Early use of antibiotics should not be ruled out

Mike Edmonds

These are exciting times for the diabetic foot. Major advances have taken place in the last decade and these have led to improved outcomes in ulcer healing and a reduced number of amputations (Edmonds, 1999). Early recognition of the at-risk foot, the prompt institution of preventive measures, and the provision of rapid and intensive treatment of foot infection in multidisciplinary foot clinics can reduce the number of amputations in patients with diabetes.

However, despite these advances, soft tissue and bone infection of the lower limbs is the most common indication for hospital admission in patients with diabetes mellitus. Furthermore, lower limb amputations, which frequently follow uncontrolled bacterial infection in these patients, account for 50% of all non-traumatic lower limb amputations (Grayson, 1995). If this situation is to be remedied, the role of infection in the natural history of the diabetic foot must be understood so that treatment can be given at an appropriately early time.

Role of neuropathy, ischaemia and infection

The feet are the target of peripheral neuropathy leading chiefly to sensory deficits and autonomic dysfunction.

Ischaemia results from atherosclerosis of the leg vessels, which in the patient with diabetes, is often bilateral, multisegmental and distal, involving arteries below the knee.

Infection is rarely the sole factor, but often complicates neuropathy and ischaemia. Nevertheless, it is responsible for considerable tissue necrosis in the diabetic foot. It is important to understand that tissue necrosis is rarely caused by an occlusive microangiopathy; more commonly, the cause is neutrophilic vasculitis secondary to soft tissue infection. Even in the neuro-ischaemic foot, neutrophilic vasculitis is often the main causative factor of tissue necrosis, although atherosclerotic large vessel disease may contribute. It is thus important to diagnose infection early and treat aggressively with antibiotics. The important question is what constitutes infection?

Definition of infection

Infection has been defined as the product of the entrance, growth, metabolic activities and resultant pathophysiological effects of microorganisms in the tissues of the patient (American College of Surgeons, 1976). From a practical point of view, infection is both a clinical and microbiological diagnosis.

Clinical diagnosis of infection

The clinical diagnosis of infection depends on the presence of purulent discharge from the ulcer, on the classic signs of inflammation around the ulcer (notably heat, erythema,

ARTICLE POINTS

1 Lower limb infections are the most common indication for hospital admission in patients with diabetes.

2 Infection must be diagnosed early and treated aggressively with antibiotics, but what constitutes infection?

3 Bacterial growth is more important than the presence of organisms in the wound.

4 Antibiotics should generally be prescribed much more readily in the neuroischaemic foot.

KEY WORDS

- Diabetic foot ulcers
- Infection
- Diagnosis
- Prompt intervention

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PAGE POINTS

1 Diagnosis of infection can be delayed because the normal clinical signs are often absent in patients with diabetes.

2 Special attention should be paid to the microbiological diagnosis of infection.

3 Recent research has shown that bacterial growth in a wound is more important than the presence of organisms.

4 Quantitative bacterial tissue cultures allow differentiation between a colonised and an infected ulcer.

5 In the absence of quantitative microbiology it is difficult to determine the true significance of a positive culture.

oedema and pain) and on the systemic signs of fever and leucocytosis. However, the manifestation of these signs of inflammation is dependent on intact nervous and peripheral vascular systems, both of which can be severely impaired in patients with diabetes, especially those with foot ulcers. Pain and tenderness may be absent because of neuropathy.

The response to injury in skin includes a local vasodilatation mediated by sensory nerve fibres, which are impaired in diabetic neuropathy (Parkhouse and Le Quesne, 1988). This leads to abnormalities in neuropeptides that play a role in the mediation of skin flare responses, in particular substance P which is a powerful mediator of vascular permeability. Erythema may be absent because of the inability of the foot to increase blood supply in response to infection. An intact tissue responds to bacterial infection by increasing blood flow more than 20-fold in the area around the infection. Furthermore, it is now established that up to 50% of patients with deep foot infection will not have leucocytosis or fever (Eneroth et al, 1997).

Trust in clinical signs alone can therefore lead to a significantly delayed diagnosis of the initial stages of infection.

Microbiological diagnosis

In view of the unreliability of clinical signs of infection, it is important to pay special attention to the microbiological diagnosis of infection. However, there is considerable controversy as to the most useful techniques for obtaining cultures, and much discussion on the interpretation of results. Isolation of bacteria from an ulcer may indicate either colonisation (when organisms multiply on the surface of the wound) or invasive infection (when the organisms are actively penetrating the soft tissues around the ulcer).

A major advance in the management of wound infection has been the discovery that the presence of organisms in a wound is less important than the level of bacterial growth. Considerable data have shown that a level of growth >100000 organisms per gram of tissue is necessary to cause wound infection and to allow for invasive sepsis for most types of bacteria (Robson, 1997). However, standard techniques of quantitative microbiology have not yet been generally established.

The importance of the numerical level of bacteria was first suggested by French army surgeons during the First World War. Subsequently, many studies from the United States Army Institute of Surgical Research have established that invasive burn wound sepsis is associated with a bacterial level of >100000/g (Robson, 1997). Krizek et al (1967) demonstrated the quantitative relationship between bacteria and skin graft survival in humans. Although all wounds were grafted purely on clinical grounds, when the bacterial counts were reviewed, the average graft survival was found to be 94% when the count was ±100000 bacteria per gram of tissue, but only 19% when the bacterial count was >100000/g tissue. With regard to decubitus ulcers, healing only occurred when bacterial counts were <100000/ml. Furthermore, despite the healthy appearance of the wound, healing did not occur if the bacterial count was >100000/ml.

In a recent study (reported by Gary Sibbald's group at the 1999 European Tissue Repair Society meeting in Bordeaux) eight patients with diabetic foot ulcers >1cm^2 had 3mm tissue biopsies of the ulcer base taken for quantitative bacteriology. Quantitative bacterial counts and organism identification were determined after 36-48 hours incubation. In this study, six out of eight patients had ≤10000 organisms colony-forming units per gram tissue, despite the absence of clinical signs of infection. The authors have since changed their clinical practice: all diabetic foot ulcers are now assessed with quantitative skin biopsies prior to the application of skin substitutes and growth factors. A repeat biopsy following treatment with a combination of antibiotics is carried out to confirm decreased bacterial burden.

Thus, quantitative bacterial tissue cultures enable differentiation between a colonised and an infected ulcer. However, techniques of quantitative microbiology are not generally available, and therefore conventional methods must be considered. Curettage of the base of ulcers and deep tissue cultures are reported as the most reliable (Gentry, 1993), but it is difficult

to obtain repeated outpatient specimens by such methods. In real life, a deep swab taken from the base of the ulcer after a good podiatric debridement should suffice.

A positive culture obviously indicates the presence of organisms. However, in the absence of quantitative microbiology, it is difficult to be sure of their true significance. Even bacteria regarded as normal flora or skin commensals may cause severe tissue damage. This includes Gram-negative organisms such as Citrobacter, Serratia, Pseudomonas and Acinetobacter. When Gram-negative bacteria are isolated from an ulcer swab, they should not be regarded as automatically insignificant. Antibiotics should generally be prescribed for positive cultures from diabetic feet, and much more readily for the neuroischaemic foot where untreated infection often leads rapidly to necrosis and major amputation.

What then is the evidence for the use of antibiotics in the treatment of uncomplicated, clinically uninfected foot ulcers which may have positive cultures?

Antibiotic treatment of non-infected ulcers

Chantelau et al (1996) found no advantage from Augmentin (co-amoxiclav) as a supplement to standard therapy in uncomplicated ulcers. However, only neuropathic ulcers were treated and, a type 2 statistical error could not be ruled out.

In a recent investigation, we studied patients with new foot ulcers, including both neuropathic and neuroischaemic ulcers, and no clinical evidence of infection. A total of 64 such patients, who consecutively presented to the foot clinic, were randomised into two groups: 32 patients received oral antibiotic treatment and 32 patients did not. All patients received standard foot care and education with follow-up in the foot clinic. Ulcer swabs were taken on admission to the study and at 2-weekly intervals.

In the non-antibiotic group, 15 patients developed clinical infection, compared with none in the antibiotic group ($P<0.001$). Seven patients in the non-antibiotic group needed hospital admission and three patients received an amputation (one major and two minor). No patients in the antibiotic group were admitted ($P<0.01$). Seventeen patients healed in the non-antibiotic group, compared with 27 in the antibiotic group ($P<0.02$).

A comparison between patients in the non-antibiotic group who developed or did not develop clinical infection found a different distribution of neuropathic to neuroischaemic ulcers: of the 15 who developed clinical infection, 7 had neuropathic ulcers and 8 had neuroischaemic ulcers; of 17 who did not develop clinical infection, 13 had neuropathic ulcers and 4 had neuroischaemic ulcers ($P<0.05$).

Furthermore, 11 of the 15 patients who developed clinical infection had positive ulcer swabs, compared with only one positlve swab in the 17 patients who did not develop clinical infection ($P<0.01$).

From this study, it was concluded that patients with diabetes and clean ulcers associated with peripheral vascular disease and positive ulcer swabs should be considered for early antibiotic treatment.

Treatment of clean diabetic foot ulcers

Previously, two contrasting views have been put forward regarding antibiotic treatment of the diabetic foot. A 'right wing' view is to give antibiotics only in the presence of clinical infection, almost disregarding microbiological diagnosis; the 'left wing' view is to give antibiotics freely to all patients with ulcers. The former carries the risk of treating infection too late, with its associated morbidity and even mortality, while the latter obviously carries a risk of inducing antibiotic resistance, which is to be deeply regretted. A middle way is needed, perhaps a little 'left of centre'.

Antibiotics should generally be prescribed for positive cultures from diabetic foot ulcers, and much more readily for the neuroischaemic foot as untreated infection often leads rapidly to necrosis and major amputation (Edmonds and Foster, 1999).

Thus for the neuropathic ulcer, at the first visit, if there is no cellulitis, discharge or probing to bone (indicative of osteomyelitis), then debridement, cleaning with saline, application of dressing and daily inspections will suffice.

For the neuroischaemic ulcer, at the initial visit, if the ulcer is superficial, oral amoxicillin

PAGE POINTS

1 There is little evidence available regarding the use of antibiotics to treat uncomplicated, clinically uninfected foot ulcers.

2 There appear to be two schools of thought regarding antibiotic treatment of the diabetic foot.

3 One view is to give antibiotics only in the presence of clinical infection.

4 The other view is to give antibitoics freely to all patients with ulcers.

5 It may be that a compromise is the best way forward until the results of much-needed clinical trials can settle the debate.

PAGE POINTS

1 Untreated infection in the neuroischaemic foot often leads rapidly to necrosis and major amputation.

2 Antibiotic should be given less readily for neuropathic ulcers than for neuroischaemic ulcers.

3 Following a positive swab, the patient could be treated with the appropriate antibiotic until a weekly repeat swab is negative.

4 In the case of severe ischaemia, antibiotics could be continued until the ulcer has healed.

5 At every patient visit, the ulcer should be examined for local signs of infection, cellulitis or osteomyelitis.

500 mg tds and flucloxacillin 500 mg qds are prescribed (if the patient is penicillin allergic, erythromycin 500 mg qds or cephadroxyl 1 g bd is prescribed). If the ulcer is deep, extending to the subcutaneous tissue, amoxicillin 500 mg tds, flucloxacillin 500 mg qds, trimethoprim 200 mg bd and metronidazole 400 mg tds are given.

At follow-up the patient is reviewed with the result of the ulcer swab. If the neuropathic ulcer shows no sign of infection and the swab is negative, treatment is continued without antibiotics.

If either the neuropathic or neuro-ischaemic ulcer has a positive swab, the patient is treated with the appropriate antibiotic according to antibiotic sensitivities until the repeat swab, taken at weekly intervals, is negative. If the neuroischaemic ulcer shows no signs of infection and the swab is negative, antibiotics may be stopped. However, in cases of severe ischaemia (pressure index < 0.5), antibiotics are continued until the ulcer is healed.

At every patient visit, examination is performed for local signs of infection, cellulitis or osteomyelitis. If these are found, action, including antibiotic therapy, is taken. ■

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