

Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment[†]

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Summary

The International Working Group on the Diabetic Foot appointed an expert panel to provide evidence-based guidance on the management of osteomyelitis in the diabetic foot. Initially, the panel formulated a consensus scheme for the diagnosis of diabetic foot osteomyelitis (DFO) for research purposes, and undertook a systematic review of the evidence relating to treatment. The consensus diagnostic scheme was based on expert opinion; the systematic review was based on a search for reports of the effectiveness of treatment for DFO published prior to December 2006.

The panel reached consensus on a proposed scheme that assesses the probability of DFO, based on clinical findings and the results of imaging and laboratory investigations.

The literature review identified 1168 papers, 19 of which fulfilled criteria for detailed data extraction. No significant differences in outcome were associated with any particular treatment strategy. There was no evidence that surgical debridement of the infected bone is routinely necessary. Culture and sensitivity of isolates from bone biopsy may assist in selecting properly targeted antibiotic regimens, but empirical regimens should include agents active against staphylococci, administered either intravenously or orally (with a highly bioavailable agent). There are no data to support the superiority of any particular route of delivery of systemic antibiotics or to inform the optimal duration of antibiotic therapy. No available evidence supports the use of any adjunctive therapies, such as hyperbaric oxygen, granulocyte-colony stimulating factor or larvae.

We have proposed a scheme for diagnosing DFO for research purposes. Data to inform treatment choices in DFO are limited, and further research is urgently needed. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords diabetes; diabetic foot; osteomyelitis; antibiotics; surgery; diagnosis; systematic review

Introduction

Osteomyelitis (infection of bone) is present in approximately 20% of cases of foot infection in persons with diabetes [1,2] and greatly increases the likelihood that the patient will require a lower-extremity amputation [3,4]. Unfortunately, there are no widely agreed guidelines for either the diagnosis of diabetic foot osteomyelitis (DFO) or its treatment, and the management of this problem is among the most controversial and challenging problems in the field. The International Working Group on the Diabetic Foot (IWGDF) recognized that DFO was an area in which guidelines for diagnosis and treatment (that could be modified according to the availability of local services and resources in different centres and communities) were needed [5,6]. To that end, they appointed an expert advisory group to suggest criteria for the diagnosis of DFO which could be used in future research, as well as to undertake a systematic review of the evidence pertaining to its treatment.

Diabetic foot osteomyelitis

Unlike most childhood osteomyelitis, DFO rarely occurs by haematogenous seeding, and almost all cases result from contiguous spread of infection from adjacent soft tissue. The soft-tissue infection usually starts as a complication of a neuropathic ulcer, but can result from penetrating injury [7] or ischaemic soft-tissue loss. Arterial insufficiency may be present but tends to play a less important role than neuropathy. Osteomyelitis therefore most often affects bones underlying sites where ulcers are most common: the toes, metatarsal heads and calcaneum. The midfoot bones are less commonly involved unless foot deformity (from neuropathic osteoarthropathy, for example) has caused ulceration.

While puncture wounds may directly inoculate pathogens into bone or joint [7], the usual trigger to bone involvement is the damage of overlying and vascularizing periosteal tissue by ulceration or soft-tissue infection. The loss of this anatomical and physiological barrier allows microorganisms to gain access, with subsequent devitalization of the superficial cortex. Extension of infection via the Haversian system leads to involvement of medullary bone and marrow, where infection may spread rapidly. Tracking of infection beneath the periosteum leads to periosteal stripping, underlying bone necrosis (forming the sequestrum) and overlying periosteal reaction with formation of new bone (the involucrum). Since osteomyelitis generally occurs by contiguous spread, the causative microorganisms are similar to those isolated from complicated soft-tissue infections [8–11]. While staphylococci (especially *Staphylococcus aureus*) predominate, many cases are polymicrobial, especially when DFO complicates chronically infected wounds or the foot is ischaemic [12].

Persistence of infection in bone has multiple underlying causes, including impaired immune and inflammatory responses (especially in necrotic bone) and reduced leucocyte number and activity, especially when microorganisms are adherent to the sequestrum [13,14]. Such adherent bacteria, in mono- or poly-microbial communities (called biofilms) [15], contain highly persistent phenotypes that resist host responses and most antibiotic agents [16]. The host response contains infection within a discrete area of the bone, leading to detachment of the sequestrum; it can then be extruded from the ulcer base, or fragments can pass through one or more sinuses to the skin surface. If the remaining bone is uninfected and covered in healthy granulation tissue, the process is arrested and wound healing is possible. If bone infection persists, however, there is further bone death, with possible spreading of soft-tissue infection. The clinical presentation of DFO can vary, depending on the site involved, the extent of infected and dead bone, any associated abscess and soft-tissue involvement, the causative organism(s) and the presence of limb ischaemia.

Apart from problems arising from differing presentations and resultant lack of consensus about how to make the diagnosis of DFO, scientific evaluation of treatments

is also hampered by issues relating to the definition of outcome. In common with expert opinion in other areas of bone infection, the term **cure** should not be used, given that very late relapse of apparently successfully treated osteomyelitis is not uncommon. The term **arrest** is used instead, to describe the situation in which there is no clinical evidence of ongoing infection in the bone. Experience suggests that the conclusion that there is arrest of infection should not be reached earlier than one year after the cessation of treatment.

The term **healing** also needs to be used with care to its meaning. In practice, it may be applied either to epithelialization of an overlying ulcer (wound healing), or to X-ray appearances that suggest that the infection is no longer active (radiological healing). Criteria for radiological healing include consolidation of ill-defined ('fluffy') periosteal reaction into a well-organized involucrum with discrete boundaries, no progression of bone lucency, union of pathological fractures associated with infection and sometimes substantial reformation of mineralized bone in areas of previous bone loss.

A scheme for the diagnosis of DFO for research purposes

Accurate diagnosis of DFO is necessary to ensure appropriate treatment. But it is also an essential prerequisite for research and for the comparison of outcomes in different studies or medical centres. These comparisons are needed to advance understanding of the best practice and to inform health care planning. Nevertheless, there are no agreed criteria for the diagnosis, or exclusion, of DFO. There are two particular problems in establishing such criteria. The first is that it may take several weeks for bone infection to produce defects on plain X-rays, so early infection may be missed. The second is that diabetic patients with peripheral neuropathy are also at risk of developing neuro-osteoarthropathy, which may closely resemble – and, indeed, co-exist with – DFO.

Osteomyelitis is considered proven if one or more pathogens are cultured from a reliably obtained bone specimen that shows bone death, acute or chronic inflammation and reparative responses on histological examination. Unfortunately, this criterion standard is infrequently achieved because bone biopsy is not widely used. The results of bone biopsy may also occasionally be misleading, and are particularly dependent on the sampling technique and specimen processing. Cultures may be falsely negative because of sampling error, prior antibiotic therapy or inability to culture fastidious organisms; likewise, they may be falsely positive because of contamination by wound-colonizing flora or skin commensals. Similarly, histological examination may be falsely positive in the face of other causes of inflammation, or falsely negative because of sampling error. In most cases, clinicians rely not on bone biopsy but on clinical presentation, combined with imaging and a variety of

laboratory investigations. Few of these have, however, been subjected to rigorous assessment. In order to create an acceptable scheme for diagnosis, the following factors were considered.

History

Underlying osteomyelitis should be considered when an ulcer fails to heal with no other obvious reason, or if the patient reports discharge of bony fragments.

Physical examination

A probe to bone test may help if properly performed after debridement of any callus or necrotic material in the wound [17–19]. A negative test substantially reduces the probability of osteomyelitis, while a positive one makes it more likely. DFO is also likely if there is visible bone or discharging bone fragments.

Plain radiographs

X-rays of the foot should be obtained if osteomyelitis is a possibility, but it may take several weeks for bony changes to become radiologically apparent. Additionally, abnormalities of a bone may be caused by Charcot neuro-osteoarthropathy [20,21]

Radionuclide bone scans

Technetium-99 bone scanning is more sensitive than plain X-rays, but is not recommended because the results are non-specific and positive scans can be caused by non-infectious processes [22].

Radionuclide white blood cell scans

Leucocyte scans may be slightly less sensitive than bone scanning, are technically more difficult and are more costly, but their specificity is typically considerably higher. Newer methods of labelling white cells are promising [23,24], as are scans using labelled anti-neutrophil antibodies [25,26]. In most instances, leucocyte scans are currently used only when magnetic resonance imaging scans (MRI) are unavailable.

Positron emission tomography (PET)

Positron emission tomography may be helpful in the diagnosis of DFO, but its role is not yet established [27].

MRI

There is general agreement that this is the most useful imaging study for diagnosing DFO, as well as for evaluating the extent of both bone and soft-tissue involvement and for planning surgery [28–31]. MRI will not always reliably distinguish between infection and acute Charcot neuro-osteoarthropathy; an accurate reading largely depends on the experience of the reporting radiologist.

Bone biopsy

Obtaining a culture and histological examination of bone will both confirm the diagnosis and potentially identify the responsible pathogen(s) and their *in vitro* antibiotic sensitivities. A bone specimen may be obtained either percutaneously (through uninfected skin) or as part of an operative procedure. If bone cannot be obtained, it is important to understand that cultures of adjacent soft tissue may give different results [32], and swabs will often overstate the number of pathogens involved. Where possible, antibiotics should be discontinued (for at least 48 h and preferably longer) before the biopsy to maximize the yield from cultures [33,34].

Formulation of the proposed scheme for the diagnosis of diabetic foot osteomyelitis

The highest quality evidence for diagnostic criteria would come from prospective studies assessing the proposed criteria against a criterion standard, such as bone culture and histology. Because of the problems with bone specimens described above, it is inevitable that future studies will need to encompass broader criteria. This makes a compelling case for reaching consensus on the relative value of integrating the results of a range of clinical, laboratory and imaging findings in the diagnosis of DFO. Schemes of this sort are common in situations where no single criterion is sufficiently reliable to make absolute decisions about the diagnosis, such as the Duke criteria for diagnosing infective endocarditis [35], and the American College of Rheumatology's criteria for certain rheumatological conditions [36–38]. Consensus diagnostic schemes will usually be used initially for research purposes, which require a greater degree of specificity, rather than in clinical practice, which requires a greater level of sensitivity. Our proposed scheme for research purposes provides a potential means to compare data from different studies, provided the diagnostic methodology has been specified in sufficient detail. Nevertheless, the clinical usefulness of the scheme will remain uncertain until it has been validated.

The levels of diagnostic certainty in our proposed scheme have been stratified into four categories (Table 1). The use of post-test probabilities to define broad levels of diagnostic certainty is deliberate, and reflects the desirability in clinical practice of using diagnostic tests with defined performance characteristics (sensitivity, specificity and likelihood ratio) to convert probability of disease into a post-test probability for each case. This will require serial mathematical calculations, as the results of each test are considered in sequence. The scheme simplifies the process by using combinations of different diagnostic criteria, the weightings of which have been derived by a consensus based on collective clinical experience. This scheme also recognizes that the diagnosis becomes increasingly or decreasingly likely as the clinical

Table 1. Proposed consensus criteria for diagnosing osteomyelitis in the diabetic foot

Category	Post-test probability of osteomyelitis	Management advice	Criteria	Comments
Definite ('beyond reasonable doubt')	> 90%	Treat for osteomyelitis	Bone sample with positive culture AND positive histology OR Purulence in bone found at surgery OR Atraumatically detached bone fragment removed from ulcer by podiatrist/surgeon OR Intraosseous abscess found on MRI OR	Sample must be obtained at surgery or through uninvolved skin Definite purulence identified by experienced surgeon Definite bone fragment identified by experienced surgeon/podiatrist
Probable ('more likely than not');	51–90%	Consider treating, but further investigation may be needed	Any two probable criteria OR one probable and two possible criteria OR , any four possible criteria below Visible cancellous bone in ulcer OR MRI showing bone oedema with other signs of osteomyelitis OR Bone sample with positive culture but negative or absent histology OR Bone sample with positive histology but negative or absent culture OR	Sinus tract; sequestrum, heel or metatarsal head involved; cloaca
Possible (but on balance, less rather than more likely)	10–50%	Treatment may be justifiable, but further investigation usually advised	Any two possible criteria below Plain X-rays show cortical destruction OR MRI shows bone oedema OR cloaca, OR Probe to bone positive OR , Visible cortical bone OR ESR > 70 mm/h with no other plausible explanation OR Non-healing wound despite adequate offloading and perfusion for > 6 weeks OR ulcer of > 2 weeks duration with clinical evidence of infection	
Unlikely	< 10%	Usually no need for further investigation or treatment	Normal MRI OR Normal bone scan	

course evolves, changing the diagnostic certainty over time. In many situations, however, the diagnosis will be either immediately evident or can be excluded with a high degree of confidence.

A systematic review of the effectiveness of treatments for diabetic foot osteomyelitis

Because guidance is urgently needed to resolve uncertainties concerning the management of this limb-threatening condition [39], a systematic search was undertaken for evidence of the effectiveness of treatments for DFO. The review was particularly aimed at answering the following questions.

- *What are the absolute and relative indications for surgery?*
- *Which surgical interventions are of value?*
- *Can osteomyelitis be treated with antibiotics alone?*
- *What empirical choices of antibiotic are sound?*
- *What is the appropriate duration of antibiotic therapy?*
- *What is the preferred route of administration of antibiotic therapy?*
- *Is there evidence for efficacy of any adjunctive treatments?*

Materials and methods

We searched the literature for all prospective and retrospective studies in any language that evaluated interventions for the treatment of DFO in people aged 18 years or older with diabetes mellitus. The search strategy employed is described in Appendix A. Eligible studies included randomized controlled trials (RCTs), case-control studies, prospective and retrospective cohort studies, interrupted time series (ITS) design, controlled before-and-after design (CBA) and uncontrolled case series, but not single-case reports. Publications were eligible for inclusion if they reported outcome of management of DFO following a specified intervention in an identifiable group with diabetes. One reviewer assessed all identified references by title and abstract to assess eligibility. We retrieved full copies of possibly eligible publications and two independent expert reviewers agreed on whether or not the publications were eligible to be included. Each included paper was then further assessed by the two reviewers, working independently, using custom-prepared data extraction sheets.

The reviewers noted the study design, patient populations, interventions, outcomes and duration of (and loss to) follow-up of included patients. Studies were also scored for methodological quality using different scoring lists developed by the Dutch Cochrane Center (www.cochrane.nl/index.html). Quality items were rated as 'done', 'not done', or 'not reported' and only those rated as 'done' contributed to methodological quality score. Equal weighting was applied to each validity criterion for

every study design. The methodological quality score was translated into a level of evidence according to the Scottish Intercollegiate Guidelines Network (SIGN) instrument as follows: (1) randomized controlled trials and (2) studies with case-control, cohort, controlled before-and-after design or interrupted time series design. Studies were also rated as: ++ (high quality with low risk of bias), + (well conducted with low risk of bias) and - (low quality with higher risk of bias), according to the methodological quality score.

Co-reviewers discussed the findings from the data extraction and the evaluation of methodological quality of each paper and reached a final decision by consensus. Extracted data were summarized in Evidence tables (see Appendix B) and described on a study-by-study narrative basis. Because of the heterogeneity of study designs, interventions, follow-up and outcomes, no attempt was made to pool the results. These Evidence tables were compiled following collective discussions (by electronic and in-person conferences) by all members of the working party, who then formulated consensus recommendations.

Results

Of 1168 papers identified in the initial search (3 of which were found by cross-referencing), 284 were selected for full paper review. Of these, 19 met the criteria for inclusion, all of which were in English. Three were controlled clinical trials, while the remainder were mainly of uncontrolled (retrospective) case series. Patients with DFO frequently formed a sub-group within a larger group of patients with infected diabetic foot ulcers and soft-tissue infections, or patients with osteomyelitis in general or ulceration from various causes. Significant selection bias was a potential problem in the majority of studies.

Absolute and relative indications for surgery

The available data, with necessary caveats on population selection and reporting bias, suggest that there is little evidence to help choose between primarily medical and primarily surgical therapy in the management of DFO. Reported success rates were generally within the range 60–90%, but no controlled studies, whether randomized or not, directly compared outcomes with the two approaches. One observational study reported that amputation and death were less common in patients receiving early surgical intervention compared with medical therapy alone [40], perhaps because of a high proportion of cases of severe deep infection in the study group. Others reported improved outcomes (higher healing rate and less antibiotic use) when limited surgery was combined with antibiotics, compared to antibiotic therapy alone [41]. Yet others have demonstrated comparable levels of success by reserving surgery only for failures of medical therapy [42].

Choice of surgical intervention

A range of foot-salvaging surgical interventions have been described, including debridement to bleeding bone marrow with epidermal sheet grafting [43], two-stage debridement with secondary closure [44] and limb amputation [45,46]. We did not include other surgical techniques described in methodologically inferior studies.

The effectiveness of non-surgical management

Studies of non-surgical management reported rates of arrest and healing comparable to those following surgery [47–50]. Two of these studies were sufficiently large to identify the following as factors associated with the failure of non-surgical treatment: more severe signs of infection with necrosis and gangrene; lower transcutaneous oxygen tension; a high serum creatinine level; and pyrexia ($>38.5^{\circ}\text{C}$) [42,51]. It was not possible to establish whether the outcome of surgery was worse in those who had previously failed to respond to non-surgical management.

Empirical choice of antibiotic

None of the selected studies demonstrated the superiority of any one antibiotic agent over another. Antibiotics with activity predominantly against Gram positive organisms (staphylococci and streptococci) [52] and broad-spectrum antibiotics with increased activity against Gram negative organisms and obligate anaerobes [53] appear equally effective. These findings confirm the results of a recent review of the antibiotic management of all types of osteomyelitis [54]. Nevertheless, it is still not known if antibiotic therapy should be selected on the basis of the sensitivities of all isolated organisms or simply against those judged most likely to be pathogenic.

Duration of antibiotic treatment

Selected studies reported responses to treatment durations ranging from 2 weeks (following aggressive surgical debridement) [4] to a mean of 42 weeks (without surgery) [50]. Results in all were comparable, and there are no reports of studies comparing treatment with antibiotics for different durations.

Route of administration

Published studies variously reported treatment with intravenous [4] or oral antimicrobials [48,50], or short-duration intravenous followed by oral therapy [55]. A single randomized study compared results with oral and intravenous antibiotics [52]. No studies in DFO have compared the outcome of administering the same agents

by different routes, or have assessed the efficacy of locally administered antibiotics, such as antibiotic-impregnated polymethylmethacrylate or calcium sulfate beads.

Effectiveness of adjunctive therapies

Successful revascularization may enable debridement and minor surgery [56], but no evidence was found to indicate that revascularization was associated with improved outcome in DFO. Similarly, no conclusive evidence demonstrates that hyperbaric oxygen therapy [57,58] improves outcome, and further well-designed and controlled studies are needed to assess its effectiveness. There is no evidence to suggest that the use of maggots (larvae), growth factors (including granulocyte-colony stimulating factor, G-CSF) or topical negative pressure therapy (e.g. vacuum-assisted closure, VAC) [59] is beneficial in the management of DFO.

Prognosis

The available evidence indicates that infection can be arrested in over 60% of cases, whether the patient is treated with surgical resection or antibiotic therapy alone. Amputation rates of 5–10% can be anticipated in cases selected for medical management, and may be higher in unselected cohorts because those requiring early surgery were not excluded.

Aftercare

Osteomyelitis commonly leads to changes in the structure and load-bearing properties of the foot, either through its direct effects on bone, or because of surgical intervention. Observational studies suggest that transfer ulcers may be more common when DFO is managed surgically as opposed to medically [60,61]. No studies specifically addressed aftercare issues in patients with osteomyelitis, as against all forms of diabetic foot ulceration.

Discussion

While there is no evidence of differences in the effectiveness of various treatment strategies, this does not mean that such differences do not exist. Important differences in both effectiveness and cost effectiveness may yet emerge from adequately powered studies that use appropriate definitions and outcome measures. The quality of published work is poor, with few controlled studies, unclear reporting and small or heterogeneous populations. The lack of standardization of diagnostic criteria and of consensus on the choice of outcome measures pose particular difficulties. The weakness of the available evidence necessarily weakened the conclusions that we could draw in this review and we urge caution

before they are extrapolated into practice. Decisions concerning clinical care should be based on individual circumstances, taking into account the needs and desires of each patient, local resources, expertise and trends in antimicrobial resistance.

Available evidence suggests that if those who need urgent surgery for life- or limb-threatening infection are excluded, surgical debridement of infected bone may not be routinely necessary and arrest of infection may be achieved with antibiotics alone in the majority of cases. Despite the lack of evidence, however, many experts feel that arrest of bone infection is facilitated by appropriate debridement of necrotic bone. The choice of antibiotic regimen may be optimized by obtaining culture and sensitivity results of a bone specimen, but empirical regimens should include anti-staphylococcal coverage. There are no data to establish the superiority of any particular route of delivery of systemic antibiotics for treating DFO. There are also no data to inform decisions on the optimal duration of antibiotic therapy, and no evidence to support the use of adjunctive therapies, such as hyperbaric oxygen, granulocyte-colony stimulating factor or larvae. Further research is urgently needed, and until more data are available from robust trials, there is limited justification for didactic recommendations of any particular treatment strategy.

Appendix A

Literature search string for each database

Search PubMed

<1966.-5/12/06>

Limits: human

Surgery (hits 638)

((("Diabetes Mellitus"[MeSH]) OR (Diabetes Mellitus) OR (Diabetes) OR (diabetic)) AND ((("Clinical Trials"[MeSH]) OR ("comparative study"[Mesh]) OR ("epidemiologic study characteristics"[Mesh]) OR (Clinical Trial*) OR (case-control stud*) OR (case control stud*) OR (cohort stud*) OR (Comparative stud*)) AND ((("Infection"[MeSH]) OR osteomyelitis OR osteitis OR ("Bone Diseases, Infectious"[MeSH]) OR ("Diabetic Foot"[MeSH]))) AND ((("Surgery"[MeSH]) OR ("Amputation"[MeSH]) OR ("Surgery, Plastic"[MeSH]) OR ("Preoperative Care"[MeSH]) OR dead space OR drain OR hardware OR bone samples OR ("Vascular Surgical Procedures"[MeSH]) OR ("Thrombolytic Therapy"[MeSH]) OR ("Costs and Cost Analysis"[MeSH]) OR ("Wound Healing"[MeSH]))

Antibiotics (hits: 265 (27 duplicates with surgery search, total 611))

((("Diabetes Mellitus"[MeSH]) OR (Diabetes Mellitus) OR (Diabetes) OR (diabetic)) AND ((("Clinical Trials"[MeSH]) OR ("comparative study"[Mesh]) OR ("epidemiologic study characteristics"[Mesh]) OR (Clinical Trial*) OR (case-control stud*) OR (case control

stud*) OR (cohort stud*) OR (Comparative stud*)) AND ((("Infection"[MeSH]) OR osteomyelitis OR osteitis OR ("Bone Diseases, Infectious"[MeSH]) OR ("Diabetic Foot"[MeSH]))) AND ((("Anti-Bacterial Agents"[MeSH]) OR ("Anti-Infective Agents"[MeSH]) OR ("administration and dosage [Subheading]"[MeSH]) OR ("Drug Administration Routes"[MeSH]) OR parenteral OR oral OR topical OR duration OR cement OR ("Methylmethacrylate"[MeSH]) OR ("Calcium Sulfate"[MeSH]) OR implant OR collagen OR ceramic OR ("Aminoglycosides"[MeSH]) OR gentamicin OR amikacin OR tobramycin OR ("Glycopeptides"[MeSH]) OR vancomycin OR teicoplanin OR ("Metronidazole"[MeSH]) OR ("Linezolid"[MeSH]) OR ("Fusidic Acid"[MeSH]) OR ("Daptomycin"[MeSH]) OR ("Monobactam"[MeSH]) OR ("Carbapenem"[MeSH]) OR imipenem OR meropenem OR ("beta-Lactams"[MeSH]) OR ("Cephalosporins"[MeSH]) OR cefuroxime OR cefazidime OR cephalixin OR ceftriaxone OR ceftiprome ("Clavulanic Acids"[MeSH]) Clavulanic Acid* OR ("Moxalactam"[MeSH]) OR ("Penicillins"[MeSH]) OR penicillin OR flucloxacillin OR oxacillin OR Methicillin OR nafcillin OR ampicillin OR penicillin OR piperacillin OR ("Tetracyclines"[MeSH]) OR tetracycline OR minocycline OR doxycycline OR ("Macrolides"[MeSH]) OR erythromycin OR azithromycin OR clarithromycin OR ("Lincosamides"[MeSH]) OR clindamycin OR ("Trimethoprim-Sulfamethoxazole Combination"[MeSH]) OR cotrimoxazole OR co-trimoxazole OR ("Quinolones"[MeSH]) OR ciprofloxacin OR ofloxacin OR moxifloxacin OR levofloxacin OR ("Anti-Infective Agents, Local"[MeSH]) OR (Silver OR Silver Sulfadiazine OR iodine)).

Search EMBASE

Database: EMBASE<1980 to 2006 dec 1st>

Search Strategy:

1. exp *Diabetes Mellitus/
2. Clinical Trial/
3. Clinical Trial/
4. exp *Comparative Study/
5. exp *Epidemiology/
6. exp *INFECTION/
7. exp *Bone Infection/
8. exp *Diabetic Foot/
9. (diabetes mellitus or diabetes or diabetic).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10. (Clinical Trial or case-control stud\$ or case control stud\$ or cohort stud\$ or Comparative stud\$).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
11. exp *SURGERY/
12. exp *AMPUTATION/
13. exp *Plastic Surgery/
14. exp *Preoperative Care/
15. (dead space or drain or hardware or bone samples).mp. [mp = title, abstract, subject headings,

- heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
16. exp *Vascular Surgery/
 17. exp *Fibrinolytic Therapy/
 18. (Costs and Cost Analysis).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 19. exp *Wound Healing/
 20. exp *Antiinfective Agent/
 21. (administration and dosage).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 22. exp *Drug Administration Route/
 23. (parenteral or oral or topical or duration or cement).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 24. exp *Methacrylic Acid Methyl Ester/
 25. exp *Calcium Sulfate/
 26. (implant or collagen or ceramic).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 27. exp *Aminoglycoside/
 28. (gentamicin or amikacin or tobramycin).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 29. exp *Glycopeptide/
 30. (vancomycin or teicoplanin).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 31. exp *METRONIDAZOLE/
 32. exp *LINEZOLID/
 33. exp *Fusidic Acid/
 34. exp *DAPTOMYCIN/
 35. exp *MONOBACTAM/
 36. exp *CARBAPENEM/
 37. (imipenem or meropenem).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 38. exp *Beta Lactam/
 39. exp *Cephalosporin Derivative/
 40. (cefuroxime or ceftazidime or cephalexin or ceftriaxone or cefpirome).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 41. exp *Clavulanic Acid/
 42. Clavulanic Acid\$.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 43. exp *Latamoxef/
 44. exp *Penicillin Derivative/
 45. (penicillin or flucloxacillin or oxacillin or Methicillin or nafcillin or ampicillin or penicillin or piperacillin).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 46. exp *Tetracycline Derivative/
 47. (tetracycline or minocycline or doxycycline).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 48. exp *Macrolide/
 49. (erythromycin or azithromycin or clarithromycin).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 50. exp *LINCOCYCIN/
 51. clindamycin.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 52. exp *Cotrimoxazole/
 53. (cotrimoxazole or co-trimoxazole).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 54. exp *Quinolone Derivative/
 55. (ciprofloxacin or ofloxacin or moxifloxacin or levofloxacin).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 56. exp *Topical Antiinfective Agent/
 57. (Silver or Silver Sulfadiazine or iodine).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
 58. 1 or 9
 59. 3 or 4 or 5 or 10
 60. 6 or 7 or 8
 61. 58 and 59 and 60
 62. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
 63. 61 and 62
 64. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
 65. 61 and 64
 66. 63 or 65
 67. 66
 68. limit 67 to human

Appendix B
Evidence tables

Reference	Study design + quality	Study population and characteristics	Diagnosis osteomyelitis	Intervention and control conditions	Outcome category	Results of primary/secondary outcomes + statistic	Evidence SIGN	Comments/weaknesses
Alkova 1996 [62]	Case series Study quality: 3/4	74 patients with severe diabetic foot infection including 49 with osteomyelitis. No specific data for osteomyelitis population. Age: mean 57 ± 10 Gender: unknown	21 of 49 with osteomyelitis, microbiologically documented. Osteomyelitis defined by infected exposed bone, and/or related findings were discovered with plain X-ray, triphasic Te scan, CT scan	Duration of therapy for osteomyelitis group, 41 ± 5 days Follow-up: 16 weeks (range 8–26)	Clinical cure and microbiological eradication	Clinical cure rate 86% (42/49) 25/32 (78%) microbiological eradication Duration of treatment 41 ± 5 days. 14 amputations (10/14 sterile bone cultures)	3	'Severe infection' not defined in this study
Bamberger 1987 [49]	Case series	51 patients with diabetes and osteomyelitis Mean age 62 ± 1 year (range 48–85)	All three of the following criteria: characteristic radiographic changes (cortical bone erosion at the site of soft tissue inflammation); clinical signs of inflammation (erythema, drainage, swelling, or warmth) or necrosis; and a wound, bone, or blood culture yielding pathologic bacteria	IV antibiotics for 4 weeks, or, IV and oral antibiotics for 10 weeks	Good outcome: resolution of clinical evidence of inflammation at the time of the last follow up examination without the need for ablative surgery Follow up period of 19 months	27 of 51 (52.9%) had good outcome. 15 received a below knee amputation, 9 a toe amputation	3	No statistical analysis between the patients within the different intervention groups
Cohen 1991 [46]	Case series Study quality: 3/4	53 patients with peripheral neuropathy (52 with diabetes) with gangrene or uncontrollable osteomyelitis All male Mean follow up 22.3 months	Not stated	Partial ray resections, transmetatarsal amputations, panmetatarsal head resections.	Definition of success: cessation of infection without transfer lesions or long-term follow-up needed	Success rate: 13/35 partial ray resections, 14/15 transmetatarsal amp, 6/7 panmetatarsal head resections	3	Unknown cases of osteomyelitis although osteomyelitis was an indication for partial ray amputation and transmetatarsal amputation This was a study of outcome of different surgical procedures data for osteomyelitis not given

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Reference	Study design + quality	Study population and characteristics	Diagnosis osteomyelitis	Intervention and control conditions	Outcome category	Results on primary /secondary outcomes + Statistic	Evidence S/GN	Comments /weaknesses
Diamantopoulos 1998 [63]	Case series Study quality: 3/4	84 patients with limb threatening infections including 49 patients with osteomyelitis (30 with peripheral arterial disease) Mean age = 62.4 years 51 male, 33 female No specific data for osteomyelitis patients	Soft tissue infection accompanied by bone erosion was classified as osteomyelitis, confirmed by histology if possible or radionuclide scan	Parenteral Clindamycin (600 mg tid) + ciprofloxacin (300 mg bid), followed by oral At discharge, patients received ciprofloxacin 1.5–2 g daily if anaerobes were undetected Duration of therapy = 6–24 months (outpatient setting)	Cure = resolution of all signs and symptoms of infection Assessment 3 weeks after the initiation of treatment	Cure in 33/49 (76.3%) Of the cured, bone incision and drainage took place in 11 patients Mean follow-up 16 months (range 2–28) Recurrent infection in 8 of 33 Overall success rate at the end of follow up 25/49 (51%)	3	Of the total population, 16 of the 18 patients who failed had osteomyelitis ($p = 0.007$) The follow-up period is short compared to the long duration of treatment
Embil 2006 [50]	Case series Study quality: 4/4	$n = 325$ consecutive patients with diabetes receiving care at a specialized wound clinic, of which 79 of 93 episodes of foot osteomyelitis (all grade 3 Wagner) Patients with foot abscess or acute osteomyelitis that necessitated debridement were excluded	At least one of the following: - Plain radiographs - bone scan - bone seen, probed or palpated	Mean duration of therapy 40 ± 30 weeks, oral route \pm short initial IV route: 2 to 4 agents, culture directed (metronidazole, ciprofloxacin, co-trimoxazole, amoxicillin/clavulic acid, clindamycin) 26 cases (28%) had bone debridement and 9 (10%) had toe amputation	Osteomyelitis in remission = resolution of both clinical findings and destructive bone changes on plain radiographs or bone scans	Remission: 75/93 (80.5%) oral alone = 53/64 (82.8%) oral + IV = 22/29 (75.8%) Patients with or without bone debridement had no significant difference in clinical response to therapy (23/26 (88%) versus 52/67 (78%), respectively; $p > .05$) Mean relapse free follow-up duration = 50 ± 50 weeks	3	Retrospective review

Grayson 1994 [2]	RCT Study quality: 8/9	Overall population = 93 diabetic patients with 96 episodes of foot infections including 59 cases of osteomyelitis No specific demographic data for patients with osteomyelitis Mean age: ampicillin/sulbactam 59 years; Imipenem/cilastin 61 years	Histopathological, radiological and clinical criteria	Aggressive surgical debridement combined with either imipenem/cilastin (N = 27) or ampicillin/sulbactam (N = 32). Duration of intravenous treatment: 12.5 days (amp/sulb), 16.5 (imi/cil)	Assessed at day 5 of therapy and at the end of intravenous therapy. Cure was defined as eradication of clinical signs of soft tissue infection	Success rate of soft tissue infection and osteomyelitis groups combined: 48/59 (81.3%). 57 of 93 total cases had a minor amputation, 4 had a below knee amputation. Cure was achieved in 22/27 (81.4% imi/cil) and 26/32 (81.2% amp/sulb) in the group of soft tissue infection and osteomyelitis combined. In the selected group of patients with osteomyelitis, cure was maintained for approximately a year in 17 (65%) of the imi/cil group and 16 (73%) of the amp/sulb treated group	1+	Comparison of ampicillin/sulbactam and imipenem/cilastin for diabetic foot infection, combined with surgical debridement, including a sub-group of cases with osteomyelitis. No specific data for the cases with osteomyelitis were given except for some follow up data
Ha Van 1996 [41]	Case series Study quality: 3/4	32 patients with diabetic foot ulcers and osteomyelitis but without critical ischaemia Mean age 59.4 years. 29/32 male. None lost to follow-up	Probe to bone and X-ray confirmation	Conservative surgery (ulcerectomy with limited resection of the infected part of the phalanx or metatarsal) plus medical treatment	Primary outcome: Healing. Secondary outcomes: time to healing, duration of antibiotic therapy, secondary surgical procedures	25 (78%) healed in 181 days. Duration of antibiotic therapy 111 days. Secondary surgical procedures in 3 patients	3	Outcomes of cases compared with 35 historical controls treated with antibiotics alone to suggest benefit of conservative surgery
Kerstein 1974 [45]	Case series, retrospective	14 male patients mean age 64.4 range 55-78 with osteomyelitis, 8 diabetic, age range 55-78	Plain radiographs and bone cultures	Transmetatarsal amputation in 4, digit amputation in 4, with intravenous antibiotics while hospitalized	Healing of wound	All healed at 6-18 months follow up		All patients initially offered major limb amputation but refused
Kumagi 1998 [44]	Case series, retrospective	33 patient with 37 wounds, 29 diabetic with 33 wounds, 17 with osteomyelitis, 18 episodes	Histological appearance of bone biopsy	Resection to bleeding healthy bone and six weeks intravenous antibiotics	Wound healing (days to healing presented)	1 failed (unhealed), one recurrence in osteomyelitis group; 2 failed (BKA) in non-osteomyelitis group, 2 lost to follow up		

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Reference	Study design + quality	Study population and characteristics	Diagnosis osteomyelitis	Intervention and control conditions	Outcome category	Results on primary /secondary outcomes + Statistic	Evidence S/GN	Comments /weaknesses
Lipsky 1997 [55]	Randomized controlled trial Study quality: 3/9	108 patients with diabetes with foot infection. Age: 61.5 years, 84% male, 54% Caucasian Type of diabetes unknown 21 (19%) patients with osteomyelitis Of these, 16 received ofloxacin and 5 ampicillin/sulbactam 12 patients in the ofloxacin group and 3 in the amp/sulb with osteomyelitis had the infected bone debrided soon after enrollment	Clinical, laboratory, and plain radiographs	Intervention: ofloxacin. controls: ampicillin/sulbactam Duration of therapy IV = 9.2 days, oral = 11.5 days for intervention and control groups with osteomyelitis combined	Cure = Disappearance of all signs and symptoms associated with active infection. Improved = incomplete abatement of the signs or symptoms. Failed = no improvement	After bone debridement: 9/12 cured and improved in the Ofloxacin group versus 2/3 in the Aminopenicillin. Without bone debridement: 3/4 cured and improved in the Ofloxacin group versus 1/2 in the Aminopenicillin group	1 –	No specific characteristic data for patients with osteomyelitis. Only 1/5 patients had osteomyelitis Comparison of Ofloxacin and Ampicillin/Sulbactam for diabetic foot infection including osteomyelitis Unclear why bone was not debrided in 6 patients when protocol indicated it should be Too few patients to draw conclusions based on these data
Lipsky 2004 [52]	Randomized open-label study Study quality: 3/9	Overall population 371. Age: 62.5 years. Gender: 71% male, type 2 diabetes: 52–61% 77 (21%) diabetic foot osteomyelitis	Actual, and presumed osteomyelitis according to individual clinicians' criteria	Intervention: Linezolid Controls: ampicillin/sulbactam. According to the bacterial profile, vancomycin or aztreonam could be added. Duration of therapy 19 ± 9 days. Evaluation in an intention to treat at the test of cure visit (+5 days after the end of trial)	Cured and improved	Intervention: 27/44 (61%), Controls: 11/16 (69%) (95% CI –34.3 to 19.5) cured and improved For the entire population studied, the number of adverse events was superior for linezolid than for ampicillin/sulbactam (26.6% versus 10.0%; $p < .001$)	1 –	No specific data for characteristics of patients with osteomyelitis. Only 1/5 patients had osteomyelitis Comparison of IV, then oral amp/sulb and linezolid (2 LZD FOR 1 A/S) for all types of diabetic foot infections including some cases of osteomyelitis Duration of antimicrobial therapy was significantly shorter in this study than in others Antimicrobial therapy mainly administered in an outpatient setting even for patients with non-critical foot ischemia

Nehler 1999 [64]	Case series, retrospective	92 patients with 97 forefoot infections. 55 extremities (56%) had osteomyelitis. All had 'clinically salvageable' forefoot infection. 32 were diagnosed on plain radiographs and have extractable results	Plain radiography	Empirical broad spectrum intravenous antibiotics and debridement surgery and primary digit amputation	Recurrence (measured by need for re-hospitalization because of infection). Eventual foot amputation	48% recurrence in osteomyelitis group, 20% in non-osteomyelitis group. Same eventual proportion of foot amputation (22%) and no difference in time to amputation	3	Observational study. A further 23 had osteomyelitis, 7 bone scan but results are not extractable from 40 others without osteomyelitis
Pittet 1999 [42]	Case series, retrospective	120 pts hospitalized for foot lesions. Investigated factors predictive of failure (fever, azotemia, prior hospitalization for DFI, gangrenous lesions). 50 patients had 'osteo & deep tissue infection'. 52 female, 53 male	Only 58 (55%) of the pts had osteomyelitis, defined by 2 blinded radiologists; clinical + X-ray + bone scan	14 (13%) had an immediate amputation. Conservative treatment successful for 57 (63%) of remaining 91	Success = healing or no infection. Failure = need for amputation or a new contiguous lesion during follow-up	Clinical failure in 15 of 34 (44%), success in 35/57 (61%) Elsewhere it is stated that 35/50 (70%) was successful and 15 (30%) failure.	3	It was classified in the article as a cohort study. Without a defined control group it is in fact a case series. The set-up is retrospective. There are some concerns about confounders, selection bias and lack of blinding.
Seidel 1991 [65]	Case series, retrospective	40 patients with diabetic neuropathic acrostyrophy of whom 12 stated to have superadded osteomyelitis	Not defined	Patients chose retrograde venous perfusion (RVP) once daily or no perfusion. All patients received Piperacillin 4G q8h. Control group also received Gentamycin 60 mg q8h, Buflomedil 50 mg q8h, Dextran 40 500 mL q8h and Heparin 5000 IU q8h. RVP group received Gentamycin 120 mg, Buflomedil 50 mg, Dexamethasone 4 mg, Lignocaine 4 mg and Heparin 2500 IU in 120 mL normal saline intravenously once daily into the extravasated limb under tourniquet control. RVP group also received additional daily Gentamycin 60 mg i.m. daily and a retard tablet of Buflomedil.	'Cured'	4/5 RVP group cured, 0/7 control group. Follow up duration not given	3	Patients allowed to chose treatment; no blinding, definitions and outcomes of osteomyelitis not stated, and all patients had abnormal radiographs

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Reference	Study design + quality	Study population and characteristics	Diagnosis osteomyelitis	Intervention and control conditions	Outcome category	Results on primary /secondary outcomes + Statistic	Evidence SIGN	Comments /weaknesses
Senneville 2001 [48]	Case series, prospective	17 pts with 20 osteomyelitic bones treated with rifampicin and ofloxacin combination therapy for median of 6 months	Bone biopsy in all	Rifampicin and ofloxacin therapy	Cure = disappearance of all signs and symptoms and no relapse. Failure = anything else	Cure in 15 (88%) at end of treatment (15/17 after 3 months; 12/14 after 6 months) and maintained in 13 (77%) at end of average period of treatment follow-up of 22 months	3	
Venkatesan 1997 [47]	Case series, retrospective	22 patients, 15 male, 7 female, median age 66, treated with antibiotics and no surgery if possible	Interruption of cortex and clinical features.	Antibiotic therapy at least 3 months	Cure = "freedom from clinical signs of inflammation or x-ray evidence."	4 patients did not respond and had amputations. Osteomyelitis recurred in one at same site. Resolution of infection in all remaining inferred from 'freedom from clinical signs of inflammation or x-ray evidence'. In all other cases medical therapy was successful in resolving osteomyelitis and there was absence of recurrence.	3	No routine follow-up x-rays. Outcome measures not clearly defined.
Wilson 1985 [66]	Case series	2 patients 57 and 73 years, males with insulin-dependent diabetes	Clinical findings and plain radiographs	Naftillin intravenous (inpatient), followed by clindamycin and cephalixin duration of therapy = 7 months. Clindamycin and metronidazole oral (outpatient). Duration of therapy 3 months.	Clinical and radiological	Follow-up 11 months after the end of treatment cured (clinical and radiological). 4 months after the end of treatment: stabilisation of the radiological abnormalities	3	First report of oral antimicrobial therapy for diabetic foot osteomyelitis

Yadlapalli 2002 [60]	Case series Chart review	58 patients with diabetes and osteomyelitis 48 male, 10 female Mean age 60 years	Clinical (grossly infected or exposed bone, probe to bone) or radiograph and radionuclide scan	47 patients with empiric intravenous antibiotic therapy 4 to 6 weeks using miscellaneous agents (ceftriaxime, ampicillin/sulbactam, cefoxitine, vancomycin). 11 patients received culture-based antibiotic therapy for a mean duration 40.3 days (range 19–90) Debridement: 34, excision of bone: 13, amputation toe or ray: 8, major amputation: 3	Healing, failure	12 failed 46 healed (79.3%) 9 persistence of ulceration. Follow up 12 months after the end of treatment.	3	Authors did not give details about culture-based antibiotic therapy 24 of 58 patients had operative procedures (41.3%)
Yamaguchi 2004 [43]	Cohort study Study quality: 5/7	11 patients with intervention, 38 patients in study, 20 patients with osteomyelitis Age range 36–84; mean age 58.1 years. Experimental, 64.8 controls for exposed bone patients. Gender: 25/38 were male; 7/2 Standard, 8/3 Experimental	Visible necrotic and infected bone with positive cultures	Epidermal sheets grafted onto foot ulcers w/o exposed bone (n = 11). In patients with exposed bone compared standard treatment (n = 9) with experimental procedure (n = 11) – bone debrided, partly excised, covered with occlusive dressing, then epidermal skin graft	Wound healing, amputation	11 pts with experimental treatment had fewer amputations (0 vs 8) and similar time to healing. No recurrence of osteomyelitis (p < 0.0001)	2	Patients chose their treatment options. Strong possibility of selection bias

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Conflict of interest

A. R. Berendt has received honoraria and consultancy fees from Merck and Pfizer; B. A. Lipsky has received research funding from or served as a consultant to Merck, Pfizer, Wyeth-Ayerst, Bayer, Cubicin, Ortho-McNeil/Johnson & Johnson; J. M. Embil has received consultancy fees from Wyeth. None of the other authors have conflicts of interest.

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