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Are antibiotic-resistant pathogens more common in subsequent episodes of diabetic foot infection?

Dan Lebowitz[a,b,1], Karim Gariani[b,c,1], Benjamin Kressmann[b,d], Elodie von Dach[e], Benedikt Huttner[b,e], Placido Bartolone[d], Nam Lê[d], Morad Mohamad[d], Benjamin A. Lipsky[b,f], Ilker Uçkay[b,d,e,*]

[a] Service of General Internal Medicine, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[b] Service of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, University of Geneva, 4, rue Gabrielle Perret-Gentil, 1211 Geneva 14, Switzerland
[c] Service of Diabetology and Endocrinology, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[d] Orthopaedic Surgery Service, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[e] Infection Control Program, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[f] University of Oxford, Oxford, UK

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SUMMARY

Background: After antibiotic therapy of an initial diabetic foot infection (DFI), pathogens isolated from subsequent episodes might become more resistant to commonly prescribed antibiotics. If so, this might require a modification of the current recommendations for the selection of empiric antibiotic therapy. This study investigated whether the Infectious Diseases Society of America (IDSA) DFI guideline recommendations should be modified based on the number of past DFI episodes.
Methods: This was a single-centre retrospective cohort survey of DFI patients seen during the years 2010 to 2016.
Results: A total 1018 episodes of DFI in 482 adult patients were identified. These patients were followed-up for a median of 3.3 years after the first DFI episode. The total number of episodes was 2257 and the median interval between recurrent episodes was 7.6 months. Among the recurrent DFIs, the causative pathogens were the same as in the previous episode in only 43% of cases (158/365). *Staphylococcus aureus* was the predominant pathogen in all episodes (range 1 to 13 episodes) and was not more prevalent with the increasing number of episodes. DFIs were treated with systemic antibiotics for a median duration of 20 days (interquartile range 11–35 days). Overall, there was no significant increase in the incidence of antibiotic resistance to methicillin, rifampicin, clindamycin, or ciprofloxacin over the episodes (Pearson's Chi-square test *p*-values of 0.76, 1.00, 0.06, and 0.46, respectively; corresponding *p*-values for trend of 0.21, 0.27, 0.38, and 0.08, respectively).
Conclusions: After the successful treatment of a DFI, recurrent episodes are frequent. A history of a previous DFI episode did not predict a greater likelihood of any antibiotic-resistant isolate in subsequent episodes. Thus, broadening the spectrum of empiric antibiotic therapy for recurrent episodes of DFI does not appear necessary.

Introduction

Patients who have had one diabetic foot infection (DFI) are at high risk of future episodes. In addition, they are usually treated with prolonged durations of therapy, often with a relatively broad antibiotic spectrum, for recurrent episodes of DFI (Uçkay et al., 2015; Uçkay et al., 2016; Uçkay et al., 2014). Antibiotic use is the major clinical risk factor for promoting antibiotic resistance (Harbarth et al., 2000). The healthcare-associated transmission

* Corresponding author at: Geneva University Hospitals and Faculty of Medicine, 4, rue Gabrielle Perret-Gentil, 1211 Geneva 14, Switzerland. Tel: +41 22 372 9828; fax: +41 22 372 3987.
E-mail address: ilker.uckay@hcuge.ch (I. Uçkay).
[1] Dan Lebowitz and Karim Gariani contributed equally as first authors.

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of resistant pathogens is likely when DFI patients are hospitalized or require frequent podiatric care in specialized centres (Agostinho et al., 2013). Having subsequent DFI episodes theoretically raises the risk of antibiotic-resistant infections developing (Zenelaj et al., 2014).

To help prevent resistance and to reduce antibiotic-related costs and adverse effects, the 2012 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of diabetic foot infections (Lipsky et al., 2012) recommend prescribing antibiotics that (1) have proven efficacy in treating DFIs; (2) cover common Gram-positive cocci; and (3) have limited coverage of Gram-negative pathogens. Commonly used empiric oral options are clindamycin, co-trimoxazole, levofloxacin, and amoxicillin–clavulanate, administered for about 1–3 weeks for soft tissue infections and 4–6 weeks for non-amputated osteomyelitis cases. These guidelines also state that chronic, previously antibiotic-treated, or severe infections usually require broader spectrum regimens (Lipsky et al., 2012), but specific recommendations cannot be given because of a lack of published comparative data. Other guidelines for DFIs also avoid offering specific empiric antibiotic suggestions for the same reason (Gariani et al., 2014).

This study was undertaken to investigate whether or not there is an effect of having a past DFI episode on the likelihood of antibiotic resistance in pathogens isolated from subsequent DFIs. This information could inform whether or not physicians should consider a past history of DFI when choosing empiric antibiotic therapy. Of note, this study was not designed to address the surgical approach to DFI or factors regarding the likelihood of achieving remission, which are addressed elsewhere (Uçkay et al., 2015; Uçkay et al., 2016; Uçkay et al., 2014; Lipsky et al., 2012; Gariani et al., 2014).

Methods and setting

This was a single-centre retrospective cohort survey of DFI patients seen during the period January 2010 to December 2016 at Geneva University Hospital. This hospital, the only public hospital in Geneva and also covering some areas of neighbouring France, has an estimated average antibiotic consumption of 59 daily defined doses (DDD) per 100 patient-days. The institution employs a clinical pathway for managing DFI that includes submitting information to a database on DFI. There were no major changes in infection prevention or antibiotic stewardship policies during the study period. As part of a hospital-wide quality programme, the medical directorate has waived the need for individual patient informed consent for the use of this clinical pathway, which includes all DFIs, independent of their severity. DL, KG, BK, and EvD, all of whom are experienced with infectious diseases databases, completed the data and built the database. A research nurse (BK) and an infectious diseases physician (IU) (Uçkay et al., 2009), both of whom specialize in caring for DFIs, supervised the accuracy of the data and distinguished between wounds that were infected versus colonized and between culture isolates that were causative pathogens versus likely contaminant or colonizing microorganisms.

Definitions and statistical analysis

The clinical pathway and DFI definition are based on the IDSA DFI guidelines (Lipsky et al., 2012) and on specialist consultation (BAL). Episodes of infection after a first DFI (within the study period) were defined as a new or recurrent DFI if they occurred in the same anatomical foot localization and presented at least 2 months after the prior episode. The aim was to exclude persistent DFIs from the final analysis. It was decided against considering all prescribing of outpatient antibiotic therapy for non-DFI-related infections or perioperative prophylaxis in the included patients.

The three pathogens predominantly isolated from microbiological culture of each individual DFI were recorded, as they were also the organisms against which treating clinicians usually targeted their antibiotic therapy. The pathogen count was censored at three microorganisms. If there was an associated surgery, the intraoperative tissue or bone specimens were taken. In non-operated cases, tissue or bone specimens were selected, if feasible. Otherwise pus was sampled. Superficial swabs without direct pus contact, as well as enrichment broth cultures, were excluded. Clinical cure was defined as the anamnestic, laboratory, and clinical resolution of the signs and symptoms of the former DFI.

The laboratory initially processed all specimens for culture in accordance with the Clinical and Laboratory Standards Institute recommendations (Performance Standards for Antimicrobial Susceptibility Testing, 2007), before switching to the European Committee criteria in 2014 (European Committee on Antimicrobial Susceptibility Testing, 2014). The standard microbiology laboratory incubation time was 5 days. Clonal typing of microorganisms was not done routinely. Focus was placed on the antibiotic resistance to four of the most frequently prescribed agents for DFIs: methicillin, rifampicin, ciprofloxacin, and clindamycin. Because antibiotic therapy would have affected bacteria that were only colonizers during the first episode, or were newly acquired in the interval between infections (Agostinho et al., 2013), it was decided to analyze antibiotic resistance epidemiologically over the time period of the study rather than for each pathogen for every episode of DFI. For example, instead of analyzing whether an *Escherichia coli* isolate cultured during a first infection was still susceptible to ciprofloxacin in the subsequent episode, it was determined whether ciprofloxacin resistance occurred among all pathogens isolated in any subsequent episode(s).

For group comparisons, Pearson's Chi-square test was used. The *p*-value for trend assessed changes over time and episodes. Stata software (version 9.0; Stata Corp., College Station, TX, USA) was used for the data analysis.

Results

Patients, episodes, and therapy

The study had access to data on a total of 1018 DFI episodes (279 in females), with a median follow-up of 3.3 years after the first DFI episode (interquartile (IQR) range 0.8–9.0 years). Among the 482 diabetic patients included in this cohort study (who had a median duration of diabetes of 15 years), 244 suffered a second DFI episode, 132 a third, 71 a fourth, 39 a fifth, 18 a sixth, 10 a seventh, 10 an eighth, six a ninth, and three a tenth. The six eleventh to fourteenth episodes involved only three patients. Overall, there were 2257 episodes, of which a total of 540 were follow-up episodes. The median interval between DFI episodes was 7.6 months (IQR 2.2–30.2 months).

The median patient age on admission was 69 years, body mass index was 28 kg/m^2, ankle-brachial index was 1.0, and C-reactive protein level was 62 mg/l. Most DFIs involved the fore-foot, but 65 (15%) involved the hind-foot and ankle and 38 (9%) involved the mid-foot. Overall, 392 (39%) episodes were complicated by underlying osteomyelitis.

The DFIs were treated with systemic antibiotics for a median duration of 20 days (IQR 11–35 days), including a median of 5 days intravenously (IQR 0–12 days). The six most frequently used antibiotic drug classes were beta-lactams ($n = 1017$), glycopeptides ($n = 116$), quinolones ($n = 91$), co-trimoxazole ($n = 49$), clindamycin ($n = 46$), and rifampicin ($n = 25$). The median number of surgical debridements was 1 (range 0–7); 596 of these involved (partial)