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The impact of the length of total and intravenous systemic antibiotic therapy for the remission of diabetic foot infections☆

Florian Haug[1,*,**], Felix W.A. Waibel[1,*], Marcus Lisy[1], Elin Winkler[1], Ilker Uçkay[2,3], Madlaina Schöni[1]

[1] Department of Orthopedics, Balgrist University Hospital, University of Zurich, Switzerland
[2] Unit for Clinical and Applied Research, Balgrist University Hospital, University of Zurich, Switzerland
[3] Infectiology, Balgrist University Hospital, University of Zurich, Switzerland

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ABSTRACT

Objective: We investigated the impact of the total length of systemic antibiotic therapy (ABT) and its initial intravenous (IV) part on clinical failure (CF) and microbiological failure (MF) in diabetic foot infections (DFIs).

Methods: In this single-center, retrospective, unmatched case-control study, we included DFI episodes treated with a combined surgical-antibiotic approach.

Results: We included 721 DFI episodes, 537 with osteomyelitis (DFO). CF occurred in 191 (26.5%) and MF in 42 (5.8%) episodes. Multivariate Cox regression analysis showed that a short ABT of 8–21 days (hazard ratio [HR] 0.4; 95% CI 0.2–0.7) was inversely associated with CF. This was also applicable for IV ABT with relatively short durations of 2–7 days (HR 0.5; 95% CI 0.3–0.8) or 8–14 days (HR 0.6; 95% CI 0.4–0.9). We failed to detect a minimal threshold of total or IV ABT predictive for CF or MF.

Conclusions: Compared with total ABT of more than 84 days and IV therapy of more than 14 days, shorter total and IV ABT yielded no enhanced risk of CF or MF. Considering the "bias by indication" that is inherent to retrospective DFI studies, the best study design concerning the duration of ABT would be a stratified, prospective randomized trial, which is currently under way in our medical center.

Introduction

Diabetic foot infection (DFI) is a frequent complication of diabetes and is associated with prolonged hospital stays (Henke et al., 2005; Lindbloom et al., 2014), a high risk of amputation (Hartemann-Heurtier and Senneville, 2008; Shank and Feibel, 2006), and long-term antibiotic therapy (ABT) (Ahluwalia et al., 2021; Gariani et al., 2020). Diabetes and DFI prevalence is increasing worldwide and so are the related costs (van Asten et al., 2018; Bus et al., 2019; Raspovic and Wukich, 2014). In addition to adequate debridement, surgery, and off-loading, systemic ABT is one of the cornerstones of therapy (Uçkay et al., 2014). DFI is probably one of the most frequent causes for inadequately prolonged ABT worldwide (Lipsky, 2016). Although there are clear guidelines available (Lipsky et al., 2020), the evidence for an optimal treatment duration and the appropriate route of administration is still weak (Ahluwalia et al., 2021; Ertuğrul et al., 2020a; Lipsky, 2016). Adverse events occur in up to 30% of all DFI regimens, and resistance against antibiotic agents is increasing (van Asten et al., 2018; Senneville and Robineau, 2017). Frequent adverse events are diarrhea (68%), nausea and inappetence (10%), renal function deterioration (9%), cutaneous rash (9%), hepatitis (5%), cholestasis (3%), mycosis (3%), leukopenia (2%), pruritus (2%), or headaches (2%) (Schindler et al., 2013). At the same time, recent studies indicate that oral ABT is as effective as intravenous (IV) therapy for most bone and joint infections (Ertuğrul et al., 2020a; Li et al., 2019), whereas oral regimens remain with shorter hospital stays and fewer complications than IV therapies (van Asten et al., 2018; Li et al., 2019; Schindler et al., 2013). Peripheral venous catheters may account for at least 6.3% of all preventable bloodstream infections (Jefferson and Mermel, 2018). Another DFI study computed that the median ABT cost reaches $969 (AUD), of which the bulk of 95.3% would only be attributed for its IV part (Commons et al., 2015).

☆ Level of Evidence: III.

** Corresponding author at: Florian Haug, MD, Department of Orthopedics, Balgrist University Hospital, Forchstrasse 340, 8008 Zürich, Switzerland.
E-mail address: florian.haug@balgrist.ch (F. Haug).
* Shared first authors.

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To avoid adverse events and possible developments of antibiotic resistance and to optimize the cost-effective treatment of DFI, the duration of total and IV ABTs should be kept as short as possible. Currently, the best approach to improve antibiotic stewardship seems to be the "individualized reduction of unnecessary or inappropriate antibiotic use" (Uçkay et al., 2019). Gariani et al published a retrospective study (Gariani et al., 2019) as well as a small prospective pilot trial in diabetic foot osteomyelitis (DFO) (Gariani et al., 2020) to determine the most appropriate duration of ABT in DFI and DFO. In the retrospective study, they found no threshold for the optimal duration of ABT to prevent treatment failures. The DFO pilot trial showed no benefit in ABT exceeding 3 weeks. Recent expert opinions and the newest International Working Group on Diabetic Foot Infections (IWGDF) guidelines conclude that ABT duration still remains one of the main controversies in the management of DFI (Ertuğrul et al., 2020b; Lipsky et al., 2020; Uçkay et al., 2019).

In this study, we investigated whether the length of total ABT and/or its IV part are associated with an enhanced risk of CF and recurrences after the therapy of DFI. These local data will serve as a guidance to larger and streamlined randomized controlled trials.

Methods

The Balgrist University Hospital is a tertiary referral center for orthopedic surgery with a specialized clinical and academic research unit for the diabetic foot. For this study, we analyzed all DFI episodes treated with a combined surgical-antibiotic approach from January 1, 2000, to March 31, 2020. The exclusion criteria were strictly conservative treatments without any surgical debridement, a postoperative follow-up of less than 6 months, major amputations, age <18 years, and insufficient documentation in the medical files. The study was approved by the local ethical committee in Zürich, Switzerland.

Primary outcomes were clinical failure (CF) and microbiological failure (MF) within 1 year after therapy, further stratified by the respective presence of osteomyelitis (DFO), gangrene, and primary versus revision surgeries. We defined CF as any clinical failure needing revision surgery, such as ischemia (Bus et al., 2019), whereas MFs were true microbiological recurrences with at least 50% of pathogens being identical with the bacteria of the index infection. We diagnosed DFO intraoperatively by the presence of bacteria in bone samples and preoperatively using x-ray examination or magnetic resonance imaging (MRI). If MRI was not possible for any reason, we replaced it with computed tomography or skeletal scintigraphy. The duration and the choice of the postoperative systemic antibiotic agents was based on the discretion of the treating surgeon and the infectious diseases consultant.

Statistical analyses

For crude group comparisons with categorical parametric variables, we used the Student *t* test or the chi-square test, as appropriate. Regarding nonparametric continuous variables, we used the Mann-Whitney *U* test. For survival data, we performed a log-rank analysis and plotted the corresponding Kaplan-Meier survival curves. The total duration of postdebridement ABT was computed as categorical and continuous data. We arbitrarily stratified the length of total ABT arbitrarily into 5 usual durations (0–7, 8–21, 22–42, 43–84, and >84 days) and the initial IV ABT into 4 categories (0–1, 2–7, 8–14, and >14 days).

We added a multivariate Cox regression analysis with the primary outcome "CF" to adjust for the large case-mix that is inherent to the DFI population. Therefore, reference was set at >84 days for total ABT and >14 days for IV ABT. For both outcomes (CF or MF), the final models consisted of the following variables: age, sex, chronic renal insufficiency, coronary artery disease, peripheral artery disease, bypass and/or angioplasty, diabetes type, nicotine abuse, prior amputations, postoperative total ABT, and the duration of IV therapy. In an ulterior step, we repeated the analyses for the strata DFO, gangrene, primary surgery, and revision surgery separately. Finally, we visually investigated a possible minimal duration level by plotting the risk of recurrences against the administered ABT durations and used SPSS software (Version 26, IBM Corp., Armonk, NY) by setting the significance level (2-tailed) at $\alpha = 0.05$.

Results

Study population

We included 721 DFI episodes in 331 different patients (79 women, 23.9%), with 570 (79.1%) primary episodes and 151 (20.9%) already revised episodes (Table 1). The mean active follow-up (physical medical controls) was 4.0 years (SD 3.5 years, range 0 days–20.1 years) after the end of index therapy. One patient died on the day of surgery because of a cardiac event and was excluded from the analyses. The mean passive follow-up (indication of problems by the patient) was 6.6 years (SD 5.3 years, range 0 days–20.5 years). During the follow-ups, 29.7% of the patients died after a mean interval of 4.1 (SD 3.6) years after therapy. The mean age at surgery was 66 (SD 11.5) years and the mean body mass index (BMI) 30.03 kg/m^2. Diabetes mellitus type II was present in 611 episodes (84.7%) and 69.6% received insulin treatment. Clinical polyneuropathy was present in 92.5% and Charcot neuroarthropathy in 12.1%. We noted peripheral artery disease in 526 episodes (73%), 108 (15%) of them at stages III and IV. Overall, 128 patients (17.8%) yielded a glomerular filtration rate ≤45 mL/min, and 48 patients (6.7%) were on dialysis. Other comorbidities included coronary artery disease (n = 325, 45.1%) and chronic immunosuppressive therapy (n = 50, 6.9%) and a history of organ transplantation (n = 17, 2.4%). In 332 episodes (46%), the patients revealed a history of contralateral minor or major amputation of the lower extremities.

Infections

We diagnosed DFO in 537 episodes (74.5%), gangrene in 14.1%, soft-tissue DFIs in 5.4%, chronic infected wounds in 5.9%, and open-toe arthritis in 0.1%. The anatomic location was the forefoot in 620 (86.0%), midfoot in 58 (8.0%), and hindfoot in 23 (3.2%) episodes. Intraoperative tissue samples revealed a polymicrobial infection in 263 episodes (36.5%) with 1.8 pathogens per sample (range, 1–6 pathogens). In 193 episodes (26.8%), at least 1 Gram-negative pathogen was involved. In total, 249 of the 883 pathogens (28.2%) were Gram-negative. Strikingly, gangrenes were significantly more associated with Gram-negative infections compared with OM (43.9% vs 25.2%). The most frequent microorganisms are listed in Table 2. In 69 episodes (9.6%), we failed to identify the causative pathogens.

Treatment

We did not use local antiseptics or topical antibiotics. The surgeons performed a partial minor amputation in 566 episodes (78.5%), an internal partial foot amputation in 119 episodes (16.5%), soft-tissue debridement in 20 episodes (2.8%), and an internal resection of infected bone with stabilization using an external Ilizarov ring fixation in 16 episodes (2.2%). We administered postoperative ABT in all episodes, of which 533 (73.9%) were IV at the start. The mean duration of IV therapy was 13 days (SD 17). The mean duration of total ABT was 36 days (SD 37) (Tables 3 and 4). We used 34 different regimens, of which the most common

Table 1
Study population.

	All episodes (n = 721)	New episodes (n = 570)	Revision episodes (n = 151)	*p*-value
Age (years), mean (SD)	66.0 (11.5)	66.0 (12.0)	65.0 (11.0)	ns
Sex (%)				**0.029**
Female	146 (20.2%)	125 (21.9%)	21 (13.9%)	
Male	575 (79.8%)	445 (78.1%)	130 (86.1%)	
Body mass index (kg/m^2), mean (SD)	30.0 (5.9)	29.8 (5.9)	30.8 (6.0)	ns
Side (%)				ns
Left	358 (49.7%)	275 (48.2%)	83 (55.0%)	
Right	363 (50.3%)	295 (51.8%)	68 (45.0%)	
Diabetes (%)				ns
Type 1	106 (14.7%)	81 (14.2%)	25 (16.6%)	
Type 2	611 (84.7%)	486 (85.3%)	125 (82.8%)	
Others	4 (0.6%)	3 (0.5%)	1 (0.7%)	
Insulin treatment in type 2 diabetes, n (%)	425 (69.6%)	326 (67.1%)	99 (79.2%)	**0.009**
Duration of diabetes (years), mean (SD)	20.0 (12.5)	20 (12)	22 (13)	ns
Neuropathy, n (%)	667 (92.5%)	525 (92.1%)	142 (94.0%)	ns
Charcot neuroarthropathy, n (%)	87 (12.1%)	74 (13.0%)	13 (8.6)	ns
PAD (%)	526 (73.0%)	411 (72.1%)	115 (76.2%)	ns
PAD stage III or IV (Fontaine)	108 (15.0%)	81 (14.2%)	27 (17.9%)	ns
Prior PTA, n (%)	380 (52.7%)	292 (51.2%)	88 (58.3%)	ns
Prior bypass surgery, n (%)	25 (3.5%)	19 (3.3%)	6 (4.0%)	ns
Coronary artery disease, n (%)	325 (45.1%)	245 (43.0%)	80 (53.0%)	**0.028**
Advanced kidney disease, n (%)	184 (25.5%)	141 (24.7%)	43 (28.5%)	ns
Dialysis	48 (6.7%)	39 (6.8%)	9 (6.0%)	ns
Kidney transplantation	12 (1.7%)	9 (1.6%)	3 (2.0%)	ns
Glomerular filtration rate ≤ 45 mL/min	128 (17.8%)	97 (17.0%)	31 (20.5%)	**0.029**
Immunosuppressants, n (%)	50 (6.9%)	37 (6.5%)	13 (8.6%)	ns
Prior organ transplantation, n (%)	17 (2.4%)	14 (2.5%)	3 (2.0%)	ns
Smoking history (%)	424 (58.8%)	327 (57.7%)	97 (64.2%)	ns
Ongoing nicotine abuse (% of smoker)	154 (36.3%)	120 (36.7%)	34 (35.1%)	ns
Alcohol abuse, n (%)	178 (24.7%)	133 (23.5%)	45 (29.8%)	ns
Already amputation on the other side, n (%)	332 (46.0%)	245 (43.0%)	87 (57.6%)	**0.005**
	306 (42.4%)	225 (39.5%)	81 (53.6%)	**0.002**
Minor amputation	26 (3.6%)	20 (3.5%)	6 (4.0%)	ns
Major amputation				
Clinical failure, n (%)	191 (26.5%)	138 (24.2%)	53 (35.1%)	**0.007**
Microbiological failure, n (%)	42 (5.8%)	31 (5.4%)	11 (7.3%)	ns
Revision (general) during FU, n (%)	407 (56.4%)	321 (56.3%)	86 (57%)	ns
Time to revision (months), mean (SD)	17.4 (28.5)	18.9 (30.5)	11.5 (17.9)	**0.032**
Major amputation during FU, n (%)	125 (17.3%)	92 (16.1%)	33 (21.9%)	ns
Death for any reason during FU, n (%)	214 (29.7%)	171 (30.0%)	43 (28.5%)	ns
Time-to-death (months), mean (SD)	49.4 (43.8)	51.9 (44.7)	39.6 (39.1)	ns
FU (months), mean (SD)	47.6 (41.9)	48.8 (43.2)	42.9 (36.3)	ns

Statistical significance is indicated in bold.
BMI = body mass index; eGFR = estimated glomerular filtration rate; FU = follow-up; ns = not significant; PAD = peripheral artery disease; PTA = percutaneous transluminal angioplasty; SD = standard deviation.

Table 2
Pathogen groups.

	All episodes (n = 721)	Osteomyelitis (n = 537)	Gangrene (n = 102)	*p*-value	New episodes (n = 570)	Revision episodes (n = 151)	*p*-value
Coagulase-negative staphylococci	219 (25.9%)	185 (28.1%)	17 (15.2%)	**0.000**	176 (25.3%)	43 (28.5%)	ns
Staphylococcus aureus	184 (21.7%)	151 (22.9%)	18 (16.1%)	**0.028**	155 (22.3%)	29 (19.2%)	**0.045**
Enterococci	83 (9.8%)	67 (10.2%)	10 (8.9%)	ns	67 (9.6%)	16 (10.6%)	ns
Streptococci	51 (6.0%)	42 (6.4%)	5 (4.5%)	ns	47 (6.8%)	4 (2.6%)	**0.017**
Pseudomonas aeruginosa	43 (5.1%)	33 (5.0%)	7 (6.3%)	ns	38 (5.5%)	5 (3.3%)	ns
Enterobacter sp.	40 (4.7%)	33 (5.0%)	7 (6.3%)	ns	36 (5.2%)	4 (2.6%)	ns
Escherichia coli	27 (3.2%)	18 (2.7%)	6 (5.4%)	ns	22 (3.2%)	5 (3.3%)	ns
Klebsiella sp.	21 (2.5%)	14 (2.1%)	4 (3.6%)	ns	17 (2.4%)	4 (2.6%)	ns

Statistical significance is indicated in bold.
ns = not significant.

single agents were ciprofloxacin (n = 331), amoxicillin/clavulanic acid (320), clindamycin (250), piperacillin/tazobactam (220), vancomycin (99), co-trimoxazole (71), and levofloxacin (47). Of note, when comparing Gram-negative to Gram-positive DFI, no significant difference was found with regard to the duration of total ABT.

Outcomes

We witnessed CF in 191 episodes (26.5%) and MF in 42 episodes (5.8%). Hence, we saw 5 times more (ischemic) treatment failures than true infection recurrences. The mean durations of total and IV ABT were not different between the episodes with and without CF (Table 5). The same applies for the outcome of MF. The plotting of the overall failure risk against the ABT duration failed to define a minimal threshold. Revision surgery was necessary in 407 episodes (56.4%) with an average of 2 revisions per patient (range, 1–13 surgeries) and a major amputation in 64 episodes (15.3%). The mean time delay to revision was 17.4 months and to major amputation, 34.5 months.

Table 3
Durations of antibiotic therapy in new episodes and revisions.

	All episodes (n = 721)	New episodes (n = 570)	Revision episodes (n = 151)	*p*-value
Duration of intravenous therapy (days), mean (SD)	13 (17)	12 (16)	16 (18)	**0.021**
Categorized information about duration of intravenous antibiotic therapy	182 (25.2%)	156 (27.4%)	26 (17.2%)	**0.010**
No intravenous therapy	20 (2.8%)	15 (2.6%)	5 (3.3%)	ns
≤24 hours	228 (31.6%)	188 (33.0%)	40 (26.5%)	**0.009**
2–7 days	149 (20.7%)	112 (19.6%)	37 (24.5%)	ns
8–14 days	120 (16.6%)	83 (14.6%)	37 (24.5%)	**0.020**
>14 days	22 (3.1%)	16 (2.8%)	6 (4.0%)	ns
Duration not documented				
Duration of overall postoperative antibiotic therapy (days), mean (SD)	36 (37)	34 (36)	43 (39)	**0.010**
Categorized information about duration of overall postoperative antibiotic therapy	61 (8.5%)	53 (9.3%)	8 (5.3%)	ns
≤7 days	290 (40.2%)	243 (42.6%)	47 (31.1%)	**0.010**
8–21 days	194 (26.9%)	147 (25.8%)	47 (31.1%)	ns
22–42 days	112 (15.5%)	82 (14.4%)	30 (19.9%)	ns
4–84 days	64 (8.9%)	45 (7.9%)	19 (12.6%)	ns
>84 days				

Statistical significance is indicated in bold.
ns = not significant; SD = standard deviation.

Table 4
Durations of antibiotic therapy for osteomyelitis vs gangrene.

	All episodes (n = 721)	Osteomyelitis (n = 537)	Gangrene (n = 102)	*p*-value
Duration of intravenous therapy (days), mean (SD)	13 (17)	12 (16)	16 (20)	ns
Categorized information about duration of intravenous antibiotic therapy	182 (25.2%)	125 (23.3%)	34 (33.3%)	**0.031**
No intravenous therapy	20 (2.8%)	12 (2.2%)	3 (2.9%)	ns
≤24 hours	228 (31.6%)	188 (35.0%)	23 (22.6%)	ns
2–7 days	149 (20.7%)	109 (20.3%)	16 (15.7%)	ns
8–14 days	120 (16.6%)	88 (16.4%)	19 (18.6%)	ns
>14 days	22 (3.1%)	15 (2.8%)	7 (6.9%)	ns
Duration not documented				
Duration of overall postoperative antibiotic therapy (days), mean (SD)	36 (37)	34 (33)	38 (41)	ns
Categorized information about duration of overall postoperative antibiotic therapy	61 (8.5%)	38 (7.1%)	14 (13.7%)	**0.024**
≤7 days	290 (40.2%)	231 (43.0%)	36 (35.3%)	ns
8–21 days	194 (26.9%)	149 (27.7%)	27 (26.5%)	ns
22–42 days	112 (15.5%)	80 (14.9%)	15 (14.7%)	ns
43–84 days	64 (8.9%)	39 (7.3%)	10 (9.8%)	ns
>84 days				

Statistical significance is indicated in bold.
ns = not significant; SD = standard deviation.

Table 5
Duration of antibiotic therapy for clinical and microbiological failure.

	Clinical failure			*Microbiological failure*		
	Yes	*No*	*p-value*	*Yes*	*No*	*p-value*
Duration of intravenous therapy (days), mean (SD)	*17 (18)*	*11 (16)*	*ns*	*13(11)*	*13 (17)*	*ns*
Categorized information about duration of intravenous antibiotic therapy, n (%)	5 (1.0)	15 (2.9)	ns	0	20 (3.9)	ns
No intravenous therapy	48 (9.3)	180 (34.8)	0.001	18 (3.5)	210 (40.6)	ns
≤24 hours	37 (7.2)	112 (21.7)	ns	10 (1.9)	139 (26.9)	ns
2–7 days	58 (11.2)	62 (12.0)	0.000	10 (1.9)	110 (21.3)	
8–14 days						
>14 days						
Duration not documented						
Duration of overall postoperative antibiotic therapy (days), mean (SD)	*47 (45)*	*32 (33)*	*ns*	*36 (32)*	*36 (37)*	*ns*
Categorized information about duration of overall postoperative antibiotic therapy	12 (1.7)	49 (6.8)	ns	2 (0.3)	59 (8.2)	ns
≤7 days	55 (7.6)	235 (32.6)	0.000	17 (2.4)	273 (37.9)	ns
8–21 days	47 (6.5)	147 (20.4)	ns	13 (1.8)	181 (25.1)	ns
22–42 days	51 (7.1)	61 (8.5)	0.000	7 (1.0)	105 (14.6)	ns
43–84 days	26 (3.6)	38 (5.3)	0.007	3 (0.4)	61 (8.5)	ns
>84 days						

SD = standard deviation.

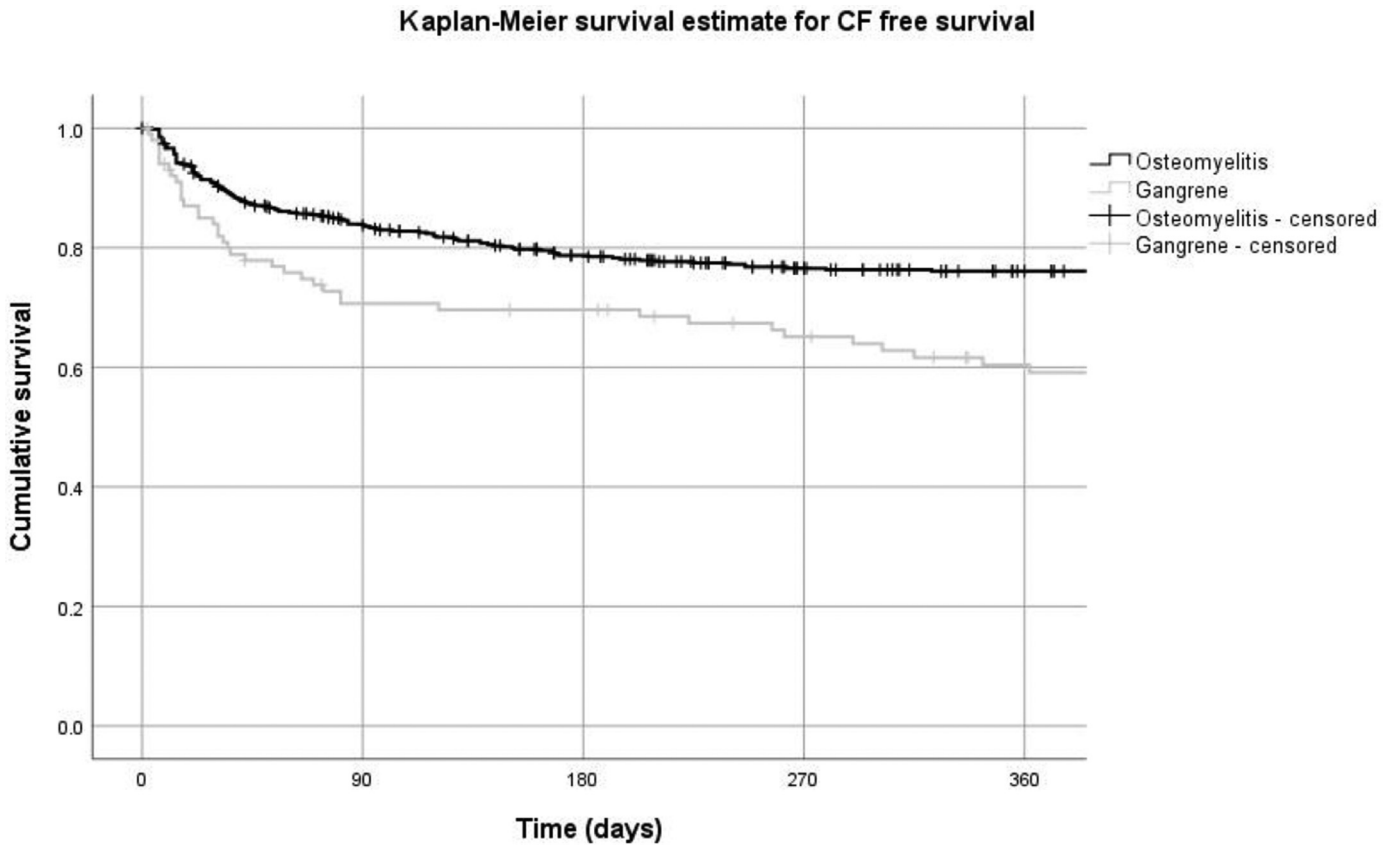

Figure 1. Kaplan-Meier survival curves regarding remission.
CF = clinical failure.

Stratified outcomes

Among the 537 DFO episodes, CF occurred in 124 (23.1%) and MF in 35 (6.5%) episodes. In cases with superinfected gangrene, CF occurred statistically significantly more often with 38.2% ($p = 0.001$) (Figure 1). MF was seen in 3.9% in this group. Overall, revision surgery was needed in 298 episodes with DFO (55.5%) versus revision surgery in 58 episodes with gangrene (56.9%). Comparing the groups with DFO and gangrene, there was no significant difference in time to CF (mean 2.8 vs 2.9 months, $p = 0.920$), time to revision (18.7 vs 14.1 months, $p = 0.269$), and time to major amputation (34.1 vs 14.9 months, $p = 0.056$). However, the time to MF was significantly shorter in DFO (2.6 vs 5.8 months, $p = 0.045$). In new DFI episodes, CF was observed in 138 (24.2%) and MF in 31 (5.4%) episodes. In revisions, CF occurred in 53 (35.1%) and MF in 11 (7.3%) episodes. Comparing new and revision episodes, there was no difference in time to CF and time to MF.

Multivariate results

Short ABT durations such as the groups of 8–21 days (hazard ratio [HR] 0.4, 95% CI 0.2–0.7) or 22–42 days (HR 0.5, 95% CI 0.3–0.9) were inversely associated with CF. Regarding the initial IV part, short prescriptions such as 2–7 days (HR 0.5, 95% CI 0.3–0.8) or 8–14 days (HR 0.6, 95% CI 0.4–0.9) were also negatively associated. In contrast, a previous contralateral minor amputation (HR 1.5, 95% CI 1.1–2.1) and a history of revascularization (HR 1.5, 95% CI 1.0–2.1) were clear risks associated with CF (Tables 6 and b). In DFOs, a contralateral minor (HR 1.8, 95% CI 1.2–2.8) or a major (HR 3.1, 95% CI 1.3–7.3) amputation was a significant risk factor for CF. Equally, we confirmed an inverse association with CF regarding the total ABT of 8–21 days (HR 0.3, 95% CI 0.2–0.7). In new episodes, the clinical need for revascularization (HR 1.7, 95% CI 1.1–2.5) was a significant risk, whereas, again, a short ABT of 8–21 days (HR 0.5, 95% CI 0.2–1.0), or short IV administrations of 2–7 days (HR 0.4, 95% CI 0.3–0.8) or 8–14 days (HR 0.5, 95% CI 0.3–0.8) still were inversely associated with CF.

We found no associations between the tested variables and MF in all regression analyses. Gram-negative DFI was not associated with MF in nonrevised DFIs (Gram-negatives vs Gram-positives: MF 6.9% vs 7.6%). This held equally true when only analyzing OM alone (MF 8.6% for Gram-negative OM vs 7.85 failure risk for Gram-positive OM).

Discussion

In this large, retrospective DFI cohort study, we found no minimal thresholds and no optimal durations concerning the total systemic ABT or the IV ABT in relation to clinical failures and microbiological recurrences. This lack of association concerned all strata: the overall study population, DFO episodes, and revision surgeries for DFI. Statistically speaking, the shorter the duration of ABT, the less the occurrence of failures, indicating a major “confounding by indication” that is inherent to many retrospective studies with a large case-mix (Jeffcoate et al., 2016). It is probable that the surgeons prolonged the duration of ABT for episodes with unsatisfactory evolutions without finally being able to reverse the risk of failure. The low number of MF (true microbiological recurrences: $n = 42$, 5.8%) compared with CF (mostly ischemic failures: $n = 191$, 26.5%) supports the fact that the ABT was sufficient for the index infection in most episodes. This is conclusive, with further data showing that only a small proportion of stump complications are caused by infections.(Dunkel et al., 2012; Uçkay et al., 2011).

Table 6a
End point clinical failure–OM vs gangrene.

	All episodes Univariate analysis, HR (95% CI)	All episodes Multivariate analysis, HR (95% CI)	Osteomyelitis Univariate analysis, HR (95% CI)	Osteomyelitis Multivariate analysis, HR (95% CI)	Gangrene Univariate analysis, HR (95% CI)	Gangrene Multivariate analysis, HR (95% CI)
Age	0.995 (0.98–1.01)	1.01 (0.99–1.02)	0.996 (0.98–1.01)	1.01 (0.98–1.03)	0.997 (0.97–1.02)	1.03 (0.98–1.1)
Female sex	0.7 (0.5–1.1)	0.8 (0.5–1.3)	**0.5 (0.3–0.9)**	**0.4 (0.2–0.9)**	1.1 (0.5–2.3)	2.4 (0.6–9.0)
Advanced kidney disease	1.3 (0.9–1.7)	0.9 (0.6–1.4)	1.3 (0.9–1.9)	0.9 (0.5–1.4)	0.9 (0.5–1.7)	0.6 (0.3–1.5)
Coronary artery disease	**1.5 (1.1–2.0)**	1.1 (0.8–1.6)	**1.6 (1.1–2.3)**	1.3 (0.9–2.0)	1.5 (0.8–2.8)	0.9 (0.3–2.6)
Bypass and/or PTA	**1.3 (1.004–1.8)**	**1.5 (1.04–2.1)**	**1.5 (1.02–2.1)**	1.2 (0.8–1.9)	1.2 (0.6–2.4)	2.5 (0.8–7.4)
Diabetes type 2	0.8 (0.5–1.1)	0.7 (0.4–1.01)	0.7 (0.5–1.1)	0.8 (0.5–1.2)	0.6 (0.3–1.3)	0.5 (0.2–1.4)
Nicotine abuse	1.3 (0.9–1.7)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	0.9 (0.6–1.4)	1.2 (0.6–2.4)	1.5 (0.5–4.1)
Prior contralateral minor amputation	**1.6 (1.2–2.1)**	**1.5 (1.1–2.1)**	**1.6 (1.1–2.3)**	**1.8 (1.2–2.8)**	**2.4 (1.3–4.6)**	**2.5 (1.1–5.5)**
Prior contralateral major amputation	1.8 (0.9–3.5)	1.8 (0.8–3.8)	2.2 (0.95–5.1)	**3.1 (1.3–7.4)**	1.1 (0.3–4.9)	2.1 (0.3–17.2)
PAD	**1.4 (1.01–2.0)**	1.1 (0.6–1.9)	1.4 (0.92–2.1)	0.9 (0.4–1.9)	2.4 (0.3–17.8)	1.9 (0.1–33.4)
Overall postoperative antibiotic therapy	**0.5 (0.2–0.9)**	0.8 (0.4–1.8)	0.6 (0.2–1.4)	0.7 (0.3–1.9)	**0.1 (0.02–0.6)**	0.3 (0.04–2.9)
≤7 days	**0.4 (0.3–0.7)**	**0.4 (0.2–0.8)**	**0.4 (0.2–0.8)**	**0.3 (0.2–0.7)**	**0.2 (0.09–0.6)**	0.4 (0.1–2.6)
8–21 days	**0.6 (0.3–0.9)**	**0.5 (0.3–0.9)**	**0.5 (0.4–0.9)**	0.5 (0.2–1.04)	0.4 (0.2–1.04)	0.4 (0.1–1.7)
22–42 days	1.3 (0.8–2.0)	0.96 (0.6–1.7)	1.3 (0.7–2.5)	1.3 (0.6–2.9)	0.6 (0.2–1.7)	0.5 (0.1–2.6)
43–84 days	reference	reference	reference	reference	reference	reference
>84 days						
Intravenous antibiotic therapy						
≤24 hours	**0.4 (0.2–0.98)**	0.4 (0.2–1.1)	0.3 (0.1–1.4)	0.4 (0.1–1.9)	n.d.	n.d.
2–7 days	**0.3 (0.2–0.5)**	**0.5 (0.3–0.8)**	**0.4 (0.3–0.6)**	0.8 (0.4–1.5)	**0.3 (0.1–0.7)**	**0.3 (0.1–0.8)**
8–14 days	**0.4 (0.3–0.6)**	**0.6 (0.3–0.9)**	**0.4 (0.2–0.7)**	0.7 (0.4–1.2)	**0.4 (0.1–0.9)**	0.4 (0.1–1.01)
>14 days	reference	reference	reference	reference	reference	reference

Statistical significance is indicated in bold.
ns = not significant; OM = osteomyelitis; PAD = peripheral artery disease; PTA = percutaneous transluminal angioplasty; SD = standard deviation.

Table 6b
End point clinical failure–new vs revision episodes.

	All episodes Univariate analysis, HR (95% CI)	All episodes Multivariate analysis, HR (95% CI)	New episodes Univariate analysis, HR (95% CI)	New episodes Multivariate analysis, HR (95% CI)	Revisions Univariate analysis, HR (95% CI)	Revisions Multivariate analysis, HR (95% CI)
Age	0.995 (0.98–1.01)	1.005 (0.99–1.02)	1.002 (0.99–1.02)	1.01 (0.99–1.03)	**0.98 (0.95–0.999)**	**0.97 (0.9–0.995)**
Female sex	0.7 (0.5–1.1)	0.8 (0.5–1.3)	0.8 (0.5–1.3)	0.9 (0.5–1.5)	0.5 (0.2–1.3)	0.6 (0.1–2.8)
Advanced kidney disease	1.3 (0.9–1.7)	0.9 (0.6–1.4)	1.3 (0.9–1.9)	1.1 (0.7–1.7)	0.98 (0.5–1.8)	0.6 (0.3–1.3)
Coronary artery disease	**1.5 (1.1–2.0)**	1.1 (0.8–1.6)	**1.5 (1.05–2.04)**	1.04 (0.7–1.6)	1.4 (0.8–2.4)	1.4 (0.7–2.6)
Bypass and/or PTA	**1.3 (1.004–1.8)**	**1.5 (1.04–2.1)**	1.3 (0.9–1.9)	**1.7 (1.1–2.5)**	1.2 (0.7–2.2)	0.99 (0.3–3.3)
Diabetes type 2	0.8 (0.5–1.1)	0.7 (0.4–1.01)	0.8 (0.5–1.3)	0.6 (0.4–1.1)	0.7 (0.3–1.2)	0.6 (0.2–1.3)
Nicotine abuse	1.3 (0.9–1.7)	1.1 (0.8–1.6)	1.2 (0.8–1.6)	0.99 (0.6–1.5)	1.6 (0.9–2.9)	1.5 (0.7–3.4)
Prior contralateral minor amputation	**1.6 (1.2–2.1)**	**1.5 (1.1–2.1)**	1.3 (0.9–1.9)	1.3 (0.9–2.0)	**2.4 (1.3–4.3)**	**2.3 (1.2–4.4)**
Prior contralateral major amputation	1.8 (0.9–3.5)	1.8 (0.8–3.8)	1.8 (0.8–3.8)	1.9 (0.8–4.5)	1.7 (0.4–7.3)	2.2 (0.5–9.9)
PAD	**1.4 (1.01–2.0)**	1.1 (0.6–1.9)	1.5 (0.98–2.2)	1.2 (0.6–2.3)	1.2 (0.6–2.3)	1.2 (0.5–2.9)
Overall postoperative antibiotic therapy	**0.5 (0.2–0.9)**	0.8 (0.4–1.8)	**0.4 (0.2–0.9)**	0.8 (0.3–2.2)	1.01 (0.3–3.8)	0.9 (0.2–3.4)
≤7 days	**0.4 (0.3–0.7)**	**0.4**	**0.4**	**0.5**	0.8	0.5
8–21 days	**0.6**	**(0.2–0.8)**	**(0.2–0.7)**	**(0.2–0.96)**	(0.3–1.8)	(0.2–1.3)
22–42 days	**(0.3–0.9)**	**0.5**	**0.5**	0.6	0.7	0.5
43–84 days	1.3	**(0.3–0.9)**	**(0.3–0.9)**	(0.3–1.3)	(0.3–1.6)	(0.2–1.4)
>84 days	(0.8–2.0)	0.96	1.2	1.003	1.5	1.2
	reference	(0.6–1.7)	(0.7–2.1)	(0.4–2.0)	(0.7–3.6)	(0.5–3.1)
		reference	reference	reference	reference	reference
Intravenous antibiotic therapy						
≤24 hours	**0.4 (0.2–0.99)**	0.4 (0.2–1.1)	0.4 (0.2–1.2)	0.5 (0.1–1.5)	0.3 (0.04–2.2)	0.2 (0.03–1.7)
2–7 days	**0.3 (0.2–0.5)**	**0.5 (0.3–0.8)**	**0.3 (0.2–0.5)**	**0.4 (0.3–0.8)**	0.5 (0.3–1.1)	0.5 (0.2–1.3)
8–14 days	**0.4 (0.3–0.6)**	**0.6 (0.4–0.9)**	**0.4 (0.2–0.6)**	**0.5 (0.3–0.8)**	0.6 (0.3–1.2)	0.9 (0.4–2.1)
>14 days	reference	reference	reference	reference	reference	reference

Statistical significance is indicated in bold.
ns = not significant; PAD = peripheral artery disease; PTA = percutaneous transluminal angioplasty; SD = standard deviation.

Duration and route of application of ABT

Various studies and guidelines show no benefit for ABT lasting longer than 6 weeks for DFO; or 2 weeks for soft-tissue DFIs (Gariani et al., 2019; Lipsky et al., 2020; Tone et al., 2015). The currently largest study concerning ABT durations in DFI (Gariani et al., 2019) equally found no threshold for the total duration of ABT or its IV part. Gariani et al. recently released an randomised controlled (RC) prospective pilot trial comparing 3 versus 6 weeks of ABT with a similar incidence for remission (Gariani et al., 2020). We confirm these results. Likewise, different IV durations cannot influence outcomes regardless of the stratum or the outcome analyzed. If the pathogen is sensitive to a specific antibiotic agent, oral ABT is not inferior to IV application for long-term treatment (Alves et al., 2012; Whisstock et al., 2020). On the basis of available literature, the new IWGDF guidelines (Lipsky et al., 2020) support

that in mild DFIs and most episodes with a moderate DFI, we can safely perform an oral ABT right from the start. In severe DFIs, the ABT is given by the parenteral route, with a switch to oral therapy after 5–7 days if the patient is improving and has no contraindications to oral regimens (Lipsky et al., 2020).

Indeed, in the entire field of orthopedic infection, (Li et al., 2019) demonstrated the noninferiority of oral ABT (after 1 week IV ABT) compared with the 6-week IV regimens. In addition, an early switch to oral therapy was associated with a shorter hospitalization owing to reduced side effects. Another promising new approach, which is currently evolving, is the local application of antibiotic agents for disruption of biofilms and prevention of recurrence. These include polymethylmethacrylate blocks, bone cement, collagen sponges, and calcium sulfate formulations (Gauland, 2011; Hutting et al., 2021; Jogia et al., 2015; Krause et al., 2009; Varga et al., 2014). Use of these agents may reduce the need for IV ABT even further (Ferguson et al., 2017; McNally et al., 2016; Varga et al., 2014).

Limitations

Our study has several limitations. First, it has a retrospective design with a substantial "confounding by indication." It is conceivable that DFI episodes with poor evolution during therapy received a prolonged ABT. Second, the study population is heterogeneous. Stratification according to different surgical factors that are known to influence the outcome should be implemented in future studies, such as adequate disruption of bacterial biofilm, resection to clear bone margins (wide or marginal), or protocolized debridement to mention a few (Ahluwalia et al., 2019; Johnson et al., 2019; Senneville and Robineau, 2017; Simpson et al., 2001) as well as various patient-related factors, such as peripheral artery disease, diabetes, and malnutrition (Abbas et al., 2015; Uckay et al., 2018; Uçkay et al., 2014). Third, because of heterogeneity of pathogens and antibiotic agents, no targeted analysis on the role of these specific pathogens or antibiotic agents was possible. Of note, we recorded a total of 81 different microbiological constellations and 34 different antibiotic regimens, especially among the Gram-negative pathogens. Fourth, our geographical localization might play a role, limiting the generatability of our findings. Gram-negative DFI is a challenge for clinicians, especially in Southern Europe and subtropical regions, such as Southern Asia (Uçkay et al., 2014) for several reasons. The proportion of (nonfermenting) Gram-negative rods in DFI is more predominant in these arid countries (up to 60%) compared with temperate areas such as Northern America or Central Europe, for which the exact reasons remain unknown. In addition, the Gram-negative rods are much more antibiotic resistant and emerging than the usual Gram-positive bacteria, for which many oral antimicrobial agents remain available. For example, Saltoğu et al. (2018) found that most Gram-negative DFI involved *Pseudomonas* spp. with a high proportion of multidrug-resistant microorganisms, leading to a prolonged IV therapy because of the nonavailability of oral agents rather than because of the clinical virulence of the infection. If there is a high proportion of multidrug resistance, the CF and MF failures risk may also increase because of that resistance (Saltoglu et al., 2018). In temperate areas and resource-rich countries where the resistance problem might be less predominant, the duration of the ABT is less driven by the clinical picture. Unsurprisingly, the total duration of our ABT did not differ between Gram-negative and Gram-positive foot infection. Likewise, the outcomes of MF were similar between both pathogen groups, suggesting that there might be no genuine difference in terms of clinical virulence between Gram-negative and Gram-positive germs. This can obviously change when the Gram-negatives are becoming multidrug resistant, which is not yet the case in our region. In such a case, the ABT would also rely more on IV administrations because of the nonavailability of performant oral agents. Of note, the proportion of *P. aeruginosa* among all causative DFI pathogens in our region ranges between 6% and 12% (Uçkay et al., 2021). Curative resection and remission are to date difficult to prove with consistence. Current studies have shown good results for routine intraoperative biopsies and percutaneous biopsies of the residual bone stump (Costerton et al., 2011; Elamurugan et al., 2011; Kosmopoulou and Dumont, 2020; Kowalski et al., 2011; Senneville et al., 2006). In case of confirmed curative resection, recent studies even suggest to limit postoperative ABT to 0–5 days (Rossel et al., 2019; Saltoglu et al., 2010). This also holds true for the guidelines for the management of simple soft-tissue infections, which suggest a maximum of 2–5 days (Uçkay et al., 2019).

Conclusion

Our study retrospectively demonstrates that in a specialized surgical diabetic foot unit for adult patients with DFI and DFO, relatively short postoperative regimens of total ABT (eg, for less than 6 weeks) do not yield an enhanced risk of CFs or MFs. The same applies for IV administrations of 2–14 days compared with more than 14 days. We were also unable to define optimal minimal threshold of ABT durations. Given the presence of substantial "confounding by indication," the best study design for our study questions would be stratified prospective randomized trials (Gariani et al., 2020; Jeffcoate et al., 2016), which are currently under way (Waibel et al., 2020).

Disclosures

All authors declare no conflict of interest.

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Authors' contributions

FH, FW, ML, EW and MS performed the data acquisition. MS, EW and IU performed the statistical analysis. FH, FW, ML, IU, EW and MS have contributed to analysis and interpretation of the data. All authors contributed by either drafting or critical revision of the manuscript. All authors have read and approved the final submitted manuscript.

Ethical approval statement

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. IRB approval was obtained. Written consent to publish potentially identifying information, such as details of the case and photographs, was obtained from the patients or their legal guardians.

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