assessed the clinical response to treatment with specific antibiotic modalities for the subgroup of 104 cases of pseudomonal DFIs compared with the clinical response to treatment with those for 914 cases without pseudomonal infections. The results of the corresponding multivariate analyses found that the duration of combined antibiotic therapy (HR, 1.0; 95% CI, 0.9-1.1), total duration

TABLE 2. Multiple Logistic Regression Analysis Assessing Factors Potentially Related to Clinical Failure in Patients Treated for Diabetic Foot Infection (Cox Regression Analyses)[a,b]

Variable	Univariate overall n=1018	Multivariate overall n=1018	Univariate *Pseudomonas* n=104	Multivariate *Pseudomonas* n=104
Female sex	1.2, 0.9-1.6	1.2, 0.9-1.7	n.d.	n.d.
Age (y)	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 0.9-1.0	1.0, 0.9-1.0
Number of surgical debridements	0.7, 0.6-0.9[c]	0.9, 0.1-1.1	1.1, 0.7-1.8	1.3, 0.6-2.7
Partial foot amputation	0.4, 0.3-0.5[c]	0.4, 0.3-0.5[c]	0.5, 0.2-1.7	0.3, 0.1-2.1
Successful angioplasty	1.1, 0.8-1.4	1.2, 0.8-1.8	0.7, 0.2-2.4	0.5, 0.1-1.9
Total duration antibiotic therapy	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 0.9-1.1
Duration parenteral therapy	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 0.9-1.0	1.0, 0.9-1.1
Duration oral antibiotic therapy	1.0, 1.0-1.0	n.d.	1.0, 1.0-1.0	n.d.
Antibiotic therapy with >1 agent	n.d.	n.d.	1.5, 0.5-4.8	n.d.
Duration of combined therapy	n.d.	n.d.	1.0, 0.9-1.1	1.0, 0.9-1.1
Presence of osteomyelitis	0.8, 0.6-1.1	0.7, 0.5-1.1	1.1, 0.3-3.5	n.d.
Pseudomonas aeruginosa isolated from infected wound	0.9, 0.5-1.6	1.0, 0.6-1.7	n.d.	n.d.

[a]n.d., not done due to interaction, the absence of medical sense, or a reduced sample size.
[b]Results expressed as hazard ratios with 95% confidence intervals; entire study population is on the left; the cases of *Pseudomonas aeruginosa* are on the right.
[c]Significant results.

of antibiotic therapy (HR, 1.0; 95% CI, 0.9-1.1), and duration of parenteral antibiotic therapy (HR, 1.0; 95% CI, 0.9-1.1) were not associated with the failure of treatment (Table 2, right side).

DISCUSSION

In our clinical pathway for the management of moderate-to-severe DFIs, the prevalence of *P aeruginosa* in the deep tissue cultures was 10%. As expected, this prevalence of *P aeruginosa* is lower than the 20%-40% reported by centers in South Eastern Asia,[1,13,14] Turkey,[23] or Iran[27] but in line with rates reported by most European and North American centers and the 8% seen among all orthopedic infections in the Geneva region in 2017.[28] In this study, we identified only 2 variables associated with pseudomonal infection: the presence of soft tissue abscesses and calcaneal DFO involvement. This is compatible with our previously published observation that *P aeruginosa* is more frequently isolated from the DFO of macerated calcaneus than from the toe.[25] However, our findings are in contrast with those of Ertuğrul et al,[23] who found that in Turkey, the only risk factor for infections caused by *P aeruginosa* was previous amputation of the lower extremity or the use of antimicrobial wound dressing.

From a therapeutic point of view, infections caused by *P aeruginosa* behaved similarly to those caused by other pathogens. Indeed, treatment with a prolonged intravenous course of therapy,[17] an oral quinolone agent for almost 3 weeks, or an initial antibiotic combination[22] each failed to enhance the rate of clinical remission. Similarly, these approaches also appeared to have no effect on the development of antibiotic resistance in the few subsequent cases of DFIs again caused by *P aeruginosa*. Some authorities have proposed, on the basis of anecdotal evidence, the use of a combination of more than 1 antibiotic agent for the treatment of DFO suspected to be caused by multiresistant pathogens, including *P aeruginosa*. For example, Tascini et al[19] published a case report detailing the treatment of DFO due to multiresistant *P aeruginosa* for 6 weeks with colistin, imipenem, and rifampin and that the combination of colistin and rifampicin was synergistic. International guidelines, such as those of IDSA[17] or IWGDF,[18] only pronounce the epidemiologic probability of pseudomonal DFIs and related empirical

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treatment, especially in (sub)tropical areas. For example, the IWGDF guidelines suggest that routine empiric antibiotic coverage for *P aeruginosa* is unnecessary in temperate areas, such as Switzerland,[18] but might be considered if *P aeruginosa* has been isolated from cultures of the affected site in the previous few weeks, in macerated skin, or in tropical or subtropical climates (weak; less evidence). Furthermore, IDSA adds exposure to aquatic milieu as a risk factor for pseudomonal (co)infections.[17] From a therapeutic point of view, for identified *P aeruginosa* infections, both the guidelines do not recommend any particular regimens, durations, or administration modes for antibiotics, suggesting that monotherapy is feasible within the general recommended durations of antibiotics. Moreover, the IDSA guidelines suggest monotherapy with piperacillin or tazobactam as starting therapy for identified pseudomonal DFIs.[17] We agree with both the guidelines.

In addition to being retrospective, our study has several other limitations. First, we may have failed to document follow-up in patients who were treated elsewhere, especially those who were only transiently living in Geneva. We believe that it is likely to be, at most, a minor issue because our center has been the largest, and the only public, hospital in the region for decades. Second, we focused our study mainly on patients with moderate or severe DFIs requiring hospitalization and potentially involving surgery. Thus, our data might not reflect outcomes in those with mild DFI. Third, although the pressure offloading of the affected limb is a mainstay of the treatment of DFIs,[1] its efficiency greatly depends on the patient's compliance, which we could not monitor in our assessments. Fourth, we compared only clinical parameters because we lacked the number of cases of pseudomonal DFIs with acquired antibiotic resistance[20] or virulence proteins,[24] required for adjustment in our multivariate analysis.

CONCLUSION

Using data from our previously validated clinical pathway,[3,29,30] we found that the prevalence of DFIs due to *P aeruginosa* was only 10%, similar to that reported by other Western countries. On the basis of our findings, we do not think that DFIs due to *P aeruginosa* require special treatment modalities (other than choosing an agent targeted at this organism) different from those used for other organisms. There is no difference! This is important because it may impact clinical care and allow for substantial antimicrobial stewardship, which is critical in the time of increasing multidrug-resistant organisms.[2] We also suggest shorter courses of parenteral antibiotics, with early transition to oral agents, which might decrease the risk of venous line complications.[17]

POTENTIAL COMPETING INTERESTS

Dr Uçkay has received a research donation from Innocoll Limited for another project.

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Abbreviations and Acronyms: **CI,** confidence interval; **DFI,** diabetic foot infection; **DFO,** diabetic foot osteomyelitis; **HR,** hazard ratio; **IDSA,** Infectious Diseases Society of America; **IQR,** interquartile range; **IWGDF,** International Working Group on the Diabetic Foot

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