

Controversies in Diagnosing and Managing Osteomyelitis of the Foot in Diabetes

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The optimal approach to diagnosing and managing osteomyelitis of the foot in diabetes is unclear. Diagnosis is based on clinical signs, supplemented by a variety of imaging tests. Bone biopsy is the accepted criterion standard for diagnosis but is not used by many. Management traditionally involves surgical removal of infected bone, combined with antibiotic therapy. However, recent studies have shown that antibiotics alone may apparently eliminate bone infection in many cases. There is also evidence that early amputation of infected digits is frequently noncurative. Agreement on criteria for diagnosing osteomyelitis is required, and randomized trials are urgently needed, to determine the relative benefits of various surgical interventions and the optimal deployment of antibiotics. We review the microbiology of osteomyelitis of the foot in diabetes, the benefits and limitations of various diagnostic procedures, and the evidence for the effectiveness of both surgical and nonsurgical approaches to management.

Underlying osteomyelitis frequently complicates ulceration of the foot in patients with diabetes. The bones involved are usually in the forefoot [1], particularly the first digit [2]. Because the foot is well perfused in most (but not all [3]) cases, signs of inflammation include diffuse, red induration; affected toes have been described as resembling a sausage [4, 5]. Bacteria gain access to bone by contiguous spread, entering from overlying soft tissue and penetrating the cortex before involving the marrow. Thus, virtually all patients present with cortical bone involvement and with features of chronic osteomyelitis. Osteomyelitis can also complicate feet distorted by neuropathic osteoarthropathy (Charcot foot); in these cases, establishing the diagnosis and eradicating the infection are particularly difficult.

Eradicating infection in bone is difficult for several reasons. Host defenses do not operate optimally in the osseous environment. Infecting bacteria can elude inflammatory cells and induce osteolysis by interacting

with host immune-system cells [6]. Moreover, the dominant pathogen, *Staphylococcus aureus*, expresses receptors (adhesins) for bone matrix proteins [7] and becomes incorporated into a relatively impermeable glycocalyx biofilm. Thus, the traditional approach to treatment of chronic osteomyelitis is by surgical resection of infected and necrotic bone. Early attempts to manage infection with antibiotics alone, or combined with limited debridement and drainage, were largely unsuccessful [8–10]. This may have resulted from the relatively poor tissue penetration of older antibiotics, especially in patients with limb ischemia. This early experience suggested that a nonsurgical approach was not particularly effective, and it became axiomatic that “curing osteomyelitis with antibiotics alone is difficult” [11] and that “surgical resection of infected areas by an experienced surgeon...down to living bone, is of critical importance” [12].

Improvements in antibiotic therapy may have changed the equation. New classes of antibiotics (especially aminopenicillin/penicillinase inhibitor combinations and fluoroquinolones, but also carbapenems and oxazolidinones) have been introduced, and there is increasing confidence in the safety of clindamycin. Many of these agents are highly bioavailable when taken

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orally and are well tolerated for long courses. The use of combination therapy, for example with rifampin, may also improve outcomes. Additionally, several new antibiotics have both the required spectrum of activity and the capacity to penetrate the glycocalix biofilm and to concentrate in the infected area [7, 10, 12]. These factors may underlie the increasing numbers of observations of remission following nonsurgical management with a prolonged course of antibiotics in cases of diabetic foot osteomyelitis. Therefore, we believe it is time to rethink the long-held principles of managing these difficult infections.

MICROBIOLOGY OF OSTEOMYELITIS IN THE DIABETIC FOOT

Polymicrobial infection. Studies of the bacteria isolated from diabetic foot infections [13–22] have reported an average of 2–5 organisms per case, depending on various clinical factors (e.g., the population studied and prior antibiotic use) and microbiological issues (e.g., the type and care with which samples are taken and the speed of transport to, and rigor of handling in, the laboratory). Osteomyelitis is most often caused by staphylococci, but they are often accompanied by other organisms [1, 23–27], especially aerobic gram-positive cocci and gram-negative bacilli. Anaerobic organisms have been isolated in up to 40% of cases in some series [1, 26], but the extent to which they contribute to the infective process is unclear [24]. Fungi (yeasts and dermatophytes) cause tinea pedis, which can serve as a portal for pathogenic bacteria, but they are rarely pathogens in osteomyelitis.

Variation between sampling sites. Different organisms thrive in different tissues, and those infecting bone are not necessarily the same as those isolated from adjacent deep soft tissue. Cultures obtained from samples taken simultaneously from bone and soft tissue have been found to be identical in only 13% [27], 19% [28], and 43% [29] of cases. In general, fewer species are isolated from the bone specimens. Because areas of infection in bone may be patchy, negative culture results may occasionally be obtained in cases of otherwise clinically overt infection [24].

DIAGNOSIS

Clinical. In most cases the foot is well perfused, and the infected part (usually the forefoot or a toe) is dull red and diffusely swollen and warm and may be discharging pus or fragments of bone. Systemic signs, such as fever and malaise, are unusual with foot infections, including those with osteomyelitis. Their occurrence usually suggests more extensive tissue necrosis with anaerobic involvement [14, 26]. When osteomyelitis occurs in an ischemic foot, inflammatory signs may be reduced, but there is usually some evidence of soft-tissue infection or necrosis.

Ulcer depth and area. Bone that is visible at the base of

a wound is likely to be infected. In a study of patients with limb-threatening infections, if bone could be felt with the tip of a sterile metal probe inserted in the wound (probe-to-bone test), then bone infection (defined histologically) was likely [30]. The procedure had a sensitivity of only 66% but was relatively specific (85%) and had a positive predictive value of 89%. Although encouraging, these findings were limited by being obtained by a single center and found in a population in which there was high pretest probability (60%) of osteomyelitis. Furthermore, the reliability of repeated tests, either by the same clinician or by others, was not assessed. Whereas the test characteristics of the procedure are as good as those of others in routine use [31], its wide adoption in clinical practice relates as much to its simplicity as to its diagnostic precision. Wound depth is an unreliable guide to the presence of bone infection in a (nondiabetic) decubitus ulcer [12].

One small study in which bone infection was defined by bone biopsy [28] found an association between the presence of osteomyelitis and the cross-sectional area (>2 cm²) of the overlying ulcer (sensitivity, 56%; specificity, 92%). Ulcers of longer duration are probably more often associated with underlying osteomyelitis, as are those that overlie bony prominences. Available evidence does not justify using any one or combination of these clinical findings as the sole criterion for diagnosing osteomyelitis.

Hematologic and biochemical investigations. Leukocytosis occurs infrequently in diabetic foot osteomyelitis [26, 32]. C-reactive protein concentrations tend to be high, but this sign is nonspecific. In one study of severe diabetic foot infections, both the neutrophil count and the C-reactive protein level were higher in those with exclusively soft-tissue infection than in those with osteomyelitis [26]. An elevated erythrocyte sedimentation rate (ESR) may be a better marker of bone infection in the diabetic foot. Armstrong et al. [32] found a high ESR in 96% of cases in which bone was involved, but this was not confirmed in another study of puncture wound infections [33]. Retrospective analysis of 2 series indicated that an ESR > 70 mm/h indicated bone infection with 100% specificity [28, 34]. The sensitivity of this finding was only 28% in one study [28] and was <50% in another [26]. Although others reported that osteomyelitis was 12 times more likely in suspected cases if the ESR exceeded 40 mm/h [24], a study of severe diabetic foot infections reported that the mean ESR in cases with osteomyelitis was only 56 mm/h, whereas in those with just deep soft tissue infection it was 75 mm/h [26]. Similarly, another study found that the mean ESR in patients with osteomyelitis was only 47.6 (±13) mm/h [35].

Imaging. The diagnostic precision of various imaging studies in diabetic foot infections has been reviewed extensively [24, 30, 36–39]. Plain radiography has poor sensitivity in the early stages [37, 40, 41], and bone infection can precede ra-

diological changes by up to 4 weeks. In patients with neuropathy, the changes seen on radiography may be indistinguishable from those of Charcot osteoarthropathy [42, 43]. Plain radiography is, however, diagnostically useful when results are initially normal but show characteristic changes (e.g., cortical destruction and periosteal elevation) weeks later. This is especially true if the affected bone is in the forefoot or hindfoot or underlies an infected ulcer in a patient without other evidence of Charcot foot.

The low sensitivity of plain radiography for acute infections has led to attempts to develop other imaging techniques. One of the first and still most commonly used techniques is the radionuclide bone scan. The sensitivity of a 3- (or 4-) phase bisphosphonate-linked technetium bone scan is certainly greater than for that of radiography in early osteomyelitis. In 1995, Eckman et al. [37] calculated a weighted average for diagnostic sensitivity for published studies of 86%; more recent studies report values from 50% [40] to 83% [41]. Specificity, however, is not good [40, 41] (averaging ~50%), because almost any type of bone disorder (including neuroarthropathy and healing osteomyelitis) can cause increased isotope uptake on a bone scan.

Other radionuclide imaging agents—for example, scans that use WBC (labeled autologous leukocytes), labeled immunoglobulin, or other infection-specific radiopharmaceuticals—generally lack the resolution of the bone scan but are more specific [39, 44, 45]. The sensitivity of these tests can be limited in some situations [40], especially in an ischemic foot. These scans may be valuable in distinguishing osteomyelitis from soft-tissue infection or Charcot-type changes, especially when combined with a bone scan [46, 47]. The labeled autologous WBC scan is relatively expensive, is technically demanding, and involves radiation exposure but can be helpful in demonstrating that an infection has resolved [28, 46].

Most clinicians agree that MRI offers the greatest diagnostic support in clinical practice. The characteristic changes seen in MRI of osteomyelitis are caused by marrow edema associated with inflammation; they include fat signal-intensity loss on T1-weighted images and high signal intensity on T2-weighted images, along with contrast (gadolinium) enhancement. Diagnostic sensitivity for osteomyelitis has generally been reported to be 90%–100% [37, 40, 41, 48]. Specificity is somewhat limited by difficulty in distinguishing osteomyelitis from other causes of marrow edema, including acute neuropathic osteoarthropathy [48]. Nevertheless, positive and negative predictive values as high as 93% and 100%, respectively, have been reported [41].

Great care must be exercised in determining the diagnostic usefulness of various imaging tests for osteomyelitis. Because each has (of necessity) been evaluated in patients selected on the grounds of clinical suspicion, it follows that the results are

heavily influenced by the pretest probability of osteomyelitis [31]. Eckman et al. [37] have used modeling techniques to argue that imaging other than plain radiography is not justified on a routine basis, but the assumptions they used in the model have been disputed [24].

Bone biopsy. Bone specimens, obtained either percutaneously or at operation, should ideally be subjected to both histological and microbiological analysis [49, 50]. The results are widely regarded to be the reference standard for identifying bone infection. Percutaneous samples are usually obtained with fluoroscopic or CT guidance, by means of a bone-biopsy needle. This procedure can often be done with little or no anesthesia (in patients with neuropathy) and is generally safe [22, 44, 45]. Unfortunately, bone biopsy procedures are expensive [24], require some experience and technical skill, and take several days to process. Furthermore, in published studies of diabetic foot infections, it is often unclear whether the diagnosis of osteomyelitis was based on histology or on microbiology and how often the results were in conflict.

Histological evidence of osteomyelitis includes bone fragmentation or necrosis with associated infiltration by leukocytes or other inflammatory cells. Gram-stained specimens may reveal microorganisms. To avoid bacterial contamination, samples should be taken aseptically through non-ulcerated skin. Biopsy of bone may yield false-negative results, either because of patchy infectious involvement or because of previous suppressive antibiotic therapy. Despite these limitations, bone biopsy remains the diagnostic criterion standard. It is, however, perhaps best reserved for cases in which other tests have proven inadequate or in which the causative organism or its antibiotic susceptibility are not readily predictable. Reaching consensus on the necessity for bone biopsy in establishing the diagnosis of bone infection will help in designing future prospective studies of the diagnosis and the management osteomyelitis.

Osteomyelitis of the digit or localized Charcot changes?

Most diabetic foot specialists are attuned to suspecting Charcot osteoarthropathy in patients with peripheral neuropathy when there is diffuse, red, and sometimes painful swelling of the mid- or hindfoot, especially when there is good arterial perfusion. However, localized Charcot involvement of the toes and forefoot may have clinical and radiological appearances similar to osteomyelitis. This could account for some cases of apparent osteomyelitis that occur with no break in the overlying skin, or in which bone fragments are observed to be discharging from an associated neuropathic ulcer. Obtaining a core of bone from affected toes is difficult; aspirates often yield just a few spicules. Although studies with direct histological comparisons have not been published, either disorder can sometimes show bone fragmentation and inflammation. Because culture results may be misleading, for the reasons discussed above, bone biopsy may need to be supplemented by MRI or radionuclide scans.

Preliminary reports suggest that conventional markers of bone turnover are of no value in differentiating osteomyelitis from Charcot arthropathy [35]. The optimal approach to this diagnostic dilemma needs to be defined.

TREATING OSTEOMYELITIS

Effectiveness of antibiotics alone, or with limited debridement. Analysis of published studies of treatment of diabetic foot osteomyelitis is difficult for several reasons. Authors have used different criteria for the diagnosis, even in the same cohort; they have often relied solely on clinical evidence supported by plain radiography. Reported results have variously included patients with “proven” and “suspected” osteomyelitis and those with osteomyelitis who did and did not have deep soft-tissue infection. Some studies have described only patients with diabetes, whereas others have included some nondiabetic patients (usually with limb ischemia). Authors have not usually specified the number of patients receiving debridement, nor its extent. The specific antibiotic agents, routes of therapy, and duration of administration have varied considerably. When patients underwent amputation, the precise indications were often not provided. The definition of outcome has been almost entirely clinical, and the length of observation of apparently disease-free patients has been variable. Finally, the majority of studies have been retrospective, uncontrolled, and undertaken in selected populations, which greatly limits their generalizability.

Notwithstanding these deficiencies, the number of reported patients managed by “conservative” (i.e., predominantly antibiotic with little or no surgical debridement) treatment now exceeds 500 (table 1), and a satisfactory response was observed in the majority [1, 2, 23, 25, 26, 36, 51–54]. This accumulated evidence suggests that it is time to revisit the traditional belief in the need for routine surgical intervention. Many experienced clinicians believe that routine excision (or amputation) of all infected bone is not necessary and that wound “debridement” and a 4- to 6-week course of antimicrobial therapy is sufficient [11]. However, the definition of “debridement” is not established. For some, it refers to the limited removal of superficial debris and necrotic soft tissue, but for others it refers to the resection of all dead—or even infected but viable—bone.

Effectiveness of surgical management. Although early and thorough surgical removal of infected bone has been long regarded as the basis for correct management [12], surprisingly little evidence supports this contention. Cure was certainly not universal in patients treated surgically in the preantibiotic era. Moreover, for >50 years, a surgical approach has almost always been combined with the use of antibiotics—albeit with varying regimens for varying durations. It follows that it is difficult to determine to what extent the antibiotics contributed to the outcome.

In this regard, 2 recent reports of the outcome following toe

amputation for infection are enlightening [55, 56]. Both involved large cohorts but were uncontrolled and retrospective reviews. Murdoch et al. [55] analyzed the outcomes for 90 patients with diabetes who underwent amputation of the hallux for a variety of reasons, including soft-tissue infection (39%) and osteomyelitis (32%). A second operation was required for 60% of patients within a mean of 10 months, and 17% proceeded to lose their limb. Similarly, Nehler et al. [56] found that in 97 episodes in which forefoot infection was managed by amputation of ≥ 1 digit, initial cure was achieved in only 38 (39%), and, of these, the infection recurred in 15 (39%). Eventual cure was achieved in only 34% of the total population. One potential explanation for these rather poor results is that patients with more severe infection were those selected for surgery. If so, a more conservative (nonsurgical) approach might have been equally ineffective. Some have suggested that prompt toe amputation represents a quick and cost-effective solution [57], but the value of this approach remains unclear.

STUDIES TO DETERMINE THE RELATIVE ROLES OF MEDICAL AND SURGICAL APPROACHES

Once consensus is reached on the criteria for diagnosing osteomyelitis, prospective trials should be undertaken to determine the relative roles of surgery and antibiotics in managing this infection. An agreed classification for diabetic foot infection would also facilitate comparison of outcomes in various centers. Studies must be randomized, controlled, and appropriately blinded. Some issues to be addressed before setting up these clinical trials follow.

Ethical concerns. Because the evidence to justify any particular approach to management is currently meager, there should be no major ethical barrier to conducting a randomized study. It is imperative, however, that patients and their caregivers be fully informed of the potential risks and benefits of both the early surgery and predominantly medical therapy arms.

Population selection. If studies are to be multicentered and if data are to be generalizable, then patient selection must be clearly defined. Factors of concern include age, race, sex, site of care (emergency ward, clinic, inpatient), and possible referral biases. It is also important to document the prevalence of vasculopathy and neuropathy.

Early surgery. The terms of reference for surgery must be established. Planned “excision” or “resection” must be distinguished from “debridement,” and the meaning of “early” must be defined. When bone is removed, dead tissue needs to be distinguished from infected but viable tissue. The training, skills, and experience of the participating surgeon(s) are crucial, and they must have a close and collegial relationship with the physician investigators.

Another confounding factor is the duration of bone infection

Table 1. Outcome of patients treated with predominantly medical therapy for osteomyelitis of the diabetic foot.

First author, reference	Year	No. of cases (n = 546)	Basis of diagnosis	Extent of local surgery	Antibiotics	Some or all iv (%)	Duration of oral ± iv therapy	Remission rate (%)	Definition of remission	Duration maintained
Bamberger [1]	1987	51	C, X, M	Not stated	Targeted	Not stated ^a	At least 10 weeks	53	Absence of signs of inflammation without the need for surgery	Until last assessment
Nix [51]	1987	24	C, X, I, P	Not stated	Ciprofloxacin ± metronidazole	None	Mean 115 days	29	Resolution of signs and symptoms	≤1 year
Peterson [23]	1989	29 ^b	C, X, I, P	Limited debridement	Ciprofloxacin	None	3 months	65	No recurrence or readmission for foot	≥1 year
Lipsky [29]	1991	20	B	Soft-tissue debridement	Targeted	65	iv ± oral 13; oral only 7	25	Wound healed, no recurrence, no need for bone resection	≥3 months (median 6.4 months)
Ha Van [52]	1996	35	C, X, P	Not stated	Broad, targeted	Not stated	Mean 246 days	57	Complete epithelialization	End of study period
Venkatesan [2]	1997	22	C, X	Limited debridement	Broad, empirical	45	Median 12 weeks	81	Absence of clinical signs ± radiographic confirmation	Median 27 months
Pittet [25]	1999	50	C, X, I, P	Occasional debridement	Broad, targeted	100	iv mean 24 days + >6 weeks oral	70	Complete healing	≥5 months
Eneroth [26]	1999	112	C, X, I, P, B, E	Incision, debridement, or bone resection	Broad, targeted ^c	95	iv median 7 days + 17/18 weeks oral	45 ^d	Intact skin for 6 months or until death (if earlier)	Unknown
Embil [36]	2000	128	No details	No details	Broad, targeted	None?	No details	80	Relapse-free	≥1 year
Senneville [53]	2001	17	C, X, I, P, B, E	Removal of necrotic bone from 2	Rifampin + ofloxacin	29	iv median 5.5 days; oral median 6 months	88	Absence of clinical signs; no relapse	Mean 22 months
Yadlapalli [54]	2002	58	C, X, I, P	All elevated; least resection possible	Broad, empirical (81%); some targeted	100	iv mean 40.3 days (range, 19–90)	79	Complete wound healing; no relapse or bone resection	≥1 year

NOTE. Different methods were used to establish the diagnosis of osteomyelitis (even within the same study): B, bone biopsy (histological or microbiological testing); C, clinical; E, erythrocyte sedimentation rate of >70 mm/h; I, imaging; M, microbiological; P, probe to bone test; X, plain radiography; ±, with or without.

^a Patients given either high-dose iv regimen or oral therapy for 10 weeks.

^b Possibly including one person without diabetes.

^c Gentamicin beads also inserted after any incision or local surgery.

^d Referring only to those who had no local surgery.

prior to inclusion in the study, because of either a delay in first referral or in confirmation of the diagnosis. Planned surgery may also be delayed in some centers because of a lack of available facilities. If surgery is delayed for any of these reasons, the protocol must address the use of preoperative antibiotics.

Antibiotic choice. Protocols would need to define the dosage, route of administration, and duration of antibiotic therapy. There are few data available on which to base these decisions, but in an era of highly bioavailable oral agents, there is little to support the recommendation to use intravenous drugs to initiate treatment [24, 58]. Most agree that if surgery is withheld, antibiotics should be continued for 4–6 weeks or more [11, 24]. Regimens must take into consideration issues such as drug costs and toxicities, allergy to antibiotics, and the prevalence of antibiotic-resistant pathogens. Study protocols would need to address delivering antimicrobials by other routes, such as topical agents or antibiotic-impregnated materials [59].

When culture and susceptibility results are available, the initial empirical antibiotic regimen should be reviewed and possibly adjusted. The patient's clinical response, as well as microbiological data, must be considered. This approach depends on the assumption that sampling is done appropriately and that cultures identify all (and only) pathogens [60].

Outcomes. Outcome measures for studies must be clinically relevant and patient centered. Amputation of the limb may result in speedy elimination of infected bone, but the price paid for this major mutilation has implications for lifestyle, mobility, and self esteem. On the other hand, foot ulcers and infections are associated with a poor quality of life and bad overall prognosis [61]. Measures of patient satisfaction, function, and freedom from recurrence, including for those whose life expectancy is limited, are therefore important parameters for any study.

Criteria must also be established for determining when bone infection has been eradicated. This determination is usually based not on microbiological studies but on clinical parameters. These may be unreliable in the neuropathic or ischemic foot, because either may affect local pain and hyperemia. Relapse may follow both surgical and nonsurgical treatment. Leukocyte and immunoglobulin scans have been shown to revert to a negative result following successful treatment [28, 46], and preliminary data suggest that scanning with ¹³¹I-labeled recombinant interleukin-8 may provide an indicator of cure [45].

COMBINED APPROACH

Some evidence suggests that the most effective approach to osteomyelitis might be a judicious combination of appropriate antibiotics and early surgery. Ha Van et al. [52] reported that local excision increased the cure rate from 57% to 78%, compared with historical controls. Similar results have been reported by Tan et al. [62] and in an unpublished Italian study

[63]. Use of MRI may improve outcome by better defining the extent of both soft tissue and bone involvement [64]. In patients with critical limb ischemia, clinicians must also consider early revascularization [3].

CONCLUSIONS

The pathophysiology of osteomyelitis in the diabetic foot creates difficulties in establishing the diagnosis and uncertainty about the optimal approach to treatment. Experts have traditionally recommended routine surgical extirpation of bone affected by this chronic infection. Available evidence suggests that a nonsurgical approach to management of osteomyelitis may be effective for many, if not most, patients with osteomyelitis of the diabetic foot. The benefits and limitations of both approaches need to be established so that appropriate therapy can be tailored to each patient's needs. This can be accomplished only with properly controlled and randomized studies. The first requirement, however, is to achieve consensus on how to diagnose osteomyelitis in clinical practice. Patients and their caregivers must also be provided information concerning different treatments and should be encouraged to be actively involved in selecting the management option.

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