Optimization of the antibiotic management of diabetic foot infections - Protocol for two randomized controlled trials

Felix WA Waibel
Uniklinik Balgrist
Martin Berli
Uniklinik Balgrist
Sabrina Catanzaro
Uniklinik Balgrist
Kati Sairanen
Uniklinik Balgrist
Madlaina Schöni
Uniklinik Balgrist
Thomas Böni
Uniklinik Balgrist
Jan Burkhard
Uniklinik Balgrist
Dominique Holy
Uniklinik Balgrist
Tanja Huber
Uniklinik Balgrist
Maik Bertram
Uniklinik Balgrist
Karin Laeubli
Uniklinik Balgrist
Dario Frustaci
Uniklinik Balgrist
Andrea Rosskopf
Uniklinik Balgrist
Sander Botter
Uniklinik Balgrist
Ilker Uçkay (ilker.uckay@balgrist.ch)
Uniklinik Balgrist https://orcid.org/0000-0002-5552-0973

Study protocol

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Abstract

Background: Few studies address the appropriate duration of antibiotic therapy for diabetic foot infections (DFI); with or without amputation. We will perform two randomized clinical trials (RCT) to reduce the antibiotic use and associated adverse events in DFI. Methods: We hypothesize that shorter durations of post-debridement systemic antibiotic therapy are non-inferior (10% margin, 80% power, ⍺ 5%) to existing (long) durations and we will perform two unblinded RCTs with a total of 400 DFI episodes (randomization 1:1) from 2019 to 2022. The primary outcome for both RCT is “remission of infection” after a minimal follow-up of two months. The secondary outcomes for both RCT are the incidence of adverse events and the overall treatment costs. The First RCT will allocate the total therapeutic amputations in two arms of 50 patients each: 1 vs. 3 weeks of antibiotic therapy for residual osteomyelitis (positive microbiological samples of the residual bone stump); or 1 vs. 4 days for remaining soft tissue infection. The Second RCT will randomize the conservative approach (only surgical debridement without in toto amputation) in two arms with 50 patients each: 10 vs. 20 days of antibiotic therapy for soft tissue infections; and 3 vs. 6 weeks for osteomyelitis. All participants will have professional wound debridement, adequate off-loading, angiology evaluation, and a concomitant surgical, re-educational, podiatric, internist and infectiology care. During the surgeries, we will collect tissues for BioBanking and future laboratory studies. Discussion: Both parellel RCTs will repond to frequent questions regarding the duration of antibiotic use in the both major subsets of DFIs, to assure the quality of care, and to avoid unnecessary excesses in terms of surgery and antibiotic use. Trial registration: ClinicalTrial.gov NCT04081792. Registered on 4th September 2019. Protocol version: 2 (15th July 2019)

Introduction

Background and rationale

Diabetic foot infections (DFI) are frequent and harbor a high burden of morbidity, costs, and recurrences [1] worldwide. Knowing the potential for poor outcomes, many clinicians tend to treat DFIs with a long antibiotic therapies, comprising side effects, spreading of antibiotic resistance, and increasing associated costs [1,3]. In contrast, scientific data from the few comparative trials available has shown that 1-2 weeks of antibiotic treatment is sufficient for most diabetic foot soft tissue infections, and 4 to 6 weeks appear adequate for (unresected) infected bone [1-3]. A randomized trial compared a 6-week against 12-week course of antibiotic therapy, without concomitant surgery, for diabetic foot osteomyelitis (DFO) and found similar outcomes. This study set the maximal duration at 6 weeks for the conservative treatment of DFO, but shorter durations have not been evaluated [4]. A pilot study in Geneva still recruits and randomizes the post-surgical antibiotic therapy between 10 and 20 days for soft tissue DFI, and between 3 and 6 weeks for DFO, and found no difference in terms of remission in two interim analyses (ClinicalTrials NCT03615807) [5]. Another recent case-control study with 1018 DFI episodes equally failed to determine an optimal duration of systemic antibiotic therapy in all substrata of DFIs, but advocated that current

therapy schema might be too long [6]. Clearly, there is room for improving antibiotic stewardship efforts in DFI [2] and an interest for randomized-controlled trials (RCT) on DFI.

Methods

Study setting

The Balgrist University Hospital in Zurich is a tertiary referral center for DFI and amputations (emergency and elective consultations with a 24-hour service) and affiliated to the University of Zurich. Regarding DFIs, it resumes a multidisciplinary team composed of four diabetic foot surgeons, three internist physicians, a hospital pharmacist, five specialized wound nurses, two podiatry nurses, musculoskeletal expert radiologists, a diabetes nurse, three nutritionists, a shoemaker, a prosthesis specialist, and up to four infectious diseases physicians who are specialized in orthopedic infections. Moreover, this team is supported by an in-house company for orthopedic footwear (Balgrist Tec) and individual adaptations of off-loading devices, a re-education unit, physical therapy, a research campus (Balgrist Campus) with a BioBank, and an Unit for Clinical and Applied Research with nine study nurses and three personnel with experience in biostatistics and investigative designs (www.balgrist.ch). This research unit runs a register for DFI's and DFOs. This register is presumably the largest in Switzerland. Our potential of recruitment oscillates between 1 to 4 new DFI episodes (hospitalized and outpatient patients) per week. This study will start at the Balgrist, but is expandable to other national or international centers.

Study: Two concomitant prospective-randomized trials

We will conduct two concomitant prospective-randomized clinical trials (RCTs) on the duration of postsurgical systemic antibiotic therapies for DFIs, including DFOs:

- First RCT (on residual infection after amputation): Its primary study question is if systemic antibiotic therapy can be shortened in amputated patients with eventual residual soft tissue infection or residual stump osteitis. The secondary study questions are the incidence of adverse events and overall costs related to the treatment.
- Second RCT (on the duration of systemic antibiotic therapy in non-resected infections): The primary study question is if antibiotic therapy can be shortened in non-amputated patients with soft tissue infections and osteitis. The secondary study questions are the incidence of adverse events and overall costs related to the treatment.

Definitions and eligibility criteria for participants

We will class DFI episodes according to the severity of infections and IDSA criteria (Infectious Diseases Society of America) [3]. Mild infection is defined as having ≥2 manifestations of local inflammation

(swelling or induration, erythema, tenderness, warmth, purulent discharge). Moderate DFI is erythema >2 cm, or involving structures deeper than the subcutaneous tissues [3]. We define DFOs as a bone infection with any positive microbiological, histological and/or radiological evidence of bone involvement. We define remission as the absence of clinical, anamnestic, radiologic and/or laboratory signs of former infection. Of note, new or persistent necrosis, fracture, Charcot deformity or ulceration can be interpreted as remission as long they are no signs of infection. The anatomical area defining DFI for the study terminates at the ankle joints, but participants are eligible with leg infections as long as these originate in their diabetic foot. Table 1 resumes the inclusion and exclusion criteria.

Interventions and study conduct

For both RCTs, we keep the current therapeutic practices. Basically, amputation or disarticulation is foreseen for DFO with advanced bone destruction and terminal (painful) ischemia, but not for DFI *per se*. The amputation level will be kept as distal and as minimal. Basically, we will perform amputation on a level determined by MRI imaging and mechanical properties. All surgeries will be performed with the participation of an experienced surgeon. The patient will be invited to participate and will be allocated to a short or a long antibiotic treatment arm; further allocation depends of the surgical indications (amputation or conservative approach). The inclusion can occur until Day 4 of surgery or of effective antibiotic therapy.

Surgical indication: amputation: If the clinicians and the patient decide for amputation, the patients participate in the First RCT. If there is residual post-amputation infection remaining either in the soft tissue or bone, the patient will be randomized as follows:

- - 1 vs. 4 days for residual soft tissue infection
- - 1 vs. 3 weeks for an eventual residual proximal stump osteitis

Stop of all antibiotics if no bacterial growth at Day 4; or according to the randomization arm.

Surgical indication: debridement without amputation: If the clinicians and the patient decide for debridement only (no therapeutic amputation), then the patient is in the Second RCT:

- 10 versus 20 days for soft tissue infections

- 3 versus 6 weeks for non-amputated osteomyelitis

If the patient cannot participate in one RCT, he/she can participate in the other (Figure 1).

Table 2 reveals the variables of interest in each of the two RCT. The follow-up will be active (regular clinical consultations by the study investigators) until 2 months postoperatively, and passive (notification of recurrence, e.g. upon telephone contact) at 12 months postoperatively.

BioBanking

If the patient is operated, we will ask to sample intraoperative tissue for BioBanking for eventual further research, or completeness of the current studies. The BioBank will store intraoperative specimens, at ambient temperature (15–25°C) in the Balgrist Campus. The storage will be anonymous for 10 years, and financed by external grants.

MRI (Magnetic resonance imaging)

At Balgrist University Hospitals, each patient suspect for DFO has a conventional X-rays and MRI examinations as part of our standard clinical protocol. For this study, no patient will have scintigraphy in addition to the MRI. The standard MRI examination will be performed before surgery as part of the usual clinical approach. We will test no new software. Both RCT will not demand for additional radiologic exams only for study reasons.

Prior antibiotic therapy

A microbiologically effective antibiotic therapy beyond 96 hours prior to screening is an exclusion criterion. In contrast, we will allow a 72-hours window before debridement, independently of the duration of prior antibiotic administration. However, if the patient requires a new antibiotic agent based on microbiological results, independently of the duration of prior ineffective antibiotic therapy, there will be no minimal windows or maximal pre-debridement antibiotic durations and the patient can be included into both RCTs.

The antibiotic therapy is administered according to the IDSA guidelines [3]. Initially, it is either empiric or targeted to the results of preoperative information. After 2-4 days, it becomes targeted to the susceptibility profile. The choice of the agent, and its administration route (oral or parenteral), is at the discretion of the treating clinicians. Nonetheless, for both RCTs, and to achieve a minimal homogeneity, we establish a list of “allowed antibiotics” (Table 3). We will avoid placebos, topical antibiotics and antiseptics; except for the eventual pre-incisional skin disinfection. Likewise, anesthesiologists will remain free to administer the routine perioperative prophylaxis (cefuroxime, vancomycin, or clindamycin

for up to three doses), if they judge it indicated. Finally, we will collect the packages of the prescriptions during the outpatient treatment; as a surrogate of "proof" of the patient's antibiotic intake.

Pregnancy and breast-feeding women

This study, all antibiotics and surgeries, have no specific relations to pregnant or breast-feeding women and their children. Additionally, the study population is likely not to reveal women at procreating age. Formally, we will not exclude pregnant and breast-feeding women, but the investigators will avoid antibiotics that are cautious for pregnant or breast-feeding women; according to the Swiss Compendium (www.compendium.ch).

Risks for the study participants

Besides the retrospective identification of patients in both RCTs, we ignore particular risks. For BioBanking specifically, a theoretical risk could be the detection of unknown pathologies. In such case, the investigators will engage to inform the patient orally or by letter; if he/she did not refuse it previously. Concerning both RCTs, a theoretical risk could be a higher incidence of recurrences in the corresponding short antibiotic arms.

Diabetic ulcer care and pressure relief

Standard diabetic ulcer foot care will include wound debridement (during hospitalization and visits and only if clinically indicated), daily care with dressing changes, pressure off-loading and professional diabetes control. Off-loading is defined as avoidance of all mechanical stress on the injured extremity. Because off-loading is so critical to the healing process, we will instruct patients to wear the device at all times except when bathing and to use a device at all times when walking or standing is required, eventually also during night rest. Strategies for off-loading will be standardized as follows: All ulcers on the bottom of the foot will be fitted with an off-loading device during the Baseline Visit 1. The size of the off-loading device (walker) will be determined based on the patient's correct shoe size. We will insert the appropriate size of the insole inserted into the device. Once the target ulcer has been debrided, cleansed, dressed and secured, we will apply the device according to the manufacturer's instructions for use.

Randomization and Allocation procedures

The unblinded allocation in a short or a long antibiotic duration arm, in both RCTs, will occur electronically 1:1 (randomization without blocked or matched variables). The result will be dichotomous.

It will be either the "*short arm*", or the "*long arm*" of antibiotic therapy. In a further step, the surgical indication (amputation vs. conservative therapy with debridement), as well as the infection site (soft tissue vs. osteitis) will finally determine the exact study arm and the corresponding antibiotic duration. We will use freely available randomization programs, e.g. (www.randomizer.org). The Principal Investigator, the Sponsor and two dedicated study nurses only will be allowed to randomize and to implement. They will conceal the randomization procedure electronically; and as printouts in the study documents.

Monitoring

The Unit for Clinical and Applied Research will assign an independent monitor (with experience in prospective-randomized clinical trials) to the study. All patient files, notes and copies of laboratory and medical test results must be available for monitoring. The monitor will verify all, or a part of the Case Report Forms (CRF), data and written Informed Consents. One monitoring visit at the investigator's site prior to the start and twice during the study will be organized by the Sponsor. Furthermore, there will be a close-out visit at the study end.

Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the competent authorities. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/ documents and to answer any questions arising.

Timetables and Study visits

For both RCT, we need 36 months each; starting in September 2019. Table 4 displays the overall study timeline. SPIRIT-Figure 2 resumes the timepoints on the study visits. Basically, all study patients will have weekly assessments, an end-of-treatment visit and a test-of-cure visit two months after. Another control will take place at 12 months, which only interests the question if there has been a recurrence during that year following the treatment. This last information can be gathered via a phone call, the patient's visit, or by the general practitioner of the patient, or the hospital's medical files. During the active study period, the assessments will be identical for both RCTs, the study objectives (primary and secondary outcomes), and their individual study arms (soft tissue vs. bone infection); with the only exception that patients in the shorter antibiotic arms will terminate the study earlier by one to three weeks. The aggregation of study-

related information, laboratory data and clinical assessments on each study visit timepoints is summarized in Table 5.

Statistical analyses, study objectives and sample sizes

Statistical approach to the study objectives and Statistical Analysis Plan (SAP)

The primary objective for both RCT's is the "remission of infection" at two months of postoperative follow-up times. The contrast to "remission" is "recurrence". We will classify recurrence as "clinical recurrence" with recurrent or new infection in the former infection site, and as "microbiological recurrence" with the same pathogen(s) as for the index infection at the same infection localization. The secondary objectives are identical for both RCTs: the risk for adverse events in each randomization arm and the overall treatment costs.

Statistical techniques, study design and sample size calculations

Statistically speaking, both RCT's are simply to analyze and simple in the design. Therefore, we renounce on a formal and separate Statistical Analysis Plan (SAP). The Sponsor and the Principal Investigator wrote the analytic strategy together. Both RCTs are exactly the same non-inferiority studies; without adaptive study designs. Moreover, we apply the same non-inferiority design for the primary outcome "remission", as well as for the secondary outcome "adverse events". Regarding the outcome "treatment costs" we do not plan any non-inferiority requirements, since DFIs are multifaceted diseases with substantial interference with other expensive pathologies. The study objectives "clinical remission" and "adverse events" will be binomial variables; the objective "overall costs" will be expressed as continuous variables.

The expected clinical remission is set at 80% for each study arm; in both RCTs. Non-inferior margins are set at 20%: power 80%, alpha 5%. Excluding some anticipated drop-outs, we need for the First RCT (residual infection after amputation) 2 x 50 episodes regarding soft tissue infections; and 2 x 50 episodes for residual DFO. For the Second RCT (duration of antibiotic therapy in non-resected DFI), we equally require 2 x 50 episodes for soft tissue infections and 2 x 50 cases for DFO (Figure 2). Hence, the total overall study population will be 400 participants, while an individual patient can participate several times in either RCT; provided that each DFI episode occurs in another infection site.

For both RCTs, a Data Monitoring Committee will perform interim analysis after the inclusion of the first 40 episodes, and again at 100 episodes; and decides upon the continuation of the studies. If there are

overt differences in terms of remission between the short and long antibiotic arms in all subsets of DFIs, we will terminate the study. During these interim analyses, we will equally check if the expected statistical power for the final analysis will not fall under our arbitrary limits of unacceptability. If this power becomes lower than 50%, we will consider the trial no more ethical. To balance a potential loss of power, we also may recruit 50 supplementary patients per RCT, if the trial has not been stopped.

Methods of data aggregation

The analyses will base on descriptive statistics (numbers, median values with ranges) and group comparisons (Pearson-χ^2-test or the Fisher-exact-test for categorical variables; the Wilcoxon-ranksum-test for (non-parametric), continuous variables. Multivariate, unmatched, cluster-controlled (on patient's level) Cox regression analyses will adjust for the large case-mix that we expect. If the study becomes multicentric, another cluster-level will be allocated to the individual hospitals. The Cox regression is the only survival analysis we will perform. We renounce on time series analyses, Log Rank tests or Kaplan-Meyer curves, because of the substantial case-mix and the limited determination of the clinical variable "antibiotic use" among all complex and mixed pathologies associated to diabetic foot problems.

Variables with a univariate association of p <0.2 will be included in the final model, while the duration of antibiotic therapy, the number of surgical debridements and the presence of angioplasties will be automatically incorporated into the final model. A minimal follow-up time of at least two months post-surgery is required to be included in the multivariable models. We will check for collinearity and interaction (effect modification) by interaction terms and Mantel-Haenzel estimates. The individual start in the Cox regression analysis will be the date of first debridement. The individual follow-up times will be censored at 12 months, death, or the date before the lost to follow-up. Since our RCTs will be prospective and the study population well balanced, we anticipate few missing data. Consequently, we plan no imputations and renounce on matched analyses. The requirement for the supposed non-inferiority will be computed using a χ^2-analysis with the real differences displayed as percentage points and 90% confidence intervals in both outcome assessments (remission; adverse events); for each RCT and for each study population separately. The (two-tailed) statistical significance level will be set at p<0.05.

Presentation of the study populations

We will publish, regarding both RCTs the outcomes "remission" and "adverse events", the intent-to-treat (ITT) and the per-protocol (PP) database. We renounce on modified ITT (mITT) populations. The ITT participants, who have signed the Consent Letter, will consist of all randomized DFI episodes, even if patients drop off the study; or if there is protocol violation. The PP population will consist of all patients completing the study and who have not deviated significantly from the protocol. Importantly, the PP analysis will be restricted to the participants who fulfil the entire protocol requirements in terms of the

eligibility, adherence to the intervention, and outcome assessment. It will represent the "best-case scenario" being studied. Both RCTs already incorporate two subgroups (soft tissue vs. bone infections). These makes a total of four subgroup analyses. There are no further subgroups planned (Figure 2). However, we keep the right to perform further (yet unidentified) subgroup analyses, if we would detect by chance any substantial particularities in the final results.

Ethical and regulatory aspects

Study registration

The study is registered in the Swiss Federal Complementary Database („Portal“) and in the international registry ClinicalTrials.gov (Number NCT04081792). This study only will make use of antibiotics that are already authorized in Switzerland for DFO and corresponding soft tissue infections. The indication and the dosage will be used in accordance with the prescribing information and international guidelines [3]. All drugs and doses in this study will be commonly used agents and related doses. The study protocol will not change without prior Sponsor and Ethical Committee’s approval. Amendments will be reported. Premature interruption will be reported within 30 days. The regular end of the study will be reported to the Ethical Committee within 90 days, the final study report shall be submitted within one year after study end. The Ethical Committee and authorities will receive annual safety reports and are informed about the study stop/end. The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Helsinki Declaration, Good Clinical Practice, and the Swiss regulatory requirements.

Patient Information and Informed Consent

We will inform potential participants about the study, its voluntary nature, procedures involved, expected duration, potential risks and benefits and any potential discomfort. All participants will be provided an Information Sheet and Informed Consent Form. The original Form stays in the study records. For the BioBank, the participants will sign a General Consent regarding personal clinical data and biologic material. The investigators will uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Subject confidentiality will be further ensured by code numbers corresponding to the computer files. For data verification, the Ethics Committee and regulatory authorities may require access to relevant medical records, including the participants’ medical history.

Early termination of the study

The Sponsor may terminate the study prematurely in certain circumstances, e.g. ethical concerns, insufficient recruitment, when the safety of the participants is at risk, respectively, alterations in accepted clinical practice making the continuation unwise, early evidence of benefit or harm of the experimental intervention. All patients will be free to withdraw from participation in this study at any time, for any reason, and without prejudice. The reason for withdrawal should be documented wherever possible. The withdrawal will not affect the actual medical assistance or future treatments. On rare occasions, the investigators may terminate a patient's participation to protect his/her best interest. After study termination, the evaluations required at the next scheduled clinical visits will remain.

Safety

During the entire study duration, all adverse events will be collected, fully investigated and documented in source documents and CRFs. The Sponsor will submit an annual safety report to the local Ethics Committee. For both RCT, a Data Monitoring Committee will perform interim analysis after the inclusion of the first 40 episodes, and again at 100 episodes; and decides upon the continuation of the studies. This Committee will consist of a urologist surgeon and an anaesthesiologist not involved in the study or in the future author lists.

Treatment by specialists

All surgeries will be performed in the participation of an experienced surgeon. The antibiotic therapy will be ordered by internists and infectious diseases physicians with therapeutic and academic experience in DFI treatments. The current medications of the study patients, as well as possible interactions, will be controlled during hospitalization by the Head of Pharmacy of Balgrist University Hospital and by the internists, on a weekly basis. The Infectious Diseases physicians and surgeons will assure this drug surveillance during the outpatient periods.

Definition and assessment of (serious) adverse events and other safety related events

An Adverse Event (AE) is any medical occurrence in a study participant, which does not necessarily have a causal relationship with the study procedure. A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that: results in death, is life-threatening, requires in-patient hospitalization or prolongation of hospitalization, persistent or significant disability. Participants with ongoing SAEs at study termination will be followed until recovery or stabilization after termination. The investigators will make a causality assessment. All SAEs shall be reported within 24 hours to the Sponsor-Investigator. SAEs resulting in death will be reported to the Ethics Committee within 7 days. Patients will AE and leaving the study, will be treated off-study, without restriction, at the study sites.

Data handling and record keeping / archiving

We will save data using the secured software REDCap®. When the study is terminated, it will be saved in the same system. During the usual clinical treatment, all healthcare workers and administrators at Balgrist University Hospital will have access to the clinical data. After the end of therapy, however, the clinical and laboratory data can only be accessed by defined persons that have contributed to the project. These persons are two dedicated study nurses, the Principal Investigator, and the Sponsor. Radiological data will be stored in the institutions' PACS systems according to the institutional standard at the Balgrist University Hospital.

Case Report Forms

We will generate an electronic Case Report Form in REDCap® for every participant and all data relevant to the study is going to be recorded by authorized persons. The participant ID numbers are automatically assigned in consecutive ascending form by the REDCap® system.

Analysis and archiving

For data analysis, we will export and analyze subject-related data from REDCap in a statistic software (IBM-SPSS and/or STATA). All health-related data will be archived in the REDCap for a minimum of 20 years. Before data export, we will remove all patient identifiers. Collection, disclosure, storage of data will be carried out in accordance with Swiss data protection regulations and the Human Research Act. The BioBank stores the intraoperative samples in accordance with laboratory guidelines as standard.

Discussion

We will seek to demonstrate the non-inferiority, in the remission of infection, of a shorter antibiotic treatment in adult patients with DFI, including DFO, with and without amputation [7]; independently of surgical debridement, the level of arteriopathy and the causative pathogens. Importantly, all study participants will have professional and regular wound debridement, adequate off-loading, eventual revascularization, and a concomitant multidisciplinary surgical, re-educational, internist and infectiology surveillance. The studies will start at the Balgrist, but will be expendable to other settings with experience in DFI. Also, the secondary outcomes "adverse events" and "overall treatment costs" will likely be less in the shorter antibiotic arms.

DFIs are associated with substantial morbidity, prolonged hospitalization, a life-long risk for lower extremity amputations and high financial costs [1,8,9]. Presented with a patient with a DFI, surgeons and

physician want to reduce the risk of poor outcomes. This often leads them to overprescribing antibiotic therapy [2]. This can take the form of prescribing an unnecessarily broad-spectrum regimen (often with combinations of agents), administering parenteral rather than oral therapy [10], or continuing therapy for a longer duration than necessary [1,2,8]. However, such an overuse is not only ineffective, but associated with risks of adverse events, increased costs and promoting antibiotic resistance. Looking at the financial side, annual direct medical costs related for diabetes in the US alone were estimated at $176 billion in 2012 [11]. In a single hospital in Trinidad and Tobago, cost for the care of only 446 DFI patients was $14 million US dollars per year [12], which the authors extrapolated to represent 0.4% of the entire gross domestic product of that country. The direct antibiotic-related costs for a DFI added up to US $1000 US dollars in Australia [13].

In a recent prospective trial randomizing the use of topical gentamicin sponges (together with systemic antibiotics) for ulcerated DFIs, AE occurred at 23% [14]. Looking at antibiotic-related AE, studies have reported high rates of kidney injuries [15], selection of resistant pathogens such as methicillin-resistant staphylococci or vancomycin-resistant enterococci [16]. The incidence of resistant pathogens reached 15% and the rate of transient renal insufficiency reached 30% in one study [15]. Other author groups reported nausea, drug-induced hepatitis, *Clostridium difficile*-colitis [17]), and central line-related problems from intravenous therapy [2,15] when treating orthopedic infections, including DFIs.

Current literature and expert opinions advocate 1-3 weeks of antibiotic therapy for soft tissue DFI and 4 to 6 weeks for bone infections, including toe arthritis [1-4,8,15]. The duration of the initial intravenous administration or an entire antibiotic course by oral antimicrobial agents alone had no effect on DFI recurrence [6,10]. There seem no thresholds for an optimal antibiotic duration, even if we analyzed 1018 different DFI episodes in 482 patients [6]. In line with these findings, previously published studies in other fields of orthopedic infections equally failed to define an optimal duration of antibiotic therapy; such as for prosthetic joint [18] or fracture-device infections [19], septic bursitis [20], native joint septic arthritis [21], long bone osteomyelitis [22], or even open fractures [23]. All these infections are strongly associated with the presence of diabetes mellitus and its complications and thus require multidisciplinary management [24].

Likewise, when a less aggressive amputation is the goal, surgeons may face the problem that there is residual infection left, even if the amputation has been performed in apparently clean tissue or bone. Hence, in daily practice, the antibiotic prescription after toe amputation *in toto*, ranges between some days of oral therapy to several weeks of intravenous administration. Moreover, the surgeons often ignore the ideal level of amputation to choose. Kowalski et al. demonstrated that patients with positive resection margins for residual post-amputation osteomyelitis had more failures than those without (44% vs. 15%, despite two weeks antibiotic therapy in both arms) [25]. Atway et al. reported a 41% incidence of positive bone margins among 27 transosseous amputations, compared to a 23% following disarticulation [26]. Positive margins were associated with worse outcome despite 25 days of post-surgical antibiotic therapy. In contrast, Mijuskovic et al. showed that the assessment of residual bone infections might overestimate the risk of osteomyelitis as defined by histology, because of contamination from soft tissue at the time of

surgery [27]. According to a retrospective analysis of a Genevian database, antibiotics could be stopped immediately after amputation if the margins were clinically and visually clean [10,28]. Clearly, the duration of antibiotic after amputation for DFI osteomyelitis remains another unresolved issue.

Despite two prospective-randomized designs and 400 different episodes, we anticipate some limitations of our project. For example, patients who are treated outside of our center may have been lost to our follow-up. However, our center is the largest public hospital for DFI in the region, so this is unlikely to be a major bias. Additionally, our minimal follow-up time of two months ranges within the time window where most recurrences occur. Second, we will focus our study practically on moderate DFIs requiring referral to a tertiary center and potentially involving surgery. Thus, our data may not reflect outcomes related to mild DFI. Third, we decided against analyzing on specific antibiotic agents used or the role of specific pathogens. There is no evidence that any specific systemic antibiotic regimen is superior for DFI treatment, or for any specific pathogen [1,16,29,30]. Fourth, pressure offloading is crucial not only for the prevention, but also for treating DFI. While the rational of such measures is easily understandable, effectively implementing them depends on the patient's adherence, which we cannot monitor during the outpatient phase of the study participation.

In conclusion, we are confident to reveal clinically important answers to frequent questions regarding the antibiotic use in DFIs, to assure the quality of care, and to avoid unnecessary excesses in terms of exams, microbiology, costs, surgery and antibiotic use.

Declarations

Ethics approval and consent to participate

The study protocol is approved by the Cantonal Ethical Commission of Zurich, Stampfenbachstrasse 121, 8090 Zürich, Switzerland (BASEC 2019-00778). We will distribute a written Informed Consent Form to the participants and inform them also orally.

Consent for publication

Not applicable.

Availability of data and materials

Minimal datasets will be available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding and insurance

The project will start with an internal grant of Balgrist University Hospital. The Association For Orthopaedic Research (AFOR) (www.afor.org) provides an unconditional donation of 10,000 Euros (AFO - RG-Forschungs-projekte-160526). Additional grants will be requested during the project. The Balgrist research insurance will be applicable (Police Nr. 14.050.565 Winterthur Insurance). We will cover study-related damages by this insurance.

Investigator and authors' information

All investigators and possible future authors currently work at Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland. The Hospital is part of the University of Zurich.

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Publication policies

The sponsor will make every endeavor to publish the data in (a) medical journal(s), to communicate the results to healthcare professionals, the public and other relevant groups. We will also present preliminary results in scientific meetings. All investigators, and eventually additional colleagues participating in the future, will be co-authors of this study according to their individual contributions.

Trial status

The study, with the actual protocol version 2, has begun on 4th September 2019. The recruitments take place since 4th September 2019 and will continue until 2022.

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Tables

Table 1 - Inclusion and exclusion criteria of both randomized clinical trials

	First randomized trial (Attempted therapeutic amputation for infection)		Second randomized trial (Only debridement for infection; conservative treatment)
·	Diabetic foot Infektion	·	Diabetic foot infection
·	Age ≥ 18 years	·	Age ≥ 18 years
·	At least two months of follow-up	·	At least two months of follow-up
·	Acceptance of local wound care, off-loading and re-vascularization (if clinically necessary)	·	Acceptance of local wound care, off-loading and re-vascularization (if clinically necessary)
		·	Osteomyelitis limited to bone contact and cortices in X-ray.
n	> 5 cm distance between amputation level and infection	·	Therapeutic amputation
·	Any concomitant infection requiring more than 5 days of systemic antibiotic therapy	·	Any concomitant infection requiring more than 10 days of systemic antibiotic therapy
·	Osteosynthesis material not removed (if any)	·	Has received > 96 hours of potentially effective systemic antibiotic therapy and the wounds been clinically improving
		·	Destructive osteomyelitis with fractures, sequestra, shattering upon contact, vanishing beyond cortical
		·	Material-related infection

Table 2 - List of prospectively assessed variables during both randomized trials

- *Patient's general descriptive characteristics*: birth date, age, sex, hospitalization number, pertinent actual and past co-morbidities, current medication, ischemia, coronary heart disease, depression, stroke, heart insufficiency, duration of diabetes, HbA1c, insulin therapy, creatinine-clearance, dialysis, hypertonia, statin use, anticoagulation, smoking habits, alcohol intake, American Society of Anesthesiologists (ASA)-Score, Frailty-Score according to Fried, patients nutritional status.
- *General diabetic foot problems*: Type and duration of pre-surgical antibiotic therapy, pre-surgical hospitalizations, pre-surgical microbiological results including antibiotic susceptibility profiles, pre-surgical podiatric care, anatomical localization of infection, type and side of foot problem, past amputations, past foot surgery, presence and type of osteosynthesis material in the foot, PEDIS-Score, Wound Score and localization (appendix), Charcot foot, transcutaneous oxygen tensions, peripheral arterial disease staging, ankle-brachial index, angioplasty, X-rays, MRI imaging and other radiological results of the foot, number and type of surgeries for the actual problem.
- *DFI*: Presence of soft tissue infection, osteomyelitis, bacteremia, iterative serum CRP, fever, pathogens and antibiotic susceptibility profiles.
- *Treatment variables*: Number and type of surgeries, amputation techniques, type of dressings, number and types of intraoperative samples, and duration, type, number sand administration route of all antimicrobials, infectiology consultations, other medical, physiotherapeutic, ergotherapeutic, and nursing consultations and notes.
- *Administrative data*: Total costs, length of hospital stay, length of re-education, number of ambulatory consultations, first and last consultation date, follow-up duration, BioBanking data.
- *Outcome parameters*: remission, clinical and microbiological recurrences, progressive ischemia, adverse events, patients' satisfaction per questionnaire at two months after end of treatment, eventual prostheses, and type of off-loading devices, re-hospitalization and re-treatment elsewhere, Frailty Score according to Fried; and the nutritional status at Test-of-Cure-visit.

Table 3 - List of allowed antibiotic treatments (empirical or targeted)

ibiotic Agent	Allowed Dosing Regimens	Allowed Total Daily Dose, Range
ofloxacin PO	750 mg q.24h or 500 mg q.12h	750 to 1000 mg
rofloxacin PO	750 mg q.24h or 500 mg q.12h	750 to 1000 mg
oxicillin/clavulanate	500/125 mg q.12h. or q.8h	1000/250 mg to 1500/375 mg
oxicillin/clavulanate	1000/200 mg q.12h or q.8h	2000/400 mg to 3000/600 mg
uroxime IV	1500 mg q.8h	4500 mg
riaxone IV	2000 mg q.24 h	2000 mg
rimoxazole PO	960 mg q.12h or q.8h	1920 mg to 2880 mg
damycin PO	300 mg or 450 mg q.6h	1200 mg to 1800 mg
ycycline PO	100 mg q.12h	200 mg
ezolid PO	600 mg q.12h	1200 mg
ezolid IV	600 mg q.12h	1200 mg
ronidazole PO	500 mg q.8h or 500 mg q.6h	1200 mg to 2000 mg
ronidazole IV	500 mg q.8h or q.6h	1500 mg to 2000 mg
comycin IV	15 mg/kg q.12h	according to serum through levels, 10-20 mg/L
openem IV	1 g or 2 g q.12h or q.8h	2 g to 6 g
eracillin/tazobactam	4000/500 mg q.8h	1200/1500 mg (12 g/1.5 g)

PO = oral therapy; IV = Intravenous therapy

Table 4 - Time table of the study

ity	2019				2020				2021				2022			
	P	S	A	W	P	S	A	W	P	S	A	W	P	S	A	W
ıission ethics committees																
ing recruitment of new sites																
cal study																
base																
im statistical analysis																
statistical analyses																
ng-up of results and ıcsript																

P = Spring, S = summer, A = autumn, W = winter

Table 5 - Assessments during the study visits in the Randomized Clinical Trials (RCT)

*First RCT (attempted therapeutic amputation) * and ***

Study Visits	Baseline Visit 1	Visit 2	Visit 3	Visit 4; End of Trial (EOT)	Visit 5; Test of Cure
Time points	*(Day 0-1)*	*(Day 8; +/-2)*	*(Day 15; +/- 2)*	*(Day 21; +/- 2)*	*6 (20-30 d after EOT)*
Identity; MRI exam	x	x	x	x	x
In- / Exclusion criteria	x		x		
Informed consent	x				
Demographics	x				
Medical History	x				x
Clinical assessment of infection	x	x	x	x	x
Intraoperative sampling	x				
Control of compliance		x	x	x	x
Adverse Event		x	x		x
Study End (Control)					x

*Second RCT (infection only debrided, conservative treatment) *, **

udy Visits	Baseline Visit 1	Visit 2	Visit 3	Visit 4	Visit 5; End of Trial (EOT)	Visit 6; Test of Cure
me points	*(Day 0-1)*	*(Day 8; +/-2)*	*(Day 15; +/- 2)*	*(Day 21; +/- 2)*	*(Day 40; +/-2)*	*(20-30 d after EOT)*
lentity; MRI exam	x	x	x	x	x	x
ı- / Exclusion :iteria	x		x			
ıformed consent	x					
emographics	x					
ledical History	x					x
linical assessment f infection	x	x	x	x	x	x
ıtraoperative ımpling	x					
ontrol of ɔmpliance		x	x	x	x	x
dverse Event		x	x	x	x	x
tudy End (Control)						x

* In both RCT, we will use clinically sampled data, laboratory and radiology results. There will be no special sampling only for the RCT.

Variables of interest: serum C-reactive protein, serum leukocytes, hemoglobulin, platelets, ASAT, ALAT, serum creatinine, radiographies.

* * A second and final control will happen at 12 months after treatment

Figures

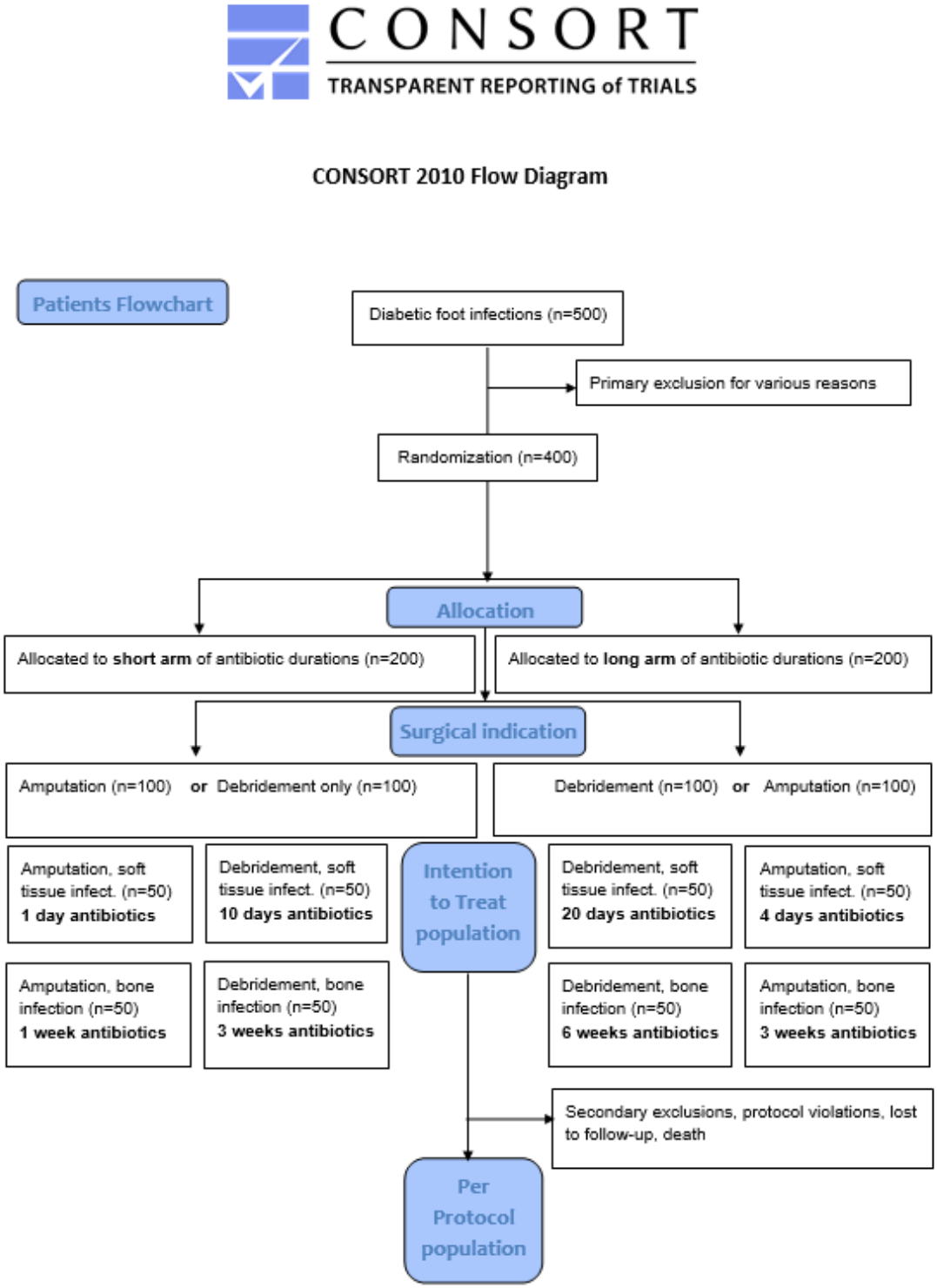

Figure 1

Study Flowchart - Consort Flow Diagram

	STUDY PERIOD							
	Enrolment	Allocation	Study visits at hospital					Test-of-Cure Visit
TIME-POINT**	$-t_{1-4}$ *and 0*	0	*0*	V_2	V_3	V_4	V_5	V_6
ENROLMENT:	X	X						
Eligibility screen	X	X						
Informed consent	X	X						
Allocation		X						
INTERVENTIONS:								
First Randomized trial			←	—	—	—	→	
Second Randomized trial			←	—	—	—	→	
ASSESSMENTS:								
Baseline variables	X	X	X					
Control variables				X	X	X		
Outcome variables						X	X	X

Visit times related to the Allocation (Inclusion) day:
V_1 = Day =, start of therapy, V_2 = Day 8 (+/- 2 days; eventually EOT visit), V_3 = Day 15 (+/- 2 days), V_4 = Day 21 (+/- 2 days), V_5 = End of treatment (EOT) visit - Day 40 (+/- 2 days) (only if still receiving treatment after V_4), V_6 = Approximately 20-30 days after the EOT visit

Baseline variables: Patient's general descriptive characteristics and general diabetic foot problems.

Control variables: Medical history and demographics. Wound score (Appendix). Determine the most appropriate route of administration (oral or IV) and empirical choice of the antibiotic. Provide adequate off-loading. Outpatients will return to the clinic (assessments can be performed in the hospital for inpatients). Record any concomitant medications as well as any additional interventions required (except wound or bone debridement performed as part of standard care). Assess adverse events of long-term antibiotic therapy. Administer appropriate ulcer debridement and cleansing.

Outcome variables: Treatment variables, Administrative data, Outcome parameters.

Figure 2

SPIRIT-Flowchart of time events of both Randomized Clinical Trials in this study

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- RevisedSPIRITFillablechecklistTRLSD1900946.pdf