The influence of skin commensals on the therapeutic outcomes of surgically-debrided diabetic foot infections

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Abstract

In diabetic foot infections (DFI), the clinically virulence of skin commensals are generally presumed to be of low virulence. In this single-center study, we divided the wound isolates into two groups: skin commensals (coagulase-negative staphylococci, micrococci, corynebacteria, cutibacteria); and, pyogenic pathogens, and followed the patients for ≥ 6 months. In 1,018 DFI episodes (392 [39%] with osteomyelitis), we identified skin commensals as the sole culture isolates (without accompanying pyogenic pathogens) in 54 cases (5%). After treatment (antibiotic therapy [median of 20 days], hyperbaric oxygen in 98 cases [10%]), 251 episodes (25%) were clinical failures. Group comparisons between those growing only skin commensals and controls found no difference in clinical failure (17% vs 24 %, p=0.23) or microbiological recurrence (11% vs 17 %, p=0.23). The skin commensals were mostly treated with non-beta-lactam oral antibiotics. In multivariate logistic regression analysis, isolation of only skin commensals was not associated with failure (odds ratio 0.4, 95% confidence interval 0.1-3.8). Clinicians might wish to consider these isolates as potential pathogens when selecting a targeted antibiotic regimen, which may equally base on oral non-beta-lactam antibiotic agents susceptible to the corresponding skin pathogens.

Keywords: antibiotic therapy; diabetic foot infections; non-beta-lactam antibiotics; skin commensals; treatment failures; associations with treatment failure

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1. Introduction

Diabetic foot infections (DFI), including osteomyelitis (DFO), are associated with high rates of treatment failure, even when treated with prolonged antibiotic therapy, adequate surgical debridement, and appropriate wound care [1]. There are multiple reasons for the poor outcomes, including limb ischemia, inadequate pressure off-loading of the foot, and a lack of patient adherence to the prescribed treatment [1]. In contrast to what many clinicians believe, the specific causative DFI pathogen is generally not a major determinant for the outcome of therapy [2-8], unless it is resistant to multiple antibiotic agents [4]. Indeed, in almost all published reports regarding DFIs, clinical or microbiological outcomes are no worse for patients infected with "difficult" pathogens such as methicillin-resistant *Staphylococcus aureus* [2], *Pseudomonas aeruginosa* [3,5], or obligately anaerobic bacteria than with other pathogens [6-8]. Even in randomized, controlled trials of treatment of DFI, the causative pathogen(s) is a negligible factor in treatment failure, compared to other parameters [9,10]. Unlike pyogenic bacteria, such as *S. aureus*, *P. aeruginosa*, *Enterobacteriaceae*, enterococci, or *streptococci*, skin commensals isolated from swab cultures are not usually considered true pathogens, even when grown repeatedly from specimens [11-14]. According to widespread clinical experience and a very few retrospective studies, skin commensals [15] (mostly coagulase-negative staphylococci [16-18], micrococci [15,16], cornynebacteria [15,16,19], cutibacteria [15,16,20,21]) demonstrate lower virulence than other bacterial genera. However, there are few published data to inform whether skin commensals are clinically associated with a better outcome after therapy for DFI. We investigate this gap in the literature.

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2. Results

Study population and infections

Using our database, we identified 1,018 DFI episodes (median age 81 years, 73% males, 610 [60%] with peripheral arterial disease). Among these, skin commensals were the sole isolates from wound cultures (without any pyogenic pathogens detected) in 54 cases (5%), and in of 23 of these 1018 (2% of all cases) the patient was diagnosed as having DFO. The proportion of DFI episodes caused entirely by pyogenic pathogens was 63% (641/1,018). Among these patients whose cultures grew at least one pyogenic pathogen (the control group), the most common isolates were *Staphylococcus aureus* (389 cases [38%]) and *Pseudomonas aeruginosa* (61, 6%) cases, but cultures yielded 30 other pyogenic pathogens (e.g., β-hemolytic streptococci or *Enterobacteriaceae*).

Overall, we detected 68 different microbiological constellations. Skin commensals were retrieved as (co)-pathogens, together with pyogenic bacteria, in 161 DFI cases (16%). Blood cultures grew organisms that we believed represented clinically plausible bacteremia in 80 episodes (8%). The median serum C-reactive protein (CRP) level among all enrolled subjects on admission was 81 mg/L. Among the 392 [39%] episodes of DFO with a positive bone culture, the diagnosis was confirmed by histology in 275 (70%), while the rest by clinical and imaging findings.

Therapy and outcomes

After treatment (including at least one surgical debridement in all, and partial amputation in 596 [58%], antibiotic therapy [45 different regimens, with a median duration of 20 days, of which 5 days were administered parenterally], hyperbaric oxygen therapy (98 cases [10%]), 251 (25%) of the episodes met our definition of clinical failure. Of these, 119 cases (12%)

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met our definition of microbiological recurrence. The follow-up duration for these episodes was a minimum of six months, and a median of 3.3 years. The six main antibiotic agents used for skin commensals were co-amoxiclav (40%; practically for all susceptible commensals), vancomycin (15%), co-trimoxazole (10%), clindamycin 8%, doxycyclin 8%, fusidic acid with rifampicin (8%). Linezolid and daptomycin were very rarely used, and only for a short period.

For further analyses, we compared the 54 DFIs solely caused by skin commensals to the 641 DFIs caused solely by pyogenic pathogens (Table 1). As noted, we censored episodes with a mixture between both types of isolates [16] and found no difference in the incidence of clinical failure between the skin commensals and pyogenic pathogens (17% vs 24 %, respectively; p=0.23) or microbiological recurrence (11% vs 17 %, respectively; p=0.23). Clinically, the study groups only significantly differed in the CRP values at admission (median of 25 mg/L vs. 105 mg/L, respectively; p<0.01). The number of surgical debridements, proportion of DFO cases, occurrence of bacteremia, and the duration of antibiotic therapy (including the parenteral part) were not significantly different between the groups. With further stratifications upon soft tissue DFI and DFO, we found no significant differences in both strata. Treating only skin pathogens among cases with only soft tissue infections revealed a similar of clinical failure rate as for the pyogenic pathogens (7/24; 29% vs 94/296; 32%, p=0.85). The same was true for the clinical failure rate for cases with DFO (2/21 vs 59/192; p=0.10).

Using multivariate adjustment with the outcome "clinical failure" (Table 2), growth of skin commensals on wound culture was not determinant of clinical failure (odds ratio 0.4, 95% confidence interval 0.1-3.8), but the presence of ipsilateral lower extremity ischemia was (OR 3.0, 95% CI 1.1-8.5). These findings were similar in a multivariate analysis for

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"microbiological recurrence" (Table 2). The Receiver-Operating-Curve (ROC) value was 0.83, representing a good accuracy of our multivariate model.

3. Discussion

In this single-center study, we did not detect any association of the clinical or microbiological outcomes of DFI with the presence of skin commensals compared with pyrogenic pathogens. Furthermore, we found that the number of surgical debridements, the incidence of bacteremia, the percentage of patients with DFO, and the length of antibiotic therapy were quite similar for the two microbiological groups. These results suggest there was not a major comparison bias in management related to the two microbiological groups. The only two differences of note between the groups was a significantly lower C-reactive protein level at admission in those with skin commensals and the association of lower extremity ischemia with a higher rate of clinical failure [22], but not microbiological recurrence [23]. Only the choice of the antibiotic agent was different. Secondly, contrary to pyogenic DFI pathogens, for which (oral) co-amoxiclav is the hallmark in the Swiss medical culture [24], we mostly used non-beta-lactam and non-quinolone antibiotic agents; with similar clinical efficacy as oral beta-lactam agents. We conclude that while skin commensals may induce a lesser degree of inflammation (CRP elevation), they do not appear to be less virulent than the classical bacteria in patients treated for DFI. Thus, there does not appear to be a reason to select less aggressive surgical or antibiotic therapy for DFIs caused by these bacteria.

Besides its retrospective nature and the large case-mix inherent to the adult DFI population, our study has other several limitations. First, we somewhat arbitrarily created two microbiological groups, one with only skin commensals and the other with only pyogenic pathogens, while in reality two-thirds of skin commensals are co-pathogens with other

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pathogenic bacteria. However, for formal comparative statistics, we had to exclude mixed-group cases in order to perform a true statistical comparison of sharply distinguished groups of interest. Similarly, our skin commensal classification was composed of many species (e.g. micrococci, *S. epidermidis* [16,18] and *S. lugdunensis* [17]), each of which might have a different level of clinical virulence or ability to cause persistent infection. Even with our large number of DFI episodes, it is not impossible to adjust for the effect of a single species in the frequently polymicrobial infections in our study population [16].

Furthermore, as we relied on classical, clinical culture techniques, we might have missed unidentified species within the microbiome [15,25]. These might have been detected by molecular methods such as "shotgun" and other DNA-enhancing techniques [12,15]. There is a growing literature assessing the effects of these “hidden” bacteria (based on standard cultures) within the microbiome or the biofilm. For example, some research groups advocate that these hidden commensals may interact with other bacteria, perhaps even promoting wound healing by inhibiting the virulent *S. aureus* [26] that are so often found in diabetic foot wounds [27,28]. Undertaking such a study would require expensive and limited academic laboratory facilities, making it beyond our routine clinical evaluation.

Lastly, some clinicians might argue that the presence of skin commensals on wound culture is more a sign of specimen contamination than of true infection, or organism selection by prior antibiotic therapy. We do not think this is so, as our diagnostic criteria are based on the IWGDF guidelines [13] and on a high proportion of histologically-confirmed DFO episodes. Moreover, on the clinical side, we managed patients with these skin commensals the same as those with every other pathogen, and still saw no difference. If these bacteria play a less

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virulent role, we think we should have found at least some hints in favor of an altered outcome when studying 1,018 episodes in the same Clinical Pathway.

Conclusion

We believe our results suggest that skin commensals isolated from DFIs are neither clinically virulent, nor more microbiologically persistent, than other bacteria. They can be treated also by oral non-beta-lactam antibiotic agents. Clinicians should therefore perhaps consider these bacteria as potential pathogens when selecting an antibiotic regimen. Further clinical confirmatory stories in other centers are needed.

4. Methods

At the Geneva University Hospitals, we have established a database (embedded in a hospital-wide Clinical Pathway for DFI [1]) for managing DFI. We examined all DFI episodes identified from April 24, 2013 to July 31, 2016 for which microbiological samples were collected from pus or intraoperative tissue specimens. We identified all pathogens from these specimens using standard culture methods [2-4]. We defined DFI based on the International Working Group on the Diabetic Foot (IWGDF) criteria [13] and a "clinical failure" as: 1) the persistence or recurrence of any clinical indication for revision surgery; 2) the development of a recurrent infection (same site, same causative pathogen[s]; 3) or the occurrence of a new infection in the same foot [9]. We defined "microbiological recurrence" as a "clinical failure" predominantly caused by the same pathogens as in the index episode. We recorded the three most frequent pathogens per episode, and censored any other quantitatively fewer common microorganisms. We developed our Clinical Pathway for DFI as a quality program, for which the patients were not required to provide individual consent. However, many of them

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concomitantly participated in at least one of the many randomized DFI trials we conducted [9,10,29,30] that required signed consent forms.

Statistical analyses

For this study, we divided the isolated microorganisms into two groups: those that we regarded, based on the literature and our extensive experience, as only *commensals* (coagulase-negative staphylococci, micrococci, cutibacteria, cornynebacteria); and *pyogenic pathogens* composed of bacteria commonly regarded as virulent isolated causing DFI. The primary objective of this study was to define the role of skin commensals in DFI by examining the likelihood of clinical remission of DFI overall, and diabetic foot osteomyelitis (DFO) separately. We compared the skin commensal with pyogenic pathogen groups using the Pearson-χ^2 or the Wilcoxon-ranksum-test, as appriopiate. In these comparisons, we only analysed infections caused entirely by skin commensals and those caused entirely due to pyogenic bacteria, excluding for these group comparisons any polymicrobial DFIs with mixed groups (i.e., pyogenic pathogens AND skin commensals). We furthermore adjusted for our large case-mix with two identical, cluster-controlled (clustering on the individual patient) multivariate logistic regression analyses with the separate outcomes “clinical failure” and “microbiological recurrence”. We performed all statistical calculations using STATA™ software (Version 14, College Station, Texas, USA).

Author’s contribution

IU: Idea, Drafting, Sponsor, Principal Investigator, Funding, Conduct, Analyses, Writing

DL: Study Conduct, Inclusion, Database

BK: Study Nurse, Conduct, Corrections, Supervision

BAL: Concept, Writing, Corrections

KG: Idea, Writing, Database

All authors have agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Zürich.

Informed Consent Statement: The project was part of a quality of Care Approach for DFI at Geneva University Hospitals. The necessity of an individual consent was waived by the Direction of the Hospital. The project approved by the Ethics Committee' of Geneva Canton (Ethical Committee NAC13-178).

Data Availability Statement: Key data are available in an anonymous form upon reasonable scientific request to the corresponding author. They are not publicly available.

Transparency declarations

All authors do not have any financial conflicts of interest and the funder has not played any decision-making role in this research.

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Table 1 - Comparison of selected factors in patients with diabetic foot infections with *skin commensals* versus *pyogenic bacteria.*

Factor	Pyogenic bacteria only n = 641	*p* value*	Skin commensals[+] n = 54
Median age (years)	80	.26	83
Osteomyelitis	251 (39%)	.62	23 (43%)
Bacteraemia associated with diabetic foot infection	71 (11%)	.21	3 (6%)
Median C-reactive protein level on admission	105 mg/L	***.01***	25 mg/L
Median number of surgical debridement	1	.18	1
Median duration of antibiotic treatment	21 days	.71	30 days
- Median duration of parenteral therapy	6 days	.88	6 days
Hyperbaric oxygen therapy	73 (11%)	.19	3 (6%)
Clinical failures (after end of therapy)	153 (24%)	.22	9 (17%)
Microbiological recurrence (with same pathogens)	111 (17%)	.24	6 (11%)

* Significant *p* values ≤ .05 (two-tailed) are displayed ***in bold and italic***.

[+] mostly coagulase-negative staphylococci, micrococci, cornynebacteria, cutibacteria

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Table 2 - Logistic regression analyses, stratified upon both outcomes "clinical failure" and "microbiological recurrence"

(Results expressed as odds ratios with 95% confidence intervals)

Outcome "Clinical failure"	Univariate	Multivariate	Multivariate	Univariate	**"Microbiological recurrence"**
Age	1.0, 1.0-1.0	1.0, 0.9-1.0	1.0, 0.9-1.1	1.0, 1.0-1.0	Age
Number of surgical debridement	***0.7, 0.6-0.8***	1.2, 0.8-1.8	2.2, 0.7-6.7	1.1, 0.9-1.3	Number of surgical debridement
Total duration of antibiotic therapy	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0	1.0, 1.0-1.0	Total duration of antibiotic therapy
Initial 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	Initial serum C-reactive protein level
Bacteraemia	0.6, 0.3-1.1	0.5, 0.1-2.8	1.8, 0.3-3.3	1.4, 0.7-2.6	Bacteraemia
Osteomyelitis	0.8, 0.6-1.1	0.8, 0.3-2.1	1.2, 0.3-4.3	0.9, 0.8-1.4	Osteomyelitis
Infection due to skin commensals	0.6, 0.3-1.3	0.4, 0.1-3.8	0.5, 0.1-4.2	0.6, 0.2-1.4	Infection due to skin commensals

*Significant results are displayed ***in bold and italic***. n.d. = not done due to interaction, absence of a medical sense, or due to reduced sample size