ORIGINAL ARTICLE

Stopping antibiotics after surgical amputation in diabetic foot and ankle infections—A daily practice cohort

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Summary

Objective: The appropriate duration of antibiotic therapy for diabetic foot infections (DFI) after surgical amputations in toto is debated. There are discrepancies worldwide.

Methods: Using a clinical pathway for adult DFI patients (retrospective cohort analysis), we conducted a cluster-controlled Cox regression analysis. Minimum follow-up was 2 months.

Results: We followed 482 amputated DFI episodes for a median of 2.1 years after the index episode. The DFIs predominately affected the forefoot (n = 433; 90%). We diagnosed osteomyelitis in 239 cases (239/482; 50%). In total, 47 cases (10%) were complicated by bacteremia, 86 (18%) by abscesses and 139 (29%) presented with cellulitis. Surgical amputation involved the toes (n = 155), midfoot (280) and hindfoot (47). Overall, 178 cases (37%) required revascularization. After amputation, the median duration of antibiotic administration was 7 days (interquartile range, 1-16 days). In 109 cases (25%), antibiotics were discontinued immediately after surgery. Overall, clinical failure occurred in 90 DFIs (17%), due to the same pathogens in only 38 cases. In multivariate analysis, neither duration of total postsurgical antibiotic administration (HR 1.0, 95% CI 0.99-1.01) nor immediate postoperative discontinuation altered failure rate (HR 0.9, 0.5-1.5).

Conclusion: According to our clinical pathway, we found no benefit in continuing postsurgical antibiotic administration in routine amputation for DFI. In the absence of residual infection (ie, resection at clear margins), antibiotics should be discontinued.

KEYWORDS
antibiotic duration, diabetic foot infections, failure, osteomyelitis, post-amputation

1 | INTRODUCTION

Diabetic foot infections (DFIs)[1-3] frequently require amputation, also because of concomitant ischaemia. In these cases, surgeons and physicians regularly debate the duration of post-amputation antibiotics, even in the absence of residual clinical signs of infection. Only a small minority of stump complications[4,5] are due to infections. Clinical practice varies worldwide: centres developed strategies using microbiological assessment of residual bone, systematic empirical continuation of antibiotics or case-by-case decision. According to an informal survey among specialized surgeons and physicians, antibiotic duration following amputation at clear margins varies between 0 days and 6 weeks. Moreover, the methods used to assess residual bone stump infection (biopsy through uninfected area with new sterile instruments vs open biopsy of the surgical site[6]) also vary significantly (*personal communications*).

International guidelines recommend post-amputation antibiotics only for remaining soft tissue infections and/or during a maximum of 2-5 days,[2,7] if bone resection was achieved at "clear margins" (low grade evidence). However, due to high rates of poor outcomes of these amputation wounds,[1] it is a common practice to prolong antibiotic therapy unnecessarily, potentially resulting in drug-related adverse effects and costs, and possible development of antibiotic resistance.[8] We previously published a retrospective study on the continuation of antibiotic prophylaxis in leg amputations and found no benefit in doing so.[5] In this study, we used our clinical pathway to question the continuation of post-amputation antibiotics.

2 | METHODS

The Geneva University Hospitals has a databank (clinical pathway) for DFI.[9] The data are prospectively entered and now retrospectively analysed. This study occurred between 1 March 2014 and 30 April 2018. Surgeons in the orthopaedic service do not perform routine microbiological assessment (histology and/or microbiological cultures) of residual bone following amputation and do not use topical antibiotics intraoperatively or on the wounds.[10,11] Specialized nurses provide professional wound care (including minimal debridement) on the ward, specifically dedicated to septic orthopaedic and amputation patients. All patients are actively followed up in our clinical pathway. The infectious diseases physicians and the surgeons deciding the duration of antibiotic therapy are part of the Pathway Committee.[9,12] As part of a hospital-wide quality programme, DFI patients participating in the clinical pathway were not required to provide individual consent for storing anonymous data. These patients also participated in other DFI trials (Ethical Committee No. 13-178).

2.1 | Definitions and criteria

We used DFI definitions based on the IDSA guidelines criteria, which require clinical signs and symptoms of inflammation.[2] We included all DFI patients that were amputated or disarticulated in toto. Distal tibia and ankle amputations were included. We excluded amputations with no clinical signs of infection, regardless of microbiology results,[13] mid-tibia amputations, implant-related DFI and patients with <2 months of active follow-up. Osteomyelitis was diagnosed using clinical features (eg, visible bone), imaging (bone lesions without prior surgery or trauma[14]) or microbiology (bacterial growth from surgically obtained bone specimens). We defined clinical failure as subsequent episodes of DFI occurring at the same location within 12 months. DFIs occurring later (ie, onset >12 months) were arbitrarily considered as new episodes. Microbiological failure was defined as recurrent DFI involving at least two of three pathogens from the index DFI recovered in deep tissue specimens. Remission was the absence of any clinical, laboratory or radiological evidence of failure at the end of follow-up. We considered antibiotics as broad-spectrum if piperacillin/tazobactam, glycopeptides, daptomycin, carbapenems or cefepime was used.

2.2 | Statistical analyses

We performed group comparisons using the Pearson chi-square test or the Wilcoxon rank-sum test. Cox regression analyses with cluster-control (random effect at patients' level) determined associations with failure. DFI episodes were censored at the last follow-up or occurrence of failure. We introduced independent variables having a *P* value ≤0.05 in the univariate analysis in a stepwise fashion in the multivariate model and checked for interaction (effect modification); antibiotic administration was automatically included into the final model. Age, total duration of antibiotic administration and duration of parenteral therapy were analysed both as continuous and categorical variables. The cut-off values of the strata were chosen according to the middle stratum positioned around the median value of that variable. We used Stata software (9.0, Stata™, College Station, TX, USA).

3 | RESULTS

3.1 | Patients

We followed 482 DFI episodes involving amputation occurring in 258 different patients for a minimal duration of 2 months and a median of 2.1 years after the index episode (interquartile [IQR] range, 0.6-6.5 years). Median age was 71 years, 118 (46%) patients were female, median body mass index 27.5 kg/m^2, median index serum C-reactive protein levels was 89 mg/L (IQR, 32-187 mg/L), median glycated haemoglobin level was 7.0 mmol/L (IQR, 6.1-8.5 mmol/L), median transcutaneous oxygen tension was 42 mm Hg (IQR, 34-52 mm Hg), and median ankle-brachial index was 0.9 (IQR, 0.7-1.2). In two-thirds (320/482; 66%) of episodes, there was peripheral arterial disease with signs of cutaneous ischaemia. In 308 cases (64%), diabetes was treated with insulin. Median duration of diabetes was 15 years (IQR, 7-23 years). Most patients were not naïve regarding prior surgery: overall, 182 patients (182/258; 71%)

had any previous surgical procedure performed on their foot or ankle.

3.2 | Infections

The DFIs predominately affected the forefoot (n = 433; 90%), of which 39 cases involved the hallux only. We localized 20 DFIs in the metatarsal region, 24 in the calcaneum, and five in the ankle; there was no septic arthritis of the ankle. Infections extended to the distal leg in 42 (9%) episodes. We diagnosed osteomyelitis in 239 cases (239/482; 50%), including 7 with sequestrae. In total, 47 cases (10%) were complicated by bacteremia, 86 (18%) presented with soft tissue abscesses, and 139 (29%) with cellulitis. By notifying the three most prevalent microorganisms per DFI episode in our pathway, we detected 102 different microbiological combinations among the study population, with the four most frequently identified pathogens being *Staphylococcus aureus* (214 episodes, of which 53 were methicillin-resistant[15]), enterococci[16] (n = 60), streptococci (n = 53) and Gram-negative pathogens[17] (n = 190, of which 35 *Pseudomonas aeruginosa* cases[18,19]). Overall, 235 episodes (49%) were polymicrobial.[19]

3.3 | Amputations and other invasive procedures

Surgical amputation included the toes (n = 155), midfoot (n = 280) and hindfoot (n = 47). Surgeons avoided amputation across overtly infected areas. All disarticulations or amputations occurred at visually safe levels. Median number of surgical interventions was 1 (IQR, 1-1 intervention), and median length of postsurgical hospital stay was 34 days (IQR, 17-56 days). All patients received specialized wound care with adequate offloading during and after hospitalization. In 178 cases (37%), endovascular revascularization was performed, and in 64 episodes (15%), patients underwent 30 sessions of hyperbaric oxygen therapy. In 28 episodes (6%), vacuum-assisted device was used for wound healing for a median duration of 7 days.

3.4 | Antibiotic administrations

Prior to admission or initial surgical procedure, 96 episodes (20%) already received systemic antibiotic therapy,[20] but exact data on duration or dosage are lacking. Following amputation, median duration of systemic antibiotic administration was 7 days (IQR, 1-16 days) and median duration of parenteral use was 5 days (IQR, 0-12 days). The entire antibiotic course was intravenous in 97 (20%) cases and oral in 69 cases (including perioperatively). In 109 cases (109/428; 25%), surgeons or physicians discontinued antibiotic administration immediately after amputation. The pathogens of these cases were not special or different from DFIs with antibiotic continuation. For example, *P aeruginosa*,[18] acknowledged as a major DFI pathogen leading to limb loss,[19] was as much present in DFIs with direct stop of post-amputation antibiotics as episodes with antimicrobial continuations (7/35 vs 102/551, P = 0.83). Overall, 128 different antimicrobial regimens were used, of which 144 (30%) included

broad-spectrum antibiotics. The five most frequently used drugs were amoxicillin/clavulanate (n = 229), quinolones (n = 104; 18 cases as the only monotherapy), co-trimoxazole (n = 43), clindamycin (n = 32; five episodes as the sole monotherapy) and rifampicin in combination therapy (n = 25).

3.5 | Outcomes

Among 482 amputation stumps, clinical failure at the same anatomical site occurred in 90 cases (17%) within one year. However, only 38 were microbiological failures (ie, due to the same microorganisms; 38/482; 8%). There was at least partial concordance of the three dominant pathogens isolated from wound cultures between the initial and subsequent DFI episodes in only 42% of cases. Hence, the majority of subsequent DFI episodes (58%) were "clinical recurrences", rather than "microbiological recurrences" according to our definitions. Additionally, progressive ischaemia without clinical DFI occurred in 38 episodes (8%). At the end of the study, 86 patients had died for various reasons unrelated to acute DFI, even if eight of them were bacteremic (for another infection) during their hospital stay.

Table 1 compares demographic, clinical and treatment characteristics for all patients, stratified according to the outcomes "clinical" vs "microbiological recurrence". Hereby, no variable was associated with failure. Of note, neither total duration of post-amputation antibiotic therapy nor immediate postoperative discontinuation of antimicrobials after surgery influenced failure rate. In the subgroup of microbiological failure, angioplasty (prior to or immediately after surgery) was protective and patients received antibiotics for a longer duration. We found no difference in clinical recurrence according to the various antibiotics we used, or when comparing the success in polymicrobial DFIs compared to monomicrobial episodes (46/109 vs 185/523; P = 0.18). Also, these would be other study questions, of which the results have been published previously.[9]

3.6 | Multivariate adjustment

In view of the considerable case-mix inherent in DFI, we performed a Cox regression analysis. Specifically, stump failures were not associated with antibiotic therapy-related variations, limb revascularization, insulin therapy, surgical interventions, use of vacuum-assisted devices, or presence of abscesses or former hindfoot osteomyelitis. Table 2 shows these results for the entire study population and separately for cases with osteomyelitis. Total duration of antibiotic therapy and intravenous antibiotic therapy (as continuous variables) had a hazard ratio (HR) of 1.0, with narrow confidence intervals (95% CI 0.99-1.01). Likewise, immediate postoperative discontinuation of antibiotics did not influence stump failure (HR 0.9, 0.5-1.5); similar results were obtained for osteomyelitis cases only (HR 1.0, 95% CI 0.5-2.1). Hyperbaric oxygen use was protective in the univariate (HR 2.0; 95% CI 1.3-2.6), but not in the multivariate analysis and the osteomyelitis episodes-only analysis (Table 2). Finally, we repeated

TABLE 1 Comparison of demographic, clinical and treatment characteristics of amputated patients with a single episode, versus those with subsequent episodes, of diabetic foot infection(s)

Total n = 482	Clinical remission n = 392	P value*	Clinical failures n = 90	Microbiological failure n = 38	P value*	Microbiological remission n = 444
Female sex	99 (25%)	0.410	19 (21%)	109 (25%)	0.905	9 (24%)
Age (median)	71 years	0.562	70 years	66 years	0.010	72 years
Body mass index (median)	27.5 kg/m^2	0.778	27.6 kg/m^2	28.5 kg/m^2	0.360	27.4 kg/m^2
Glycosylated haemoglobulin (median)	7.0 mmol/L	0.864	7.0 mmol/L	8 mmol/L	0.031	7 mmol/L
Transcutaneous oxygen (foot; median)	28 mm Hg	0.580	30 mm Hg	30 mm Hg	0.236	28 mm Hg
Clinical arterial insufficiency	261 (67%)	0.984	59 (66%)	23 (61%)	0.167	297 (71%)
Ankle-brachial index (median)	0.9	0.938	1.0	1.0	0.184	0.9
Bacteremic infection	43 (11%)	0.081	4 (4%)	4 (11%)	0.921	43 (11%)
Serum C-reactive protein (median)	89 mg/L	0.262	88 mg/L	111 mg/L	0.417	88 mg/L
Insulin-dependent diabetes mellitus	220 (56%)	0.143	54 (60%)	22 (63%)	0.912	252 (64%)
Presence of an abscess	69 (18%)	0.596	17 (19%)	6 (16%)	0.659	80 (16%)
Presence of osteomyelitis	188 (48%)	0.136	51 (57%)	24 (63%)	0.081	215 (48%)
Calcaneal osteomyelitis	22 (6%)	0.379	3 (3%)	0 (0%)	0.133	25 (5%)
Presence of a sequestrum	5 (1%)	0.446	2 (2%)	1 (3%)	0.549	6 (2%)
Angioplasty	142 (36%)	0.503	36 (40%)	7 (18%)	0.014	171 (39%)
Number surgical interventions (median)	1	0.605	1	1	0.800	1
Duration antibiotic treatment (median)	15 days	0.139	18 days	23 days	0.001	15 days
>21 days compared to ≤21 days	163 (66%)	0.290	43 (48%)	22 (58%)	0.049	184 (41%)
Duration parenteral therapy (median)	5 days	0.809	6 days	5 days	0.571	5 days
>7 days compared to ≤7 days	208 (53%)	0.418	52 (58%)	17 (45%)	0.236	243 (55%)
Post-amputation antibiotic stop	90 (23%)	0.705	19 (21%)	6 (16%)	0.295	93 (23%)

*Significant P values ≤0.05 (two-tailed).

theses multivariate analyses for cases undergoing angioplasty. In this latter substratum, total duration of post-amputation antibiotics or their immediate interruption equally did not alter outcomes (HR 1.0, 95% CI 1.0-1.0) and HR 0.4, 95% CI 0.2-1.2), respectively.

4 | DISCUSSION

This study of adult DFI patients from a defined clinical pathway shows that the duration of antibiotic administration following radical amputation did not affect microbiological or clinical failure. This was equally true when interrupting antibiotic therapy immediately after wound closure and when analysing osteomyelitis cases alone. Our study, with a total of 482 amputations in the infected diabetic foot, is to the best of our knowledge the largest existing single-centre database of its kind. It is unlikely that our findings are related to insufficient sample size. Also, since we included all hospitalized patients, this study reflects real-life conditions at our centre's clinical practice, thus reducing selection bias. Our rate of clinical recurrence (17%) is similar to that reported in the literature (15%,[20] 18%[21] and

19%[6] depending on the studies). This is equally true regarding our microbiology-confirmed recurrence rate of 8%, which is shared by other groups (6%-8%,[22] 9%,[6] and 8%[23]) as well.

The literature on duration of antibiotic therapy in amputated DFI is sparse and consists mostly of expert opinions.[2,7,24,25] Available original data mainly concern two questions. Firstly, prevention against surgical site infection[26] following major amputation, not specifically in DFI. Studies unanimously advocate the use of prophylactic antibiotics generally for 0-48 hours[5,27] and up to 5 days.[25,28] Secondly, residual infection, with authors supporting culture of intraoperative bone samples from residual stumps,[21,29] rather than from the removed bone.[30] Kowalski et al[21] demonstrated that amputated DFI patients with positive resection margins for residual osteomyelitis (histologically or microbiologically) revealed more treatment failures and re-amputations than those without (44% vs 15%, despite a similar 2 week intravenous antibiotic therapy in both arms). Atway et al reported a 41% incidence of positive bone resection margins among 27 trans-osseous amputations, compared to a 23% incidence following disarticulation.[29] Positive margins were associated with worse outcome despite a

TABLE 2 Univariate and multivariate analyses of factors potentially related to failure in amputated diabetic foot infections (cluster-controlled Cox regression) *(Results expressed as hazard ratios with 95% confidence intervals)*

Total n = 482	All episodes	n = 482	Only former osteomyelitis	n = 239
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Female sex	0.9, 0.5-1.5	0.9, 0.5-1.6	1.1, 0.5-2.1	0.9, 0.5-2.0
Age (continuous variable)	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-2.0
Age ≥60 y	1.1, 0.6-2.1	nd	1.2, 0.6-2.4	nd
Glycosylated haemoglobin level	1.0, 0.9-1.2	nd	1.0, 0.8-1.2	nd
Insulin therapy	1.5, 0.9-2.4	nd	1.2, 0.6-2.4	nd
Serum C-reactive protein level	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0. 1.0-1.0
Bacteremia	0.5, 0.2-1.3	nd	0.6, 0.2-1.9	nd
Ankle-brachial index	1.0, 0.3-2.8	nd	0.8, 0.1-5.4	nd
Transcutaneous oxygen (midfoot)	1.0, 1.0-1.0	nd	1.0, 1.0-1.0	nd
Transcutaneous oxygen (mid-leg)	1.0, 1.0-1.0	nd	1.0, 1.0-1.0	nd
Body mass index	1.0, 0.9-1.1	nd	1.0, 0.9-1.1	1.0, 0.9-1.1
Past history of foot surgery	1.0, 0.9-1.2	1.0, 0.9-1.2	0.9, 0.7-1.1	0.9, 0.6-1.3
Presence of abscess	1.2, 0.7-2.0	nd	1.2, 0.6-2.6	nd
Presence of osteomyelitis	1.5, 0.9-2.3	1.4, 0.8-2.3	nd	nd
Metatarsal amputation vs. forefoot	1.1, 0.6-1.7	nd	1.2, 0.6-2.3	nd
Ankle amputation vs. forefoot	0.4, 0.1-1.3	nd	0.6, 0.1-2.6	nd
Number surgical interventions	0.9, 0.7-1.1	0.9, 0.7-1.2	1.1, 0.8-1.5	1.2, 0.9-1.7
Angioplasty	1.1, 0.7-1.7	1.0, 0.6-1.7	1.0, 0.5-1.9	1.3, 0.6-3.0
Vacuum-assisted closure	1.0, 0.9-1.1	nd	1.1, 0.9-1.2	nd
Duration total antibiotic administration	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0
>1-≤3 d compared to 0 d	0.8, 0.4-1.6	0.9, 0.5-1.9	0.9, 0.4-2.1	1.1, 0.5-2.8
>3-≤7 d compared to 0 d	0.6, 0.3-1.3	0.7, 0.3-1.6	0.5, 0.2-1.4	0.6, 0.2-1.8
>7-≤14 d compared to 0 d	1.1, 0.6-2.0	1.4, 0.7-2.8	0.9, 0.4-1.9	1.1, 0.5-2.9
Duration parenteral administration	1.0, 1.0-1.0	nd	1.0, 1.0-1.0	nd
>1 wk IV antibiotic therapy	1.3, 0.8-2.1	nd	1.7, 0.9-3.2	nd
Immediate stopping post-amputation	1.0, 0.6-1.7	0.9, 0.5-1.5	1.3, 0.6-2.5	1.0, 0.5-2.1
Hyperbaric oxygen therapy	**2.0, 1.2-3.6**	1.9, 0.9-4.2	1.9, 0.8-4.3	1.7, 0.6-4.7

nd, not done.

median duration of 25 days of postsurgical antibiotic therapy. In contrast, side results of a Turkish prospective randomized multi-centre trial are in line with our findings. According to Saltoğlu et al, and provided a total excision of infected bone, five days of postsurgical antibiotic continuation were largely sufficient,[23] even if their study was not designed for the precise study question of post-amputation antibiotic continuation.

Besides the fact that our study is retrospective withloss or lack of data for certain variables, it has several limitations. Firstly, patients who were subsequently treated outside of our centre may have been lost to follow-up. However, our centre is the largest, and the only public, hospital in the region with a large catchment area. Indeed, patients seeking medical care consult mainly at our hospital, making this an unlikely major bias. Secondly, we did not analyse the antibiotic agents that were used, or the role of specific pathogens. This is based on the lack of evidence that any specific systemic antibiotic regimen is significantly superior for treatment of DFI, regardless of the involved pathogens.[1,13,15] Our study population and pathogens recovered were consistent with those reported in the literature.[1,6] Moreover, antibiotic regimens often change throughout treatment course for these complex cases. In our study, 109 antibiotic regimens were changed during the course of therapy for a given infection episode. Likewise, we did not routinely assess residual stump osteomyelitis in patients undergoing atrial amputation. However, recent studies doubt about the accuracy of these specimens,[11] especially when they were sampled through the operation site. Thirdly, it is noteworthy that wound care, especially pressure offloading of the affected limb, is crucial for treating DFI.[1] While the rationale of such measures is easily understandable, effectively implementing them

depends on the patient's adherence, which we could not monitor in our assessment. Fourthly, we defined remission as the absence of any clinical, radiological or laboratory signs of recurrent or new DFI at the site of prior infection, within one year following treatment of the prior DFI episode. In DFI, microbiological patterns of consecutive DFI episodes are only congruent in two-thirds of cases at most,[31] and new ischaemia, noncompliance, as well as inadequate anatomical positioning may lead to new infections at the same location. Hence, we overestimate the true risk of recurrence having more to do with patient's compliance or progressive ischaemia[1] rather than with antibiotic effects. Fifthly, there is certainly bias from confounding by indication; for example, patients who were suspected to have an unfavourable outcome might be those who were prescribed longer antibiotic courses. Only prospective randomized trials could help to fully circumvent this bias inherent to every retrospective study. Therefore, we renounced on formal propensity score analyses in our very heterogeneous study population. Finally, we included all DFI patients hospitalized for in toto amputations in order to reproduce routine clinical settings at best. This should not be confused with DFIs with proven postsurgical residual osteomyelitis. For this specific population, continuation of systemic antibiotic for 3-4 weeks[21] is warranted.

In conclusion, in our daily practice clinical pathway including 482 consecutive DFIs, continuation of postsurgical antibiotic administration or immediate interruption was not associated with treatment failure, provided that surgeons performed amputations with clear bone margins. Therefore, favouring efficacious antibiotic stewardship in the DFI population,[8] our findings support immediate interruption of antibiotic therapy following routine amputations, provided that residual infection is absent.

CONFLICT OF INTEREST

AR, BK, KG, DL, MAb, PT and DS declare no conflict of interest. IU has received research donations from Innocoll Ltd. for another project. MAs has worked on another investigator-initiated research project mandated by *SwissNoso* that was funded by Pfizer USA.

AUTHORS CONTRIBUTION

AR involved in data sampling, conduct and writing; DL and BK involved in data sampling, conduct, supervision and correction; KG involved in data sampling and concept; Both MAb, MAs involved in concept and writing; PT and DS involved in data sampling, clinical work and writing; IU involved in data sampling, clinical work, conduct, supervision, analyses and writing.

ETHIC STATEMENTS

This work is part of a Clinical Pathway for Diabetic Foot Infections and a quality programme. Individual informed consent was not necessary.

DATA ACCESSIBILITY

Data are stored with the corresponding author and available upon individual request.

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