Initial antibiotic therapy for postoperative moderate or severe diabetic foot infections: Broad versus narrow spectrum, empirical versus targeted

Nieuwland, Arend J ; Waibel, Felix W A ; Flury, Andreas ; Lisy, Marcus ; Berli, Martin C ; Lipsky, Benjamin A ; Uçkay, İlker ; Schöni, Madlaina

DOI: https://doi.org/10.1111/dom.15228

Received: 25 April 2023 | Revised: 12 July 2023 | Accepted: 14 July 2023

DOI: 10.1111/dom.15228

ORIGINAL ARTICLE

WILEY

Initial antibiotic therapy for postoperative moderate or severe diabetic foot infections: Broad versus narrow spectrum, empirical versus targeted

Arend J. Nieuwland MD[1] | Felix W. A. Waibel MD[1] | Andreas Flury MD[1] | Marcus Lisy MD[1] | Martin C. Berli MD[1] | Benjamin A. Lipsky MD[2] | İlker Uçkay MD[1,3,4] | Madlaina Schöni MD[1]

[1]Department of Orthopedic Surgery, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

[2]Department of Medicine, University of Washington, Seattle, Washington, USA

[3]Infectiology, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

[4]Unit for Clinical and Applied Research, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

Correspondence
İlker Uçkay, MD, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland.
Email: ilker.uckay@balgrist.ch

Funding information
Universitat Zurich

Abstract

Aim: To retrospectively evaluate clinical and microbiological outcomes after combined surgical and medical therapy for diabetic foot infections (DFIs), stratifying between the empirical versus the targeted nature, and between an empirical broad versus a narrow-spectrum, antibiotic therapy.

Methods: We retrospectively assessed the rate of ultimate therapeutic failures for each of three types of initial postoperative antibiotic therapy: adequate empirical therapy; culture-guided therapy; and empirical inadequate therapy with a switch to targeted treatment based on available microbiological results.

Results: We included data from 332 patients who underwent 716 DFI episodes of surgical debridement, including partial amputations. Clinical failure occurred in 40 of 194 (20.6%) episodes where adequate empirical therapy was given, in 77 of 291 (26.5%) episodes using culture-guided (and correct) therapy from the start, and in 73 of 231 (31.6%) episodes with switching from empirical inadequate therapy to culture-targeted therapy. Equally, a broad-spectrum antibiotic choice could not alter this failure risk. Group comparisons, Kaplan–Meier curves and Cox regression analyses failed to show either statistical superiority or inferiority of any of the initial antibiotic strategies.

Conclusions: In this study, the microbiological adequacy of the initial antibiotic regimen after (surgical) debridement for DFI did not alter therapeutic outcomes. We recommend that clinicians follow the stewardship approach of avoiding antibiotic de-escalation and start with a narrow-spectrum regimen based on the local epidemiology.

KEYWORDS
diabetic foot infections, empirical, postsurgery, targeted antibiotic treatment

Congress workshop: Parts of this manuscript were presented as a poster at the 82th Swiss National Annual Congress for Orthopaedic Surgery and Traumatology (*swissorthopaedics*), 22-24 June 2022, in Basel, Switzerland.

1 | INTRODUCTION

Diabetic foot infections (DFIs) are an increasing burden for both patients and healthcare systems, leading to substantial morbidity,[1–5] high financial costs, and possibly the development of antimicrobial resistance induced by treatment with broad-spectrum antibiotic regimens. Many published studies of antibiotic therapy for DFI have focused on comparing specific regimens,[1,5] routes of administration, or treatment durations.[4] Only a few, however, have considered outcomes associated with the spectrum of antibiotic therapy, especially based on infection severity.[1] Many clinicians fear failing to adequately cover the potential causative pathogens with their initial antibiotic choices. Thus, they often initiate empirical therapy with a broad-spectrum, often intravenous, regimen. When culture results (especially from intraoperatively obtained specimens) become available, clinicians frequently switch to a targeted oral regimen, often selected independently of the severity of infection. As this so-called 'de-escalation' approach is not evidence based, it should perhaps be abandoned in favour of a regimen based on antibiotic stewardship principles.[2]

We hypothesize that for patients with localized DFIs and no evidence of a systemic inflammatory response or suspected bacteraemia, it is not necessary to cover all potential pathogenic microorganisms from the start, especially after undertaking surgical debridement. During the first few days of treatment, adequate surgical debridement may be even more important to curing infection than selecting the right antibiotic agents. Unfortunately, it would be difficult to test our hypothesis by conducting a prospective randomized trial. For example, it would be unethical to randomize patients to inadequate empirical therapy. Furthermore, the appropriateness of therapy can only be defined in retrospect, based on culture and sensitivity results that are not available at the time of randomization. By contrast, we can retrospectively evaluate the clinical and microbiological outcomes after combined surgical and medical therapy for DFIs, stratifying between the empirical versus the targeted nature of the antibiotic therapy.

2 | METHODS

2.1 | Setting and database

The Balgrist University Hospital is a regional referral orthopaedic centre for diabetic foot problems. We conducted a retrospective cohort study of all adult DFI patients seen in our hospital from 1 January 2000 through 31 March 2018 whose treatment included surgical debridement, including partial lower extremity amputations. Our exclusion criteria were patients who had a clinical follow-up time of less than 6 months; required a major lower extremity amputation; had incomplete documentation of their clinical course; or had an orthopaedic implant-related DFI. For our microbiological data, we only used results of specimens taken intraoperatively or, exceptionally, from deep sampling of pus.

2.2 | Study definitions

For this study, we summarized findings based on categorizing patients into one of three different antibiotic choice strategies that we defined. We have analysed these data separately in the following text, tables and figures. We defined 'adequate empirical therapy' as an antibiotic regimen for which the agents correctly targeted all isolated pathogens from the start. We used the term 'empirically inadequate therapy' if the initially selected empirical (not based on culture results) choice was incorrect (some or all of the isolated bacteria were resistant to all of the agents), but the antibiotic regimen was revised based on the culture results when they became available. Very often, the spectrum of coverage was also narrowed when clinicians switched to a targeted regimen. We defined 'culture-guided therapy' as an antibiotic regimen choice that was based on microbiological results that were available from the start of therapy. We further classified the initial antibiotic therapy, based on our own opinions, as 'narrow spectrum' or 'broad spectrum'. We considered therapy broad spectrum if it included the use of cefepime, glycopeptides, carbapenems, daptomycin, ceftazidime, piperacillin-tazobactam or aminoglycosides. Narrow-spectrum antibiotic agents were quinolones, penicillins, first–third generation cephalosporins (except for ceftazidime), tetracyclines, clindamycin and co-trimoxazole. Broad and narrow spectra were classified based on the initial antibiotic choices, and not fixed throughout the course. In our centre, initial broad-spectrum empirical antibiotics are regularly switched to narrower, targeted regimens based on the results of cultures of intraoperative tissue samples. We defined 'resistant pathogens' as those that showed resistance to co-amoxiclav, the antibiotic most frequently used for treating DFIs in Switzerland.[6]

We defined 'remission' after treatment as the absence of any clinical, imaging or laboratory findings suggesting failure of treatment after a minimal follow-up of 6 months after the end of therapy. We defined 'clinical failure' as the need for any surgical revision, or the occurrence of a new DFI episode requiring antibiotic treatment, at the same anatomical site of the foot. Hence, a clinical failure could have many causes, such as progressive or new ischaemia, late development of a diabetic foot ulcer, a bone fracture or a new infection episode. We defined 'microbiological recurrence' as a failure specifically caused by the same pathogen(s) identified from the index (prior) infection. As we lacked microbiological typing of recurrent bacterial strains, we relied on the species identification together with the antibiotic susceptibility testing results.

2.3 | Statistical analyses

For group comparisons, we used the chi-square test for categorical variables, and the student *t*-test for parametric, continuous variables. For non-parametric variables, we used the Mann–Whitney *U*-test. We performed separate risk factor analyses for the endpoints 'clinical failure' and 'microbiological recurrence', using univariate and multivariate Cox regression analyses. For both outcomes, the final models consisted of the following variables: antibiotic treatment strategy; age; biological sex; treatment with broad-spectrum antibiotic therapy; diabetes type; presence of osteomyelitis; presence of peripheral arterial disease; and prior lower extremity amputation(s). We censored the regression model at the date of

TABLE 1 Characteristics of the study population

	All episodes ($n = 716$)
Mean age, y (SD)	66.2 (± 11.6)
Female sex, *n* (%)	147 (20.5%)
Mean body mass index, kg/m^2 (SD)	30.0 (± 5.9)
Diabetes type, *n* (%) • Type 1 • Type 2	 107 (14.9%) 603 (84.2%)
Presence of osteomyelitis, *n* (%)	523 (73.9%)
Chronic renal insufficiency, *n* (%)	355 (49.6%)
Peripheral arterial disease, *n* (%)	526 (73.5%)
Coronary arterial disease, *n* (%)	320 (44.7%)
Smoking history, *n* (%)	421 (58.8%)
Preoperative antibiotic therapy, *n* (%)	529 (73.9%)
Duration of the preoperative antibiotic-free period ('window')	4 days (median)
Total duration antibiotic therapy (median, interquartile range)	22 (14-42) days (median)
Duration of intravenous therapy (median, interquartile range)	8 (5-14) days (median)
Adequate empirical therapy, *n* (%)	194 (27.1%)
Initial use of broad-spectrum antibiotics[a], *n* (%)	498 (69.6%)
Culture-guided therapy, *n* (%)	291 (40.6%)
Inadequate empirical therapy, *n* (%)	228 (31.8%)
Clinical failure, *n* (%)	190 (26.5%)
Microbiological recurrence, *n* (%)	44 (6.1%)
Death for non-infectious reasons of the diabetic foot, *n* (%)	210 (29.3%)

Abbreviations: *n*, number; SD, standard deviation.
[a]Broad-spectrum antibiotic agents = glycopeptides; carbapenems; daptomycin; ceftazidime; cefepime; piperacillin/tazobactam; aminoglycosides.

clinical failure, microbiological recurrence, death for any reason, or the last medical (surgical) control in our clinic. Importantly, we did not censor after a maximal follow-up time in cases with an event-free follow-up. In addition to the multivariate analyses, we compared survival data using a log-rank test and plotted them with Kaplan–Meier curves. We used SPSS (IBM, version 26) and STATA software (version 15, College Station, TX).

3 | RESULTS

3.1 | Study population and infections

We included a total of 716 DFI cases that occurred in 332 adults (253 males, 79 females; median age 66 years; median body mass index 28 kg/m^2; Table 1). Bone was infected in 523 (73%) of cases. Of all the DFIs, 86% involved the forefoot, 8% the midfoot and 3% the hindfoot (2% in the calcaneus).[7] The type of diabetes was type 2 diabetes in 84% of cases. Angioplasty of the involved lower extremity was performed in 373 cases (52%). The duration of clinical follow-up after therapy for DFIs ranged from 0.5 to 20 (median 2.9 [interquartile range 1.4-5.0]) years. In our surgical clinic, very few of the cases were classified as mild or severe, according to the Infectious Diseases Society of America (IDSA) criteria.[1] The majority were of moderate severity[1] and were often complicated by limb ischaemia.[8] However, we cannot provide the exact proportion of cases in each severity category because of the retrospective nature of our assessment and the overlapping case mix of infection severity with osteomyelitis[1] and/or ischaemia.[8] Also, there are several classification schemes targeting different aspects of DFI disease, which is multifaceted. For example, the IDSA system[1] is pertinent for classifying infected ulcers with osteomyelitis, whereas the more recent Wound-Ischaemia-Foot Infection classification is best for evaluating the interaction of infection with concomitant ischaemia.[8] At the inclusion of the last episode on 11 December 2018, 91 patients (27%) had died, all from non-infectious causes, after a median of 3.3 years following their index infection.

3.2 | Pathogens

Among the study population, our microbiology laboratory (Medizinische Mikrobiologie, Universitätsspital Zurich) identified 99 different microbiological constellations from cultures of wound specimens. The five most frequently isolated pathogen groups[1] were coagulase-negative staphylococci (32.8%, $n = 235$), *Staphylococcus aureus* (27.1%, $n = 194$), *Enterococcus* spp. (11.9%, $n = 85$), *Streptococcus* spp. (7.8%, $n = 56$) and *Pseudomonas* spp. (6.4%, $n = 46$). In 231 episodes (32%), the infection was polymicrobial. In 112 DFI cases (112/716; 16%), at least one of the predominant pathogens was (naturally, or intrinsically) resistant to co-amoxiclav, which is the 'standard' drug used for treating DFIs in Switzerland.[6] In this study, we have only reported microorganisms that we considered causative pathogens of the DFI. Because we aim to collect specimens for culture aseptically (usually intraoperatively), and all our patients had diabetes, all the isolates cultured (including those commonly viewed as of low virulence) are infectious agents.

3.3 | Antibiotic regimens

Preoperative antibiotic therapy was administered in 529 (73.9%) of our DFI cases. The treating clinicians (most frequently general practitioners) prescribed 59 different regimens and dosing schemes, with a mean preoperative duration of treatment of 11 days. Postoperatively, the mean total duration of antibiotic therapy was 19 (range 1-193) days, of which the initial 5 days was administered intravenously (range 1-50 days). Overall, we prescribed 71 different treatment regimens, based on the isolated pathogens, their susceptibility profiles, potential drug interactions, the clinicians' personal choice and the other existing

TABLE 2 Associations of the initial postoperative antibiotic choice with final outcomes

Early postoperative antibiotic therapy	Clinical failure ($n = 190$)	Remission ($n = 526$)	*P* value
Adequate empirical treatment throughout the course	40	192	Not significant
Culture-guided (and correct) therapy from the start	77	131	Not significant
Empirically inadequate therapy with a switch to correct targeted and narrowed therapy	73	203	Not significant

TABLE 3 Cox regression analyses of outcomes for 'clinical failure' and 'microbiological recurrence' (the results are expressed as hazard ratios [HRs] and 95% confidence intervals [CIs])

	Clinical failure ($n = 190$)		Microbiological recurrence ($n = 44$)	
	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)
Antibiotic therapy[a]				
- Adequate empirical	Reference 1	Reference 1	Reference 1	Reference 1
- Culture-guided	1.4 (0.9-2.0)	1.1 (0.6-1.9)	***2.7 (1.0-7.3)***	1.1 (0.4-3.3)
- Empirically inadequate	***1.7 (1.1-2.5)***	1.1 (0.6-2.0)	***3.7 (1.4-9.8)***	1.5 (0.5-4.4)
Age	1.0 (0.99-1.01)	0.99 (0.98-1.01)	1.0 (0.97-1.02)	1.0 (0.97-1.02)
Female sex	0.7 (0.5-1.0)	0.7 (0.4-1.1)	0.5 (0.2-1.2)	0.5 (0.2-1.4)
Narrow-spectrum antibiotics[b]	Reference 1	Reference 1	Reference 1	Reference 1
Broad-spectrum antibiotics[c]	***1.7 (1.2-2.5)***	***1.8 (1.2-2.8)***	1.6 (0.8-3.2)	1.5 (0.7-3.2)
Presence of osteomyelitis	1.0 (0.7-1.6)	1.0 (0.6-1.6)	1.3 (0.8-1.9)	1.4 (0.9-2.2)
Peripheral arterial disease	***1.6 (1.1-2.3)***	1.2 (0.8-1.8)	1.1 (0.5-2.1)	0.7 (0.3-1.6)

Note: Statistically significant results are in bold italic.
[a]See text for definitions.
[b]Narrow-spectrum antibiotic agents = quinolones; penicillins; first–third generation cephalosporins; tetracyclines; clindamycin; co-trimoxazole.
[c]Broad-spectrum antibiotic agents = glycopeptides; carbapenems; daptomycin; ceftazidime; cefepime; piperacillin/tazobactam; aminoglycosides.

co-morbidities of the patient. In 35% of cases, the treating clinicians started therapy with several antibiotic agents simultaneously.

Using our scheme, the initial therapy was classified: 'adequate empirical' in 194 cases (27%); 'culture-guided' from the start in 291 episodes (41%); and 'empirically inadequate' in 228 cases (32%) (Table 1). In only three patients, no antibiotic therapy was started initially, but each had residual bone samples. These episodes concerned cultures of a specimen of bone taken after the surgeons had removed all infected bone. Among all cases, using our definition, the initial antibiotic choice was broad spectrum for 386 (54%) of the DFI episodes. During the course of therapy, the initial antibiotic regimen was changed in 473 (66%) of the DFI episodes. The reasons for change were mostly to de-escalate treatment (narrow the spectrum or switch from intravenous to oral administration). Only one-third of patients continued with the initially prescribed antibiotic regimen to the end of treatment.

3.4 | Clinical failures and microbiological recurrences

Overall, there were 190 cases (26.5%) classified as a clinical failure by our definition. Among DFI episodes, clinical failure ultimately occurred in 40 of 194 (20.6%) episodes treated with 'adequate empirical therapy' throughout the course of treatment, in 77 of 291 (26.5%) episodes treated with a correct 'culture-guided' regimen from the start, and in 73 of 231 (31.6%) episodes treated with 'empirically inadequate therapy' that was switched to a correct (and mostly narrowed) targeted regimen (Table 2). The clinical failures were related to several factors, including foot ischaemia, new infection episodes and the appearance of a new (uninfected) foot ulcer. Few of the failures were infectious, that is, caused by another, new, DFI. Only 44 microbiological recurrences (6.1%) occurred after the end of therapy for the index episode. These occurred in five of 194 (2.6%) cases after 'adequate empirical therapy'; in 19 of 291 (6.5%) cases with 'culture-guided therapy' therapy; and in 20 of 231 (8.7%) cases with initial 'empirically inadequate therapy' (Table 2). Of note, the incidence of multidrug resistance among the bacteria isolated in cases of clinical failure (i.e. a potential selection by prior antibiotics) was only 2%.[1]

3.5 | Multivariate adjustments

The case mix of patients included in our study population was large. By univariate Cox regression analysis, the following variables were associated with clinical failure: switch-to-targeted treatment (hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.1-2.5); broad-spectrum therapy (HR 1.7, 95% CI 1.2-2.5); documented presence of coronary heart disease (HR 1.4, 95% CI 1.1-1.9), peripheral arterial disease

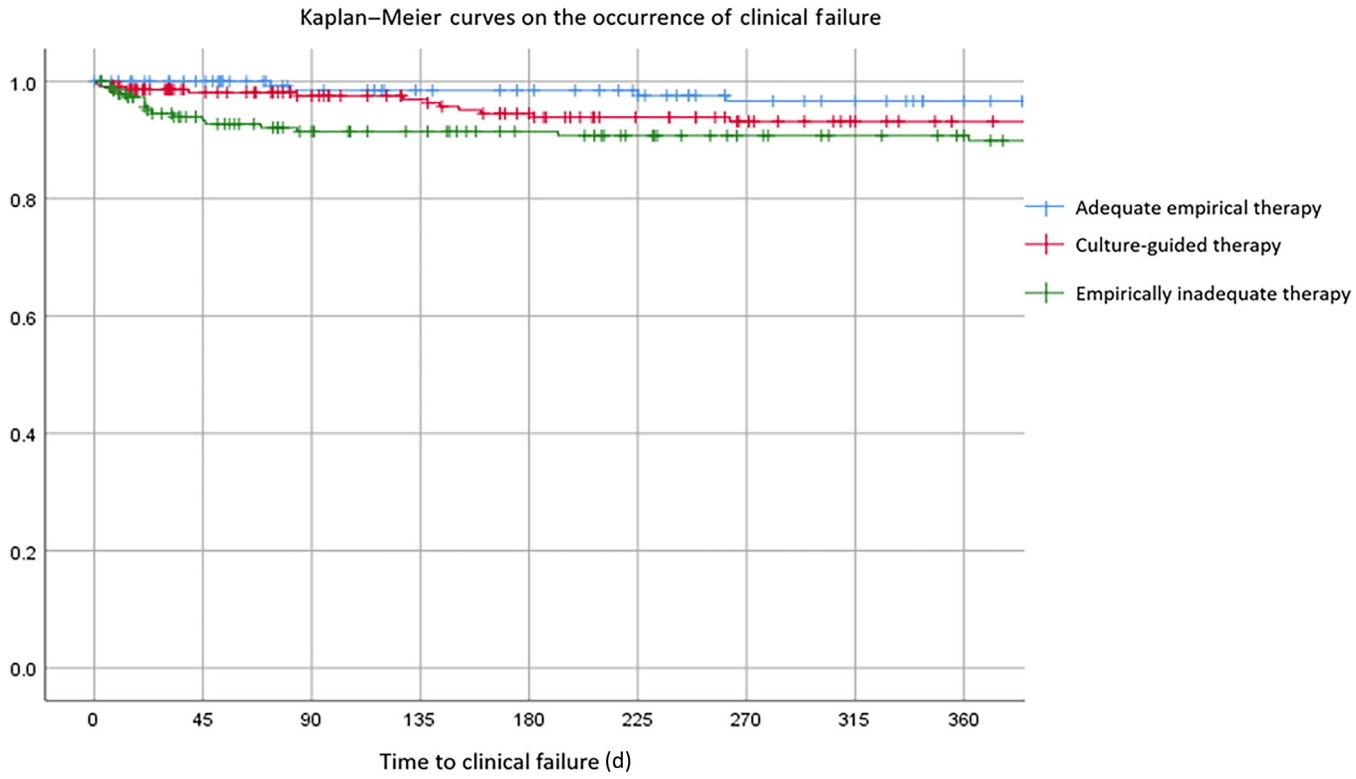

FIGURE 1 Kaplan–Meier survival estimate curves regarding surgical revisions.

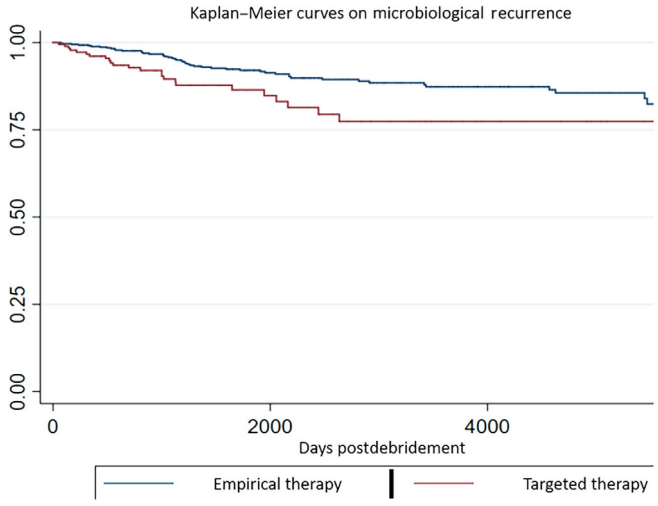

FIGURE 2 Kaplan–Meier survival estimate curves regarding microbiological recurrences, which we consider to be the most important outcome specifically related to the antibiotic treatment in diabetic foot infections.

(HR 1.6, 95% CI 1.1-2.3) or history of previous amputation (HR 2.0, 95% CI 1.0-3.8) (Table 3). The presence of osteomyelitis was not associated with clinical failure. In the corresponding multivariate analysis, the only factors that remained significantly associated with clinical failure were initial broad-spectrum antibiotic therapy (HR 1.8, 95% CI 1.2-2.8) and documented coronary heart disease (HR 1.4, 95% CI 1.0-2.0) (Table 3). Compared with 'adequate empirical therapy', neither 'culture-guided therapy' nor 'empirically inadequate therapy' with a delayed switch to targeted regimens was associated with 'clinical failure' or 'microbiological recurrence' (Table 3).

3.6 | Survival data

The Kaplan–Meier curves on the occurrence of clinical failure after surgical revisions are shown in Figure 1. Figure 2 displays the Kaplan–Meier curves for microbiological recurrence, showing insignificant differences (log-rank test; $P = .13$) between 'empirically inadequate' and 'culture-guided' therapies over a surveillance period of several years.

3.7 | Use of initial broad-spectrum antibiotic therapy

Use of an initial broad-spectrum antibiotic regimen did not prevent 'clinical failure', but was positively correlated with it. We interpreted this as confounding by indication. Use of broad-spectrum agents was, however, associated with the need for revascularization (192/373 [51%] episodes with vascularization vs. 176/387 [45%] cases without; $P = .09$), major amputations ($P < .01$) or osteomyelitis ($P < .01$).[1]

4 | DISCUSSION

The results of our investigation show that, for patients who underwent surgical operations for a DFI, therapy with an initial empirical

postoperative antibiotic regimen was as effective as targeted culture-guided therapy, whether the initial empirical choice was adequate (based on results of culture) or not. While others may be, we are not surprised by our findings. The selection of an antibiotic regimen is only one part of the multifaceted management of DFIs, which requires concomitant attention to appropriate wound care, pressure off-loading, optimized glycaemic control and assessment for possible need for revascularization or other surgery.[3] In the literature, few if any antibiotic-related variables have been found to influence key treatment outcomes.[1,4,6,7,9–19]

We agree with the International Working Group on the Diabetic Foot/IDSA infection guidelines position that an initial, empirical broad-spectrum antibiotic regimen should be reserved for severe (septic) DFI cases, unless it is administered as targeted or empirical treatment for known or suspected multidrug-resistant pathogens.[1,18] Unfortunately, many clinicians also select broad-spectrum antibiotic coverage in locally complicated DFI cases marked by ischaemia, destructive osteomyelitis or multiple co-morbidities. Some are seeking the possibility of better tissue (especially bone) penetration of intravenous formulations, which are often associated with a broader spectrum than oral drugs.[18–20] Available studies suggest, however, that even if in vitro data show differences in oral bio-availability or penetration into the infected bone, almost none show that any specific oral or intravenous agents result in better outcomes than others.[6,21,22] Our own retrospective data show that, even for DFI episodes associated with significant ischaemia, the use of intravenous (compared with oral) antibiotic agents does not alter the outcomes.[9]

In the absence of strong evidence favouring the administration of initial broad-spectrum regimen therapy for all or most DFIs, are there methods that help clinicians decide when they might select this approach for individual patients? Theoretically, we could consider using existing laboratory methods, such as new molecular microbiological innovations, to identify pathogens more rapidly,[23] or guide our pre-emptive choice by determining if there is body colonization (e.g. anterior nares) with multiresistant pathogens. However, these innovative and comparatively new techniques have been developed for addressing monomicrobial bloodstream infections, which are rare in the typically polymicrobial setting of chronic DFIs.[23] Additionally, the required equipment is comparatively expensive, and not available in many settings. Furthermore, using molecular identification of healthcare-associated methicillin-resistant *Sta. aureus* (MRSA) body carriage does not necessarily predict methicillin resistance in soft-tissue infections,[24] including for the diabetic foot. Indeed, a patient colonized with MRSA may simultaneously have a foot infected with a methicillin-susceptible *S. aureus*.[25] Likewise, anal carriage of extended-spectrum-beta-lactamase–carrying gram-negative rods[26] does not predict a gram-negative orthopaedic infection among patients hospitalized in septic isolation orthopaedic wards with a high proportion of DFI patients.[26]

One simple, inexpensive and traditional approach to selecting antibiotic therapy is to examine a Gram-stained smear of appropriately collected infected specimens. In stable DFI patients who have undergone wound debridement, clinicians might wait for the results of a bedside-collected sample before starting antibiotic treatment. This approach has been investigated by clinicians in Tanzania[27] and practised in Geneva, Switzerland, by one of the authors of this study (IU). The Tanzanian study investigated the predictive accuracy of the Gram-stained smear of tissue specimen, which was processed and interpreted by a trained microbiology technician.[27] They found an overall positive predictive value of the Gram stain ranging from 86% to 100% for the growth of bacteria with a corresponding gram profile. Specifically, smears showing gram-negative organisms were 82% predictive of growth of gram-negative organisms. There were just two discordant stain/culture pairs, giving 96.4% congruency between the Gram-stain appearance and ultimate culture results.[27] Even if such a waiting approach seems possible (given the lack of a negative impact of a wrong initial choice), our study did not address this particular question. Of note, clinicians should not see the presence of Gram-negative bacteria as requiring immediate antipseudomonal therapy, which would trigger excessively broad treatment for many patients in most parts of the world. Also, the local microbial epidemiology (pathogens and their susceptibilities), the severity of the infection and the clinical context play an important role in the selection of the empirical antibiotic therapy.[28]

An alternative to the Gram-stain method is staining with agents such as Acridine orange.[29] Clinicians should also use their various senses when examining the wound, including visual interpretation of the finding, and characteristics of any odour, especially regarding the presence of *Pseudomonas aeruginosa*. However, the limited data suggest that results for the clinical guesses made regarding the infective agents in infected foot wounds, without any laboratory help, are disappointing.[28] Other possible aids (where available) might include the use of fluorescent light sources, and rapid diagnostic assays such as PCR.[28]

In our literature review we found only one previous publication that addressed a similar study question to the one we posed in this study. Schindler et al.[30] followed 342 orthopaedic implant infections for a median of 3.5 years. The median duration of empirical postsurgical antibiotic treatment was 3 days, before switching to a targeted antibiotic regimen. The empirical antibiotic choices (269, 79%) adequately covered the causative pathogen(s), but they were too broad in 32% of all episodes. Multivariate Cox regression analysis showed that neither selecting correct antibiotic coverage, nor prescribing broad-spectrum therapy (HR 1.1, 95% CI 0.8-1.5), affected the final remission rates. The authors called for a more rational use of empirical antibiotic agents, especially after surgical intervention, a sentiment with which we agree.

Our study has obvious limitations. Besides its retrospective design and the corresponding 'confounding by indication', our cohort primarily consisted of moderate or severe DFI cases that underwent surgical procedures. Thus, we cannot address the relevance of our results to mild DFI episodes, or on a strictly non-operative pharmaceutical management of DFIs. Secondly, our clinic employs infectious diseases physicians who are highly specialized in orthopaedic and diabetic infections,[1,12–14] which might theoretically reduce the likelihood of an inadequate choice. Thirdly, by concentrating on our study question, we chose not to analyse the impact of other variables that have been separately investigated, such as the antibiotic-related costs, adverse events of broad-spectrum

therapies,[12,13,28] quality of wound debridement,[14] total duration of postoperative antibiotic treatment,[4,12,13] glycaemic control,[2,15] malnutrition,[16] or other immune suppressed states beyond that of diabetes.[17] Fourthly, because we live in a resource-rich, small city with a low endemicity of multiresistant pathogens, our outcomes could be different from those in settings with a high endemicity of community-acquired resistances. Lastly, we only had very few microbiological recurrences (6% of cases). While the statistical analyses regarding clinical failures are adequate, it could be underpowered and less conclusive for the few recurrence cases.

In conclusion, while it is almost always preferable to use the results of appropriate collected cultures and antibiograms to tailor a targeted antibiotic regimen for moderate or severe DFIs, sometimes this is not possible. In our study, after the surgical debridement of moderate or severe local DFIs,[5] the clinical efficacy of 'adequate empirical therapy' was similar to that of 'culture-guided therapy', and to that of a delayed switch from 'empirically inadequate therapy' to a targeted antibiotic regimen. Likewise, we found that selecting an initial broad-spectrum antibiotic regimen, compared with an initial narrow-spectrum regimen, failed to reduce the overall risk of clinical failure in treating localized DFIs. Our findings are important regarding employing effective antibiotic stewardship in the global management of DFIs.[1–3,18] We therefore advocate for considering a narrow-spectrum postoperative antibiotic regimen in stable patients with local DFIs that have been surgically debrided.[2,30]

AUTHOR CONTRIBUTIONS

Conceptualization: FWAW, IU and MS. Methodology: FWAW, IU and MS. Validation: FWAW, ML, AF and MS. Investigation: AJN, MS, IU, AF, ML, MCB and FWAW. Resources: MS, FWAW, ML, IU and MCB. Data curation: AJN, IU and MS. Data collection: AJN, MCB, AF, MS and IU. Data analysis: MS and IU. Analysis verification: IU and MS. Writing, original draft preparation: AJN, AF, IU, ML and MS. Writing, review and editing: AJN, FWAW, MS, BAL and IU. Visual: IU. Supervision: IU, FWAW and MS. Project administration: AJN, FWAW, IU and MS. All authors have agreed to the published version of the manuscript.

ACKNOWLEDGEMENTS

We are indebted to the study nurses of the Unit for Clinical and Applied Research (UCAR) for their invaluable help. Open access funding provided by Universitat Zurich.

CONFLICT OF INTEREST

Each of the authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15228.

DATA AVAILABILITY STATEMENT

Key data may be available in an anonymized form upon scientific request to the corresponding author.

ORCID

İlker Uçkay https://orcid.org/0000-0002-5552-0973

REFERENCES

1. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:132-173.
2. Uçkay I, Berli MC, Sendi P, Lipsky BA. Principles and practice of antibiotic stewardship in the management of diabetic foot infections. *Curr Opin Infect Dis*. 2019;32:95-101.
3. Uçkay I, Gariani K, Pataky Z, Lipsky BA. Diabetic foot infections: state-of-the-art. *Diabetes Obes Metab*. 2014;16:305-316.
4. Gariani K, Lebowitz D, von Dach E, Kressmann B, Lipsky BA, Uçkay I. Remission in diabetic foot infections: duration of antibiotic therapy and other possible associated factors. *Diabetes Obes Metab*. 2019;21:244-251.
5. Byren I, Peters EGJ, Hoey C, Berendt A, Lipsky BA. Pharmacotherapy of diabetic foot osteomyelitis. *Expert Opin Pharmacother*. 2009;10:3033-3047.
6. Gariani K, Lebowitz D, Kressmann B, et al. Oral amoxicillin-clavulanate for treating diabetic foot infections. *Diabetes Obes Metab*. 2019;21:1483-1486.
7. Waibel FWA, Klammer A, Götschi T, Uçkay I, Böni T, Berli MC. Outcome after surgical treatment of calcaneal osteomyelitis. *Foot Ankle Int*. 2019;40:562-567.
8. Mills JL Sr, Conte MS, Armstrong DG, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischaemia, and foot infection (WIfI). *J Vasc Surg*. 2014;59:220-234.
9. Altmann D, Waibel FWA, Forgo G, et al. Timing of revascularization and parenteral antibiotic treatment associated with therapeutic failures in ischemic diabetic foot infections. *Antibiotics (Basel)*. 2023;12:685.
10. Selva Olid A, Sola I, Barajas-Nava LA, et al. Systemic antibiotics for treating diabetic foot infections. *Cochrane Database Syst Rev*. 2015;9:Cd009061.
11. Peters EJ, Lipsky BA, Aragon-Sanchez J, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32:145-153.
12. Gariani K, Pham TT, Kressmann B, et al. Three weeks versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: a prospective, randomized noninferiority pilot trial. *Clin Infect Dis*. 2021;73:1539-1545.
13. Pham TT, Gariani K, Richard JC, et al. Moderate to severe soft tissue diabetic foot infections: a randomized, controlled, pilot trial of post-debridement antibiotic treatment for 10 versus 20 days. *Ann Surg*. 2022;276:233-238.
14. Haug F, Waibel FWA, Lisy M, Winkler E, Uçkay I, Schöni M. The impact of the length of total and intravenous systemic antibiotic therapy for the remission of diabetic foot infections. *Int J Infect Dis*. 2022;120:179-186.
15. Moret CS, Schöni M, Waibel FWA, et al. Correction of hyperglycemia after surgery for diabetic foot infection and its association with clinical outcomes. *BMC Res Notes*. 2022;15:264.
16. Uçkay I, Yogarasa V, Waibel FWA, et al. Nutritional interventions may improve outcomes of patients operated on for diabetic foot infections: a single-center case-control study. *J Diabetes Res*. 2022;2022:9546144.
17. Uçkay I, Schöni M, Berli MC, et al. The association of chronic, enhanced immunosuppression with outcomes of diabetic foot infections. *Endocrinol Diabetes Metab*. 2022;5:00298.
18. Lipsky BA, Senneville E, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36:3280.

19. Abbas M, Uçkay I, Lipsky BA. In diabetic foot infections antibiotics are to treat infection, not to heal wounds. *Expert Opin Pharmacother*. 2015;16:21-32.
20. Betz M, Landelle C, Lipsky BA, Uçkay I. Letter to the editor concerning the review of Prof. Sheldon L. Kaplan "recent lessons for the management of bone and joint infections"-bacteriostatic or bactericidal agents in osteoarticular infections? *J Infect*. 2015; 71:144-146.
21. Preiss H, Kriechling P, Montrasio G, et al. Oral Flucloxacillin for treating osteomyelitis: a narrative review of clinical practice. *J Bone Jt Infect*. 2020;5:16-24.
22. Abbas M, Rossel A, de Kraker MEA, et al. Association between treatment duration and mortality or relapse in adult patients with *Staphylococcus aureus* bacteraemia: a retrospective cohort study. *Clin Microbiol Infect*. 2020;26:626-631.
23. Emonet S, Charles PG, Harbarth S, et al. Rapid molecular determination of methicillin resistance in staphylococcal bacteraemia improves early targeted antibiotic prescribing: a randomized clinical trial. *Clin Microbiol Infect*. 2016;22:946.
24. Reber A, Moldovan A, Dunkel N, et al. Should the methicillin-resistant *Staphylococcus aureus* carriage status be used as a guide to treatment for skin and soft tissue infections? *J Infect*. 2012; 64:513-519.
25. Landelle C, Iten A, Uçkay I, et al. Does colonization with methicillin-susceptible *Staphylococcus aureus* protect against nosocomial acquisition of methicillin-resistant *S. aureus*? *Infect Control Hosp Epidemiol*. 2014;35:333-527.
26. Agostinho A, Renzi G, Haustein T, et al. Epidemiology and acquisition of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in a septic orthopedic ward. *Springer Plus*. 2013;2:91.
27. Abbas ZG, Lutale JK, Ilondo MM, Archibald LK. The utility of gram stains and culture in the management of limb ulcers in persons with diabetes. *Int Wound J*. 2012;9:677-682.
28. Uçkay I, Holy D, Schöni M, et al. How good are clinicians in predicting the presence of *pseudomonas* spp. in diabetic foot infections? A prospective clinical evaluation. *Endocrinol Diabetes Metab*. 2021;4:00225.
29. Cunningham G, Seghrouchni K, Ruffieux E, et al. Gram and acridine orange staining for diagnosis of septic arthritis in different patient populations. *Int Orthop*. 2014;38:1283-1290.
30. Schindler M, Gamulin A, Belaieff W, et al. No need for broad-spectrum empirical antibiotic coverage after surgical drainage of orthopaedic implant infections. *Int Orthop*. 2013;37:2025-2030.

How to cite this article: Nieuwland AJ, Waibel FWA, Flury A, et al. Initial antibiotic therapy for postoperative moderate or severe diabetic foot infections: Broad versus narrow spectrum, empirical versus targeted. *Diabetes Obes Metab*. 2023;1-8. doi:10.1111/dom.15228