Diabetic foot osteomyelitis

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Abstract

Bone infection in the diabetic foot is always a complication of a preexisting infected foot wound. Prevalence can be as high as 66%. Diagnosis can be suspected in two main conditions: no healing (or no depth decrease) in spite of appropriate care and off-loading, and/or a visible or palpated bone with a metal probe. The first recommended diagnostic step is to perform (and if necessary to repeat) plain radiographs. After a four-week treatment period, if plain radiographs are still normal, suspicion for bone infection will persist in case of bad evolution despite optimized management of off-loading and arterial disease. It is only in such cases that other diagnosis methods than plain radiographs must be used. \textit{Staphylococcus aureus} is the most common pathogen cultured from bone samples, followed by \textit{S. epidermidis}. Among enterobacteriaceae, \textit{Escherichia coli}, \textit{Klebsiella pneumonia} and \textit{Proteus sp.} are the most common, followed by \textit{Pseudomonas aeruginosa}. Surprisingly, bacteria usually considered contaminant (as coagulase negative staphylococci (CNS) and \textit{Corynebacterium} sp.) have been documented to be pathogens in the osteomyelitis of diabetic foot. Traditional approach to treatment of chronic osteomyelitis was by surgical resection of infected and necrotic bone. But new classes of antibiotics have both the required spectrum of activity and the capacity to penetrate and concentrate in the infected bone. Recently, several observations of osteomyelitis remission following non-surgical management with a prolonged course of antibiotics have been published. Lastly, combined approach with local bone excision and antibiotics has been proposed. Prospective trials should be undertaken to determine the relative roles of surgery and antibiotics in managing diabetic foot osteomyelitis.

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Résumé

Ostéite du pied diabétique.


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Mots clés : Pied diabétique ; Ostéite ; Revue générale
Dealing with osteomyelitis can be difficult in the management of diabetic foot infection because of the presence of many controversial aspects such as the definition of various terms, diagnostic strategy and therapeutic options [1–3]. But, in recent years, many efforts have been made to arrive at nearly consensual guidelines [4,5].

1. Epidemiological data

Individuals with diabetes have an approximately 25% lifetime risk of developing a foot complication. Over half of foot wounds in such patients may eventually become infected, and most of these will involve only the soft tissue. Prevalence of bone involvement is variable, depending on the context: it is higher in a selected cohort with infected wounds, and lower in a less-specific population. When clinically severely infected foot ulcers are considered, the prevalence of osteomyelitis may be as high as 66% [6]. When consecutive series of outpatients attending a diabetic foot clinic are involved, osteomyelitis prevalence is between 10 and 20% [7,8].

2. Pathophysiology

Bone infection in the diabetic foot is always a complication of a preexisting infected foot wound. Bone contamination results from the spread of infection from soft tissue in an ongoing process that can take several weeks. Major pathogens adhere to bone by expressing adhesion factors for components of bone matrix. Pus spreads into vascular channels, raising the intrasosseous pressure and impairing blood flow. Ischaemic bone necrosis results in the separation of devascularized fragments called ‘sequestra’. Microorganisms, neutrophil infiltration and congested or thrombosed blood vessels are the principal findings in acute osteomyelitis. One of the distinguishing features of chronic osteomyelitis is necrotic bone, which can be recognized by the absence of osteocytes.

Most ulcers responsible for the spread of infection to underlying bone are located around the fifth and first metatarsal heads, and the distal phalanx of the great toe [9]. In the absence of a clinical foot ulcer, osteomyelitis is unlikely, even when bone lesions are present on imaging (false-positive imaging data).

Chronic wound infection is the main risk factor for ulceration and secondary spread to bone [10]. Consequently, all factors that contribute to prolongation of healing time will increase the risk of osteomyelitis. Indeed, an inefficient off-loading of a foot ulcer, a well-known factor for non-healing, greatly increases the incidence of osteomyelitis [11,12].

3. Microbiology

The microbiological aetiology of foot osteomyelitis in diabetic patients is similar to that of the contiguous soft-tissue infection, which is not surprising as the former is a consequence of spread of the latter. This means that diabetic foot osteomyelitis is usually polymicrobial, although fewer numbers of isolates are usually found in bone compared with soft-tissue infections [13]. In nearly every series reported in the literature, *Staphylococcus aureus* was the most common pathogen cultured from bone samples, followed by *Staphylococcus epidermidis*. Among the Enterobacteriaceae, *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus* sp. are the most common, followed by *Pseudomonas aeruginosa*. The number of obligate anaerobes depends largely on the method of sampling and transportation of bone fragments. However, in a recent study in which all bone samples were directly inoculated with Rosenow’s broth, obligate anaerobes were identified in only 5% of patients [14]. Among obligate anaerobes, *Finegoldia magna* (ex *Peptostreptococcus magnus*) and other anaerobic peptococci are the most prevalent bacteria, with *Bacteroides* sp. being rarely cultured from these infections [15].

Surprisingly, bacteria that are usually considered contaminants [such as coagulase-negative staphylococci (CNS) and *Corynebacterium* sp.] have been documented as pathogens in osteomyelitis of the diabetic foot [16,17]. CNS species have been cultured in up to 50% of cases in at least four series of bone-culture-proven osteomyelitis [14,15,18,19]. However, the pathogenic role of these organisms should only be considered when bone fragments have been taken with all proper precautions to avoid contamination by colonizing flora, and when histological examination is consistent with a diagnosis of osteomyelitis [13].

It is not clear whether multiresistant bacteria, especially methicillin-resistant *S. aureus* (MRSA), represent an increasing problem, as it is with skin and skin-structure infections.

Microbiological data from four series are presented in Table 1.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Aerobic gram-positive cocci</td>
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<tr>
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<td><em>Enterococcus</em> sp.</td>
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<td>8</td>
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<tr>
<td>Other</td>
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<td>10</td>
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<td>–</td>
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<tr>
<td>Aerobic gram-negative bacilli</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
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<tr>
<td><em>Pseudomonas</em> sp.</td>
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<td>11</td>
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<td>70</td>
<td>83</td>
<td>–</td>
</tr>
<tr>
<td>Organisms (n)/bone samples (n)</td>
<td>1.54</td>
<td>–</td>
<td>2.25</td>
<td>–</td>
</tr>
</tbody>
</table>

4. Positive diagnosis

4.1. Physical examination

Osteomyelitis must be considered as a potential complication of any deep ulcer. But depth is often not clinically apparent. As a consequence, any foot wounds should be carefully and systematically explored at each consultation with a sterile blunt metal probe. Diagnosis can be suspected under two main conditions: no healing (or no depth decrease) in spite of appropriate care and

Table 1

Microbiological aetiology of osteomyelitis of the foot in diabetic patients (values given as percentage of total number of microorganisms)
off-loading, and/or visible or palpable bone with a metal probe (called a ‘positive probe-to-bone test’).

The ability of the PTB test to predict osteomyelitis was explored in three studies. In the first [6], severely infected wounds were assessed for detectable bone by probing, and the positive predictive value of the test for osteomyelitis was 89%. In the two other studies [7,8], the PTB test was evaluated in consecutive patients attending a diabetic foot clinic (no selection). In this case, the positive predictive value of the test was around 55%, but its negative predictive value was over 95%. What we can conclude is that, in the presence of a clinically-infected wound, a positive PTB test is highly suggestive of osteomyelitis, but a negative result does not refute the diagnosis. On the other hand, in the presence of any wound (with no apparent infection), the PTB test is not sufficient to suggest osteomyelitis, but osteomyelitis is highly unlikely if the PTB test is negative. Under such conditions (a non-infected wound and a negative PTB test) and in the absence of depth decrease, two explanations other than osteomyelitis should be explored: insufficient off-loading or insufficient arterial vascularization.

Where there are no specific clinical symptoms of diabetic foot osteomyelitis, one symptom is highly suggestive: the so-called ‘sausage’ deformity [20], where the toe is swollen and erythematous, with obliteration of the normal toe contour. Given this feature in association with local ulceration (of the toe or of the adjacent metatarsophalangeal joint), underlying osteomyelitis is certain.

4.2. Laboratory examination

Leucocytosis is a poor indicator of foot osteomyelitis: the white blood cell (WBC) count is normal in 50% of cases, and an increased WBC count can be seen in soft-tissue or systemic infection [21].

In the absence of an inflamed ulcer on physical examination, an erythrocyte sedimentation rate (ESR) above 70 mm/h is highly suggestive of osteomyelitis (positive predictive value of 100%) [19]. However, in 70% of cases of osteomyelitis, the ESR is less than 70 mm/h.

Other interesting laboratory findings (C-reactive protein and procalcitonin) have not been properly evaluated in diabetic foot ulcer with suspected osteomyelitis.

4.3. Microbiological examination

4.3.1. Value of microbiological tests

The definition of what constitutes reliable microbiological documentation in cases of osteomyelitis is still controversial. It has been suggested that the results of superficial sample cultures do not correlate with those of bone [15,22]. A recent study in patients who had not been given antibiotic therapy for at least four weeks before biopsy found low correlation rates between results from cultures of swabs taken from the ulcer surface and those of bone fragments taken transcutanously via an area of normal skin [14]. Correlation rates varied according to bacterial species, with a significantly higher rate with S. aureus than with other organisms, but which nevertheless remained too low (about 40%) to be useful in clinical practice [14]. It is now generally admitted that bone biopsy performed with proper precautions is still the sole technique that reliably allows identification of the true pathogens involved in bone infection [1]. It would be, however, interesting to compare correlations between cultures resulting from transcutanous needle aspiration, as described by Kessler et al. [23], and those resulting from transcutanous bone biopsy.

4.3.2. Value of bone biopsy

Bone biopsy is useful for reliably recovering the pathogens responsible for bone infection and for determining their profile of susceptibility to antimicrobial agents. It is also claimed to be the gold-standard test for diagnosing osteomyelitis [4]. Thus, there are two indications for a bone biopsy:

- Bone biopsy to recover pathogens

  Antimicrobial treatment of skin-structure infections complicating diabetic foot ulcers is often empirical because of the risk of rapid worsening of the infection. In cases of osteomyelitis, it is necessary to identify the pathogens responsible for the infection as it will determine the treatment options. When non-conservative surgical treatment is performed, such identification may not be necessary. But when a medical treatment is intended, it has to be based on reliable sample cultures because of the need for prolonged therapy. In such cases, bone bacteriological analysis, to be interpretable, must be the result of a strictly applied procedure: no antibiotic therapy for two to four weeks (to avoid false-negative results), and a transcutanously (via normal skin) obtained bone biopsy (to avoid contamination from the ulcer; see below);

- Bone biopsy to make a positive diagnosis of osteomyelitis

  The simplest test to make a positive diagnosis of bone infection is to carry out successive plain radiography (see below, and Fig. 1). In certain rare conditions, when osteomyelitis appears to be doubtful, bone biopsy may be carried out for diagnosis (see below, and Fig. 1). A positive diagnosis is established by culture growth and/or histological findings, in which case, two bone fragments are necessary: one for histological examination, and another for bacteriological analysis. Histological findings include aggregates of inflammatory cells (neutrophils, lymphocytes, histiocytes and plasma cells), erosion of trabecular bone and marrow changes (from loss of normal marrow fat to fibrosis and reactive bone formation).

  The absence of histological abnormalities on bone examination can help physicians to interpret both negative cultures or positive cultures involving only skin bacterial flora. Histological findings and/or positive culture for pathogens (when performed under perfect conditions) are sufficient to confirm an osteomyelitis diagnosis. But, in the presence of CNS or Corynebacterium sp., histological examination must support a diagnosis of bone infection.

  Histological analysis has been said to have a better sensitivity than culture growth [24] probably because cultures are often performed under flawed conditions (a negative culture due to antibiotic treatment). In one study [25], microbiological
examination had a sensitivity of 92% and a specificity of 60% for diagnosing osteomyelitis, but the bone specimens had been obtained during surgery (and thus, had a high risk of bacterial contamination).

4.3.3. How to perform a bone biopsy

Although bone biopsy is generally considered the gold standard, it is rarely performed in routine practice because of the expense and the possible (though unlikely) adverse events. A single centre has recently established the safety of transcutaneous bone biopsy of the foot in diabetic patients, involving trained orthopaedic surgeons [14]. When feasible, a bone biopsy should be performed without passing through an open wound to avoid contamination by colonizing organisms [13]. Bone biopsy can generally be done with little or no anaesthesia in patients with profound peripheral neuropathy. Histological examination may help to confirm the presence of osteomyelitis, but is of no interest for microbiological documentation. To reduce the number of false-negative results, patients should not have received any antibiotic therapy for two to four weeks before the biopsy because of the prolonged release of these drugs from bone [14,26]. Although percutaneous bone biopsies can be easily obtained under fluoroscopic or computed tomographic (CT) guidance, the use of a bone biopsy needle rather than an open surgical biopsy may lead to false-negative results by missing the osteomyelitic area.

4.4. Imaging tests

4.4.1. Plain radiographs

Radiographs are readily obtained and relatively inexpensive. The classic radiographic triad for osteomyelitis is demineralisation + periosteal reaction + bone destruction. Radiologically evident bone damage beneath an ulcer should be considered...
osteomyelitis unless proven otherwise. However, it may take as many as 14 days after the onset of bone disease for it to become evident on radiography. For this reason, the accuracy of plain radiography for early diagnosis is only about 50–60%, with a sensitivity of around 60% and a specificity of around 80% [19,27–29]. These rates suggest that there are few false-positive results, but a considerable rate of false negatives early in the course of the disease. However, characteristic progressive changes can be seen on serial plain radiographs repeated after two or four weeks [20,30]. For this reason, in most cases, it is simpler and less expensive to obtain successive radiographs (with the patient on appropriate care and off-loading) instead of using other, more sophisticated imaging techniques. Indeed, according to IDSA guidelines [4], when osteomyelitis is uncertain, a second radiograph should be obtained after two to four weeks before embarking on additional imaging studies.

4.4.2. Bone scanning (scintigraphy)

Bone scanning with 99mTc diphosphonates has a high sensitivity (about 75%), but low specificity (40%) [19,28,29]. Focal hyperperfusion, focal hyperaemia and focal bony uptake on delayed images are considered diagnostic of osteomyelitis, although the same pattern may also be seen in neuroarthropathy and cellulitis, conditions that regularly coexist in the diabetic foot. So, a negative result can be suggestive (osteomyelitis is unlikely), but the number of false positives is much too high. Furthermore, a bone scan may remain positive for months after successful therapy. So, bone scintigraphy cannot confirm whether an infectious disease process is present in bone.

4.4.3. Labelled autologous leucocyte scanning

Leucocytes are labelled in vitro with 111In indium oxine or 99mTc-HMPAO and then injected back into the patient. Patients are scanned 4 and 24 hour later. Labelled leucocytes do not usually accumulate at sites of new bone formation without infection (neuroarthropathy), so the risk of false-positive results should be low. But the major limitation of leucocyte imaging is the poor spatial resolution (there is no way to distinguish bone from soft-tissue infection), making the number of false-positive results likely to be high [19]. To precisely identify the site of leucocyte deposition (bone or soft tissue), it is necessary to also do a bone scan. Labelled leucocyte scanning along with a bone scan is highly accurate (90% sensitivity, 70–90% specificity) [25,30]. Labelling with 99mTc-HMPAO provides better imaging characteristics than with 111In indium oxine.

However, there are problems with this imaging technique: it is not currently available; it is expensive; it requires trained laboratory personnel to handle blood samples; and the patient has to spend two days having the test done.

4.4.4. Antigranulocyte scintigraphy (AGS)

There have been many attempts to develop an agent that can be injected directly into patients to selectively bind circulating granulocytes in vivo. 99mTc-labelled antigranulocyte antibody scintigraphy is one result. The preparation of labelled antibodies requires a short time, and no sterile laboratory facilities are required. Evaluations of early one-hour [31] and four-hour [32] imaging reported 90% sensitivity and 70% specificity. In patients with early high uptake intensity, further delayed images are unnecessary but, in patients with early mild uptake intensity, delayed imaging (24 h) is recommended. But again, the technique is expensive and not currently available.

4.4.5. Magnetic resonance imaging (MRI)

MRI is a currently available imaging modality that reveals active medullary osteomyelitis as an area of abnormal marrow with decreased signal intensity on T1-weighted images that corresponds to an area of high intensity on T2-weighted images [33]. But the main problem with this technology is that marrow oedema may give MR signal intensities similar to those of osteomyelitis [33]. Consequently, MRI sensitivity is good for detecting osteomyelitis (90%), but specificity may range from 70–80% [29,34,35] or less [25,36]. The typical MRI findings seen in patients with chronic neuroarthropathy can be distinguished from those of osteomyelitis [34]. But, in patients with acutely evolving neuropathic osteoarthropathy (acute Charcot foot), signal intensity changes within the bone marrow are similar to those observed in osteomyelitis [37].

4.4.6. Positive diagnosis algorithm

Where osteomyelitis is clinically suspected, the recommended first step is to perform (and, if necessary, repeat) plain radiography (Fig. 1). This will allow a diagnosis of osteomyelitis to be made in most cases. After a four-week treatment period, if the ulcer depth does not decrease and plain radiographs are still normal, then three diagnoses are likely: off-loading has not been properly applied; arterial perfusion is not optimal; and/or osteomyelitis is present. Bone infection will remain likely where there is disease progression in spite of optimal management of off-loading and arterial disease. It is only in such cases that diagnostic methods other than plain radiography need to be used. We propose the diagnostic process shown in Fig. 1. Bone scanning (scintigraphy) is useful when negative. But, if positive, MRI or a bone biopsy is recommended. Labelled autologous leucocyte scanning and antigranulocyte scintigraphy should be kept for difficult differential diagnosis with acute Charcot foot.

5. Differential diagnosis

The only differential diagnosis for osteomyelitis is neuroarthropathy of the foot. In fact, neuroarthropathy can induce destructive bone lesions with the same appearance as bone infection on plain radiographs. However, in the absence of an ulcer, diagnosis is easy: bone damage is the result of neuroarthropathy. A problem arises when a foot ulcer is present on a chronic Charcot foot, with bone lesions localized beneath the ulcer seen on radiography. In the absence of any symptoms of clinical infection, and a negative PTB test, bone infection is unlikely. But, if there is exposed bone and clinical disease progression in spite of appropriate care, then MRI may be useful. If there is persistent doubt as to the diagnosis, then labelled autologous leucocyte scanning or antigranulocyte scintigraphy could be performed.
6. Osteomyelitis treatment

The traditional approach to treatment of chronic osteomyelitis has been by surgical resection of infected and necrotic bone. It was generally thought that removal of the infected bone was necessary for permanent cure of chronic bone infection, as the success rates obtained using antimicrobial therapy alone were disappointing. But new classes of antibiotics have both the required spectrum of activity, and the capacity to penetrate and concentrate in infected bone. Recently, several observations of osteomyelitis remission following non-surgical management using a prolonged course of antibiotics have been published. In fact, the combined approach of local bone excision with antibiotics has been proposed. Prospective trials need to be undertaken to determine the roles of surgery and antibiotics in the management of diabetic foot osteomyelitis.

6.1. Therapeutic strategies

6.1.1. Traditional surgical management

The traditional surgical treatment of osteomyelitis consists of removal of all necrotic and infected tissue down to living bone. The goal of such an approach is to quickly resolve the bone infection. A short course of antibiotics is also used. But this strategy exposes patients to the risk of re-ulceration related to new pressure areas and to changes in foot biomechanics. Murdoch et al. [38] showed that, after great toe or first ray amputation, 60% of patients had a second amputation within a year of the procedure. The risk is even greater because this traditional approach often removes healthy bone segments along with infected bone. For example, metatarsal head or even digit infection is treated by total ray amputation. When multiple digits are involved, a transmetatarsal amputation is performed even if the metatarsal heads are not infected [39]. In this regard, the technique is not what could be called ‘conservative’ surgery. This traditional approach has not been compared with other treatments. Nehler et al. [40] reported a success rate of 34% (healing without amputation) in a cohort of 97 forefoot infections, 56% of which were osteomyelitis;

6.1.2. Conservative surgery or medicosurgical management

Medicosurgical treatment involves antibiotic therapy with conservative surgery. Conservative surgery refers to limited resection of the infected digit or metatarsal bone, with no resection of non-infected bone. It can involve removing a single metatarsal head, or one or two phalanges, but not amputation.

Fig. 2. Medicosurgical treatment of osteomyelitis: limited resection of an osteomyelitic second metatarsal head.
of any ray (Fig. 2). Antibiotic therapy consists of four to six weeks of treatment following surgery. Off-loading during healing is a major component of the medical part of treatment. It has been suggested that such a medicosurgical approach could lead to an increased healing rate compared with medical treatment alone, but this assumption requires further investigation [11,41].

Nevertheless, the conservative surgical approach probably increases the risk of re-ulceration related to changed foot biomechanics, even though the risk is less than with traditional surgery, where more bone segments are removed. Unfortunately, published studies do not include prolonged clinical and radiological follow-ups that evaluate the rates of recurrence of osteomyelitis (as usually recommended for chronic osteomyelitis in other settings) and of foot ulcers. Again, this possible limitation of the medicosurgical approach to osteomyelitis requires further investigation;

### 6.1.3. Medical management

Interestingly, a few recent studies have reported satisfactory clinical success using only medical drugs (antibiotic treatment alone; see below) for diabetic patients with foot osteomyelitis [42–47]. Senneville et al. [14] reported an 85% healing rate at the six-month follow-up, and Venkatesan et al. [42] achieved an 80% resolution of osteomyelitis over a median follow-up period of 27 months. Such a medical strategy does not expose patients to the risk of re-ulceration related to new pressure areas and changed foot biomechanics. But the antibiotic treatment is long (12–24 weeks), and vigorous off-loading is necessary until the ulcer heals. Healing time could be more prolonged than with the medicosurgical approach, but this needs further investigation. Also, an important issue that has not been evaluated in most studies is to determine the extent of bone destruction that can be

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Therapy</th>
<th>Dosage/24h</th>
<th>Route of administration</th>
<th>Dose interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>Oxa/cloxacin ± Gentamicin</td>
<td>100–150 mg/kg/day</td>
<td>i.v</td>
<td>4 h or 6 h</td>
<td>Until specimens are taken in case of sepsis</td>
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<td>FQa + Rifampicin</td>
<td>4 mg/kg/day</td>
<td>i.v</td>
<td>24 h</td>
<td>Oral route as soon as possible</td>
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<tr>
<td>FQa + Clindamycin</td>
<td>600–800 mg/day</td>
<td>i.v/oral</td>
<td>8–24 h</td>
<td>Oral route as soon as possible</td>
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<tr>
<td>MRSA</td>
<td>Vancomycin or Teicoplaninb ± Gentamicin</td>
<td>1 g/60 min then 40 mg/kg/day</td>
<td>i.v</td>
<td>Continuous IV 3–5 doses/12 h, then 24 h</td>
<td>Adjust to serum assays&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rifampicin + Fusidic acid</td>
<td>20 mg/kg/day</td>
<td>i.v/oral</td>
<td>12 h</td>
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<td>Rifampicin + TMP-SMX</td>
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<td>i.v/oral</td>
<td>12 h</td>
<td>Renal and bone marrow toxicity</td>
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<tr>
<td>GNB</td>
<td>FQa + 3&lt;sup&gt;d&lt;/sup&gt; G CP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>600–800 mg/day</td>
<td>i.v/oral</td>
<td>8–24 h</td>
<td>Consider FQ monotherapy</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Imidazole</td>
<td>1.5 g/day</td>
<td>i.v/oral</td>
<td>8 h</td>
<td>FQ + [clindamycin or FQ] if Propionibacterium acnes</td>
</tr>
</tbody>
</table>

<sup>a</sup> Fluoroquinolones (ofloxacin, levofloxacin).
<sup>b</sup> Consider teicoplanin if renal impairment.
<sup>c</sup> Adjust dosage to obtain plateau concentrations of 30 mg/l for vancomycin and trough concentrations of 30–40 mg/l by HPLC for teicoplanin.
<sup>d</sup> Fluoroquinolones (ofloxacin, levofloxacin, ciprofloxacin).
<sup>Pro</sup> Third-generation cephalosporin (ceftriaxone, cefotaxime); consider cefazidime, cefepime or other beta-lactam agent with anti-<i>Pseudomonas</i> sp. activity combined with ciprofloxacin or levofloxacin in case of pseudomonal infection.

### 6.2. Antimicrobial treatment

The few available clinical studies in the literature of antimicrobial treatment of osteomyelitis in diabetic foot ulcers do not provide definitive helpful conclusions. Also, the study designs are not consistent, especially in terms of the definition of bone infection, the definition of successful treatment, and whether or not there was post-treatment follow-up. In most cases, bacterial documentation was not reliable, as it was based on the results of superficial sample cultures; in most of the studies, bone biopsy was not performed. When the results of bone-biopsy cultures are reported, they usually referred to deep-tissue samples taken during debridement rather than true biopsies, and the studied patients constituted only part of the studied cohort.

The antimicrobial agents usually administered to patients treated medically for foot osteomyelitis were fluoroquinolones, clindamycin and rifampicin — agents that reach the highest concentrations in bone, and maintain activity against surface-adhering, slow-growing, and biofilm-producing microorganisms. These antimicrobial agents also have the highest risk of resistant-mutant selection and should, therefore, only be administered in effective combinations (where both agents are active against the pathogens) to prevent the emergence of resistant bacteria (especially with rifampicin). To ensure that drug combinations are fully active against pathogen(s) involved in bone infection, the choice of agents should ideally be based on the results of bone cultures [48–50].

Given that rifampicin, fusidic acid and fluoroquinolones tend to select for resistance in infections with high inoculums, these

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agents should not be used as first-line therapy in patients with acute soft-tissue infections, but should be reserved for foot osteomyelitis when bone specimens are available. Table 2 shows the antimicrobial therapy for diabetic foot osteomyelitis as recommended by the French guidelines for the management of diabetic foot infections [5].

There are little reliable data for the optimal duration of antimicrobial therapy. It probably depends on the persistence of infected bone and its nature (dead or vital, fragmented or not). Over the past several decades, it has been recommended that antimicrobial therapy be applied for at least four weeks in patients with chronic bone infection. This may not be true with antimicrobial agents that have complete oral bioavailability such as levofloxacin, rifampicin and fusidic acid. At present, the proposed treatment period is two to five days where there is no residual infected tissue (postamputation), two to four weeks where there is residual infected soft tissue (but not bone), four to six weeks where there is residual infected but viable bone, and three months or more in cases of persistent bone necrosis [4].

References


