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

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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

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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)

lower extremity amputations. Overall, 610 (60%) cases were clinically considered as ischemic, 98 underwent angioplasty, and 98 received hyperbaric oxygen therapy.

Pathogens

Among the 1018 DFI episodes, the number of episodes with two pathogens was 381 (37%) and the number with three pathogens was 163 (16%). The five most frequently isolated microorganisms were *Staphylococcus aureus* (325 episodes), coagulase-negative staphylococci ($n = 35$), *Enterococcus faecalis* ($n = 40$), *Streptococcus agalactiae* ($n = 26$), and *Pseudomonas aeruginosa* ($n = 61$). *S. aureus* was the predominant pathogen in all episodes of recurrent infection (from 1 to 13). *S. agalactiae* and coagulase-negative staphylococci were rarely encountered beyond episode 7, whereas enterococci and *P. aeruginosa* were found equally in higher episode numbers. Among the 365 DFIs occurring at least three times, the three dominant pathogens showed partial concordance between episodes only 43% of the time (158/365). In 57% of episodes, the pathogens isolated were unrelated to those found in the prior episode.

Antibiotic resistance across episodes in the study and the medical centre

The incidence of antibiotic resistance of DFI isolates to methicillin, rifampicin, clindamycin, and ciprofloxacin did not increase significantly over subsequent DFI episodes (Chi-square test p-values of 0.76, 1.00, 0.06, and 0.46, respectively). In contrast, there was a tendency towards lower rates of antibiotic resistance from episode 1 to 3, with p-values for trend of 0.21, 0.27, 0.38, and 0.08, respectively. Table 1 shows the comparison of rates of antibiotic resistance for all clinical isolates in DFI episodes 1–3. Table 2 reveals the rates of resistance to antibiotics of some of the key pathogens at the study institution during the period investigated.

The rate of resistance to methicillin of *S. aureus* isolates in these DFI episodes was not higher than the average for the clinical strains at the medical centre in 2011 (75/325 vs. 605/2630, $p = 0.98$). Moreover, the *S. aureus* strains of the DFI patients had a lower level of resistance to clindamycin (74/325 vs. 736/2630, $p = 0.05$) and rifampicin (11/325 vs. 26/2630, $p = 0.01$), and tended to have lower rates of resistance to ciprofloxacin (61/325 vs. 605/2630, $p = 0.08$). *P. aeruginosa* also tended to have lower rates of resistance to ciprofloxacin in DFI patients compared to all clinical isolates in the medical centre (9/61 vs. 98/1230, $p = 0.08$). When analyzing the 61 Pseudomonas DFI isolates separately, the difference in ciprofloxacin resistance across episodes 1 to 3 and overall was not statistically significant (Chi-square test, $p = 0.87$), which was confirmed in the trend analysis ($p = 0.42$). Overall, while the proportion of antibiotic resistance decreased over the episodes for DFI patients (Table 1), it remained stable for all other clinical isolates at the institution (Table 2).

Table 1
Rates of antibiotic resistance according to the increasing number of episodes of diabetic foot infection.

All pathogens causing DFI, by episode			*p*-Value[a]
Episode 1	Episode 2	Episode 3	
49%	23%	14%	0.21
53%	25%	11%	0.08
54%	23%	8%	0.38
46%	23%	17%	0.27

DFI, diabetic foot infection.
[a] *p*-Value for trend.

Discussion

In this single-centre cohort study involving 1018 episodes of DFI in 482 adult patients, the concordance of the three dominant wound pathogens was only 43% for subsequent episodes, while the pathogens isolated were unrelated to those in the prior episode in nearly two-thirds of cases. Based on the microbiological findings, many so-called DFI recurrences are probably new episodes.

From the first episode of DFI, the rates of resistance of wound isolates of *S. aureus* and *P. aeruginosa* were significantly higher than those of all clinical isolates in the study institution. Moreover, while the proportion of antibiotic resistance for DFIs decreased over time, it remained stable for all other clinical isolates at the institution during the 6-year study period, for which there is no apparent explanation. No increased occurrence of new or specific bacterial species with the increasing number of DFI episodes was detected. The duration of antibiotic therapy administered to the patients was consistent with the recommendations in widely used DFI guidelines (Lipsky et al., 2012; Gariani et al., 2014). The choice of antimicrobial agents, largely consisting of oral amoxicillin–clavulanate, clindamycin, or fluoroquinolones, was similar to the experience reported by large Veterans health networks in the USA (Fincke et al., 2010). Regarding the microbiological profile of DFI pathogens, the present data are consistent with those of reports from Central European and North American institutions, which have shown a predominance of *S. aureus* and other aerobic Gram-positive pathogens (Uçkay et al., 2014; Harbarth et al., 2000; Charles et al., 2015). This finding is in contrast to those reported in publications from (sub)tropical countries in Asia and Africa, which have shown a predominance of Gram-negative pathogens, especially *P. aeruginosa* (Uçkay et al., 2014).

This study has several limitations, the most important being that the assessment of resistance patterns was restricted to methicillin, ciprofloxacin, rifampicin, and clindamycin (Czekaj et al., 2011). The severity grading of the DFI (e.g., according to the IDSA guidelines (Lipsky et al., 2012)) was not uniformly assessed, nor was resistance to other antibiotics, such as co-trimoxazole (Harbarth et al., 2015), linezolid, tetracyclines, daptomycin, glycopeptides, piperacillin–tazobactam, colistin (Valour et al., 2013), or carbapenems, which are occasionally used for methicillin-resistant *S. aureus*, sepsis, or non-fermenting Gram-negative

Table 2
Rates of antibiotic resistance in all clinical isolates of the selected key pathogens during the study period—entire hospital.

Antibiotic	MSSA			*Streptococcus agalactiae*			*Pseudomonas aeruginosa*		
Year	2010	2013	2016	2010	2013	2016	2010	2013	2016
Methicillin	0%	0%	0%	0%	0%	0%	-[a]	-[a]	-[a]
Clindamycin	11%	12%	17%	22%	22%	20%	-[a]	-[a]	-[a]
Rifampicin	1%	1%	1%	0%	0%	5%	-[a]	-[a]	-[a]
Ciprofloxacin	3%	4%	3%	-[a]	-[a]	-[a]	8%	10%	9%

MSSA, methicillin-susceptible *Staphylococcus aureus*.
[a] Drug not used for this organism.

bacteria. This choice was made based on the relatively small number of DFI episodes that were treated with these other antibiotic agents and the expectation that all of the Gram-positive pathogens would be susceptible to linezolid (Valour et al., 2013), daptomycin (Jugun et al., 2013), and glycopeptides.

Second, the results should not be interpreted as suggesting that new pathogens were selected by ongoing antibiotic therapy, as commonly occurs in clinical practice (Al-Mayahi et al., 2015). In this study, only patients who had an antibiotic-free interval of several weeks before experiencing a new episode of DFI were included. This antibiotic-free time window is a good compromise between selecting recurrent episodes (up to a quarter of further DFI episodes recurred at 2 months) and new DFIs. No other publication appears to have mentioned the median duration until onset of antibiotic resistance in DFIs.

Third, this study was solely epidemiological and thus did not prospectively investigate the development of a specific antibiotic resistance for a given pathogen in an individual patient. Taking into account the considerable variation in DFI microbiology among episodes, such a detailed individualized analysis was not feasible when analyzing over 1000 events.

Fourth, infection prevention programmes, such as the promotion of hand hygiene or antibiotic stewardship, might have reduced the prescription of selected antibiotics and indirectly decreased the overall resistance to these antibiotics. However, it is believed that the influence of these hypothetical programmes is small, because most such programmes target a reduction in nosocomial infections and not the antimicrobial resistance, and many DFIs are treated in the community and involve many different antibiotics. There are also no scientific data to indicate that antibiotic stewardship programmes directly reduce the resistance patterns of DFIs. Additionally, there was no major change in these policies at the study institution during the study period.

Fifth, DFI episodes treated elsewhere or before the study period might have been missed, especially for patients residing in Geneva for only a few years. However, because the study centre has been the largest and the only public medical centre for several decades, it is believed that this is unlikely.

Finally, the results might reflect the situation in many Western countries, but cannot be generalized to other regions in resource-poor countries or those in which there is a high burden of community- and healthcare-associated antibiotic-resistant pathogens, where over-the-counter antibiotic agents are widely available, or that have a high prevalence of non-fermenting Gram-negative rods in DFIs (Uçkay et al., 2014).

In conclusion, based on the results of this study, it is suggested that for medical centres similar to this one, the current IDSA recommendations for the empiric oral antibiotic treatment of recurrent mild to moderate DFIs (Lipsky et al., 2012) do not need to be modified to encourage broader spectrum coverage based on a history of past DFI episodes. It would be beneficial for these results to be confirmed at other sites, especially in prospective, patient-level studies.

Ethical approval

Not required for this review.

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Conflict of interest

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Author contributions

All authors contributed to the writing and reviewing of the manuscript.

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