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MAJOR ARTICLE

Enterococci in Diabetic Foot Infections: Prevalence, Clinical Characteristics, and Outcomes

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Background. Diabetic foot infections (DFIs) are frequently polymicrobial, yet the relevance of each isolated pathogen, remains ill-defined. Specifically, the prevalence and pathogenicity of enterococcal DFIs and the impact of targeted antienterococcal treatment remain elusive.

Methods. We collected demographic, clinical, and outcome-related data on patients admitted with DFIs to the Hadassah Medical Center diabetic foot unit between 2014 and 2019. The primary outcome was a composite of in-hospital death or major amputation. Secondary outcomes included any amputation, major amputation, length of stay (LOS), and 1-year major amputation or mortality rate.

Results. Enterococci were isolated in 35% of 537 eligible DFI case patients, who were notable for a higher prevalence of peripheral vascular disease, increased levels of C-reactive protein, and higher Wagner scores. Infection in enterococci-positive individuals was mostly polymicrobial (96.8% vs 61.0% in non–enterococci-infected patients; $P < .001$). Enterococci-infected patients were more likely to undergo amputation (72.3% vs 50.1%; $P < .001$) and had longer hospital stays (median LOS, 22.5 vs 17 days; $P < .001$), but the primary end point of major amputation or in-hospital death did not differ between groups (25.5% vs 21.0%; $P = .26$). Appropriate antienterococcal antibiotics were used in 78.1% of enterococci-infected patients and, compared with results in untreated patients, were associated with a trend toward a lower rate of major amputations (20.4% vs 34.1%; $P = .06$) but longer hospitalization (median LOS, 24 vs 18 days; $P = .07$).

Conclusions. Enterococci are common in DFIs and associated with higher rates of amputation and longer hospitalization. A reduction in major amputation rates with appropriate enterococci treatment is suggested retrospectively, meriting validation by future prospective studies.

Keywords. amputation; diabetic foot infection; enterococci.

Diabetic foot infections (DFIs) constitute a common, difficult-to-treat complication of diabetes mellitus, associated with adverse outcomes, including hospitalization, amputation (in up to 20% of cases), and death [1]. DFIs typically begin with a soft-tissue ulcer that becomes infected and may progress to osteomyelitis, especially in patients with risk factors including peripheral vascular disease (PVD), uncontrolled hyperglycemia, peripheral neuropathy, arthropathic deformities, disabilities such as reduced vision, and maladaptive behavior [2]. Most DFIs are polymicrobial, with aerobic gram-positive cocci, especially staphylococci, constituting the most common causative organisms. Treatment includes multidisciplinary care encompassing proper wound dressing, pressure off-loading, optimization of glycemic control, antibiotics, revascularization, and surgical intervention (ranging from debridement to amputation) [3, 4].

Enterococci, common gastrointestinal commensals associated with a variety of infections, including urinary tract infection, bacteremia, and endocarditis [5], are variably reported in DFIs. Nonetheless, the true prevalence of enterococci in DFIs remains unclear, with some studies suggesting a rate as low as 8% [6, 7] while others report rates of up to 65% [8–11]. Furthermore, the clinical significance of enterococci isolated from a polymicrobial-infected diabetic foot ulcer (DFU) remains unclear. In the current study, we explored the role of enterococcal infection in patients who presented to our institution with a DFI, aiming to identify predictors of enterococci infection and its associated outcomes, while assessing whether appropriate antienterococcal treatment affects those outcomes.

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METHODS

Study Setting

This retrospective study was conducted in the diabetic foot unit of Hadassah Medical Center, a 1100-bed tertiary medical center in Israel. According to our in-hospital established protocols for medical and surgical treatment of DFU, deep wound cultures are obtained in all patients presenting with an infected DFU when feasible, excluding cases of dry necrosis or superficial infection. Wound cultures are obtained after disinfection with alcohol-based chlorhexidine gluconate preparation and include deep tissue, bone biopsy specimens, or true pus, while the use of swab samples is strongly discouraged. A substantial portion of cultures are attained during surgery after debridement of superficial tissues. The study was approved by the local Helsinki committee of Hadassah Medical Center (HMO-20-0958), and the requirement for informed consent was waived owing to the study's retrospective design.

Inclusion and Exclusion Criteria

All patients admitted to the diabetic foot unit between 1 January 2014 and 31 December 2019 with an acute DFI diagnosis were included in the study. Acute DFI was defined by a presence of ≥2 signs of inflammation (local erythema, tenderness, pain, or induration) or the presence of purulence, in accordance with International Working Group on the Diabetic Foot (IWGDF) and Infectious Diseases Society of America guidelines [3, 4, 10]. Patients hospitalized in the Diabetic Foot Unit without a positive wound culture or those with superficial swab specimen cultures (unless frank pus was obtained) were excluded, as well as patients with a positive blood culture and a possible alternative source for bacteremia.

Data Collection

Data were retrospectively retrieved from the hospital's electronic medical records, as well as from the national Ministry of Health database. For each admission, we recorded the patient's medical history (including the type of diabetes, PVD, chronic kidney disease, ischemic heart disease, and smoking), as well as documentation of hospitalization within the prior 6 months and antibiotics received in the 3 months before admission. Laboratory parameters on admission, including white blood cell count and blood glucose, creatinine, and C-reactive protein (CRP) levels were also collected. The SINBAD (Site, Ischemia, Neuropathy, Bacterial infection, Area, Depth) and Wagner ulcer classification scores were ascertained according to the wound description in the chart. Infection severity was based on the Infectious Diseases Society of America classification and determined by the description of local signs of infection, as well as by evidence of systemic infection [3].

Osteomyelitis was defined as a positive bone culture or evidence of osteomyelitis at imaging [3, 4]. Neuropathy was determined based on the physical examination findings documented by the medical team at admission or the presence of classic plantar neuropathic ulcers. Major amputation was defined as an amputation above the ankle. Mortality data were retrieved from regularly updated hospital and national registry records. Data regarding the occurrence of major amputations within a year after discharge were extracted from the Ministry of Health registry, which routinely collects data regarding inpatient procedures. We included only cultures obtained during the first 2 weeks of hospitalization, because in some cases surgical removal of osteomyelitis or extensive debridement occurred a week or more after the initial admission.

In patients with enterococcal DFI, we recorded the antibiotic regimen given, the route of administration and duration of treatment, including in-hospital treatment and recommended postdischarge treatment. Antibiotic treatment was defined as appropriate if it included an antienterococcal antibiotic with good bone penetration (penicillin, ampicillin, piperacillin, imipenem, meropenem, vancomycin, daptomycin, linezolid, chloramphenicol, or doxycycline) [12] while being adequate according to susceptibility results provided by the microbiology laboratory. Antibiotic regimens lasting <3 days were excluded. The duration of treatment was defined as appropriate if it lasted (1) ≥1 week for mild soft-tissue infection; (2) ≥4 weeks for osteomyelitis that was not completely surgically removed; (3) ≥2 days after complete surgical resection of osteomyelitis, with no suspected residual soft-tissue infection; or (4) ≥1 week when residual soft-tissue infection was suspected after surgical resection [3, 10]. In line with recently published studies, an oral route of antibiotic administration was considered appropriate [13, 14].

Outcomes

The primary outcome was the composite end point of major amputation or in-hospital mortality. Secondary outcomes included (1) in-hospital major amputation, (2) in-hospital death, (3) any amputation during hospitalization, (4) length of stay (LOS), (5) death during the first year after discharge, and (6) major amputation during the first year after discharge.

Statistical Methods

Outcomes were analyzed and compared between enterococci-infected patients (with a culture positive for enterococci, including the following *Enterococcus* species: *E. faecalis, E. faecium, E. avium, E. raffinosus, E. gallinarum,* and *E. casseliflavus*) and non–enterococci-infected patients and between enterococci-infected patients who were appropriately treated and those who were not. Continuous variables are presented as mean with standard deviation (SD), and categorical variables as number and percentage, with χ^2 and t tests used to compare categorical and continuous variables between these groups, respectively, and Mann-Whitney test used when continuous

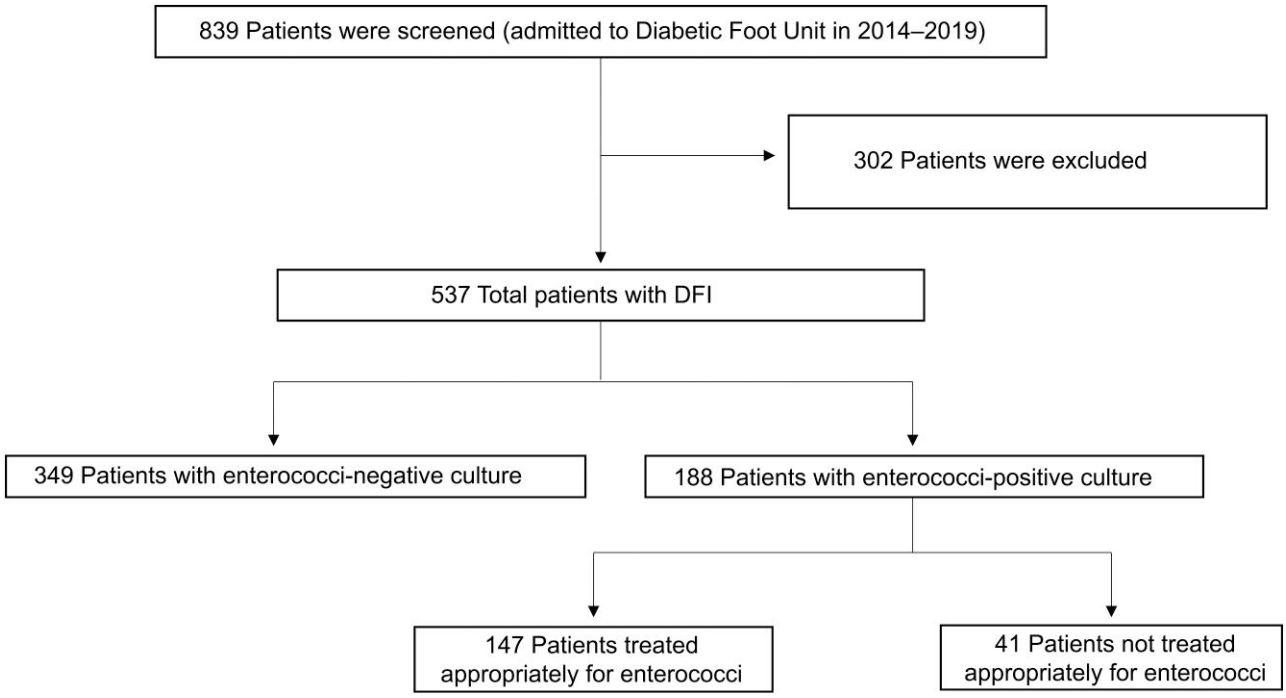

Figure 1. Patient enrollment and disposition (CONSORT [Consolidated Standards of Reporting Trials] diagram). The main exclusion criteria were a possible reason for hospitalization other than diabetic foot infection (DFI) and/or the lack of a positive deep tissue culture.

variables were markedly skewed from normal distribution. The associations between covariates and primary and secondary outcomes in multivariate analysis was assessed using logistic regression analysis. All variables without high multicollinearity and with P values <.05 in the unadjusted model were included in the adjusted model, and all unadjusted and adjusted odds ratios and 95% confidence intervals are presented. We used IBM SPSS statistics software, version 27, to generate the statistical analyses for this study.

RESULTS

During the study period, 839 patients with DFI were admitted to the diabetic foot unit in our medical center, of whom 537 were eligible for the study (Figure 1). Most cultures (84.4%) were obtained from deep soft tissue or bone, and 15.6% from frank pus. Enterococci were isolated in 188 cultures (35.0%), at a median of 3 and a mean (SD) of 4.22 (3.99) days after admission, compared with 1 and 2.34 (3.32) days, respectively, for cultures without enterococci ($P < .001$).

As empirical antibiotic treatment was initiated in 63.3% of patients (340 of 537) before culture was obtained, enterococci-infected patients were exposed to antibiotics before microbe isolation for a longer time than non–enterococci-infected patients (for a mean [SD] of 3.39 [3.578] and a median of 2 days vs 2.05 [3.27] and 1 day, respectively; $P = .009$). Similar empirical antibiotic regimens were used in both groups; thus, 78.7% (118 of 150) of the enterococci-infected and 72.1% (137 of 190) of the non–enterococci-infected patients were treated with ≥24 hours of an antibiotic regimen that did not cover enterococci, before diagnostic biopsy specimens were obtained ($P = .16$). Most of the enterococci isolated (88.8%) were *Enterococcus faecalis,* and 93% of all enterococci isolated were sensitive to ampicillin, with only 2.1% resistant to vancomycin (Supplementary Table 1).

Predictors of Infection With Enterococci

Baseline characteristics of enterococci-infected versus non–enterococci-infected patients are presented in Table 1. The former were more likely to have a diagnosis of PVD or osteomyelitis and higher CRP levels and Wagner scores on admission. Notably, previous hospitalization in the 6 months and antibiotic treatment in the 3 months before admission were not associated with a higher prevalence of enterococcal infection.

The patients' bacteriological profile is presented in Table 2. DFIs with enterococci were more likely to involve a polymicrobial infection and were positively associated with extended-spectrum β-lactamase (ESBL)–producing gram-negative organisms and anaerobes and negatively associated with methicillin-susceptible or methicillin-resistent *Staphylococcus aureus* and other streptococci.

Table 1. Characteristics of Patients With or Without Enterococcal Infection

Characteristic	All Patients (N = 537)	Patients With DFI, No. (%)[a] Enterococci-Positive Culture (n = 188)	Enterococci-Negative Culture (n = 349)	*P* Value
Male sex	408 (76.0)	143 (76.1)	265 (75.9)	.97
Age, mean (SD), y	62.3 (12.2)	63.0 (11.0)	61.8 (12.8)	.25
Type 2 diabetes	499 (92.9)	173 (92.0)	326 (93.4)	.55
Insulin treatment	365 (68.0)	132 (70.2)	233 (66.8)	.41
Current smoking	108 (20.1)	34 (18.1)	74 (21.2)	.39
IHD	241 (44.9)	89 (47.3)	152 (43.6)	.40
PVD	350 (65.2)	138 (73.4)	212 (60.7)	.003
Osteomyelitis	282 (52.5)	111 (59.0)	171 (49.0)	.03
Previous amputation	212 (39.5)	80 (42.6)	132 (37.8)	.28
Hospitalization in past 6 mo	329 (61.3)	123 (65.4)	206 (59.0)	.15
Renal function at admission[b]				
eGFR >60 mL/min/1.73 m²	217 (40.4)	67 (35.6)	150 (43.0)	.21
eGFR 30–60 mL/min/1.73 m²	156 (29.1)	56 (29.8)	100 (28.7)	
eGFR <30 mL/min/1.73 m²	62 (11.5)	28 (14.9)	34 (9.7)	
Dialysis	102 (19.0)	37 (19.7)	65 (18.6)	
Antibiotic therapy in past 3 mo	337 (62.8)	124 (66.0)	213 (61.0)	.26
Glucose, mean (SD), mmol/L	12.6 (6.6)	13.0 (7.1)	12.5 (6.3)	.41
WBC count, mean (SD), 10^3 cells/μL	13.5 (5.9)	13.9 (6.4)	13.3 (5.7)	.27
CRP, mg/dL	15.2 (10.8)	16.6 (11.6)	14.5 (10.2)	.03
Total SINBAD score, mean (SD)	4.6 (1.0)	4.7 (1.0)	4.6 (1.1)	.12
Wagner score				
1–2	45 (8.4)	11 (5.9)	34 (9.7)	.006
3	222 (41.3)	65 (34.6)	157 (45.0)	
4–5	270 (50.3)	112 (59.6)	162 (45.3)	

Abbreviations: CRP, C-reactive protein; DFI, diabetic foot infection; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; PVD, peripheral vascular disease; SD, standard deviation; SINBAD, site, ischemia, neuropathy, bacterial infection, area, depth; WBC, white blood cell.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Patient Outcomes by Enterococcal Infection

Overall (N = 537), the median LOS (interquartile range [IQR]) was 19 (11.0–31.0) days. During hospitalization, 311 patients (57.9%) underwent amputation, categorized as major amputation in 111 (20.7%) (above the knee in 28 [5.2%] and below the knee in 83 [15.4%]). The primary composite end point of major amputation and/or in-hospital death did not differ between enterococci-infected and non–enterococci-infected patients (25.5% vs 21.0%, respectively, $P = .26$) (Figure 2). The in-hospital major amputation rates were similar between the groups (44 of 188 enterococci-infected patients [23.4%] vs 67 of 349 [19.2%] without enterococci infection; $P = .25$). Likewise, the 1-year mortality rates were similar in enterococci-infected and non–enterococci-infected patients (42 of 188 [22.3%] and 69 of 349 [19.8%], respectively; $P = .48$). The 1-year major amputation rate was lower in enterococci-infected patients (0 of 188 [0%] vs 4 of 349 [1.1%] for non–enterococci-infected patients), but this difference but did not reach statistical significance ($P = .30$).

Enterococci-infected patients had longer hospital stays than non–enterococci-infected patients (median LOS [IQR], 22.5 [15–34] vs 17 [10–30.5] days, respectively; $P < .001$) and were more likely to undergo any amputation during hospitalization (136 of 188 [72.3%] vs 175 of 349 [50.1%], respectively; $P < .001$). This difference was predominantly driven by higher rates of minor amputations in the enterococci-infected group (92 of 188 [48.9%] vs 108 of 349 [30.9%]; $P < .001$). Moreover, enterococcal infection emerged as an independent predictor of any amputation in a multivariate analysis, as well as higher Wagner score, while PVD trended (Supplementary Table 2).

Appropriate Antienterococcal Antibiotic Treatment and Patient Outcomes

Appropriate antienterococcal antibiotic treatment was used in 147 of 188 enterococci-infected patients (78.1%) (Figure 3 and Supplementary Table 3). Most of the antibiotics were intravenously administered (71%), with piperacillin-tazobactam the most prevalent regimen (24%) and with an overall median treatment duration of 14 days. Oral treatment, mostly with amoxicillin, was used in 29% of cases, with an overall median treatment duration of 21 days. Collectively, the median durations of oral and intravenous treatment were 21 and 14 days, respectively, with a trend toward a shorter antibiotic regimen noted in patients undergoing major amputation. Importantly, we found no demographic, clinical, or bacteriological differences

Table 2. Concomitant Bacteria in Patients With or Without Enterococcal Infection

Bacteria	Patients With DFI, No. (%)[a]			*P* Value
	All Patients (N = 537)	Enterococci-Positive Culture (n = 188)	Enterococci-Negative Culture (n = 349)	
Polymicrobial	395 (73.6)	182 (96.8)	213 (61.0)	<.001
No. of bacterial isolates in culture, mean (SD)	2.2 (1.0)	2.8 (0.9)	1.9 (0.9)	<.001
MRSA	53 (9.9)	11 (5.9)	35 (12.0)	.02
MSSA	66 (12.3)	9 (4.8)	57 (16.3)	<.001
GN bacteria				
ESBL producing	145 (27)	61 (32.4)	84 (24.1)	.04
Non–ESBL producing[b]	229 (42.6)	89 (47.3)	140 (40.1)	.11
Pseudomonas	59 (11.0)	14 (7.4)	45 (12.9)	.054
Anaerobes	208 (38.7)	95 (50.5)	113 (32.4)	<.001
Streptococci	143 (26.6)	30 (16.0)	113 (32.4)	<.001
CoNS	48 (8.9)	12 (6.4)	36 (10.3)	.13

Abbreviations: CoNS, coagulase-negative staphylococci; DFI, diabetic foot infection; ESBL, extended-spectrum β-lactamase; GN, gram-negative; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SD, standard deviation.

[a]Data represent no. (%) of patients unless otherwise specified. Enterococci in positive cultures included *Enterococcus faecalis, Enterococcus faecium,* and *Enterococcus avium*).

[b]Non-*Pseudomonas,* non–ESBL-producing GN bacteria.

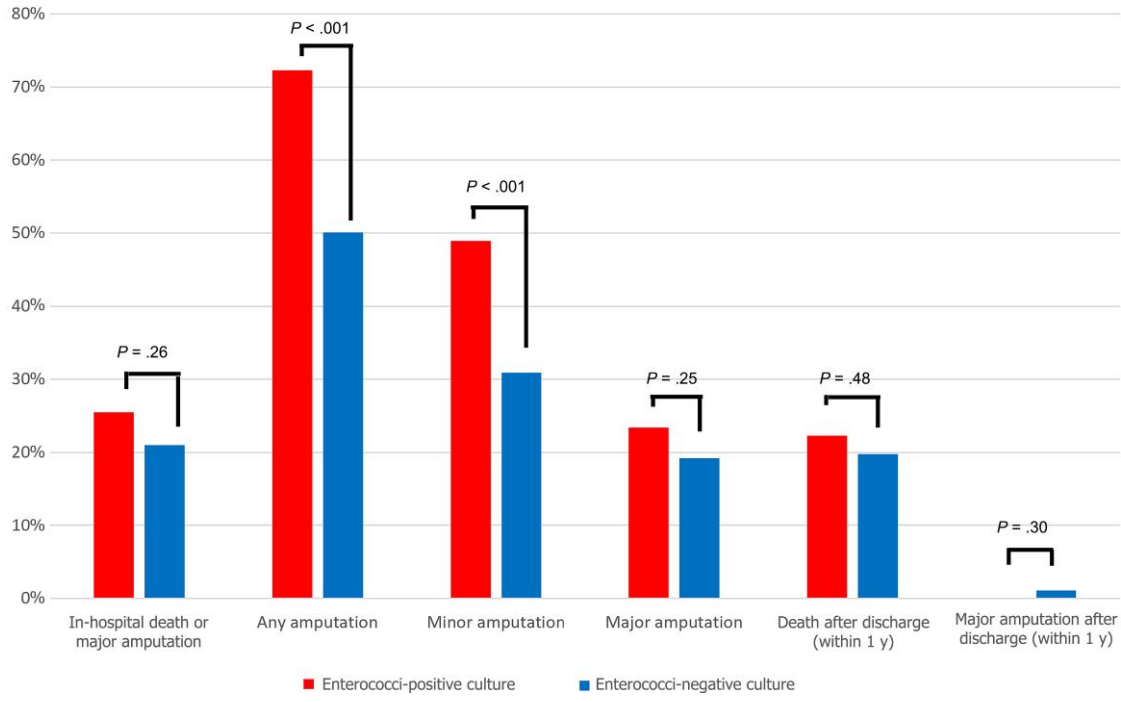

Figure 2. Outcomes in patients with diabetic foot infection, with or without enterococci-positive culture. Major amputation was defined as amputation above the ankle; minor amputation, as amputation below the ankle.

between treatment groups, except for a lower rate of MSSA co-infection in enterococci-infected cases that were appropriately treated than in those that were not (2.7% vs 12.1%, respectively; $P = .01$) (Supplementary Table 4).

In enterococci-infected patients, a trend was noted toward a lower rate of major amputations in those who were appropriately treated compared with those who were not (20.4% vs 34.1%, respectively; $P = .06$), coupled with a longer hospital stay in those who were appropriately treated (median LOS [IQR], 24 [16–32] vs 18 [12–38] days in non–appropriately treated patients; $P = .07$). The composite outcome of major amputation and/or in-hospital death did not differ

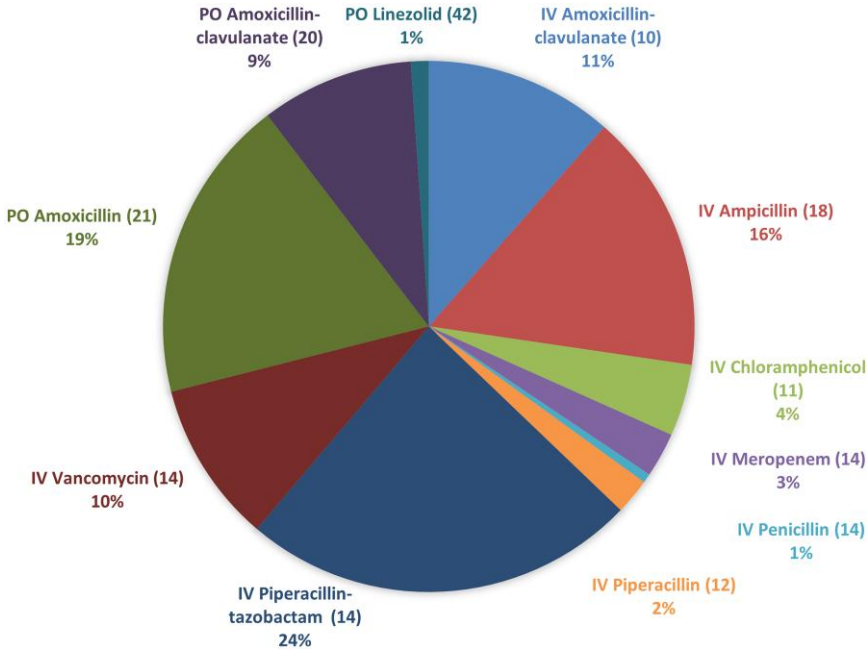

Figure 3. Antienterococcal antibiotic regimens; all antibiotics not identified as oral were administered intravenously. Median treatment durations are noted parenthetically, and percentages indicate the proportion of patients treated with each regimen.

between the groups (23.8% vs 34.1%; $P = .18$). Likewise, the rates of minor amputation (50.3% and 43.9%, respectively; $P = .47$) and the 1-year mortality rates (21.7% vs 24.3%; $P = .72$) were similar in enterococci-infected patients who were appropriately treated and those who were not.

DISCUSSION

In this retrospective study of hospitalized patients with DFI, enterococci were found to be an independent predictor of any amputation and were associated with a longer LOS, whereas appropriate antienterococcal treatment trended toward a lower rate of major amputations coupled with a longer LOS. The prevalence of enterococcal infection in our cohort was 35.0%. Similar rates (39.5%) were reported by Anvarinejad et al from Iran [15], which were much higher than those reported by Senneville et al from France [6] and van Asten et al from the United States [7] (each reporting enterococcal infections constituting 8% of DFIs), as well as Pontes et al in Brazil (with enterococcal infections constituting 17.9% of DFIs) [16]. Conversely, Shettigar from India [8] and Semedo-Lemsaddek from Portugal [9] each reported a 60% rate of enterococcal isolation in DFIs, constituting 65% and 83% of biofilm producers, respectively. This inter-study variability might be explained by patient characteristics, geographic variations in prevalence, and the different treatment protocols and antibiotic stewardship used in the different locations. Variations in culture acquisition, processing, and reporting techniques can also contribute to such variability, as reflected by the high rate of anaerobic bacteria in wound cultures noted in our study (38.7% overall).

The polymicrobial infection of patients with enterococcal DFI (96.8%), as well as the correlation between enterococcal DFIs and PVD, higher CRP, and worsened Wagner score, likely reflect the natural history of DFIs. Typically, streptococci and staphylococci are present early in the course of DFI, whereas enterococci and antibiotic-resistant organisms (such as ESBL) dominate at later stages, being selected by previous antibiotic treatment. Surprisingly, hospitalization in the 6 months and antibiotic treatment 3 months before admission were not associated with a higher prevalence of enterococcal infection. Of, note, cultures from enterococci-infected patients were obtained after longer exposure to empirical antibiotic treatment than those from non–enterococci-infected patients (mean [SD] exposures, 3.39 [3.58] vs 2.05 [3.27] days). However similar empirical antibiotic regimens that do not cover enterococci were used in both groups (72.1% [137 of 190] of the non–enterococci-infected and 78.87% [118 of 150] of the enterococci-infected patients; $P = .16$).

Enterococci-infected patients in our study had significantly higher rates of in-hospital amputation (72%) than non–enterococci-infected patients (50%). These results were consistent in a multivariate analysis and could signify that enterococci are not merely an "innocent bystander" colonizer but rather a clinically important pathogen in this setting. The higher rate of minor amputations noted in enterococci-infected patients is likely attributed to a limb salvage approach. Since it is

plausible (although hard to prove) that *Enterococcus* constitutes a real pathogen in this clinical context, appropriate and typically intravenous enterococci-targeting antibiotic therapy was used in the first 14 days in most cases (78.1%). A subsequent year outcome analysis did not identify any postdischarge major amputations in enterococci-infected patients, compared with 4 in non–enterococci-infected patients. These data may suggest that our combined limb salvage approach, consisting of a minor amputation followed by long-term intravenous treatment, is appropriate and does not result in a higher rate of long-term complications. This approach is supported by a previous study that endorsed specific antienterococcal treatment in DFIs in which the pathogen is cultured [11], but it should be further explored by comparing different treatment modalities in controlled studies.

Although our study does not provide unequivocal results supporting the need for specific antienterococcal treatment in polymicrobial infections, it is one of the first to evaluate both the prevalence and likely importance of an appropriate antimicrobial therapy with respect to clinical outcome. Current guidelines do not provide specific recommendations for enterococci-mediated DFIs, with regard to the administration route and duration of antibiotic treatment, the necessity for using bone-penetrating antibiotics, or the need for combination therapy, given high rates of reported biofilm production in this context [3, 4, 10]. While combination therapy is recommended in other enterococcal infections, such as endocarditis, its efficacy in enterococcal bone infections remains questionable [17, 18]. The multiple antibiotics administered via different routes for varying durations in our study preclude a clear conclusion as to the optimal treatment regimen, meriting further investigation in large prospective studies.

Our trial has several limitations stemming from its retrospective nature. First, ulcer severity scoring was based on patient file description of the DFI, a process subject to misclassification bias. Second, patients with extensive necrosis, who often underwent major amputation with no prior bone imaging or biopsy, were underdocumented for osteomyelitis. In addition, our data collection is based on the history documented in hospital records, without retrospective access to other hospital or community medical records, leading to some information gaps (eg, recent antibiotic treatment, including type of antibiotics used and treatment duration, and previous admissions). Our analysis indicated a longer empirical treatment period until diagnostic cultures were obtained in the enterococci-infected patients, which might bias our culture results. Finally, although our statistical analysis included multivariate analyses indicating that enterococcal DFI is independently associated with a higher rate of any amputation, given the complexity of factors involved in DFI we cannot exclude the possibility that this result is related to other factors that could be colinear factors in our analysis, such as PVD, a higher Wagner score, osteomyelitis, renal disease, and ESBL-producing gram-negative pathogens.

In conclusion, this large retrospective cohort demonstrates that enterococcal DFIs are likely more common than previously reported and are associated with PVD, osteomyelitis, higher CRP levels, and higher Wagner scores at admission. Enterococci were found to be an independent predictor of any amputation and were associated with longer LOS, whereas appropriate antienterococcal treatment also trended toward a greater LOS but with a lower rate of major amputations. Until more supportive evidence is made available, our data might suggest a beneficial effect of targeted antienterococcal therapy in decreasing major amputations. Prospective randomized studies of antienterococcal treatment are essential to determine the direct role of this pathogen in DFIs and the benefit of targeted treatment.

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.

Notes

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