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MAJOR ARTICLE

Empirical Antibiotic Therapy in Diabetic Foot Ulcer Infection Increases Hospitalization

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Background. We evaluated the outcomes associated with initial antibiotic management strategies for infected diabetic foot ulcers (DFUs) diagnosed in an outpatient multidisciplinary center.

Methods. Consecutive outpatient individuals with infected DFUs, stratified according to Infectious Diseases Society of America infection severity, were followed for 1 year from the initial antibiotic administration to treat acute infection. The main outcomes were hospitalization rates for a diabetes-related foot complication within 30 days of diagnosis and requiring an amputation or death during follow-up. Outcomes were analyzed by regression analysis, accounting for demographics, clinical characteristics, and antibiotic therapy.

Results. Among 147 outpatients with infected DFUs, 116 were included. Infections were categorized as mild (68%), moderate (26%), and severe (6%). Empirical antibiotics (not culture-guided) were prescribed as initial treatment in 39 individuals, while 77 received culture-based antibiotics. There were no differences in demographic or clinical characteristics between the antibiotic administration groups, except for a higher body mass index and prevalence of chronic kidney disease in the empirical cohort. Forty-two infected DFU patients required hospitalization within 30 days of diagnosis for the same reason. The relative risk for hospitalizations was 1.87 greater in those with mild infections when treated with empirical antibiotics compared with culture-directed antibiotics. There were no differences in amputations and/or death at 1 year follow-up.

Conclusions. These data support obtaining tissue culture to guide antibiotic therapy, regardless of DFU infection severity, to decrease hospitalizations.

Keywords. antibiotic; diabetic foot; hospitalization; infection; ulcer.

Diabetic foot ulcer (DFU) infections are a common problem in clinical and hospital settings. Most DFU infections occur in the skin and soft tissue structures, although they can also manifest as osteomyelitis when osseous structures are involved. It is well established that the estimated lifetime risk of developing DFU for a person with diabetes is up to 35%, and >40% of DFU patients become infected during clinical care [1–4]. Individuals who develop a DFU infection have a 155-fold increased risk of amputation compared with those who do not [5], and in 85% of lower extremity amputation events, amputations are preceded by the presence of a DFU [6, 7].

Several national and international society guidelines have been developed to guide clinical care for people with DFU infections [6, 8]. These guidelines recommend evaluating for peripheral arterial disease, employing local wound care, wound debridement of all nonviable tissue, and incorporating offloading strategies to promote wound healing for DFU [6, 8, 9]. When DFU infections occur, they can be categorized based on local signs of inflammation and/or presence of systemic involvement [6] such as no, mild, moderate, and severe infection [6].

Regardless of disease severity, when treating DFU infections, it is currently recommended to obtain a deep tissue culture to guide antimicrobial therapy [6, 8, 9]. The use of a superficial wound swab for microbial evaluation of infection is discouraged by both the Infectious Diseases Society of America (IDSA) and International Wound Group Diabetic Foot (IWGDF) [6, 8, 10, 11]. When cultures are not obtained, empirical antibiotic selection should target the most likely pathogen(s), such as *Staphylococcus aureus* and *Streptococcus* spp. [6, 8, 12], and consider medical history and associated comorbidities. However, IDSA recommendations, based on low-quality evidence, note that culture-guided therapy may be unnecessary for mild DFU infection [6, 8]. How these recommendations have been implemented at the point of care and influenced usual care

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practices and hospitalization rates following DFU infection treatment in the outpatient setting has not been amply studied.

Thus, the objective of this study was to compare the effects of empirical vs culture-guided antibiotic therapy antibiotic regimens for DFU infections on 30-day hospitalization rates for diabetes-related foot complications. Secondary outcomes were rates of amputations and death at 1-year follow-up in this population and potential factors driving a selected intervention strategy.

METHODS

This was a retrospective cohort study performed from January to December 2019 in adult persons with diabetes diagnosed with acute-onset DFU infection in the outpatient (ie, clinical) setting at the University of Michigan Health System Diabetes/Podiatry clinics. Cases were identified with a cohort analysis tool, Data Direct, via International Classification of Diseases (ICD) 9/10 codes (Supplementary Appendix A). DFU infections were categorized according to IDSA DFI guidelines [6] by the treating physician at the time of care utilizing institutional standardized foot exam documentation. This study was approved by the University of Michigan Institutional Review Board.

Data on the antibiotic treatment strategy (empirical or culture-guided antibiotic therapy) were extracted with the same Data Direct analysis tool.

The empirical cohort was defined as individuals who received an antibiotic prescription at the time of initial treatment that was not based on microbiological culture results. The culture-guided cohort was defined as an individual who received an antibiotic after tissue culture data, including gram-stain, became known. In this cohort, the time between the visit and antibiotic prescription (in hours) was recorded. Both cohorts received standard of care according to best practices as outlined by the IWGDF [13].

Outcomes Definition

The primary outcome was 30-day hospitalization rates for a diabetes-related foot complication after initial diagnosis of incident DFU infection. Hospitalizations due to conditions not related to diabetes-related foot complications were excluded. Secondary outcomes were rates of lower extremity amputation and a binary assessment of death at 1 year from initial diagnosis. All patient data and outcomes were verified for each individual via manual curation by the first author.

Analysis

A data set was constructed to assess hospitalization rates within 30 days of DFU infection diagnosis for consecutive patients. Demographic information, laboratory values, select comorbid conditions including Charlson Comorbidity Index (CCI) [14–16], including chronic kidney disease [CKD], defined as decreased kidney function [estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) for ≥3 months, irrespective of the cause [17], and coronary artery disease (CAD), and outcomes were recorded from the medical records. Laboratory values included white blood cell count (WBC) obtained immediately following the outpatient encounter. Hemoglobin A1c (HbA1c) values within 3 months before the outpatient encounter were used. Toe brachial index (TBI) and absolute toe pressures (in mmHg) from the affected limb were reported, as they are more accurate than ankle brachial index testing in patients with diabetes and use of TBI avoids concerns pertaining to noncompressible arteries that are not uncommon in persons with diabetes [9, 18]. All DFU individuals who did not have infection were excluded.

Binary logistic regression analysis of the primary outcome of hospitalization was performed. Associations between clinical characteristics and outcomes were evaluated using the Student or Welch's t testing for continuous variables and χ^2 tests for categorical variables. All associations found to be statistically significant at the $P < .10$ level in the univariate analysis were collectively considered for multivariable analysis. For descriptive statistics, mean and standard deviation were reported. For relative risk (RR) calculations, 95% CI and number needed to treat (NNT) are reported. Data were analyzed using RStudio software [19]. All P values are 2-sided, and findings were considered statistically significant at $P < .05$.

RESULTS

During 2019, 147 consecutive DFU individuals were identified as having a new diagnosis of DFU infection. Among these, 31 were excluded due to lack of follow-up data at 30 days [10] and absence of clinical infection at the DFU site [19]. The rest of 116 individuals had a DFU infection according to IDSA guidelines; 39 of these were initially managed with empirical antibiotics, and 77 were managed with culture-guided therapy (Figure 1). The most common IDSA category of infection at initial presentation in the outpatient was mild infection in 68% of individuals, followed by IDSA-moderate and -severe infections in 26% and 6%, respectively. Severity of DFU infection did not vary significantly among cohorts.

The demographic and other characteristics of the included individuals are shown in Table 1, contrasting those in the empirical antibiotic management cohort with those in the culture-based antibiotic cohort. As seen, there were no differences in age, percent women, race, CCI, smoking status, affected foot, prior history of a lower extremity amputation, or prior osteomyelitis between groups (all $P > .05$). The empirical treatment cohort had a higher mean body mass index and a higher prevalence of CKD (both $P < .05$). In the culture-guided cohort, the mean time between diagnosis and antibiotic prescription was 54.4 ± 15.2 hours.

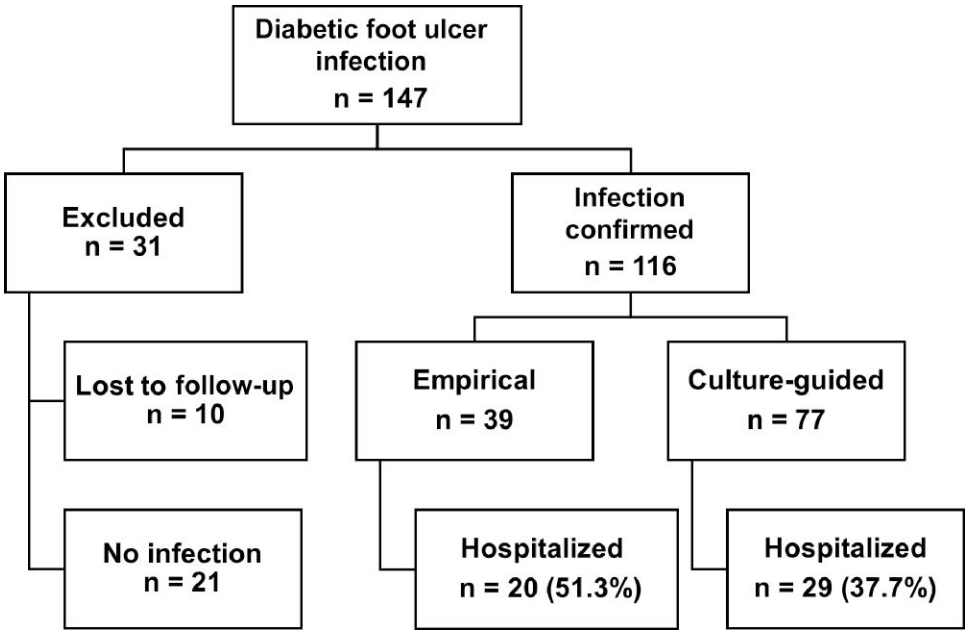

Figure 1. Study participant eligibility flow chart.

Table 1. Demographics and Other Characteristics

	Total (n = 116)	Empirical (n = 39)	Culture-Guided (n = 77)	*P* Value
Age, y	58 ± 11	59 ± 13	59 ± 11	.5
Male sex	89 (76.7)	30 (77)	59 (76)	1.0
Race				
White	105	35	70	1.0
Non-White	11	4	7	…
BMI, kg/m^2	33 ± 6	34 ± 6	32 ± 6	.02[a]
T1DM	5 (4.3)	2 (5.1)	3 (3.9)	1.0
Left foot	52 (44.8)	21 (53.8)	31 (40.3)	.1
Smoker	23 (19.8)	8 (21)	15 (19)	1.0
Current	3 (13)	2 (25)	1 (7)	…
Former	20 (87)	6 (80)	14 (93)	…
CCI (IQR)	5 (3)	5 (2)	5 (4.5)	.4
History of amputation	48 (41.4)	14 (35.9)	34 (44.1)	.4
CKD	33 (28.4)	16 (41.0)	17 (22.1)	.049[a]
CAD	44 (37.9)	19 (48.7)	25 (32.5)	.1
IDSA category				
Mild	79 (68.1)	25 (64.1)	54 (70.1)	.5
Moderate	30 (25.9)	12 (30.7)	18 (23.4)	.5
Severe	7 (6.0)	2 (5.1)	5 (6.5)	1.0
History of osteomyelitis	20 (17.2)	8 (20.5)	12 (15.5)	.6
Time to antibiosis, h	…	…	54.4 ± 13.2	…

Data are presented as No. (%) or mean ± SD, unless otherwise indicated.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; IDSA, Infectious Diseases Society of America; IQR, interquartile range; T1DM, type 1 diabetes mellitus.

[a] $P < .05$.

Similarly, pertinent laboratory values including HbA1c and WBC, as well as TBI, and toe pressures on the affected limb were equivalent between cohorts ($P > .05$) (Table 2).

No covariate was associated with the primary outcome of hospitalization at $P < .10$ in univariate analysis, and therefore multivariable regression was not performed.

Primary and Secondary Outcomes

The average rate of 30-day hospitalization was 42.2% (n = 49). Overall, there was no significant difference in the rates of hospitalization between the empirical and culture-guided treatment cohorts (51% vs 38%, respectively). The relative risk of hospitalization for culture-based management was 0.7 (95% CI, 0.6–1.1; $P = .18$).

Next, data were analyzed by infection severity grade, demonstrating differences in 30-day hospitalization rates. In those with mild DFU infection (68% of all individuals included), 13 of 25 DFU individuals treated with empiric antibiotics required hospitalization, compared with 15 of 54 DFU individuals treated with culture-guided antibiotics. Thus, the relative risk of hospitalization in the mild DFU infection group was 1.87 times higher in those patients who received empirical treatment (95% CI, 1.05–3.72; $P = .036$) than those in the culture-guided cohort. Those with mild DFU infection managed based on culture-guided antibiotics were less likely to require hospitalization at 30 days ($r = -0.5$; $P < .05$). The NNT for mild DFU infection using culture-guided therapy to prevent hospitalizations was ~4 (4.4). There was no difference in the rates of hospitalization for those with IDSA-moderate or -severe DFU infection between empiric and culture-based antibiotic therapy (both $P > .1$).

The average rate of lower extremity amputation in this entire cohort was 24.1% (n = 28). Partial foot amputations (ie, minor

Table 2. Laboratory and Noninvasive Vascular Study Characteristics

Lab Value	Total (n = 116), Mean ± SD	Empirical (n = 39), Mean ± SD	Culture-Guided (n = 77), Mean ± SD	*P* Value
HbA1c	8.7 ± 2.1	8.3 ± 1.7	8.9 ± 2.3	.2
WBC	10.4 ± 5.3	10.4 ± 4.0	10.5 ± 5.9	.9
TBI (affected foot), mmHg	0.84 ± 0.40	0.82 ± 0.35	0.84 ± 0.42	.4
Toe pressure (affected foot), mmHg	116.7 ± 55	116.0 ± 32.2	117.1 ± 63.7	.9

Abbreviations: HbA1c, hemoglobin A1c; TBI, toe pressure index; WBC, white blood cell.

Table 3. Primary and Secondary Outcomes

	Total (n = 116), No. (%)	Empirical (n = 39), No. (%)	Culture-Guided (n = 77), No. (%)	*P* Value
Primary outcome				
Hospitalization ≤30 d	49 (42.2)	20 (51.3)	29 (37.7)	.2
Hospitalized by IDSA severity				
Mild	28 (57.1)	**13 (52.0)**	15 (27.8)	.04[a]
Moderate	14 (28.6)	5 (41.6)	9 (50)	.7
Severe	7 (14.3)	2 (100)	5 (100)	1.0
Secondary outcomes in following year				
Amputation	28 (24.1)	9 (23.1)	19 (24.6)	.7
Minor (% of amputations)	20 (71.4)	7 (77.8)	13 (68.4)	NS
Major (% of amputations)	8 (28.5)	2 (22.2)	6 (31.6)	NS
Death	8 (6.9)	2 (5.1)	6 (7.8)	.7

Abbreviations: IDSA, Infectious Diseases Society of America; NS, not significant.

[a] $P < .05$.

amputations) accounted for 71.4% of all amputations performed. There was no difference in the rates or types of amputations performed for either cohort (Table 3). Eight individuals (6.9%) died in the 12 months following initial DFU infection outpatient diagnosis, 2 and 6 in the empirical and culture-guided cohorts, respectively.

DISCUSSION

These data indicate that in general there was adherence to clinical practice guidelines in usual care, as a majority of outpatient DFU infections managed at our multidisciplinary diabetic foot center were treated with culture-guided antibiotic therapy. However, we also found that despite these guidelines, empirical antibiotic therapy continued to be applied in approximately one-third of the cohort with DFU infections, particularly in those categorized as mild. Although the hospitalization rates were similar between the empirical cohort and the culture-guided cohort, in subgroup analysis categorized by infection severity at initial presentation, we found that culture-guided therapy is protective against hospitalization for those with mild DFU infection.

These findings have important clinical care implications because the majority of DFU infections initially diagnosed in the outpatient setting were mild and could be managed with debridement and close follow-up, in support of historical precedent [20–22]. Mild DFU infection is defined by the IDSA as an infection involving skin and subcutaneous tissue [6]. As wound debridement is part of the standard of care for DFU [6, 8, 9], it provides an ideal opportunity to collect (deep) tissue to direct antibiotic therapy. Thus, consistently implementing the practice of obtaining tissue culture to guide antibiotic therapy will have a high yield to prevent hospitalizations, as highlighted by a low (~4) NNT.

We did not find differences in the 30-day hospitalization rates in those with moderate or severe DFU infection, which is likely explained by more proactive hospitalization in individuals with more severe DFU infection, who were also more likely to present with hemodynamic instability and more comorbidities (particularly more chronic kidney disease and more obesity, which both affect immune status). Hence, there is a need for higher-acuity care in those with more severe DFU infections (Table 1). As expected, all patients in this study who presented to an outpatient clinic had relatively modest comorbidities, and median CCI scores were similar between management groups. We could not identify specific factors among demographics and/or clinical characteristics that could explain why empirical therapy was selected. In addition, patients had similar laboratory and noninvasive vascular results before the development of DFU infection.

The frequency of lower extremity amputations, either partial foot or major, occurring within 1 year of acutely diagnosed DFU infection treatment was 24.1%. It compared favorably with our previous reports for diabetic foot amputation rates at our institution [23–25]. We attribute this to the study design, which included an exclusively outpatient-managed cohort. Surprisingly, our death rate was higher than expected at ~7%, but this may be attributable to the coronavirus disease 2019 pandemic. Upon abstraction of data, none of the deaths were directly related to diabetic foot complications.

There is evidence to suggest that stratifying clinical management using IDSA risk categories by skin and soft tissue infection or osteomyelitis results in improved outcome assessment [26, 27]. Initial IDSA characteristics demonstrated no difference in infection severity among cohorts. There were also no differences in rates of hospitalizations among patients with moderate and/or severe DFU infection (Table 3). In fact, the majority of outpatient DFU infections were mild (~68%), and this DFU infection category excludes patients with suspected or confirmed osteomyelitis. Thus, further investigation is warranted to determine if hospitalization rates are disparate when deeper structures are involved in DFU infection managed in the outpatient setting [26, 27].

This study has several strengths. It is one of the few studies to address the impact of empirical antibiotic use in the management of infected DFUs in the outpatient setting. Additionally, individuals with infected DFUs were followed longitudinally to determine amputation rates. Finally, this study highlights the real-world practice patterns of teams managing the diabetic foot following international guidelines.

There are also some limitations. First, the study was performed at a single academic institution with a specialized multidisciplinary DFU management team and with established infrastructure that promotes implementation of the standards for DFU infection management at the point of care. We did not account for the decision-making involved in an admission other than to record the hospitalization event due to a diabetes-related foot complication. Second, this was a retrospective cohort study, which may induce some bias and an inability to identify causation. The risk of bias was mitigated by using an authoritative guideline for infection assessment [6] and using consecutive patients. Third, the reduced sample size, particularly in the more severe infections, limited some of the outcome analyses. Finally, microbiological data from the culture-guided cohort were reviewed to ensure that culture data were used to prescribe a relevant antibiotic. They were not used to evaluate pathogenicity of an organism present upon culture or admission.

In conclusion, these novel data identify culture-guided therapy as a strategy to prevent hospitalization for mild DFU infections presenting in the clinical setting, which are most often encountered in the outpatient setting. Although empirical antibiotic treatment is recommended for mild DFU infection by several guidelines, our data challenge these guidelines and older practices of not obtaining tissue culture in mild infection to guide therapy. Thus, it is recommended that DFU infection treatment involve culture-directed antibiotic therapy and that this practice be uniformly applied across all DFU infections to prevent hospitalization. Further research is needed to identify sensitive rapid diagnostic techniques that can be easily implemented to guide therapy at the point of care in a personalized manner to improve outcomes and reduce hospitalizations.

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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Patient consent. This study was approved by the University of Michigan Institutional Review Board (HUM00166943).

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Potential conflicts of interest. All authors: no reported conflicts of interest.

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