Study Protocol: Optimization of the surgical and medical management of diabetic foot infections

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Study protocol
Abstract

Background: Few studies address the appropriate duration of antibiotic therapy for diabetic foot infections (DFI); with or without amputation. We 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 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 1st RCT allocates the 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 2nd RCT randomizes the conservative approach 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 have professional wound debridement, adequate off-loading, angiology evaluation, and a concomitant surgical, re-educational, internist and infectiology care. During the surgeries, we collect tissues for BioBanking and future laboratory studies.

Discussion: Both parallel RCT will enable to prescribe less antibiotics for DFI; for a conservative therapy and after amputation. 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 worldwide and harbor a high burden of morbidity, costs, and recurrences [1]. 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 and found similar outcomes. This study set the maximal duration at 6 weeks for the conservative treatment of diabetic foot osteomyelitis, 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 osteomyelitis, and finds no difference in terms of remission in interim analyses (ClinicalTrials NCT03615807) [5]. Another recent case-control study with 1018 DFI episodes equally fails 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, 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 two personnel with experience in biostatistics and investigative designs (www.balgrist.ch). Our study starts at the Balgrist, but is expandable to other national or international centers.

Study Objectives

The academic research questions cannot be separated from each other. Essentially, we build up a retro- and prospective cohort assessing the epidemiology of DFI in adult patients. The retrospective part includes the years 2014 to August 2019, when most patients started to sign a General Informed Consent regarding clinical data. Additionally, we conduct two prospective randomized clinical trials (RCT) embedded in the ongoing cohort:

- RCT (Randomized trial 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 osteomyelitis. The secondary study objectives are the evaluation if the histologic and microbiological extent of osteomyelitis correlates with the current gold standard in MRI, and the costs.
- RCT (Randomized trial on the duration of systemic antibiotic therapy in non-resected diabetic foot infections): The primary study question is if antibiotic therapy can be shortened without adverse effects on remission in non-amputated patients with soft tissue infections and osteitis. Secondary objectives are the same as in the 1. RCT.

Definitions and eligibility criteria for participants

DFI is defined 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]. Remission is defined as the absence of clinical, anamnestic, radiologic 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. Study Figure 1 resumes the inclusion and exclusion criteria.

Interventions and study conduct

We will collect clinical, radiological and laboratory data from each DFI episode. 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 and for 10 years. If the patient cannot participate in one RCT, he/she can participate in the other (Figure 2). Table 1 reveals the variables of interest in each of the two RCT. SPIRIT-Figure 3 resumes the timely assessment of these variables.

For this cohort and associated side studies, we do not change the current therapeutic practices. Basically, amputation or disarticulation is foreseen for osteomyelitis 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. All surgeries will be performed with the participation of an experienced surgeon. The patient will be invited to participate in one of the two RCTs; depending on the surgical indications (amputation or conservative treatment):

Surgical indication: amputation: If the clinicians and the patient decide for amputation, the patients are invited to participate in the 1. RCT. Basically, we perform amputation on a level determined by MRI imaging and mechanical properties. If there is residual post-amputation infection remaining either in the soft tissue or bone, the patient participates in the randomization:

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

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

Surgical indication: debridement without amputation: If the clinicians and the patient decide for debridement only (not amputation), then the patient is invited to participate in the 2. RCT:

- 10 versus 20 days for residual soft tissue infections
- 3 versus 6 weeks for non-amputated osteomyelitis

MRI (Magnetic resonance imaging)

At Balgrist University Hospitals, each patient suspect for DF osteomyelitis 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 MRI. The standard MRI examination will be performed before surgery, without testing new software. The cohort and both RCT will not demand for additional radiologic exams only for study reasons.
Prior and concomitant antibiotic therapy

A microbiologically effective antibiotic therapy beyond 96 hours prior to screening is not permitted. However, a 72-hours window before debridement is permitted, independently of the duration of prior antibiotic administration. If the patient requires a new antibiotic agent based on microbiological results; independently of the duration of prior ineffective antibiotic therapy, there are no minimal windows or maximal pre-debridement antibiotic durations. The antibiotic therapy is administered according to the IDSA guidelines [3]. Initially, antibiotic therapy is either empiric or targeted to the results of preoperative informations. After 2−4 days, antibiotic therapy 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 2). The investigators must chose among them, unless the pathogens are very special. We will not test new indications for antibiotic therapy. Only the duration of the therapy will be determined. We avoid placebos, topical antibiotics and antiseptics; except for the pre-incisional skin preparation. Likewise, anaesthesiologists remain free to administer the routine perioperative prophylaxis (cefuroxime, vancomycin, or clindamycin for up to three doses), if they judge it indicated.

Pregnancy and breast-feeding patients

This cohort, 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, pregnant and breast-feeding women are not excluded. The investigators will avoid antibiotics that are not liberated for pregnant or breast-feeding women, according to the Swiss Compendium (www.compendium.ch).

Risks for the participants

Besides the retrospective identification of patients, we ignore particular risk regarding the cohort or BioBanking. For BioBanking specifically a theoretical risk could be the detection of unknown pathologies, if there would be a further work-up of the intraoperative samples. In such case, the investigators engage to inform the patient orally or by letter; if he/she did not refuse it previously. Concerning 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 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, patients will be instructed 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. The size of the off-loading device
(walker) will be determined based on the patient’s correct shoe size; and not by randomization. The appropriate size of the insole will be inserted into the device. Once the target ulcer has been debrided, cleansed, dressed and secured, the device will be applied according to the manufacturer’s instructions for use.

Outcomes of interest

For the cohort and BioBanking, we will collect scientific data and material for future studies and quality assessments. Concerning the randomized trails, Table 4 summarizes the scheduled outcome parameters.

Allocation

The unblinded allocation in both RCT occurs electronically 1:1 (randomization without blocked or matched variables).

Monitoring

The Unit for Clinical and Applied Research has assigned 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 CRFs, 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 authority or CEC, respectively. 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. All involved parties will keep the patient data strictly confidential.

Participant timetable

The cohort is unlimited and also might retrospectively assess DFI episodes since 2014. For both RCT, we need 36 months each; starting in August 2019. Table 3 shows key time events.

Statistical analyses and sample size

There is no minimal number for the cohort. In contrast, both RCT are non-inferiority studies with categorical analyses and without adaptive study designs. The expected recurrence risk is 80%. Non-inferior margin for all analyses is set at 20%: power 80%, alpha 5%. We need for the 1. RCT (residual infection after amputation) 2 x 50 episodes regarding soft tissue infections; and 2 x 50 episodes for
residual osteomyelitis. For the 2. 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 osteomyelitis. For both RCT, a Data Monitoring Committee performs interim analysis after the inclusion of the first 50 episodes, and again at 100 episodes; and decides upon the continuation of the studies. This Committee will consist of investigators not applicated in the study. The intent-to-treat (ITT) population will consist of all randomized patients. The per-protocol (PP) population will consist of all participants completing the study and who have not deviated significantly from the protocol. The analyses will base on descriptions, group comparisons and multivariate, unmatched, cluster-controlled (on patient's level) Cox regression analyses adjusting for the large case-mix that we expect.

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).

Categorization of this study

This study only makes use of antibiotics that are already authorized in Switzerland for diabetic foot osteomyelitis and the corresponding soft tissue infections. The indication and the dosage are used in accordance with the prescribing information and international guidelines. All drugs and doses in this study are commonly used treatment methods. The study protocol will not be changed without prior Sponsor and Ethical Committee’s approval. Premature interruption is reported within 30 days. The regular end of the study is reported to the Ethical Committee within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported. 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 Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP), and the Swiss regulatory authority’s requirements.

Patient Information and Informed Consent

Our institution has a standardized procedure for recruiting participants, based on the in- and exclusion criteria. 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 Cohort and the BioBank, the participants sign a General Consent regarding personal clinical data and biologic material.

Participant privacy and confidentiality
The investigators 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 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 are 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 serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms.

**Treatment by specialists**

All surgeries will be performed in the participation of an experienced surgeon. The antibiotic therapy is ordered by internists and infectious diseases physicians with therapeutic and academic experience in DFI treatments. The current medications of the operated study patients, as well as possible interactions, will be controlled by the Head of Pharmacy of Balgrist University Hospital once a week.

**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. An AE can therefore be any unfavorable and unintended symptom. 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 make a causality assessment. All SAEs are reported within 24 hours to the Sponsor-Investigator. SAEs resulting in death are reported to the Ethics Committee within 7 days. The Sponsor-Investigator will report the safety signals within seven days to the local Ethics Committee. Patients will AE and leaving the study, will be treated off-study, without restriction, at the study sites.

**Periodic reporting of safety**
An annual safety report on the participant is submitted once a year to the local Ethics Committee. We, moreover, perform statistical interim (futility) analyses.

**Data handling and record keeping / archiving**

Data is only saved using the secured software REDCap®. When the study is terminated, it will be saved in the same system. Data can only be accessed by defined persons that have contributed to the project. Radiological data will be stored in the institutions’ PACS systems according to the institutional standard at the Balgrist University Hospital.

**Case Report Forms**

An electronic Case Report Form will be generated 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. Corrections can only be made by authorized persons.

**Analysis and archiving**

For data analysis, subject-related data from REDCap will be exported and analyzed in a statistic software (IBM-SPSS and/or STATA). All health-related data will be archived in the REDCap. Before data export, all patient identifiers are removed. All data will be stored for a minimum of 10 years. Collection, disclosure, storage of data is 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**

Our cohort with two embedded RCTs seeks to demonstrate a clinically relevant non-inferiority of a shorter antibiotic treatment in adult patients with DFI, with and without amputation [7]; independently of surgical drainage, the level of arteriopathy and the pathogens. Importantly, all 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 start in Zurich, but are expendable to other settings with experience in DFI.

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 may add 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 recent 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 analyze 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 transosseus 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 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 his/her study participation.

In conclusion, we are confident to reveal some answers to frequent questions regarding the antibiotic use in DFIs, to assure the quality of care, determine an optimal amputation level, and avoid unnecessary excesses in terms of exams, microbiology, surgery and antibiotic use.

**Declarations**

*Ethics approval and consent to participate*

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

*Consent for publication*

Not applicable.

*Availability of data and materials*

The datasets are available from the corresponding author on reasonable request.

*Competing interests*

The authors declare that they have no competing interests.

*Funding and insurance*

The project starts with an internal grant of Balgrist University Hospital. Additional financing and grants are requested during the project. The Balgrist research insurance is applicable (Insurance police Nr. 14.050.565 Winterthur Insurance). Any damage developed in relation to study participation is covered by this insurance.
Authors’ information

All authors work at Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland. The Hospital is affiliated to the University of Zurich.

Acknowledgments

We are indebted to all teams of Balgrist University Hospital and Balgrist Tec for support, to the Zentrallabor Zürich for laboratory analyses, and to the Institute of Medical Microbiology, University of Zurich, for the bacterial analyses. This work is supported by the Swiss Center for Musculoskeletal BioBanking, Balgrist Campus AG, Zürich, Switzerland.

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 takes place since 4th September 2019 and will continue until 2022.

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### Figures

| Inclusion Criteria | RCT 1 | RCT 2 | Cohort |
|--------------------|-------|-------|--------|
| • Diabetic foot infection | • Age ≥ 18 years | • Diabetic foot infection | • Since 2014 signed general informed consent |
| • Age ≥ 18 years | • At least two months of follow-up | • Age ≥ 18 years | |
| • At least two months of follow-up | • Acceptance of local wound care, off-loading and re-vascularization (if clinically necessary) | • At least two months of follow-up | |
| • Acceptance of local wound care, off-loading and re-vascularization (if clinically necessary) | • Osteomyelitis limited to bone contact and cortices in X-ray. | • | |

| Exclusion Criteria | RCT 1 | RCT 2 | Cohort |
|--------------------|-------|-------|--------|
| • >5 cm distance between amputation level and infection. | • Amputated diabetic foot infection | • Rejection of general consent |
| • Any concomitant infection requiring more than 5 days of systemic antibiotic therapy | • Any concomitant infection requiring more than 10 days of systemic antibiotic therapy | | |
| • Eventual osteosynthesis material not removed | • Has received > 96 hours of potentially effective systemic antibiotic therapy and the wounds are clinically improving. If a patient is not improving or deep-tissue culture results indicate that the infecting pathogen is not susceptible to that antibiotic, the patient may be enrolled at any time. | | |
| | • Destructive osteomyelitis with fractures, sequestra, shattering upon bone contact, and radiological vanishing of bone beyond cortical. | | |
| | • Material-related infection | | |

### Figure 1

Study Criteria
Figure 2

Study Flowchart
Table 1: SPIRIT - Flowchart of the enrolments and assessments during both randomized-controlled trials

| TIME-POINT** | Enrolment | Allocation | Study visits at hospital | Test-of-Cure Visit |
|--------------|-----------|------------|--------------------------|---------------------|
| t1, t2, 0    | X         | X          | V1, V2                   | V5                  |
| Eligibility screen | X       | X          | V2, V3                   |                     |
| Informed consent | X      | X          | V3, V4                   |                     |
| allocation   | X         |            | V4, V5                   |                     |

**Visit times related to the Allocation (Inclusion) day:**
- V1 = Day 0, start of therapy, V2 = Day 8 (+/- 2 days; eventually EOT visit), V3 = Day 15 (+/- 2 days), V4 = Day 21 (+/- 2 days), V5 = End of treatment (EOT) visit - Day 40 (+/- 2 days) (only if still receiving treatment after V4), V6 = 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 3

SPIRIT-Flowchart of the enrolments and assessments during both randomized-controlled trials

**Supplementary Files**

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

- SPIRITFigure3.doc