Osteomyelitis in the diabetic foot: what lies beneath

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Summary

Osteomyelitis is an important cause of delayed healing of foot ulcers in diabetics, increasing the risk of amputation. There is limited evidence on which to base decisions regarding the role of surgical versus conservative treatment, the optimal duration of antibiotic therapy and the most effective agent. However, it is clear that early diagnosis provides the best chance of successful conservative treatment. This opportunity is frequently missed because patients with neuropathy do not seek treatment promptly and clinicians sometimes fail to recognise the signs of infection, which may be subtle in patients with diabetes. Even in severe, limb threatening infections, patients with diabetes can have little or no systemic symptoms. Thorough clinical evaluation of the patient and their wound is the first step to improving the detection of infection and osteomyelitis. This should be followed by baseline and follow-up X-rays for wounds that are large, deep, longstanding or recurrent. Investigation with nuclear scans or magnetic resonance imaging is useful when radiological signs are inconclusive. When conservative treatment is implemented too late or fails to result in resolution, timely amputation of a toe or distal aspect of the foot may reduce morbidity and preserve function. Determining the stage at which surgery or amputation is indicated is a challenging but important clinical decision based on the location and severity of the osteomyelitis, peripheral arterial disease and preference of the patient.

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Introduction

Most health professionals and patients with diabetes are aware that diabetes increases the risk of amputation. The majority of these amputations are preceeded by foot ulcers that become infected [1,2], thus a window of opportunity exists during which prompt management of infection can greatly alter the outcome. Failure to detect local wound infection in patients whose defenses are impaired by diabetes means that infection can deteriorate rapidly leading to involvement of deeper structures including bone. These deep infections are less likely to respond to conservative treatment alone, thus increasing the risk of amputation [3]. For these reasons, the early recognition of soft tissue infection is a critical step in preventing osteomyelitis and amputations. The aim of this article is to outline the clinical features of infection and osteomyelitis in patients with diabetes and to discuss the management of osteomyelitis based on the literature and experiences of our multidisciplinary diabetic foot clinic.

In the diabetic foot, osteomyelitis occurs via contiguous spread from an adjacent infected wound in 94% of cases [4]. These ulcers are typically present over bony prominences or as a result of deep penetration injury and the progression to osteomyelitis can be rapid. People with diabetes are more susceptible to infection than the non-diabetic [5], particularly when diabetes is poorly controlled, as hyperglycaemia impairs the immune response to infection. Despite this, the diagnosis of infection

is often delayed or the extent of infection underestimated [6] providing the opportunity for infection to progress to bone in a high proportion of foot ulcers in diabetics. The first barrier to prompt detection of infection is neuropathy. Peripheral neuropathy is the predominant risk factor for foot ulceration in people with diabetes, hence most ulcers are neuropathic in origin. As these ulcers are characteristically painless, patients rarely understand the serious implications of their wound (Figure 1). As a consequence, they present late and may be uncertain as to the true duration of their wound. Even when patients decide to seek treatment the referral pathway is not always straightforward. The management of diabetic foot disease does not fall under any one specialty, thus presenting a problem when patients consult a series of health professionals, losing valuable time before appropriate treatment is commenced. While specialised multidisciplinary clinics providing access to the various medical and surgical specialties, nursing and podiatric care in a single clinic are ideal for the management of diabetic foot disease, these services are not available in many areas.

Detecting infection requires careful clinical assessment and is not greatly reliant on tests [6,7]. The key is to look carefully for signs of inflammation such as redness, swelling and warmth. Inflammation in association with a wound indicates that the microorganisms within the wound are multiplying and

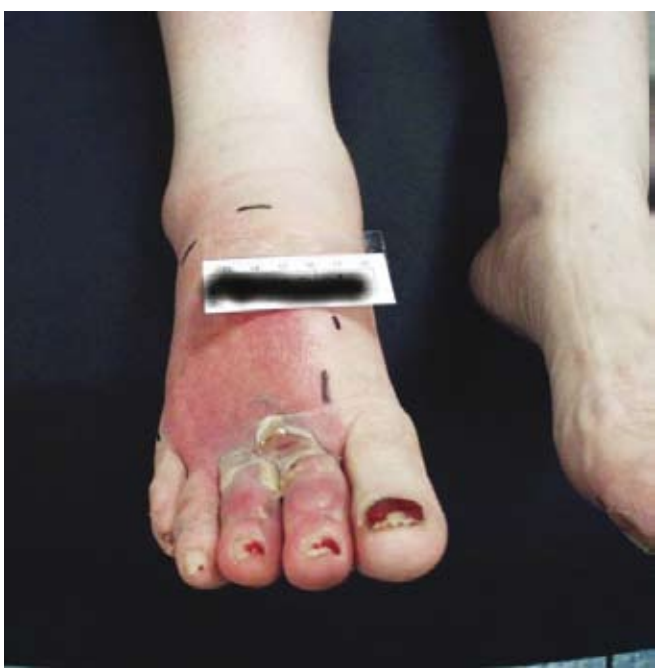

Figure 1. Initial presentation of 31-year-old woman with Type 1 diabetes who trod on glass three weeks prior. Note the acute cellulitis and enlargement of the 2nd and 3rd toes. She was systemically unwell but had not sought treatment until the day of this photo.

of sufficient number and virulence to result in the immune response of the host. The International Consensus Working Group on Diagnosing and Treating the Infected Diabetic Foot (IWGIDF) provides us with the following definition of infection: "In the absence of systemic signs (such as fever), the presence of two or more of the following clinical signs constitutes infection: redness, warmth, induration, pain, tenderness. They also indicate that necrosis, fetid odour, or failure of a properly treated wound to heal are features 'suggestive' of infection" [7]. These signs can be present locally, around the wound but it is equally important to examine the rest of the foot and leg for any generalised swelling or redness.

In our experience, swelling is a key indicator of infection. Owing to the multiple causes of foot swelling (for example, renal disease, cardiac disease or musculoskeletal pathology) this may be seen by some as an unreliable sign. However, swelling from infection is somewhat different in its presentation. It occurs adjacent to the wound site and may be observed to follow the compartments of the foot or extend up the leg in more severe cases. If patients are able to relate the history, it is learned that the swelling develops relatively quickly over a period of days (or more rapidly), is unilateral and fails to resolve with rest. We also rely on the presence of warmth, using our hands or more objectively, a digital scanner to measure skin temperature. By comparing the affected site with the corresponding area on the unaffected foot, we can record the difference attributed to infection. With the exception of patients who have markedly different vascular supply between limbs or those with concomitant disease of the contralateral foot such as Charcot's arthropathy, measuring temperature difference is very useful in diagnosing infection and monitoring response to treatment.

A failure to recognise these signs of infection, particularly in chronic foot ulcers, may be partly explained by an absence of pain, dampening of the inflammatory response in those with arterial disease and impaired leukocyte function in people with diabetes [8]. Even in severe infections, these patients can present as systemically well [9], or have only vague flu-like symptoms. The effect is suboptimal management of infection [6], setting the stage for osteomyelitis

Osteomyelitis

The IWGIDF defines osteomyelitis as infection involving the bone marrow, while the term osteitis is applied to infection of the cortical bone only [10]. However, in the literature, many authors continue to make the diagnosis radiologically [11,12]

on the basis of erosion of cortical bone and the presence of sequestra that are loose fragments of infected bone. However, plain X-ray may not be specific enough to differentiate between osteitis and osteomyelitis.

The prevalence of osteomyelitis varies between patient populations and with the diagnostic criteria used. In our outpatient diabetic foot clinic, 18% of patients treated had radiological evidence of osteomyelitis. On the other hand, another study indicates a 68% prevalence of osteomyelitis, confirmed with bone biopsy and culture in a cohort of diabetic patients admitted to hospital with severe foot infections [13].

Diagnosing osteomyelitis

Clinical features

As with soft tissue infection, detecting osteomyelitis requires a high level of clinical suspicion as the classic inflammatory signs of infection can be more subtle in diabetes, particularly in ischaemic feet [9]. Nevertheless, there are some clinical features that suggest osteomyelitis. A wound that deteriorates or in which healing is delayed despite adequate wound care and reasonable blood flow, should be investigated for osteomyelitis. Similarly, wounds that are deep, probe to bone [14], >2cm [13], recurrent or associated with peripheral arterial disease, are more likely to be complicated by osteomyelitis.

Due to the high probability of osteomyelitis in deep wounds, assessment should include gently probing the base using a sterile blunt metal probe. This will identify any deep sinus and if bone is present this will be readily appreciated as a hard surface within the tissue. In one study, the probe to bone test demonstrated a predictive value of 89%, with sensitivity 66% and specificity 85% [14]. This predictive value may overestimate the power of the test as it was performed on patients with severe wounds and a strong likelihood of osteomyelitis. Nevertheless, we view the 'probe to bone' test as a key component of wound assessment that should be performed routinely to screen for osteomyelitis. In our clinic, a presumptive diagnosis is made in most cases where bone is probed and treatment is commenced while awaiting the results of more accurate tests. We believe this is the safest approach given the speed with which infections can deteriorate in these patients.

Ulcers on the toes extend to bone very quickly owing to the lack of soft tissue. Toes with osteomyelitis typically develop a 'sausage-like' appearance with diffuse redness and cylindrical swelling extending the whole length of the toe (Figure 2). In their case series of 14 patients, Rajbhandari et al also describe

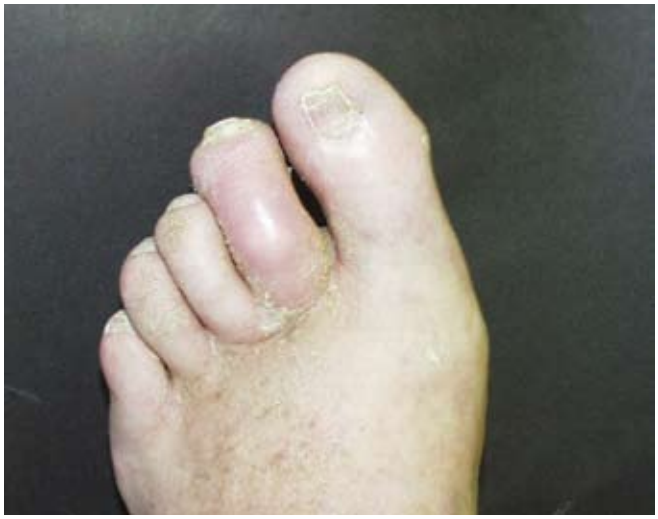

Figure 2. A 'sausage toe'.

this typical appearance. All infections were associated with a neuropathic ulcer on the affected toe or adjacent metatarsal that had been present for a mean of 7 weeks (1-38 weeks) [15]. Plain radiographs confirmed the presence of bone erosions consistent with osteomyelitis in 12 patients and 7/8 patients who underwent bone scanning also had increased uptake consistent with bone infection [15].

Investigations

When osteomyelitis is clinically suspected, a plain X-ray may be all that is needed to confirm the diagnosis [16,17]. When ordering X-rays, it is prudent to request more than one view and to specify the location of suspected osteomyelitis on the request form. The latter minimises the frustration caused when the X-ray beam is not appropriately aimed at the area in question, making it difficult to visualise minor changes. Interruptions of the cortex of the bone or periosteal reactions are seen in the milder forms, while bone destruction is seen in more advanced cases. A 'normal' X-ray does not rule out osteomyelitis as bone changes may not be seen during the early stage. A follow-up X-ray two to four weeks later may subsequently show progressive changes of osteomyelitis [9,18]. For wounds in which healing is delayed or when the wound is deep, it is important to repeat X-rays every six weeks or when clinically indicated as a means of monitoring for osteomyelitis. Despite its limitations, X-ray is a very useful method for the diagnosis of osteomyelitis when used together with clinical assessment.

Additional imaging studies may be needed if X-ray findings are equivocal despite a high clinical suspicion. During the early phase, radionuclide studies such as bone scan and white cell scan are more sensitive than X-rays but are not

specific [19,20]. The suspected area of osteomyelitis will show an increase in radioisotope uptake, but many other bone pathologies will show the same findings (fracture, arthritis, malignancy, contiguous infection) [18]. Therefore, these tests have been overtaken by magnetic resonance imaging (MRI) scans. MRI has been shown to have the highest sensitivity and specificity (>90%) for diagnosing osteomyelitis [21] and is becoming increasingly accessible. The underlying pathology of bone marrow oedema and inflammation in osteomyelitis gives rise to characteristic MRI features. The osteomyelitic bone will have low signal (dark) in T1-weighted images and high signal (bright) in fat-suppressed T2-weighted images. Following gadolinium contrast administration, high signal (bright) will be noted in fat-suppressed T1-weighted images. Unfortunately, Charcot's osteoarthropathy, a differential diagnosis that often needs to be excluded in diagnosing osteomyelitis, affects the bone marrow signal intensity in the same way, giving rise to the same MRI findings. However, in experienced centres the two entities can generally be distinguished by assessment of the location and pattern of the signal abnormality and the associated findings in adjacent bones and joints [22-24].

Bone biopsy for culture and histology provides the only definitive proof for the diagnosis of osteomyelitis [25]. Unfortunately, appropriate procedures have to be followed, experience and technical skill are required, and false negative results may be obtained. Because of this bone biopsy is not always practical and so is not commonly used [10,11,13,26,27].

White cell counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are three markers often used as aids in diagnosis or assessment of severity of infection [9]. However, in diabetic patients they are neither sensitive nor specific, even in cases of severe infection or osteomyelitis [28,29].

Treatment of osteomyelitis

The control of soft tissue infection is the first priority in preventing osteomyelitis and amputation. Systemic (generally oral) antibiotics need to be commenced without delay. Debridement is almost always indicated. Deep collections of pus evidenced by fluctuant swelling require surgical drainage and deep infections that rapidly result in necrosis of underling tissue, will also need surgical debridement. For wounds with localised infection, sharp debridement aids healing by removing necrotic tissue and callus. Preferably, this should be performed in the setting of multidisciplinary wound care or a diabetic foot clinic by an appropriately skilled podiatrist. When the vascular supply is inadequate, such as when pulses are impalpable or studies demonstrate inadequate blood flow for healing, intervention from the vascular specialist should be sought urgently before debridement. In cases of inadequate blood supply, debridement may be contraindicated.

Surgical resection of infected bone is traditionally considered the only definitive treatment of osteomyelitis. However, in our experience, conservative treatment with systemic antibiotics can be curative if started early. There is some research supporting this conservative approach [30,31], but there is a paucity of evidence to guide antibiotic choice and the duration of treatment required for osteomyelitis [7]. As the initial choice of antibiotic is empiric, agent(s) that target the most likely pathogen, *Staphylococcus aureus* [4], are used to prevent unnecessary delays in treatment [32]. Other commonly found pathogens are *Staphylococcus epidermidis*, streptococci, and Enterobacteriacea [25]. Bone biopsy is the only definitive method for identifying the infective organism(s), as concordance between wound cultures and bone biopsy is poor [7,13,32]. When bone culture results are available, this may direct a change in antibiotic but in most cases, clinical response to treatment provides the most valuable guide to the appropriateness of the agent selected. A clinical response to antibiotics should be evident within 48-72 hours. Therefore, a change in antibiotic or dose is indicated if there is no improvement in redness, swelling or warmth.

Lipsky suggests a minimum of four weeks of intravenous antibiotics, at least initially for osteomyelitis, with a shorter course of systemic antibiotics when infected bone is resected [7]. In practice, due to shortage of inpatient facilities, this is often not possible in Australia. There is evidence that because of the high bioavailability of some drugs, conservative treatment using prolonged oral antibiotics is successful in selected patients and this is described by the IWGIDF [4,7,26]. In our clinic, cases of mild osteomyelitis are treated high dose oral antibiotics for two to three months. Clindamycin and dicloxacillin alone or in combination are commonly used agents, as they have good bone penetration and high bioavailability [7]. Fluoroquinolones (eg ciprofloxacin) may also be employed but their use is limited by the development of resistance and in Australia by government regulation. For chronic infections clindamycin can be given in doses of 150 mg or 300 mg qid and is generally well tolerated. Patients are warned to report severe diarrhoea (watery diarrhoea >4 per day) as there is some risk of pseudomembranous colitis, a serious side effect of that requires cessation of the drug. Dicloxacillin is given in doses of 500 mg to 1000 mg qid. Rifampicin together with fucidic acid is useful

when Methicillin-resistant *Staphylococcus aureus* (MRSA) is known or suspected, or if the patient is allergic to penicillin. Intolerance (such as severe nausea or vomiting), allergy, or severe renal impairment can all restrict antibiotic choice. In some cases antibiotic treatment is ceased for such reasons, necessitating a surgical approach.

Treatment of osteomyelitis will benefit from close involvement of orthopaedic and vascular surgeons with expertise in diabetic foot disease. This enables the patient to be presented with timely conservative (if possible) and surgical options as required. A prognosis can be given and a timeline for the expected duration of oral therapy can be explained to the patient. When patients with osteomyelitis have severe peripheral arterial disease, the surgical opinion is sought from our vascular surgeons. They will optimise blood flow using surgical or endovascular procedures when possible and perform any necessary surgery, including amputation to the level where healing can be expected.

When conservative treatment is attempted but fails to result in clinical and or radiological improvement after two months of appropriate treatment, continued conservative treatment is unlikely to result in cure. Determining which patients will respond to conservative treatment alone and those who will require surgery presents a clinical challenge with few studies on which to base the decision. The following factors will influence the decision:

Severity of infection and extent of bone destruction

An early diagnosis of osteomyelitis based on the presence of small area(s) of erosion on X-ray provides an opportunity for successful treatment with oral antibiotics (Figure 3). Radiographic evidence of extensive erosion and bone loss with large, loose fragments (sequestra) carries a less positive prognosis (Figure 4). Systemic antibiotics may not be able to penetrate bone that has become necrotic and in these cases some surgical resection of bone is most likely needed, followed by a short course of culture directed systemic antibiotics. Overtly destroyed bone generally requires surgery to remove all infected tissue. Of key importance for any surgery involving the diabetic foot is consideration as to the biomechanics of the foot post-surgically. For example, leaving behind bony prominences or taking most but not all of the metatarsals means that pressure can be localised on these sites when the patient resumes walking. This sometimes requires amputating more than the infected bone. For example, when more than one metatarsal is affected, performing a transmetatarsal amputation may provide a more viable

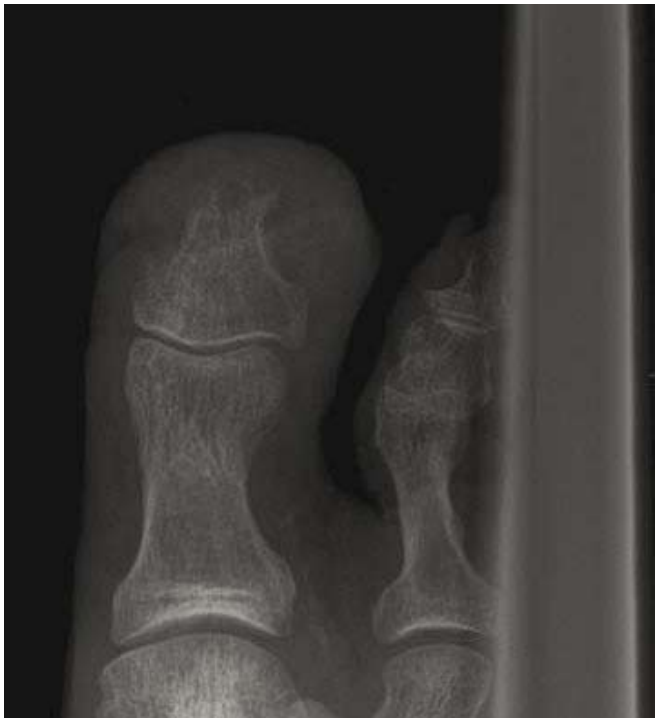

Figure 3. Erosion of tip of the distal phalanx of the hallux.

weightbearing surface, thus providing a better chance of avoiding future ulceration and amputation. Pressure areas must always be addressed with orthoses and footwear aimed at redistributing plantar pressure to lessen the risk of ulceration elsewhere on the foot.

Anatomic site of infection

Long bones of the metatarsal or toes are not only more amenable to treatment with systemic antibiotics, but their removal surgically has less impact on the function of the foot. However, amputation of the great toe has a very different long-term prognosis compared to loss of a lesser toe. Hallux amputation is associated with more subsequent foot deformity and increased risk of further amputation [33,34]. Timing of surgery to avoid spread of infection is again important, as removing only the distal portion of the toe has a less detrimental effect on forefoot alignment and function than removal of the base of the toe.

The potential for transfer of pressure to an adjacent toe or metatarsal following amputation needs to be assessed and preventive measures, such as appropriate insoles, orthodigital devices and footwear, are often needed to protect these vulnerable areas from breakdown following surgery.

Osteomyelitis affecting the tarsal bones is more difficult to detect. This is because visualisation using radiographs can be unclear due to superimposition of bone and there may

be co-existing neuropathic joint disease that has a similar radiographic presentation. Tarsal bones cannot readily be resected to remove osteomyelitic bone and proximal amputation (even below-knee amputation) may be needed to preserve function. Calcaneal osteomyelitis has a high likelihood of below-knee amputation.

The effect of surgically removing part of the foot must also be balanced against the impact of long-term antibiotic therapy that exposes patients to side effects, may be poorly tolerated and has the potential for encouraging resistant strains of bacteria. A lesser toe is more expendible in terms of the long-term prognosis of the foot than amputation of a hallux. However, not all patients accept this view and will vehemently pursue treatment if it can save any toe.

The goal of healing should not outweigh the overall aim to preserve patient quality of life. While research in the area of quality of life for people with diabetic foot disease is lacking, some findings suggest that people with amputations have better quality of life than those with foot ulcers [35]. We have found the best approach is not to avoid the option of amputation as a treatment, particularly when this involves minimal removal of bone. Speaking with another patient who has undergone an amputation can be reassuring to people who are making a decision about their own surgery.

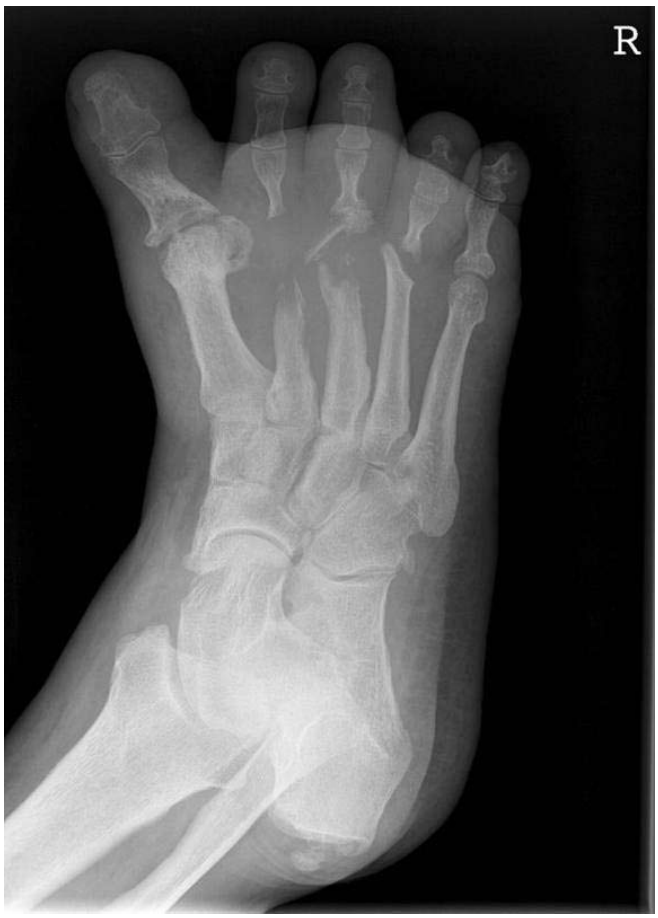

Figure 4. Advanced osteomyelitis with significant loss of bone.

Presence of peripheral arterial disease (PAD)

Sufficient blood flow must be present for the systemic antibiotic to reach the bone in adequate concentration as to be beneficial. There are little data to accurately determine the stage at which PAD interferes with antibiotic effect, but patients with impalpable or reduced pulses or those with an ankle brachial index of <0.8 should be reviewed by a vascular surgeon to determine the options for revascularisation. When blood flow is inadequate and cannot be improved, surgery to remove infected bone to the level of tissue viability may be indicated if curing osteomyelitis is the goal of treatment. Unfortunately, the level of amputation may need to be significantly higher than the level of the infection in order to have sufficient perfusion to heal the amputation site.

Patients with arterial disease often represent a poor surgical risk owing to their co-morbidities. Living with a chronic wound may better serve patient interests in these cases. Instead of curing the osteomyelitis, the goal becomes prevention of amputation through 'control' of infection. Control in this instance is defined as containing the infection to the local area while preventing spread to adjacent areas.

There is some question as to the definitive method for determining when osteomyelitis has been cured. We use follow-up X-rays to assess the radiological signs of resolution and these results are correlated with the clinical presentation of the foot. Relapse of osteomyelitis can occur so patients need to be reminded to inspect their feet regularly and report any signs that could indicate recurrence of infection. White cell scans can also be useful to determine when infection has resolved as they are specific for infection [9]. In this instance, correlation with a bone scan is not necessary.

Conclusion

Early diagnosis of soft tissue infection is of great importance in the prevention of diabetes related amputation and requires careful assessment of the clinical signs of swelling, redness and warmth. The likelihood of osteomyelitis is high when the diagnosis of infection is delayed or when the extent of infection is underestimated. Once infection has progressed to involve bone, prompt detection of osteomyelitis provides the best chance of successful conservative treatment. Detecting osteomyelitis requires a high level of clinical suspicion for wounds that are deep, large, longstanding, recurrent or

associated with PAD. The clinical features of bone within the wound or a 'sausage toe' are indicative of osteomyelitis. To confirm the diagnosis, various imaging procedures are available. However, plain radiographs, which are readily available and relatively inexpensive, will often suffice.

In approaching treatment, the relative merits of surgical and medical treatment should be considered together with the patient related factors such as the severity and location of the wound, the presence of PAD and the patient ability to tolerate antibiotics. Surgery is often indicated and we should not assume that amputation is the worse case scenario in terms of patient quality of life, particularly if the timing of surgery results in distal limb-saving amputation.

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