

How Do Preoperative Antibiotics Affect Culture Yield in Diabetic Foot Infections?

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The impact of preoperative antibiotics on culture of diabetic foot infection samples has not been studied. We found that increasing exposure to preoperative antibiotics was associated with less frequent growth of streptococci and anaerobes and more culture-negative results. In contrast, the yield of *Staphylococcus aureus* and Gram-negative bacilli was unaffected.

Keywords. diabetes; diabetic foot infection; perioperative antibiotics; *Staphylococcus aureus*.

There are 22 million adults living with diabetes mellitus in the United States, 4 times more than 30 years ago [1]. Diabetes remains a leading cause of lower extremity amputation; approximately 4 per 1000 adults with diabetes undergo amputation in their lifetime with 85% of these amputations preceded by a diabetic foot infection (DFI) [2]. Optimal management of DFI is imperative to prevent amputation.

In accordance with the Infectious Diseases Society of America (IDSA) guidelines, antibiotics are typically initiated early in a hospital stay for patients with DFI, although debridement and acquisition of deep tissue samples may not occur immediately. The impact of preoperative antibiotics on DFI operative cultures is unknown. Previous authors have shown that a single perioperative antibiotic administered before operations for suspected prosthetic joint infection is not associated with a larger proportion of negative cultures [3, 4]. The effect of multiple days of antibiotics on operative cultures has been studied in revision hip arthroplasty [5], mixed orthopedic infections [6], pediatric osteomyelitis [7], and pyogenic vertebral osteomyelitis [8, 9]

with conflicting results. The effect of preoperative antibiotics on DFI cultures has not been studied.

Negative cultures may lead to inappropriate antibiotic choice; the prescribed regimen may be either excessively broad, predisposing patients to antibiotic-related side effects, or excessively narrow, leading to persistence of infection. The objective of this study was to evaluate the impact of preoperative antibiotics on tissue culture in patients with DFI.

PATIENTS AND METHODS

Study Setting and Population

This was a retrospective cohort study of inpatients with moderate or severe DFI treated at a safety net academic hospital between July 1, 2012 and June 1, 2016. Eligible patients were identified through query of a clinical database of patients referred to the musculoskeletal infectious diseases consultation service. The musculoskeletal infectious diseases consultation service has been the sole provider of infectious diseases consultations to the orthopedic and podiatric providers for over 8 years.

To be eligible for inclusion, patients must have had tissue or bone culture taken from a debridement procedure in the operating room. Patients who had bedside debridement procedures, those who did not have cultures sent from the operative procedure, and those who initiated treatment at another facility were excluded. To avoid sampling bias, the first eligible tissue or bone sample was included; subsequent tissue or bone samples were excluded from analyses. Similarly, only the first DFI episode was included for patients with multiple DFI episodes during the study period.

Data Collection

Demographic information, past medical history, DFI severity [10], culture results, and antibiotic exposure were abstracted from the electronic medical record. Antibiotic exposure, including perioperative antibiotics, was determined for the 7 days before surgery by calculating the time that elapsed between the first dose of antibiotics and the time that the specimen was received by the microbiology laboratory. Antibiotics were started and continued through the surgery in most cases. In rare cases, antibiotics were administered for a brief amount of time and then discontinued; for these cases, the hours of antibiotic were calculated by multiplying the number of doses by the dosing interval prescribed by the provider. For example, if vancomycin were prescribed for 2 days at 24-hour dosing interval and then discontinued for 3 days before surgery, then the hours of vancomycin exposure would be 2 × 24 hours or 48 hours. The total antibiotic exposure was determined by the summation of all hours of individual antibiotics that the patient received before surgery.

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Microbiology Methods

Microbiologic specimens were transported to the clinical microbiology laboratory in sterile containers. Specimens were processed per routine laboratory protocol and set up for both aerobic and anaerobic bacterial cultures. Aerobic media plates were incubated at 35°C and checked daily for growth for 5 days. Anaerobic media plates were incubated at 35°C in an anaerobic environment and checked daily for growth beginning on the second day for a total of 5 days. Isolates were identified using biochemical testing. An isolate was considered positive if there was any quantity of bacterial growth.

Statistical Analysis

Descriptive statistics were used to determine the frequency of comorbid conditions, the types of DFI treated, the types of bacteria isolated, and the hours of antibiotics administered to the patients. The primary outcome was the proportion of tissue cultures that were culture negative in the absence or presence of preoperative antibiotics. Because the number of hours of antibiotic administration is positively skewed, Wilcoxon's rank-sum test was used to determine whether there were differences in distributions of the number of days of antibiotic administration for bacteria presence/absence groups. The χ^2 test was used to determine whether at least 1 dose of antibiotics was associated with a smaller proportion of bacterial growth. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The Colorado Multiple Institutions Review Board approved this study.

RESULTS

There were 381 patients hospitalized for moderate or severe DFI during the study period. Of these, 143 were excluded for the following reasons: recurrent infection ($n = 103$), no operative culture taken ($n = 37$), and cultures taken at an outside hospital ($n = 3$). Of the included 238 patients, 78.2% were male ($n = 186$). The median age was 55.5 years (interquartile range [IQR], 49.3–62.2), and glycosylated hemoglobin level was 9.3% (IQR, 8.0–11.2). Tobacco abuse was reported by 27.7% ($n = 66$), and 15.5% ($n = 37$) were homeless. Most DFI were classified as moderate ($n = 170$, 71.4%).

Samples consisted of bone cultures ($n = 194$, 81.5%) and tissue or abscess contents ($n = 44$, 18.5%). Streptococci were most frequently isolated ($n = 125$, 52.5%), followed by anaerobic bacteria ($n = 111$, 46.6%), *Staphylococcus aureus* ($n = 108$, 45.4%), and *Enterobacteriaceae* species ($n = 45$, 18.9%). The most common preoperative antibiotics administered were vancomycin ($n = 175$, 73.5%; median 63.4 hours [IQR, 34.7–112.3]) and piperacillin-tazobactam ($n = 78$, 32.8%; median 35.0 hours [IQR, 12.0–64.5]) (Table 1). Although 21% ($n = 50$) of patients received no preoperative antibiotics, the median total antibiotic exposure for those who did receive antibiotics was 100.5 hours (IQR, 44.3–166.7).

Patients with culture-negative results received more total antibiotic exposure than patients whose cultures grew any bacteria (median 213.2 vs 80.1 hours, $P < 0.001$) (Figure 1). Patients

Table 1. Microbiology and Preoperative Antibiotic Characteristics of a Hospitalized Cohort With Moderate and Severe Diabetic Foot Infection

Microbiology Characteristics	n (%)
<i>Staphylococcus aureus</i>	108 (45.4)
Methicillin-susceptible <i>S aureus</i>	73 (30.7)
Methicillin-resistant <i>S aureus</i>	24 (10.1)
Coagulase-negative <i>Staphylococcus</i>	96 (40.3)
Streptococci	125 (52.5)
α -hemolytic <i>Streptococcus</i>	42 (17.6)
β -hemolytic <i>Streptococcus</i>	81 (34.0)
γ -hemolytic <i>Streptococcus</i>	28 (11.8)
<i>Enterococcus</i> species	31 (13.0)
Vancomycin-resistant <i>Enterococcus</i>	2 (1)
<i>Enterobacteriaceae</i>	45 (18.9)
<i>Proteus</i> species	17 (7.1)
<i>Escherichia coli</i>	13 (5.5)
<i>Klebsiella</i> species	9 (3.8)
<i>Enterobacter</i> species	6 (2.5)
<i>Morganella</i> species	4 (1.7)
<i>Serratia</i> species	3 (1.3)
<i>Citrobacter</i> species	3 (1.3)
Not speciated or other	15 (6.3)
<i>Pseudomonas aeruginosa</i>	8 (3.4)
Anaerobic bacteria	111 (46.6)
Culture negative	18 (7.6)
	n (%)
Preoperative antibiotic characteristics	median hours (IQR)
Vancomycin	175 (73.5) 63.4 (34.7–112.3)
Piperacillin-tazobactam	78 (32.8) 35.0 (12.0–64.5)
Cefepime	20 (8.4) 33.9 (12.0–56.4)
Clindamycin	17 (7.1) 16.0 (8.0–24.0)
Ampicillin-sulbactam	14 (5.9) 39.0 (12.0–95.8)
Levofloxacin	9 (3.8) 63.0 (24.5–75.3)
Cefazolin	9 (3.8) 40.0 (22.2–136.6)
Ceftriaxone	8 (3.4) 62.9 (36.0–128.6)
Metronidazole	5 (2.1) 67.3 (56.3–85.8)
Other antibiotic	9 (3.8) 47.4 (20.9–98.9)

Abbreviation: IQR, interquartile range.

whose tissue culture grew streptococci received a shorter total antibiotic exposure than those that did not grow streptococci (median 65.7 vs 108.1 hours, $P = .001$); similarly, patients whose tissue culture grew anaerobic bacteria received fewer hours of total antibiotic exposure than those that did not grow anaerobic bacteria (median 60.5 vs 120.5 hours, $P < .001$). The median total antibiotic exposure did not differ for those cultures that grew or did not grow *S aureus* (median 83.7 vs 82.9 hours, $P = .981$), *Enterococcus* species (89.1 vs 83.5 hours, $P = .878$), or *Enterobacteriaceae* (79.4 vs 86.9 hours, $P = .811$).

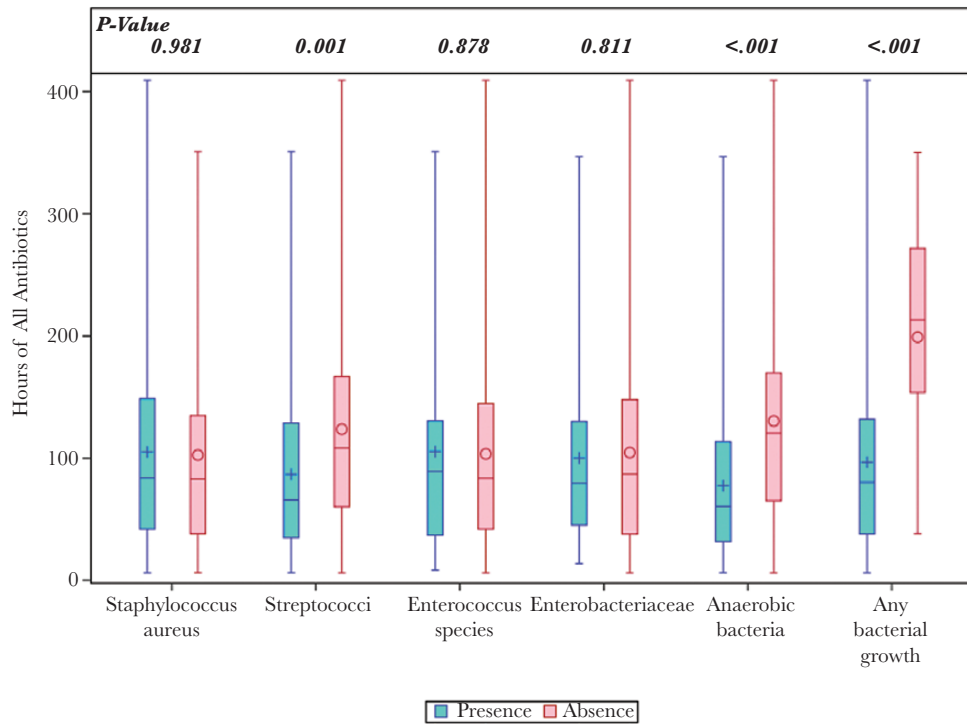


Figure 1. Box plot of the total hours of antibiotics versus the proportion of cultures that grew select bacteria in patients with moderate and severe diabetic foot infection. The box plot figure summarizes hourly distribution of all antibiotics among each bacteria group within bacteria presence and absence. The hourly mean (ie, symbol '+' or 'o'), median (horizontal line within the rectangular box), upper and lower quartiles (upper and lower ends of the rectangular boxes), and minimum and maximum values (bottom and highest tick mark at the ends of the lines) are displayed for each bacterial grouping. The plot overall provides a quick visual summary that easily shows center, spread, range, and any outliers for the hourly antibiotic distributions.

Patients who received at least 1 dose of antibiotic with spectrum active against methicillin-resistant *S aureus*, *Enterobacteriaceae*, or *Pseudomonas aeruginosa* did not exhibit less frequent growth of the respective pathogens.

In contrast, anaerobic bacteria trended toward less frequent growth when at least 1 dose of antibiotic with spectrum active against anaerobic bacteria was administered (Table 2).

Table 2. Frequency of Bacterial Growth When At Least One Dose of Antibiotic With Spectrum Active Against the Bacteria Was Administered

Organism	Active Antibiotic	Organism Growth in Presence of Active Antibiotic n (%)	Organism Growth in Absence of Active Antibiotic n (%)	PValue
MRSA	Vancomycin	16 (9.6)	8 (11.1)	.729
	Daptomycin			
	Linezolid			
<i>Enterobacteriaceae</i>	Ceftriaxone	21 (17.5)	24 (20.3)	.576
	Cefepime			
	Ampicillin-sulbactam			
	Piperacillin-tazobactam			
	Levofloxacin			
	Moxifloxacin			
	Gentamicin			
<i>Pseudomonas aeruginosa</i>	Cefepime	2 (2.1)	6 (4.4)	.356
	Piparicillin-tazobactam			
	Levofloxacin			
	Gentamicin			
Anaerobes	Ampicillin-sulbactam	37 (38.9)	74 (51.7)	.053
	Piperacillin-tazobactam			
	Metronidazole			
	Clindamycin			

Abbreviation: MRSA, methicillin-5resistant *Staphylococcus aureus*.

DISCUSSION

This study found that increasing duration of preoperative antibiotic exposure was associated with less frequent growth of streptococci and anaerobes and more frequent culture-negative results. Increasing preoperative antibiotic exposure did not appear to impact the growth of *S aureus*, *Enterococcus* species, and *Enterobacteriaceae*.

The impact of preoperative antibiotics on culture yield is debated in the literature. Zhorne et al [7] reported that longer durations of preoperative antibiotics were associated with more culture-negative results in cases of pediatric hematogenous osteomyelitis. Similarly, in a retrospective cohort of patients with mixed orthopedic infections, Al-Mayahi et al [6] found that 19% of patients who received preoperative antibiotics had culture-negative results, whereas only 6% of those who did not receive preoperative antibiotics had culture-negative results. In contrast, Ghanem et al [11] found no statistical difference in the proportion of negative tissue cultures between patients with total knee arthroplasty infection who were exposed and not exposed to perioperative antibiotics. Likewise, Burnett et al [4] reported no culture-negative samples after perioperative antibiotics were administered in a series of 26 infected total knee arthroplasty infections. We hypothesize our results differed from these authors because the durations of antibiotics used in these studies (ie, a single perioperative dose) were insufficient to impact the culture results.

Almost 80% of our patients with moderate or severe DFI received antibiotics before operative cultures. In the presence of preoperative antibiotics, bacterial growth from tissue cultures can be challenging to interpret. Some providers may treat with prolonged broad-spectrum antibiotics regardless of culture results, assuming that pathogens were sterilized by preoperative antibiotic treatment. The literature supports the notion that some bacteria require a longer duration of antibiotics to eradicate infection; for example, the IDSA prosthetic joint infection guideline [12] recommends 4 to 6 weeks of antibiotics for septic arthritis due to Gram-negative bacilli and 3 to 6 months for septic arthritis due to *S aureus*. Extrapolating this information, other providers may choose narrow therapy, hypothesizing that a highly susceptible bacteria was formerly present and sterilized, and that a hardy bacteria, such as *S aureus*, was not present if it did not grow.

Strengths of this study were the inclusion of only deep operative tissue specimens and characterization of the hours of antibiotics received by each patient. This was a single-center retrospective study; results may not be applicable to patients in regions where DFI pathogens may be different. The study was unable to assess the impact of acute versus chronic infection

and severity of peripheral arterial disease on cultures. Finally, the amount of time on preoperative antibiotics may have been influenced in part by the pathogen. For example, aggressive bacterial species may have necessitated more emergent surgery than indolent bacterial species. A future, larger study may be able to describe the impact of individual antibiotics on culture yield.

CONCLUSIONS

In conclusion, this study found that increasing duration of preoperative antibiotic exposure was associated with less frequent growth of streptococci and anaerobes and more frequent negative cultures. These data may provide some guidance for clinicians who are considering de-escalation of therapy for patients with DFI.

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