The treatment of diabetic foot infections

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Successful treatment of infection in the feet of patients with diabetes mellitus remains a challenge. Although the diagnosis of infection remains a clinical decision, presentation in feet rendered insensate from diabetic neuropathy plus co-existing vascular insufficiency means presentation is often atypical. Wounds frequently yield polymicrobial growth and differentiating commensal from pathogenic organisms can be difficult; isolates from diabetic foot wounds are often multidrug resistant. Affected patients often have many other co-morbidities, which not only affect the choice of appropriate antimicrobial regimen but also impede healing. Further, much contention surrounds the management of osteomyelitis, with the merits and role of surgery still undecided. In this review we briefly consider the epidemiology and pathogenesis of diabetic foot disease, before discussing emerging best microbiological practice and how this fits with the multidisciplinary approach required to tackle this difficult clinical problem.

Keywords: diabetes, microbiology, osteomyelitis

Diabetic foot disease: a costly problem

Diabetes mellitus (DM) is a complex metabolic disorder with an ever-increasing prevalence. An estimated 2.6 million people are thought to have DM in the UK at present, with this likely to reach close to 4 million by 2025. Among the many complications associated with diabetes, issues related to foot disease represent a significant and often challenging clinical problem. The proportion of patients with DM who develop foot infections is ~2% per year in the UK, with the annual prevalence of such infections in this population reaching 5%. Patients with diabetic foot disease are over-represented in hospital inpatient populations and, despite often prolonged and repeated admission, many come to amputation. Indeed, diabetes is the most common cause of non-traumatic limb amputation, with a foot ulcer being an antecedent event in the majority of cases.

Pathogenesis of diabetic foot disease

The development of a foot ulcer invariably involves the convergence of several pathological mechanisms. Diabetic peripheral sensorimotor neuropathy is a key factor in the majority of cases. As a result of damage to sensory nerves, minor trauma (from something as seemingly trivial as an ill-fitting pair of shoes or walking barefoot on unfamiliar terrain) can go unnoticed. Neuropathy can also deform the architecture of the foot to such a degree that joints and digits are placed in mechanically unfavourable positions, making them highly vulnerable to injury.

Once the skin has been breached, continued mobilization on a broken area impairs the healing process. Inevitably, direct contiguous spread of microbes on the skin follows on, with colonization and infection of superficial and then deeper tissues likely if the process is allowed to proceed unchecked. Both the healing process and the response to infection are further compromised by vascular insufficiency, which is commonly present in patients burdened with complications of diabetes. Each pathological driver—inappropriate weight-bearing due to neuropathy, ischaemia and infection—needs tackling for resolution of the ulcer but the major focus of this review will be the infection burden.

Presentation and diagnosis of infection in the diabetic foot

Clinical diagnosis

One major problem facing the management and study of diabetic foot disease is that there is no unifying standard that defines infection. Classic features such as purulence, erythema, pain, swelling and systemic upset can all be present but none is pathognomonic of infection. Indeed, as a result of peripheral neuropathy, limb-threatening lesions can present entirely without pain and the concomitant ischaemia present in many limbs also means that the florid inflammatory response typically seen in a severe soft tissue infection may be greatly muted.

Despite these challenges, a variety of scoring systems for foot lesions have been used in the literature. For example, the Wagner score classifies a wound from grade 0 (pre- or post-ulcerative lesion) through a range of increasing depth and severity to grade 5 (whole-foot gangrene). It does not, however, distinguish aetiology. The University of Texas system also uses a stepwise progression in grading (0–3) depending...
upon depth of wound and, additionally, takes account of the presence of infection and/or ischaemia. In neither classification, however, is there the ability to record infective burden. The classification developed by the Infectious Diseases Society of America (IDSA) is a simple, validated system that ranks infected wounds as mild, moderate or severe (Table 1) and appears to be a reliable and useful tool for predicting relevant clinical outcomes, such as the need to be admitted to hospital and amputation. It is noteworthy that the ‘severe’ category—that associated with the highest percentage rate of amputation—is reliant upon assessing systemic clinical (blood pressure, pulse, temperature) and laboratory (acidosis, glucose levels, white cell count) parameters, indicating that an assessment of the patient as a whole is as critical as examination of the wound.

**Microbiological diagnosis**

Once a clinical diagnosis of infection has been made, the next challenge is to determine the aetiology so that rational and appropriate therapy can be instigated. Important clues as to potential pathogens can be garnered from the clinical history. Infection in a very recently acquired superficial ulcer is likely to be due to aerobic Gram-positive cocci (for example staphylococci) while a long duration of ulceration, increased depth/severity and antecedent therapy are likely to increase the chances of the wound yielding both polymicrobial growth (often comprising aerobic and anaerobic Gram-positive and Gram-negative bacteria) and resistant organisms (Figure 1). Because the skin has an indigenous microbial flora, great care must be taken not only in obtaining a sample for microbiological analysis but also in interpreting the result. Invariably, a positive laboratory culture can only suggest the presence of infection and must be correlated with clinical findings. A simple superficial swab across the ulcer runs the great risk of isolating commensal organisms unrelated to the infection, leading to misdirected treatment against an innocent bystander rather than focusing on the pathogenic culprit. When used, swabs should always be taken from the base of a lesion after debridement of superficial slough and necrosis. Ideally, biopsy of tissue from a debrided ulcer base or, if applicable, extruded bony fragments, offers more useful material for microbiological analysis.

Even when such best practice is observed, there remains a degree of subjectivity in analysis. Preliminary data employing the wound infection (modified from reference 11) classification developed by the Infectious Diseases Society of America (IDSA) is a simple, validated system that ranks infected wounds as mild, moderate or severe (Table 1) and appears to be a reliable and useful tool for predicting relevant clinical outcomes, such as the need to be admitted to hospital and amputation. It is noteworthy that the ‘severe’ category—that associated with the highest percentage rate of amputation—is reliant upon assessing systemic clinical (blood pressure, pulse, temperature) and laboratory (acidosis, glucose levels, white cell count) parameters, indicating that an assessment of the patient as a whole is as critical as examination of the wound.

**Response to the laboratory result**

There are no data to validate the treatment of culture-positive wounds when the clinical appearance is not one of infection. Indeed, responding solely to laboratory findings without reference to the clinical scenario puts patients at unnecessary risk of antibiotic-associated side effects and is likely to increase the prevalence of drug-resistant organisms. Current best practice advocates immediate treatment in the face of clinical infection, with initial therapy directed against the ‘most likely’ pathogens, aiming for revision of this empirical choice on the basis of culture results and clinical progress. Thus Gram-positive cocci are invariably involved in mild and moderate infection and should respond to antistaphylococcal therapies such as semi-synthetic penicillins (e.g. flucloxacillin), while recent antecedent therapy increases the likelihood of Gram-negative bacilli (GNB) also being involved, necessitating the addition of β-lactam/β-lactamase inhibitor combinations or fluoroquinolones.

Oral agents are adequate for mild and moderate infections. However, severe infections invariably require intravenous therapy covering Gram-positive cocci [with a low threshold to use a glycopeptide to cover the possibility of infection with methicillin-resistant *S. aureus* (MRSA)], GNB and anaerobes. Moreover, it is our view that a severe infection with clinical evidence of systemic involvement, such as spiking temperature or

**Table 1.** IDSA classification of wound infection (modified from reference 11)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td>More than two of:</td>
<td>Patient is systemically well and metabolically stable but has any of:</td>
<td>Infection in a patient with systemic toxicity or metabolic instability</td>
</tr>
<tr>
<td>• Purulence, erythema, pain, tenderness, warmth or induration</td>
<td>• Cellulitis extending &gt;2 cm</td>
<td></td>
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<tr>
<td>• Any cellulitis/erythema extending ≤2 cm around ulcer</td>
<td>• Lymphangitis</td>
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<tr>
<td>• Infection is limited to skin/superficial subcutaneous tissues</td>
<td>• Spread beneath fascia</td>
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<tr>
<td>• No local complications or systemic illness</td>
<td>• Deep tissue abscesses</td>
<td></td>
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<tr>
<td></td>
<td>• Gangrene</td>
<td></td>
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<tr>
<td></td>
<td>• Muscle, tendon, joint or bone involved</td>
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rigors, should trigger evaluation by an experienced surgeon. A collection within the foot may be best served by surgical intervention to limit further spread and tissue loss, reduce the septic burden on the patient and allow collection of appropriate material for microbiological investigation, which should optimize the likelihood of pathogen detection and initiation of correctly targeted treatment at the earliest possible juncture.

Drug-resistant organisms and diabetic foot infections

Drug-resistant organisms are over-represented in samples obtained from diabetic foot ulcers. A study from a secondary care multidisciplinary diabetic foot clinic in Melbourne, Australia is typical of many such units, in that patients attending had a high prevalence of MRSA. Of 653 specimens from 379 patients, MRSA was isolated from 23%. Chronicity of ulcer, previous in-patient care and chronic kidney disease (CKD) each independently predisposed patients to MRSA infection.

But does isolation of a drug-resistant organism matter? A French study in 2008 looked to determine the impact of multidrug-resistant (MDR) organisms on healing rates 1 year after discharge in 188 patients admitted for an infected foot ulcer. Organisms identified included MRSA, Enterobacteriaceae resistant to third-generation cephalosporins, Pseudomonas aeruginosa resistant to two antibiotics from among ticarcillin, ciprofloxacin, ceftazidime and imipenem, and Enterococcus spp. resistant to glycopeptides. The complexity of the ulcers in the study can be judged by the fact that two-thirds were graded as moderate or severe, >70% were judged to be neuroischaemic ulcers and around a quarter of the lesions yielded resistant organisms. The presence of MDR organisms was associated with a higher incidence of lower-limb amputation (35.6% versus 11.2% in non-MDR infection), with the majority (87.5%) of these amputations being minor. After adjustment for other factors, however, multivariate analysis indicated that the presence of MDR bacteria did not affect healing time. This is in keeping with a similar study directed by investigators in Nottingham UK, where Game et al. found no evidence that the presence of MRSA was associated with a significant difference in healing time or percentage of healed wounds. In the case of the French study, this may be a direct consequence of prescribing practice in the unit in question being vigilant to the high prevalence of MDR organisms seen locally, with the first-line antibiotic regimen frequently including an agent active against MRSA given immediately after obtaining specimens for culture, to be reassessed thereafter according to the microbiological results.

Guidelines for therapy

One of the major difficulties in developing guidelines for therapy is the lack of randomized controlled trial evidence to support them. The lack of a standardized objective definition of infection and its subsequent eradication, the heterogeneous influences from variation in vascular supply, position and duration of ulceration, the variability in strategies to prevent weight bearing through the affected tissue and the diverse multiple co-morbidities invariably found in patients with diabetic foot disease are just some of the many factors that conspire to make study design challenging. Industry is also unlikely to offer financial support to evaluate the comparative efficacy of generic antibiotic agents long-since off patent. In addition, any guidelines relating to the use of antimicrobial therapy must factor-in local susceptibility and resistance data. Thus, in the face of an increasing clinical problem, there remains unsatisfactory uncertainty about the optimal route and effective duration of antimicrobial treatment. At present, the situation is one of consensus agreement from multidisciplinary panels of experts assimilating other published guidelines and the limited available support from published studies, rather than guidance backed by rigorous trial data. One such example is that of the Scottish working group who contend that local differences across the
country in causative organisms and their susceptibility to specific agents are insignificant enough to make such a document valid in most instances. This approach has much merit, emphasizing as it does the importance of a multidisciplinary approach to management, the categorization of infection on clinical grounds and the acknowledgement that, although culture-supported specific targeted therapy is the gold standard, there must be a role for initial empirical treatment.

Osteomyelitis

The significance of diagnosing osteomyelitis in diabetic foot infections is clear; it increases refractoriness to antibiotic treatment and is associated with an elevated risk that lower-limb amputation, either minor or major, will subsequently be required.20,21 The correct determination of the presence or absence of osteomyelitis therefore carries high clinical importance. In theory, the diagnosis should be an easy one to make since, put simply, osteomyelitis is infection of bone. In practice, however, it remains a challenging condition. The gold standard for diagnosis is the culture of pathogenic organisms from an isolated bone culture in the presence of characteristic histological changes suggesting necrosis, inflammation and reparative processes. However, such biopsies are infrequently taken and are not infallible: false negatives can result from poor sampling or samples being taken after antibiotic therapy; false-positive microbiology can be introduced by contamination and other inflammatory conditions can mimic the histological findings. A diagnosis is more usually made on clinical suspicion (refractory infections, bone visible or palpable on probing the ulcer, failure to respond to antibiotics) in conjunction with one or more imaging modalities.

Plain radiographs are readily available in most centres and represent the first imaging step if osteomyelitis is suspected. The films, ideally weight-bearing and in two projections, may demonstrate the discrete areas of radiolucency, cortical destruction and loss of trabecular patterning found in early osteomyelitis. Periosteal reaction, sclerosis and osteogenesis may follow (Figure 1). However, radiographic features only typically start to appear after at least 2 weeks and can be mimicked by other processes such as Charcot neuroarthropathy or trauma.10 If the plain radiograph findings are equivocal, magnetic resonance imaging (MRI) should be considered as it is the most sensitive and specific imaging modality in diabetic foot infections for diagnosing and assessing the extent of both bone and soft tissue involvement. Osteomyelitis is seen as areas of decreased signal on T1 imaging/high signal on T2 imaging and MRI can also demonstrate intraosseous abscess formation and breaching of the cortex. Soft tissue involvement can be further evaluated with the use of gadolinium enhancement. Diagnostic yield is reliant on experienced radiological reporting but provides a sensitivity and specificity of ~90% and ~80%, respectively.22 As such, MRI can prove extremely valuable in informing diagnosis, extent and thus management of osteomyelitis in diabetic foot infections. CT can also prove superior to plain radiography in demonstrating the described bony radiological features of osteomyelitis. However, MRI gives superior imaging of the soft tissues and is the preferred modality. Radionuclide bone scanning and white cell scanning also have their place when the diagnosis is unclear but a full review of their role lies outside the remit of this review.23

Consensus criteria for diagnosis of osteomyelitis

An established consensus view on the diagnosis of osteomyelitis is yet to emerge but is an important aim both for informing treatment and to enable meaningful comparison of management strategies in determining best practice. Recent work under the auspices of the International Working Group on the Diabetic Foot (IWGDF) has attempted to formulate a criteria-based approach to diagnosis in the manner already accepted for similarly diagnostically challenging conditions such as infective endocarditis or various rheumatological conditions.24 This aims to classify osteomyelitis as definite, probable, possible or unlikely, based on a combination of clinical, microbiological and radiological features as well as response to antimicrobial therapy (Figure 2). Each criterion is in turn weighted as indicating either possible or probable infection. The decision to treat for osteomyelitis is then based on this probability. This approach has not been validated in practice but represents a quantum leap forward towards standardizing diagnosis and the decision to treat.

Management of osteomyelitis

Once the diagnosis has been made and the decision to treat taken, there is currently no evidence-based consensus view on the best way to manage osteomyelitis in the diabetic foot. Broadly, the approach is either conservative or surgical. The choice of treatment is all too often based on local prejudices and facilities with surprisingly little evidence to drive the development of robust guidelines. For many years, harking back to the days of limited antibiotic availability and effectiveness, the surgical removal of infected bone was held to be paramount. More recently, a primarily medical approach has been advocated, with the view that appropriate antibiotic and adjunctive treatments can obviate the need for surgery. So who is correct? No randomized controlled trials addressing this question exist. The group responsible for postulating the consensus criteria approach to diagnosis described above went on to undertake a systematic literature review of the effectiveness of osteomyelitis treatment in the diabetic foot and Fran Game of the Nottingham Foot Ulcer Trials Unit also recently evaluated this question. Both drew similar conclusions: there is little evidence to support the case for early surgical intervention but, equally, there are no robust comparative data to conclude that there is a significant difference in outcome after either primarily surgical or conservative management.24,25

Role of surgery

A handful of limited observational studies do support the case for surgery. ‘Successful’ treatment after surgery is reported in ~60%–90% of cases though how this is defined is somewhat nebulous.24 One retrospective series analysis suggested that surgical intervention within the first 3 days reduced the subsequent need for lower-limb amputation (10/77 patients) when compared with initial therapy with antibiotics alone (24/87).26 Henke et al.27 also report that delaying surgery leads to an increased risk of major amputation. Others indicate that limited surgical intervention improves the degree of healing
and limits the required degree of antibiotic therapy usage when compared with conservative management only. Aragon-Sanchez et al. advocate the use of early minimal debridement in conjunction with antibiotics and subsequent minor or major amputation as required. All of these studies are limited observational series and the inclusion criteria, indications for surgery and endpoint measures are ill defined and vary considerably. A pragmatic view would consider that there will be cases where surgery is absolutely required (e.g. a large collection of pus in a patient with systemic signs of sepsis) but there is not convincing evidence to mandate early surgery in all cases or sufficient clarity in the literature to adequately define when surgery becomes a necessity. As a minimum, consideration is needed to determine whether an intervention has an acceptable chance of resulting in a sound, weight-bearing unit with a low chance of ulceration in the future. We also believe antibiotic therapy alongside surgical treatment remains obligatory.

**Medical treatment**

Conservative management, based primarily on antibiotic therapy alone, was found to eradicate diabetic foot osteomyelitis in >60% of cases when 500 case reports were reviewed. A series of patients treated this way in a single centre showed arrest of the infection in 80% of cases, though 37% of their total of 147 cases of osteomyelitis did in fact undergo early surgery, suggesting that there remains a clinical judgement call to be made in all presentations. Major amputation rates and relapse rates have been shown to be equivalent between primarily conservative management and where initial minor surgery is used. Medical management is not without its problems. The mean duration of antibiotic therapy in the Game series was 61 days while others have suggested that treatment for 6 months is required in up to 50% of cases. Such prolonged courses of antibiotics potentiate the side effects, discourage compliance and encourage the development of drug-resistant organisms. It is, therefore, a priority to optimize antibiotic therapy. Surgery may be one route to reducing the need for antibiotics as suggested above. There is little evidence, however, to inform choice of antibiotic or route of administration. Antistaphylococcal agents and broad-spectrum antibiotics have been shown to be equally efficacious and, despite the frequent preference for parenteral administration in osteomyelitis, there is little evidence to support its superiority over oral therapy.

In the absence of high-quality comparative data, we suggest that each presentation must be evaluated on its own clinical merits and that the need for surgery should be judged throughout the course of treatment by an experienced clinical team, in the knowledge that antibiotic therapy alone may prove effective in some cases.
Beyond antimicrobial therapy in diabetic foot infections

Successful treatment of infection in a diabetic foot often requires interventions beyond the prescription of even correctly targeted antimicrobial therapy. Appropriate and aggressive attention needs to be given to the wound bed and the surrounding tissue. This includes removal of necrotic or poorly vascularized tissue from the surface and edges of the wound, which may be done in a clinic environment by sharp debridement, but if the nature of the wound dictates, may require a more invasive procedure in the controlled environment of the operating theatre. A major factor in the failure of chronic wounds to heal is the continued, unchallenged trauma to the wound bed as a result of continued weight bearing in an insensitive neuropathic foot. Effective redistribution of this pathological pressure is a critical adjunct to successful healing This may be as intensive as a total contact plaster cast to redistribute the force but can be as simple as instituting a non-weight bearing policy on the affected foot. A lesion occurring on a limb with clinical evidence of impaired blood flow mandates consideration of revascularization, via either bypass or endovascular intervention. This is particularly important with infection in the presence of arterial disease, as penetration of antibiotic into infected tissue may be poorer. It is worthwhile highlighting the sinister combination of ischaemia and infection. In an Italian study looking at 564 patients presenting with critical limb ischaemia, two-thirds of them also had clinical evidence of infection. Despite 95% of the patients undergoing a revascularization procedure, at follow-up 6 years later, 50% of the patients were dead. The fact that coronary artery disease was the leading cause of death is also testament to the fact that diabetic foot disease has a predilection to occur in patients already overburdened with disabling co-morbidities, in particular cardiovascular pathologies.

Successful delivery of these key interventions can only be done with the involvement of a multidisciplinary team, which requires the expertise of a whole range of professionals ranging from diabetologist, orthopaedic surgeon and specialist podiatrist right through to orthotist, diabetes specialist nurse and plaster technician. The concept of a team approach is core to recent documentation produced by a Diabetes UK specialist foot care services working group, in which effective integration of the input of different healthcare professionals is highlighted as being essential for effective management of disease of the foot in diabetes.

The lack of robust validated protocols to guide treatment of infection in the diabetic foot can engender a feeling of therapeutic nihilism, but to take such a stance risks unjustly dismissing beneficial interventions and condemning a fragile patient group to undeserved suffering and debility. We welcome the recent initiative supported by the UK National Institute for Health and Clinical Excellence (NICE) to develop clinical practice guidelines on the inpatient management of diabetic foot problems and look forward to the results of properly constructed trials to inform treatment of this difficult clinical problem.

References


Transparency declarations

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