

# Use of antibiotics in uninfected ulcers may do more harm than good

William Jeffcoate

## ARTICLE POINTS

**1** Due to the scarcity of controlled research in the field, decisions concerning foot care are based as much on experience and belief as on fact.

**2** Inappropriate use of antibiotics may do harm by encouraging the development of resistant strains.

**3** The diagnosis of infection is *primarily clinical*, supported by microbiological data.

**4** The only published controlled trial in 'clean' (but microbiologically infected) neuropathic ulcers showed that antibiotics had no apparent benefit.

**5** The urgent need for controlled trials in this area could be facilitated by the adoption of newly published classifications of foot ulcers.

## KEY WORDS

- Diabetic foot ulceration
- Antibiotics
- Osteomyelitis
- Neuropathy

## Introduction

**Diabetic foot ulcers are disabling and potentially limb-threatening lesions that are exacerbated by infection. The lack of consensus among healthcare practitioners on how best to manage infection in the diabetic foot ulcer can be largely attributed to the paucity of hard scientific data. Both articles below address the issue of how to ascertain pathogenic infection. The first article urges caution before commencing antibiotic therapy because of the potentially serious consequences — evidence of soft tissue infection is suggested as the crucial deciding factor. The second article advocates early antibiotic treatment for 'clinically clean' neuroischaemic ulcers to prevent necrosis and amputations.**

Ulceration of the diabetic foot carries with it a prognosis that is potentially appalling, and it is a source of frustration to healthcare professionals that the scope for therapeutic intervention is so limited. Moreover, current practice is largely based on experience and opinion, and the scientific evidence to justify certain management choices is thin (Connor, 1999; De and Scarpello, 1999; Mason et al, 1999). Thus, when confronted with a potentially limb-threatening problem, a specialist will feel the need to do everything he/she can to improve outcome, and will be under pressure to omit nothing which might help, especially if it is unlikely to do harm.

The prescription of antibiotics is easy in the Western world, and it is not surprising that most doctors have a low threshold for their use in any foot lesion — just in case it might help. As often as not, however, non-specialists prescribe antibiotics inappropriately — using preparations with inadequate spectrum, inadequate dose and duration, or when they are unnecessary. The inappropriate use of antibiotics may clearly do harm, either by causing side-effects such as pseudomembranous colitis, or by encouraging multiresistant species (Goldstein et al, 1996; Tentolouris et al, 1999).

Thus, specialists in the management of the diabetic foot have to exercise careful judgment to ensure that antibiotics are prescribed sparingly and with maximum effect; they should only be prescribed when

there is evidence of infection and when there is evidence that their use will improve outcome. The trouble is that while nobody would disagree with these principles, the scientific evidence is so scant that specialists will exercise their judgment differently.

## Diagnosis of infection

The clinical diagnosis of infection presents little problem in the limb that is normally perfused, but signs may be masked when it is ischaemic. If blood flow is restricted, the classic signs of inflammation will be attenuated, and there may be no clues to the presence of soft tissue infection; however, the experienced specialist will be sensitive to any small increase in exudate, and will also consider whether infection is responsible for the onset of pain around the ulcer. The presence of an odour is also helpful — although it may be due to an infection either of living tissue or simply of superficial debris.

The neuropathic limb is, however, typically well-perfused, even abnormally well-perfused on occasion, with bounding pedal pulses when there is associated neuropathic arteriovenular shunting (Ward, 1982). In such circumstances, the clinical problem is the reverse: warmth and swelling of the foot may suggest infection when perhaps there is none. Fever is a poor guide because systemic involvement is uncommon (Sapico et al, 1982), and assessment of white cell count, erythrocyte sedimentation rate and C-reactive protein are similarly unhelpful.

**Swabs**

Many studies have been undertaken of the spectrum of organisms which may be isolated from lesions of the diabetic foot. It is known that when infection is present multiple species of organism may be involved. The studies that have been done with the greatest care (generally those involving the fewest patients) isolated the greatest number of organisms, including both Gram-positive and Gram-negative species (Jeffcoate et al, 1987). Anaerobic organisms are commonly present, although they may not be isolated unless the swab is handled with particular care.

Sadly, it is not possible to handle routine clinical samples with sufficient rigour. When surface swabs are taken, the organisms most likely to be identified are simply those which are most robust and able to withstand the conditions of transport, i.e, skin commensals and *Staphylococcus aureus*. Thus, the isolation of *S. aureus* from a surface swab taken in clinical practice does not necessarily mean that there are no other organisms present (Figure 1).

**Colonisation and infection**

Moreover, the isolation of *S. aureus* from a surface swab of an ulcer does not necessarily mean that it is pathogenic: staphylococci are widespread in the environment and will readily colonise and thrive on any surface wound. Only when microorganisms cause infection do they interfere with normal healing. Thus, the isolation of an organism such as *S. aureus* from a surface swab is compatible with, but not diagnostic of, infection. If infection is present, the isolation of *S. aureus* alone does not exclude the presence of other pathogenic organisms (Figure 2).

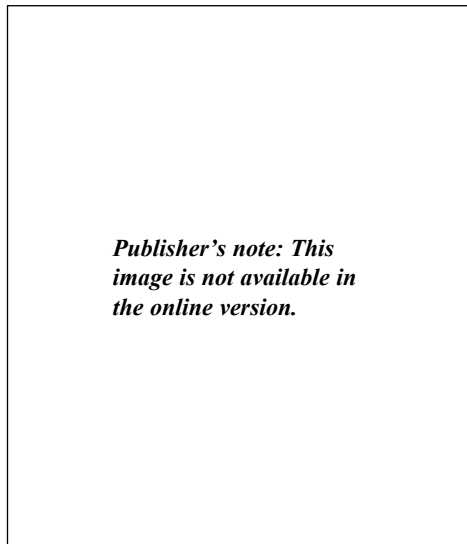
Thus, the diagnosis of clinical infection is partly microbiological, but mainly clinical. It is acknowledged that both microbiological tools and clinical signs may be misleading. Even so, an attempt must be made to restrict the use of antibiotics to cases with some supporting evidence of soft tissue infection; the use of swabs alone is insufficient.

**Superficial infection and slough**

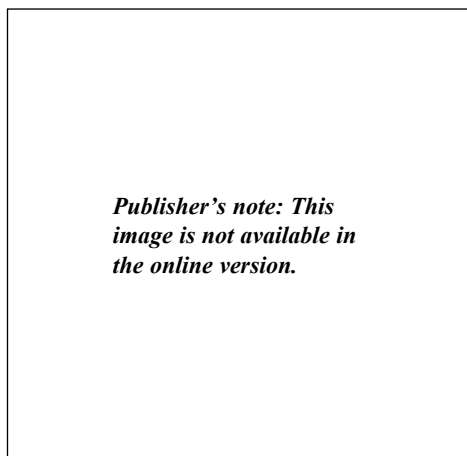
One particular problem relates to the presence of slough on the wound surface. This will inevitably harbour large numbers

of microorganisms, which will hinder healing by the release of locally acting enzymes, toxins and cytokines. It is accepted that as systemic antibiotics are unlikely to be effective against such superficial infection in devitalised tissue, slough should be removed by sharp debridement, regular cleansing and the use of desloughing agents.

What has not been accepted hitherto, however, is the use of topical antibiotics, which are traditionally held to be ineffective, likely to cause skin sensitisation, and to encourage the breeding of resistant strains. Nevertheless, it is now possible that this view should be challenged, since recent studies



*Figure 1. If antibiotics are prescribed for an infected wound, the choice should be based on all the organisms that are likely to be present — not just those which are robust enough to survive transport to the laboratory.*



*Figure 2. Clinically clean wounds will be readily colonised by bacteria such as S aureus, which will be isolated from a surface swab. Such colonisation needs to be distinguished from infection.*

**PAGE POINTS**

**1** Swabs do not distinguish between colonisation by bacteria and infection.

**2** Unless surface wound swabs are handled with speed and efficiency, the cultures they yield may be misleading.

**3** *S. aureus* will readily colonise any bare wound.

**4** The possible option of topical application of antimicrobial agents for established superficial infection needs to be reconsidered.

**PAGE POINTS**

**1** The only controlled, published trial has shown no benefit from the use of antibiotics in clean neuropathic ulcers.

**2** The number of organisms to be isolated from the surface of a wound is not affected by the use of broad spectrum antibiotics, but their sensitivity to antibiotics is.

**3** Duration of antimicrobial therapy is an issue because ulcers many persist for many months and swabs at all stages will continue to grow bacteria.

**4** As antibiotics encourage resistant organisms, there is a risk that any secondary infection of bone will be harder to eradicate.

**5** Newly published classifications may prove invaluable in the conduction of controlled trials, which are so urgently needed.

have shown that at least one topically active agent, pexiganan, is as effective as oral ofloxacin in 'mildly infected' ulcers (Lamb and Wiseman, 1998; Lipsky, 1999). Clearly the nature of such superficial infection needs to be carefully defined, but there is a need for further appropriately controlled studies, in which topical and systemic antimicrobials are compared with each other, and when appropriate, to placebo.

**Antibiotics for clinically non-infected ulcers**

One of the few placebo-controlled trials of antibiotic use for diabetic foot ulcers is that of Chantelau and colleagues (1996), which is particularly relevant to this debate. In this meticulous study, 44 patients with superficial and deep neuropathic (ankle:brachial systolic index > 1) ulcers were randomised to double-blind treatment with an appropriate broad-spectrum antibiotic regimen (amoxicillin/clavulanic acid). Even though all ulcers except one were infected (i.e. potentially pathogenic organisms were isolated from surface swabs), there was no difference in outcome between the two groups.

Foster and colleagues (1998) reported very different results in another randomised, but apparently otherwise uncontrolled study, but their data have only been presented in abstract form. Thus, the data of Chantelau et al (1996) are the best available, and indicate that the benefit to be derived from the use

of antibiotics in clean neuropathic ulcers is at best slight, and probably non-existent.

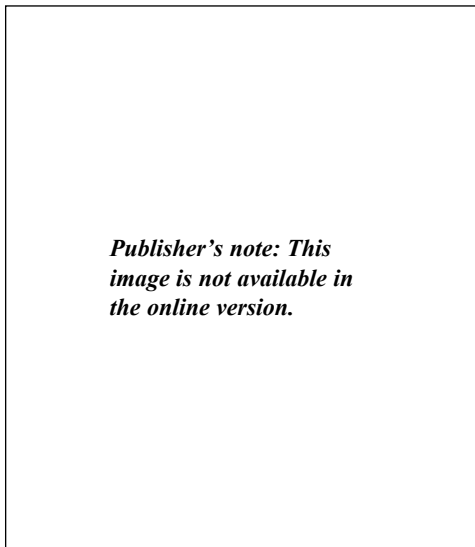
An interesting observation made in this study was that the deployment of such an appropriate antibiotic regimen made no difference to the number of organisms isolated from ulcers at either six days or the end of the study. We have also found that the use of antibiotics made no difference to the total number of isolates (Jones et al, 1985), as have others (Sapico et al, 1984). If it is believed that the evidence of isolates from surface swabs is sufficient to indicate the presence of infection which should be treated, then it must be accepted on the same evidence that the treatment is ineffective. While it is obvious that antibiotics are beneficial in the management of infection that is clinically apparent, this observation emphasises the danger of drawing the wrong conclusions from the results of microbiological investigations.

**Unresolved issues**

While a case can be made for the use of broad-spectrum antibiotics in clinically uninfected ulcers, there is no guidance as to how long the treatment should be continued. The available evidence is that antibiotics do not sterilise wounds, and hence the duration of treatment cannot be determined by the use of swabs. Similarly, clinical signs of infection cannot be used since there will be none. As it is unlikely that antibiotics will be continued until the ulcer has healed (which in our experience is after a median of 12 weeks), the course of treatment must be determined by factors that are entirely unscientific. If the presence of *S. aureus* at day one is an indication of significant infection, why not *S. aureus* at day 61?

**Dangers of inappropriate antibiotic use**

Apart from patient-related adverse events, the main danger is the likelihood of encouraging the development of resistant organisms. Not only will these enter the overall germ pool and ultimately endanger others with unrelated disease, they could also have an adverse effect on the index patient. The resistant organisms will colonise the ulcer under review, and are a



*Publisher's note: This image is not available in the online version.*

**Figure 3. Infection of bone with MRSA (multiply resistant *Staphylococcus aureus*) may be very difficult to eradicate and may threaten the whole limb.**

potential cause of spreading infection. The greatest risk with a neuropathic ulcer is the development of osteomyelitis (Lipsky 1997), which may well be limb-threatening if the dominant infective organism is resistant to usual antimicrobial therapy (Figure 3).

### Conclusions

The correct use of antibiotics will save limbs and lives, but decisions concerning best practice are currently hampered by the scarcity of robust scientific data. Such published evidence as there is, however,

suggests that they are not necessary in the management of ulcers that are clinically clean, although there remains a desperate need for further controlled clinical trials in this area.

It is to be hoped that the adoption of standardised criteria for the classification of ulcers (Armstrong et al, 1998; Macfarlane and Jeffcoate, 1999) may facilitate the performance of such multicentre trials in the future. In this respect the option of topical treatment offers hope of a new therapeutic approach. ■