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Article

Therapy of Non-Diabetic Foot Infections after Orthopedic Foot and Ankle Surgery: The Duration of Post-Debridement Antibiotic Treatment Does Not Alter Failure Risk

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Abstract: Whereas there is an increasing number of scientific publications investigating the optimal antibiotic treatment for diabetic foot infections, we are lacking corresponding data in the adult non-diabetic (postsurgical) foot infection population. We therefore established one of the largest single-center databases on this topic and retrospectively investigate failures of a combined surgical and antibiotic therapy for surgical site foot infections. Overall, 17.4% of the episodes experienced any therapeutic failures; especially among the infected ankle prostheses. In contrast, neither the age, the biological sex, pathogens, the duration of post-debridement antibiotic treatment, the number of surgical debridement, or the use of negative-pressure wound care could alter the failure risk. In multivariate logistic regression analyses, the duration of postsurgical antibiotic use was completely indifferent (as a continuous variable with odds ratio 1.0, 95% confidence interval 0.96-1.03), or when stratified into inter-tertiary groups. Our results potentially enable shorter applications of systemic antibiotics in favor of a better stewardship in the non-diabetic adult population. Consecutive prospective-randomized trials are under way to identify eligible patient populations for a potentially shorter durations in surgical site infections after elective foot and ankle surgery.

Keywords: adult foot and ankle surgery; infection; surgical site infections; surgical debridement; duration of antibiotic treatment; treatment failures; total ankle prostheses

1. Introduction

According to available scientific literature, most surgical site infections [1] (SSI) after elective foot and ankle surgery in otherwise healthy adults may occur to incidences between 1.9% [2] and 4.2% [3]. In contrast, among adult diabetic patients, this incidence can reach 9.1% or more [4,5]. Classical risk factors for SSI include the patient's co-morbidities (American Society of Anesthesiologists' Scores 3 to 5), revision surgeries, large metallic implants, long operation times [1], inadequate perioperative antibiotic prophylaxis, use of allografts, bone substitutes, smoking, and postoperative wound problems [2,6-8]. In traumatic foot surgery, and especially in open fractures [9], this risk culminates up to 33% in Gustilo grade IIIc open fractures [9,10], and is also marked by the selection of multi-resistant Gram-negative pathogens by concomitant excess, and prolongation, of prophylactic antibiotic use. Another factor that the clinicians know and which is difficult to assess in retrospective studies, is the patients' malcompliance to wound care and off-loading.

Despite an increase of orthopedic foot procedures all over the world in recent years, most literature on antibiotic treatment of foot infections target adult diabetic patients and (implant-free) diabetic foot infections (DFI) [11]. However, DFIs are a distinct clinical entity that mostly lack the hallmark of established polyneuropathy or progredient (terminal) ischemia to DFI patients and

heavily complicate their therapeutic approach. In turn, DFI patients usually lack implant-related infections [12]. Other considerations are about correction of hyperglycemia [13] and the extent of surgical debridement versus minor amputations, which remains a valuable option in diabetic foot osteomyelitis [14]. The lack of optimal compliance to off-loading is probably the only common feature that non-diabetic foot infection patients share with the classical DFI population. Furthermore, the differences between both entities do not only concern epidemiological features, but also therapeutic success. In DFIs, overall clinical failure after treatment is high and recurrence (albeit mostly with different germs) occurs in around 1 of 4 patients, independently of the microbiological adequacy of the initial antibiotic regimen [11].

Our research center largely published on therapeutic failures and complications in DFIs [13-16]. The aims of this current study are different: We investigate the remission (or inversely failure) rate of SSI therapies in adult elective foot and ankle surgery. We renounce on investigating specific risk associations with SSI in foot surgery, which has been published in a prior article [2]. Importantly, we hypothesize that the duration of postsurgical antibiotic treatment, and the number of surgical debridement in the operating theater, does not influence the risk for failures, leaving room for a better antibiotic and surgical stewardship [17] for these infection patients. Ultimately, our retrospective results enable us to tailor future prospective-randomized studies in orthopedic foot infections [18].

2. Materials and Methods

We retrospectively analyzed all SSI after elective foot and ankle surgeries in our tertiary foot center; an orthopedic referral center at the Balgrist University Hospital in Zurich, Switzerland, from January 2014 to August 2022 [2]. We used data mining from the hospital's own medical databases and confirmed the presence of SSI by controlling the individual electronic files. We included all SSI (first time episode) in adult elective foot and ankle surgeries in our patients older than 18 years with a minimum surveillance of two years after the start of therapy; and with detailed information available during database closure (August, 1st 2024). The definition of SSI based on international criteria [1,2].

The minimal set of required variables for each infection episode were information about the index surgery, surgical and antibiotic therapies during follow-up, information on the biological sex, age, body mass index (BMI), diabetes mellitus yes or no, pathogens (especially *Staphylococcus aureus* yes or no), presence of total ankle prosthesis (TAA), immobilization (off-loading), the duration of systemic antibiotic prescription in days, the number of surgical debridement for infection and the use of negative-pressure wound devices [19] during hospitalization or in the outpatient setting. Exclusion criteria were described in a previous study [2,20] and briefly resumed as recurrent infection episodes, amputations without residual infection, infection episodes with prior emergency index surgery, external patients that we treated only partially, open fractures [9,10], foot infections extending beyond the ankle (e.g. gas gangrene, necrotizing fasciitis and other rapidly spreading severe soft tissue infection), insufficient documentation, antibiotic therapy relying mostly on local (topical or intraosseous) antibiotic therapies [2], atypical pathogens such as *Actinomyces* spp., fungi or mycobacteria, concomitant severe and remote infections such as endocarditis or brain abscesses, and, most importantly, the presence of a community-acquired DFI with ischemia, chronic infected foot ulcers, and/or severe polyneuropathy. In contrast, a patient with a well-regulated concomitant diabetes mellitus was allowed to be included in the study if he/she had developed a SSI (e.g. diabetic patient with a non-ischemic SSI of his/her orthopedic hardware in the foot).

2.1. Study Objectives and Definitions

We performed a classical case-control study with two separate primary outcomes: Remission after the minimal follow-up, and Microbiological Recurrences. The latter were defined as an infection recurrence at the same anatomical localization, following the end of the antibiotic therapy, with the same pathogen (s) as in the index infection episode. A new infection with a new pathogen, or at a different anatomical localization (e.g. in the other foot) counted as a "Clinical Failure". The differentiation between "Clinical Remission" and "Microbiological Recurrence" based on our

assumption that overall failure might be due to a panoply of explanations, whereas a Microbiological Recurrence would rather reflect a failure of the antibiotic therapy *per se*. Remission was a complete absence of any clinical, laboratory, and/or radiological evidence of a new or persistent problem.

2.2. Statistical Analysis

We used descriptive statistics and compared groups with the Pearson- χ^2 , Fisher-exact and Wilcoxon-rank-sum-tests, as appropriate. To adjust for the large case-mix, we added a univariate and multivariate, unconditional, logistic regression analyses. We included 5 to 8 predictor variables per outcome variable [21] and checked key variables for collinearity and interaction. We used Stata™ software (version 15.0, Stata Corporation, College Station, Texas, USA) and considered *P*-values ≤ 0.05 (two-tailed) as significant.

3. Results

3.1. Study Population

We included 69 adult patients with “non-diabetic surgical site foot infections”, of whom 61% were biological males (42 patients) and 39% women (27 patients). Of the 69 patients, nineteen (28%) yielded diabetes mellitus and eighteen cases (26%) presented with an infected TAA [22]. Overall, the median age and the median BMI were 59 years and 29.4 kg/m² respectively. Other variables such as the duration of antibiotic use and the number of surgical debridement were equally distributed among both groups (Table 1).

3.2. Diagnosis of Infection

Besides the clinical suspicion of infection (purulent wound discharge, erysipelas, lymphangitis, dolor, rubor, calor, and/or *functio laesa*), we microbiologically confirmed infection by several deep tissue and bone samples (mostly intraoperative specimens) sent for microbiological cultures and histology; and sonication in case of implants. Additional microbiological examinations by polymerase chain reaction were occasionally ordered. The incubation period for all intraoperative cultures was 14 days, independently of prior antibiotic prescription. In the intraoperative samples, we retrieved a total of 52 different bacterial constellations (68% monomicrobial versus 32% polymicrobial infections). The three most frequently detected individual pathogens were (methicillin-susceptible) *Staphylococcus aureus* in 29% (20 episodes), followed by *S. caprae /capitis* and (methicillin-resistant) *S. epidermidis* in 6% of the episodes each; the latter two mostly in implant-related infections.

3.3. Therapy of Infection

Basing on international SSI definitions [1,2] and the exclusion of recurrent episodes, practically all our infections were considered as “acute” and treated by a combined approach of surgical measures, nursing approach, professional wound care, internist consultations, and with a (targeted) systemic antibiotic therapy. The median number of surgical debridement for SSI was 1 (range, 1-4 interventions, IQR, 1-2 surgeries), whereas the number of past surgeries before the onset of SSI ranged from 1 to 17. The number of surgeries did not differ significantly between both groups (Table 1), and 26%, or 18 patients, had additional negative-pressure wound care. There is no hyperbaric oxygen therapy in our center.

The median duration of systemic antibiotics treatment after the first debridement lasted for a median of 42 days (interquartile range (IQR), 31-76 d, 95% confidence interval (CI), 42-48 d). Upon stratification, 27% of patients witnessed less than 6 weeks of systemic antibiotic therapy, 15% between 6 and 12 weeks, and 28% for more than 12 weeks of antimicrobial therapy. In the early years of the cohort (2014 to June 2018), the initial 7-14 days of antibiotic treatment occurred parenterally. Afterwards, the initial intravenous part was reduced to 3-5 days [23]. The daily doses of the agents corresponded to the upper limits of the Swiss recommendations (www.compendium.ch) and were

only reduced in case of cachexia or renal insufficiency. We did not use antimicrobial agents in dressings. Among the entire study population, we noted 135 different antibiotic regimens administered sequentially or concomitantly. Parenteral or oral co-amoxiclav was the most frequent regimen (42% or 27 patients), followed by clindamycin (11%; 7 patients), co-trimoxazole (9%; 6 patients) or vancomycin (6%). Rifampicin combination occurred in six (9%) cases.

Therapy also included different types of immobilization, namely with a dorsal splint in neutral position in 52% (36 patients), no device-related immobilization in 33% (23), and a lower leg cast in 7% (5 patients). The devices were regularly controlled, in an outpatient basis, in our specialized center. Our specialized personnel and the surgeons classified the compliance as sufficiently good. If we would have been aware of a major compliance issue in wearing the cast, we would have excluded the patient by study criteria.

3.4. Outcomes of infection therapies

We cured 83% (n=57) of all SSI episodes at the first therapeutic approach. Inversely, 17.4%, or a total of 12 patients, sustained a "Clinical Failure" after the end of treatment, of which 13%, or 9 patients, were "Microbiological Recurrences" (Table 2) according to our study definitions; with the identical pathogen as in the index infection.

Table 1. Patient characteristics in surgical site infections in foot and ankle surgery.

	Overall SSI	Remission	Clinical Failure	p-value
	n = 69 (%)	n = 57 (82.6%)	n = 12 (17.4%)	
Sex				
Female	27 (39)	25 (44)	2 (17)	
Male	42 (61)	32 (56)	10 (83)	0.079
Median age (years)	59 (49-73.5)	59	61	0.232
Median BMI (kg/m²)	29.4 (26-32.3)	29.4	29.4	0.665
Diabetes mellitus	19 (28)	11 (19)*	8 (67)*	0.001
Total ankle prostheses	18 (26)	11 (19)*	7 (58)*	0.005
<i>Staphylococcus aureus</i>	20 (29)	17 (30)	3 (25)	0.738
Duration antibiotics (days)	42 (range, 31-76)	42 (range, 42-58)	47 (range, 11-120)	0.093
≤ 6 weeks	27 (39)			
> 6 and < 12 weeks	14 (20)			
≥ 12 weeks	28 (41)			
Negative-pressure care	18 (26)	15 (26)	3 (25)	1.000
Surgeries (median number)	1 (1-2)	1	1	0.096

Footnote: Data are shown in absolute numbers (% in brackets) or median values (in brackets; range). * Significant p-values are printed in **bold italics**.

3.5. Associations with Clinical Remission and Microbiological Recurrences

We added a univariate and multivariate logistic regression analysis to adjust for the large case-mix (Table 2). Regarding the outcome of "Microbiological Recurrence," we had only nine cases. This paucity excluded a multivariate adjustment. Hence, only univariate results are shown regarding the

"Microbiological Recurrence". Concerning "Clinical Remission", the only (inverse) significant association were diabetes mellitus (odds ratio 0.12) and the presence of an infected TAA (OR 0.17 in the univariate; and 0.10 in multivariate analysis). Patient characteristics such as age, sex or BMI, or an infection due to *S. aureus*, did not influence Remission. Likewise, the use a negative-pressure wound care or the number of surgical debridement did not alter all outcomes. Importantly, the duration of postsurgical antibiotic treatment had absolutely no role; with an odds ratio of 1.0 associated to a very narrow confidence interval (0.96-1.02) as continuous variable, and similar values in stratified analyses. Of note, the goodness-of-fit result was insignificant and the receiver-operating-curve (ROC) value yielded 83%; reflecting a very good accuracy of our final model. We are confident that our results are very likely not underpowered.

Table 2. Case-mix adjustments in logistic regression analyses.

	SSI Remission n = 57 (82.6%)		Microbiological Recurrence n = 9 (13%)
	Univariate (OR, 95% CI)	Multivariate (OR, 95%)	Univariate (OR, 95% CI)
Sex			
male	0.26 (0.05-1.28)	0.36 (0.03-4.36)	2.50 (0.48- 13.06)
Age (years)	0.97 (0.93-1.01)	0.98 (0.92-1.04)	1.02 (0.98-1.07)
Body mass index (kg/m ²)	0.97 (0.84-1.12)	-	1.01 (0.85-1.19)
Diabetes mellitus	0.12 (0.03-0.47)	-	4.11 (0.97-17.41) *
Total ankle prosthesis	0.17 (0.05-0.64)	0.10 (0.02-0.73)	4.52 (1.06-19.29)
<i>Staphylococcus aureus</i>	1.28 (0.31-5.30)	0.57 (0.08-4.18)	0.67 (0.13-3.53)
Duration of antibiotics	1.00 (0.98-1.02)	1.00 (0.96-1.03)	1.00 (0.99-1.02)
≤ 6 weeks	1 (default)	1 (default)	1 (default)
> 6 and < 12 weeks	1.04 (0.17-6.54)	1.75 (0.11-27.36)	1.33 (0.20-9.08)
≥ 12 weeks	0.64 (0.16-2.57)	0.75 (0.01-53.55)	1.33 (0.27-6.61)
Negative-pressure care	1.07 (0.26-4.49)	0.29 (0.03-2.95)	1.50 (0.33-6.75)
Number of debridement	2.43 (0.63-9.40)	2.04 (0.47-8.93)	0.55 (0.15-2.09)

Footnote: Data as odds ratios with 95% confidence intervals. Significant results are in *bold and italics*. BMI and diabetes were excluded from multivariate analysis due to substantial interaction.

4. Discussion

We cured 83% of our orthopedic foot SSIs at the first therapeutic approach, with one debridement and a targeted systemic antibiotic therapy. The postsurgical duration of antibiotic use did not influence the "Remission", any "Clinical Failure", or a "Microbiological Recurrence" with the same pathogen. Formally, prolonging the antibiotic prescription beyond six weeks did not alter the fate of therapy. Indeed, in multivariate logistic regression analyses, the duration of postsurgical antibiotic use was completely indifferent when computed as a continuous variable (odds ratio 1.0, 95% confidence interval 0.96-1.03), or stratified into three large groups composed of 6-week's steps. Similarly, the patient's age, sex, the BMI, the number of surgical debridement, the use of negative-pressure wound, or the involvement of *S. aureus* could not alter the final outcomes. The only significant associations with more "Clinical Failures" were diabetes mellitus [4] and an infected TAA [22], both probably associated to wound problems in the aftermath of debridement.

These latter findings are not surprising. The ideal surgical strategy for infected TAA remains unknown [22]. Meticulous debridement, antibiotics, and implant retention (DAIR) in acute TAA infection are considered as an acceptable option, without much differentiation between the prosthesis types. If performed, DAIR should be done meticulously, ensuring that all necrotic or infected tissues are removed and modular parts of the prosthesis, if any, exchanged. The infected joint should also be irrigated with antiseptic solutions. Equally concerning TAA infections, these general prerequisites for DAIR are formally not different from those for other prosthetic infections. However, the success of DAIR in TAA is particularly poor [22]. The best evidence is reported by Kessler et al. [24]. The

authors investigated 34 cases of TAA infections, of which 21 were treated by DAIR. Remission using the DAIR procedure was achieved only in two-thirds of all cases (14 of 21, 67%), which is a lower success rate as for hip or knee arthroplasty DAIRs [24]. We think that the DAIR procedure in TAA should be rigorously discussed and should be a routine approach for every acute SSI. The alternatives of arthrodesis, or a two-stage exchange (mostly with transient external fixation) might be better in complicated cases.

Our general findings are in line with the literature of non-diabetic foot SSIs [2,8] and similar to our own experience in the field of (ischemic) DFI [11,13,14,25]. For sure, there is an overestimated effect of the prolongation of antibiotic use among orthopedic surgeons in terms of precautionary benefits. For DFI, a recent review concluded that the duration of systemic antibiotic therapy for osteomyelitis should never be more than 4-6 weeks [25], independently of the underlining surgical approach. This also applies for non-diabetic foot infections. With our good retrospective results, we currently target prospective-randomized trials aiming to reduce the overall exposure to therapeutic antibiotic agents in infected orthopedic patients. Concretely, in the SALATIO trials, we randomize implant-free foot infections between three and six weeks of antibiotic prescription [18] and thus reduce the usual antibiotic therapy to the half. Likewise, in case of infected implants, the randomization is between six and twelve weeks of antibiotic treatment [18].

Our study has limitations. i) The retrospective nature, with some heterogeneity in the patient characteristics, may lead to possible biases by confounding. ii) Likewise, the study was conducted in a single-center, tertiary referral center, which might also hamper the generalizability of our findings. iii) We cannot state about the general compliance (i.e. the correct intake of prescribed antibiotics or adequate immobilization and wound care). For example, one study examining risk factors for DFI stated that as much as 72% of the affected patients were non-compliant with the treatment [26], suggesting that non-compliance could become a very important and underreported risk factor of therapeutic failures.

5. Conclusions

In our case-control study, the duration of post-surgical antibiotic therapy does not influence remission or failure risks in the adult non-diabetic foot infect population. Hence, the mere prolongation of the antibiotic therapy will not reverse other shortcomings of the therapeutic approach in this patient population, leaving room for a better antibiotic stewardship in future randomized trials.

6. Patents

Author Contributions: Conceptualization, M.S., L.S.-B, I.Y, and I.U.; methodology, I.Y., L.S.-B. and P.F.; formal analysis, I.U., L.S.-B.; investigation, L.S.-B., I.U., P.F., and I.Y.; resources, A.V., S.B., I.U., and S.W.; data curation, L.S.-B., I.Y., and I.U.; writing—original draft preparation, L.S.-B., S.W. and I.U.; writing—review and editing, M.S., I.U., S.B., A.V., S.W.; visualization, M.S. and I.U. supervision; I.U. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The local ethics committee at the University of Zurich approved our study (BASEC 2022-01755). The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of University of Zurich (BASEC 2022-01755 on 22 October 2022).” for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Patients who did not provide their general informed consent upon hospitalization for surgery were excluded from analysis.

Data Availability Statement: We might share anonymized key data upon reasonable scientific request to the corresponding author.

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