Comparison of three antimicrobial strategies in diabetic foot infections post-amputation

Samarth P. Shah (iD), Ana Negrete, Timothy Self, Jaclyn Bergeron and Jennifer D. Twilla

Abstract

Background: The 2012 Infectious Disease Society of America (IDSA) guidelines recommend antimicrobial treatment of diabetic foot infections (DFIs) post-amputation, but the optimal route and duration are poorly defined.

Objective: The objective of this study was to determine whether the selection of a specific antimicrobial treatment modality affected hospital and patient outcomes.

Methods: This was a retrospective review of hospital admissions of adults admitted to ourhealthcare system with a primary diagnosis of DFIs post-amputation. The groups were separated into patients who received intravenous antimicrobials (IV), oral antimicrobials (PO), or no antimicrobials (NA). Outcomes included average length of stay among others.

Results: Of the 200 patients screened, 120 patients were included (IV $n = 72$; PO $n = 20$; NA $n = 28$). No statistically significant differences were identified in average LOS (IV $= 9.97 \pm 5.85$, PO $= 8.83 \pm 7.37$, NA $= 9.33 \pm 5.91$ days; $p = 0.73$). However, post-operative (post-op) LOS was significantly shorter in the PO group (PO $= 3.43 \pm 2.56$, IV $= 7.34 \pm 5.95$, NA $= 5.81 \pm 4.18$ days; $p = 0.0001$).

Conclusion: The results of our study indicate that a PO antimicrobial treatment strategy post amputation for DFIs has the potential to decrease post-op LOS without increasing the risk of readmission. Based on the results of our study, we feel consideration should be given to transition to oral antimicrobials soon after amputation to facilitate discharge and decrease the utilization of intravenous antimicrobials.

Keywords: amputation, antimicrobial stewardship, diabetes, diabetic foot infection, surgery

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Introduction

Patients with diabetes are at risk for lower extremity skin and skin structure infections (SSTI). These infections, defined as diabetic foot infections (DFIs), can be associated with considerable morbidity and mortality. Based on the research by the American Diabetes Association (ADA), foot ulcers are estimated to occur in 15% of patients in the United States, with recent research suggesting that the rates could be as high as 25%.[1–9] Compared with nondiabetics with lower-extremity infections, diabetics have a tenfold greater risk of hospitalization along with an increased risk of amputation if an ulcer is left untreated.[1–9]

Although the 2012 Infectious Disease Society of America (IDSA) guidelines recommend treatment of DFIs post-amputation with antimicrobials, the optimal route and treatment duration are poorly defined.[10] For patients who undergo amputation secondary to DFIs, treatment with either intravenous or oral antimicrobials is recommended based on patient specific factors. The route of treatment is dictated by the amount of residual dead or infected bone and the state of the

soft tissues, which is often a decision made by an individual provider or care team.[10] In addition, evidence for the utilization of antimicrobials after amputation is derived from perioperative surgical prophylaxis studies evaluating the rate of infection after amputation, which limits its applicability in the diabetic population.[10] To the best of the authors' knowledge, research in the area of optimal antimicrobial treatment strategies in patients with DFIs post-amputation is limited, thus warranting additional investigation. The purpose of this retrospective study is to review hospital outcomes based on the selection of antimicrobial therapy along with route chosen in hospitalized patients presenting with DFIs who underwent amputation.

Methods

Study design and participants

A retrospective review of adult patients admitted to our healthcare system composed of five adult hospitals, who underwent an amputation secondary to a DFI between August 2011 and August 2016, was conducted. Patients were identified through a corporate financial services database using ICD-9 codes of 84.11 (amputation of toe), 84.12 (amputation through foot), or 84.15 (other amputation below knee). Inclusion criteria were patients greater than 18 years old, an inpatient admission for DFI, and an amputation secondary to DFI. Exclusion criteria included documentation of an above-the-knee amputation. Approval for this study was granted by the University of Tennessee Health Science Center Institutional Review Board.

Treatment groups were assigned based on the antimicrobial regimen route selected within 24 h after post-operative (post-op) antimicrobials were completed. The groups were separated into intravenous (IV), oral (PO), and no antimicrobials (NA). Patients that were continued on IV antimicrobials 24 h after post-op antimicrobials were completed were placed into the IV antimicrobial group. Patients who were transitioned to PO antimicrobials within 24 h after completion of post-op antimicrobials were placed into the PO antimicrobial group. Patients that did not receive antimicrobials after completion of post-op antimicrobials were placed into the NA group. In the event the patient was discharged within 24 h after the procedure, the discharged antimicrobial regimen

dictated the group the patient was placed into (i.e. if discharged on home IV antimicrobials, patient placed into the IV antimicrobial group). Owing to the fact that IV antimicrobials are continued for 24 h after amputation as part of post-surgical prophylaxis, we chose to define that as our timeframe for transition to therapy to ensure post-surgical prophylaxis antimicrobials did not affect the definition of the group the patient was placed into.

Post-op antimicrobials utilized were differentiated into anti-methicillin resistant staphylococcus aureus (anti-MRSA) agents, anti-pseudomonal beta-lactams, beta-lactams, and miscellaneous agents. Anti-MRSA agents were defined as vancomycin, daptomycin, and linezolid. Anti-pseudomonal beta-lactatams that were available on formulary were meropenem, piperacillin-tazobactam, and cefepime. Lastly, fluoroquinolones, metronidazole, sulfamethoxazole-trimethoprim, and tetracyclines were defined as miscellaneous antimicrobials.

Outcomes

The primary outcome of the study was to determine if the selection of a specific antimicrobial treatment modality would have an impact on post-op length of stay (LOS) and overall LOS. Secondary outcomes that were assessed include 30-day readmission (TDR), rates of treatment failure (TF), overall antimicrobial days, and rates of *Clostridium difficile* associated diarrhea (CDAD) within 30 days.

Patient demographics, pertinent laboratory findings, and baseline vitals were collected upon admission. Home antimicrobial therapy was obtained via medication history documented in the electronic medical recorded by a certified pharmacy technician and subsequently verified by a pharmacist. Documentation of surgical margins was obtained from the post-op note in the electronic medical record.

TF was defined using three exclusive components. The first aspect of TF was escalation of antimicrobial therapy. Escalation of antimicrobial therapy was clearly defined as the addition of an agent to the current regimen to broaden out coverage or a switch to an agent that would provide a broader spectrum of coverage (i.e. ceftriaxone to meropenem). The second aspect of TF was defined as the development of sepsis at any point during
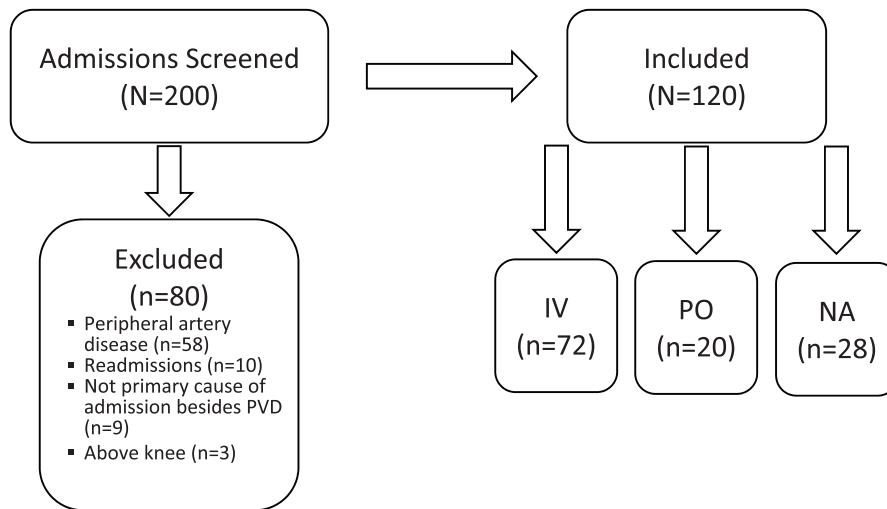
Figure 1. Patient selection.

inpatient hospitalization. The development of sepsis was based on the sepsis-3 definition of at least two of the following: change in mental status per the medical record, respiratory rate greater than or equal to 22, or systolic blood pressure (SBP) less than 100.[11] Lastly, the need for additional surgical intervention was the final component of TF. The need for additional surgical intervention was defined as an unplanned surgical procedure that involved removal of bone within 5 days of amputation. If the patient met any of the three criteria described above, the patient was deemed to have TF. Overall antimicrobial days were included the number of days the patient was on antimicrobials after post-op antibiotics were discontinued. In the instance of a patient being discontinued on IV or PO antibiotics, the predefined stop date was used to determine the overall antimicrobial days. Rates of CDAD were collected based on an inpatient admission to our healthcare system or any available clinic notes.

Statistics

Length of stay was reported as the mean with a standard deviation due to it being normally distributed. Readmission rates, TF, and CDAD were reported in percentages. Antimicrobial days were reported as a mean with a standard deviation. Statistical tests were performed using the SPSS® Program Version 24.0, released in 2016. The χ^2 test was performed when analyzing nominal data.

The one-way analysis of variance (ANOVA) test was performed when analyzing continuous data.

Results

Among the 200 admissions screened at all the study sites, 120 admissions met inclusion criteria (IV $n = 72$; PO $n = 20$; NA $n = 28$) (Figure 1).

Baseline characteristics were similar between the three groups with the exception of a baseline white blood cell count (WBC) and incidence of chronic kidney disease (CKD) (Table 1). Baseline WBC was significantly higher in the IV group ($p = 0.02$), while CKD was significantly higher in the NA group ($p = 0.04$).

Positive blood, urine, surgical, and wound cultures were collected as well as documentation of surgical margins. There were 42 patients (35%) that had positive wound culture results. A Gram-positive organism was reported for 37 (88%) of the wound culture results, with the primary organisms identified as *Staphylococcus aureus* and *Enterococcus faecalis*. A total of 18 (51%) of the wound cultures were polymicrobial.

There were 40 positive surgical cultures, with MRSA being the most prominent microbe isolated. Eleven (28%) of the surgical cultures were polymicrobial. Full antimicrobial data from our study is provided in Tables 2 and 3. A total of 11

Table 1. Patient demographics.

Patient demographics	IV (n = 72)	PO (n = 20)	NA (n = 28)	p-value
Age (years)*	58.7 ± 12.79	59.2 ± 14.5	61.4 ± 12.8	0.65
Female, n (%)	20 (28)	4 (20)	10 (35.7)	0.49
African American, n (%)	45 (62.5)	12 (60)	15 (53.6)	0.72
White blood cell count (cells/mm^3)*	12.7 ± 6.91	10.5 ± 4.01	10.1 ± 5.49	0.02
Hemoglobin A1c (%)	9.8 ± 2.91	9.7 ± 2.78	9.6 ± 3.9	0.98
ICU admission, n (%)	4 (5.6)	0 (0)	1 (3.6)	0.54
Hypertension, n (%)	48 (66.7)	13 (65)	10 (67.9)	0.98
Coronary artery disease, n (%)	19 (26.4)	6 (30)	10 (35.7)	0.66
Chronic kidney disease, n (%)	19 (26.4)	4 (20)	14 (50)	0.04
Peripheral artery disease, n (%)	14 (19.4)	5 (25)	9 (32.1)	0.40
qSOFA‡	0 ± 0.49	0 ± 0.49	0 ± 0.49	1

*Data presented as mean ± standard deviation.
‡Data presented as median ± standard deviation.
qSOFA, quick Sepsis-related Organ Failure Assessment.

Table 2. Wound culture results.

Positive wound culture (n = 35)	
Gram-positive organisms	**31**
• *Staphylococcus aureus*	10
• *Enterococcus faecalis*	10
• *MRSA*	8
• *Staphylococcus epidermis*	3
Gram-negative organisms	**9**
• *Enterobacteriaceae*	5
• *Acinetobacter lwoffii*	3
• *Pseudomonas aeruginosa*	2
Polymicrobial, n (%)	18 (51)

Table 3. Surgical culture results.

Positive surgical culture (n = 40)	
Gram-positive organisms	**33**
• *MRSA*	12
• *Staphylococcus epidermis*	8
• *Staphylococcus aureus*	7
• *Enterococcus faecalis*	2
Gram-negative organisms	**11**
• *Enterobacteriaceae**	15
• *Acinetobacter baumannii*	1
Polymicrobial, n (%)	11 (28)

*3 Enterobacter cloacae culture results

patients (9%) had positive blood cultures with 6 (8%) in the IV group, 1 (5%) in the PO group, and 4 (14%) in the NA group. Antimicrobial coverage of these cultures revealed that 70 patients (76%) that were receiving IV or PO antimicrobials were on combination therapy providing both Gram-positive and Gram-negative coverage. A full breakdown of antimicrobial agents utilized is provided in Table 4. Lastly, 38 patients (31.7%) had surgical margin descriptions, with 32 patients

Table 4. Post-operative antimicrobials utilized.

Anti-MRSA (*n* = 68)	Antipseudomonal beta-lactam (*n* = 64)
• Vancomycin (*n* = 58)	• Meropenem (*n* = 25)
• Daptomycin (*n* = 6)	• Piperacillin-tazobactam* (*n* = 22)
• Linezolid (*n* = 4)	• Cefepime (*n* = 17)
Beta-Lactams (*n* = 25)	**Miscellaneous (*n* = 29)**
• Augmentin (*n* = 6)	• Ciprofloxacin (*n* = 8)
• Ceftriaxone (*n* = 3)	• Metronidazole (*n* = 6)
• Cephalexin (*n* = 3)	• SMX/trimethoprim (*n* = 2)
• Cefazolin (*n* = 3)	• Minocycline (*n* = 2)
Combination Therapy, *n* = 70 (76%)	

Source: Piperacillin-tazobactam on national shortage during study time-frame

(26%) with clean margins and 6 patients (5%) with unclean margins. Most patients (82 patients; 68%) did not have descriptions of margins in their surgical note (Table 5).

Primary and secondary outcomes
The overall average LOS in the IV group was 9.97 ± 5.95 days compared with 8.83 ± 7.37 in the PO group and 9.33 ± 5.91 in the NA group ($p = 0.73$). The groups were equally distributed and there were no outliers that were excluded. The average LOS post-op, however, was significantly different. In the IV group, post-op LOS was 7.34 ± 5.95 days compared with 3.43 ± 2.56 days in the PO group and 5.81 ± 4.18 in the NA group ($p = 0.0001$). TDRs were similar among all three groups with 15.3% in the IV group, 15% in the PO group, and 10.7% in the NA group ($p = 0.84$).

There was a difference in the incidence of TF. In the IV group TF occurred in 16 patients (22.2%) compared with 1 patient (5%) in the PO group and 3 patients (10.7%) in the NA group. Of the 16 patients in the IV group that had TF, there were 6 patients that met multiple criteria for TF. Analyzing the cause of TF further in the IV group, we found that a total of eight (11.1%) patients had an escalation of therapy, while eight patients (11.1%) had unplanned surgery. The other reasons for TF were development of sepsis ($n = 3$, 4.2%) and death ($n = 2$, 2.8%). Of the eight patients that failed due to an escalation in therapy, five of those patients were escalated in their antimicrobial therapy due to surgical or wound cultures that finalized after initial antimicrobial therapy was selected.

Upon discharge, 56 patients (47%) were discharged with antimicrobials. The most utilized oral agent that patients were discharged on was amoxicillin/clavulanic acid. A total of nine patients (17%) were discharged with IV antimicrobials. Looking specifically at overall antimicrobial days we identified that the PO group had a statistically significantly longer duration of total antimicrobial days at 17.8 ± 16.24 compared with 11.8 ± 12.42 in the IV group and 3.8 ± 6.40 in the NA group ($p = 0.001$). A complete breakdown of inpatient, outpatient, and overall antimicrobial days is provided in Table 6. No differences in rates of *Clostridium difficile* associated diarrhea was noted between the groups (IV group $n = 2$, PO group $n = 0$, NA group $n = 1$).

Discussion
The results of our study revealed that selection of a specific antimicrobial modality based on route of treatment of DFIs post-amputation can affect hospital outcomes. In our study, we identified that post-op LOS was significantly shorter in the PO treatment group compared to both the IV and

Table 5. Description of surgical margins.

Description	IV (*n* = 72)	PO (*n* = 20)	NA (*n* = 28)	*p* value
Undocumented, *n* (%)	53 (73.6)	12 (60)	17 (60.7)	0.74
Clean, *n* (%)	14 (19.4)	8 (40)	10 (35.7)	
Not clean, *n* (%)	5 (6.9)	0 (0)	1 (3.6)	

Table 6. Overall antimicrobial days.

Outcome	IV (*n* = 72)	PO (*n* = 20)	NA (*n* = 28)	*p* value
Inpatient antimicrobial days	5.3 (± 3.43)	3.4 (± 2.64)	1.6 (± 2.24)	0.001
Outpatient antimicrobial days	6.5 (± 10.9)	14.4 (± 16.6)	2.3 (± 6.04)	0.002
Total antimicrobial days	11.8 (± 12.42)	17.8 (± 16.24)	3.8 (± 6.40)	0.001

NA groups without an increase in readmission rates.

Previous studies regarding optimal antimicrobial strategies in patients undergoing amputation secondary to DFIs are scarce. Lipsky and colleagues compared sequential IV fluoroquinolone/beta-lactam therapy with PO fluoroquinolone/beta-lactam therapy in patients with DFIs.[12] In their study (*n* = 127), they determined that clinical cure rates were similar when transitioned to an oral regimen after IV therapy.[12] Although this information is crucial in confirming that oral antimicrobials are a safe option in patients with DFIs, the ability to apply these results to a patient population consisting of patients post-amputation is limited based on their small number of patient that were post-amputation (*n* = 18).[12]

Sadat and colleagues compared the difference on infection rates and hospital LOS in patients with amputations when treated with a 5-day antimicrobial regimen compared to a 24-hour regimen after amputation.[13] This study used flucloxacillin or vancomycin in addition to gentamicin or ciprofloxacin, and metronidazole intravenously. Patients were transitioned to oral therapy as soon as appropriate beyond the first 24 h. In their study (*n* = 76), they saw a statistically significant reduction in wound infection rates and reduced hospital LOS, however only 46% (*n* = 35) of those patients were diabetics.[13]

In contrast to these studies, we evaluated a high-risk only population (diabetes mellitus diagnosis) that all received amputation. Given the differences in healing as well as microorganism involvement in our study patients compared with populations in previous studies, it is interesting to find that in accordance with these studies that a PO option may be sufficient at preventing further infection.

After review of our laboratory and culture data, it is important to note that the WBC was significantly higher in the IV group compared with the PO and NA group. This may have influenced providers selection of route of antimicrobial therapy as WBC is a known lab value analyzed to determine the severity of infection. This potential selection bias makes it hard to interpret if patients presenting with criteria suggestive of a more serious infection warrant an IV treatment strategy. Although the baseline WBC was significantly higher in the IV group, the median quick Sepsis-related Organ Failure Assessment (qSOFA) score, which suggests high risk of poor outcome in patients with suspected infection, was similar across all three groups.[14] In addition, it is interesting to note that culture results were similar to culture results in the previous studies.[12,13] Lipsky *et al.* found that 45% of patients had polymicrobial culture results.[12] Our results showed a similar number with 51% of wound cultures being polymicrobial, but surgical cultures were only

polymicrobial 28% of the time. This could be due to surgical cultures finalizing as *Staphylococcus epidermis* seven out of eight times. Knowing that *S. epidermis* is normal skin flora; this could have skewed our findings.

The majority of post-op antimicrobial regimens included an anti-MRSA agent (i.e. vancomycin, daptomycin, linezolid) along with an anti-pseudomonal beta-lactam (i.e. meropenem, piperacillin-tazobactam, cefepime). Of note, we may have seen an increase in combination of cefepime and metronidazole owing to piperacillin-tazobactam being on national shortage during the study period, and the combination of cefepime and metronidazole was used as a therapeutic alternative to monotherapy with piperacillin-tazobactam. Not only are culture results part of the antimicrobial selection process but even more important may be the review of surgical margins post-op. As the guidelines provided by the IDSA recommend an antimicrobial regimen based on the margin at the amputation site,[10] this is one key area that can definitely be improved to ensure that a proper antimicrobial regimen is being utilized. As mentioned previously, 38 patients (31.7%) had documented description of surgical margins on the post-op report limiting the applicability for interpretation of appropriate antimicrobial utilization. Owing to the lack of documentation, we are unable to determine whether the addition

Analyzing our primary outcome, no difference in overall LOS between the groups was identified. However, when breaking that down into post-op LOS, a significant reduction in the PO group compared with the IV and NA group was observed. This result could be expected due to an ease in transitions of care with insurance approval and overall set up of oral antimicrobial regimens compared with a patient being discharged on IV antimicrobials. In addition, the majority of patients started on IV antimicrobials stayed a full 7 days post-surgery to complete a 7-day course of antimicrobial therapy as deemed necessary by the provider. It is also important to note that four patients in the IV group, compared with zero in the PO and one in the NA group required ICU admission, which can potentially impact the overall length of stay. Owing to LOS being a burden on our entire healthcare system, transitioning patients to oral therapy may be a consideration because we did not see any difference in clinical outcomes, such as TF and TDR.

TF in the IV group is also an aspect that warrants discussion. In our study, eight patients had an escalation in antimicrobial therapy (i.e. ceftriaxone to meropenem) owing to a positive surgical culture that finalized after the amputation was completed. It could be presumed that the results of the culture influenced the healthcare provider's decision to alter the patient's antimicrobial therapy to cover the microorganism that grew, however this may have been an unnecessary action. As the amputation removed the aspect of the bone that was infected, and the culture was taken from an aspirate of the amputated bone, the prevailing need to change antimicrobial therapy may be obsolete.

Although the prior studies provide information vital in treatment of patients with DFIs and amputations separately, their results are difficult to generalize due to the lack of patients who underwent an amputation solely for DFIs. In comparison to the two prior studies mentioned,[12,13] our study sought out to determine the difference in outcomes in patients specifically post-amputation due to DFIs. Based on our study we feel that transitioning a patient from IV antimicrobials to oral antimicrobials was not only safe but also effective. Our study expands on the work done by previous authors and demonstrated that various antimicrobial strategies could be used in treatment of DFIs post-amputation. Moreover, our study establishes the possibility of the benefit of using PO therapy over IV therapy. The one key area in which significant benefit was observed was in terms of post-op LOS and TF. Although TF has not been clearly defined in this patient population previously, we determined that an escalation in antimicrobial therapy, need for additional unplanned surgical intervention, or clinical deterioration (development of sepsis or death) was the optimal definition due to the effect it can have on clinical outcomes.

There are several limitations to our study that warrant consideration. This was a retrospective review, which relied on ICD-9 and ICD-10 coding for amputation and DFIs; therefore, admissions may have been miscoded and, more importantly with regards to one of our outcomes, readmissions may have been missed. Specifically, if a patient presented to a hospital outside of our healthcare system. Although a limitation, we felt that it was still worthwhile to evaluate readmission rates as this presents a very real-world

scenario of some patients being lost to follow up as they may follow up at a different facility than the facility which performed the surgery. Furthermore, the retrospective nature limited the use of was not protocolized methodology, which could have led to gaps in documentation subsequently affecting our results. An important aspect of this limitation is with the low number of patients with surgical margin clearance documented on the post-operative report, which prevents interpretation of how well the surgery was at removing infected tissue and bone. This could ultimately impact the need for continued antimicrobial therapy. Lastly, it is important to note that patients may have been treated longer with IV antibiotics due to confounders based on specific provider's subjective assessment of the patient's severity of illness, baseline comorbidities, and any surgical findings.

Physician practice patterns could also not be accounted for due to not having a protocolized approach in prescribing of antimicrobial regimens after an amputation was completed. Owing to readmissions and patients being discharged on antimicrobials, we were also unable to assess compliance with outpatient antimicrobials.

Although the limitations of our study are important to consider, it is also imperative to realize the lack of evidence available regarding the optimal antimicrobial strategy in patients with DFIs undergoing amputation. Owing to the prevalence of diabetes and the risk of developing DFIs, the morbidity associated with this disease is quite high. Length of stay and TDR are a huge burden on the healthcare systemic thus warranting further evaluation. By reporting these outcomes, we hope that this study may provide an impetus for development of an ideal antimicrobial treatment strategy for patients with DFIs who undergo amputations.

Conclusion

In summary, our results suggest that antimicrobial treatment for DFIs post-amputation with PO agents lead to a significant decrease in post-op LOS when compared with IV antimicrobials or no antimicrobials. To the best of the authors' knowledge, this is the largest study conducted specifically in post-amputation patients owing to DFIs. The ability to provide adequate coverage for a patient and expedite their discharge has the potential not only to impact patient's LOS, but also decrease their exposure to IV antimicrobials and unnecessary utilization of broad spectrum antimicrobials.

Conflict of interest statement
All authors declare that they have no conflicts of interest. The views expressed in this manuscript reflect the authors' point of view and do not represent the position of the institution.

Ethics approval and consent
Our study was approved by The University of Tennessee Health Science Campus Institutional Review Board (approval number 16-04872-XP). The study was a retrospective chart review and did not require written informed consent prior to enrollment in the study.

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