Antibiotic treatment of diabetic foot infections: what's new?

Benjamin A Lipsky

ARTICLE POINTS

1 Inappropriate therapy for a diabetic foot lesion too often leads to amputation of the foot.

2 In the past, antibiotic therapy was usually parenteral; other options are now available.

3 Recent studies of antibiotic therapy for diabetic foot infections have now made evidence-based choices of antibiotic possible.

4 The recommended agents for treating such infections are constantly changing as new data on their efficacy and resistance become available.

5 The inclusion of an infectious diseases clinician in the foot care team is vital to successful treatment.

KEY WORDS
- **Diabetic foot lesions**
- **Infection**
- **Antibiotic therapy**

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Introduction

This is the first in a series of articles that aim to provide an up-to-date overview of the important principles underlying successful therapy of diabetic foot infections. Written by leading international experts in diabetic foot infections, the articles will present thoughtful, evidence-based, and perhaps controversial, comments on those aspects of treatment felt to be most in need of further study. We hope that readers will contribute to the debate and invite your comments.

Neuropathy and vascular disease are clearly the major risk factors for foot lesions in people with diabetes. Infection of a foot lesion is, however, often the final common pathway leading to amputation of the foot (Pecoraro et al, 1991; Reiber et al, 1992).

Assessment of an infected diabetic foot lesion

Before antibiotic therapy for an infected diabetic foot lesion can be commenced, the lesion must be carefully evaluated, and an attempt made to determine its probable cause and severity (Lipsky and Berendt, 1999).

- *Appropriately performed cultures and carefully selected diagnostic tests* are usually needed to assess the infected wound properly and to plan proper treatment (Lipsky, 1990b; Caputo et al, 1999).
- *Wound debridement*, for both diagnostic and therapeutic purposes, is needed in almost all cases. This may be a minor procedure performed in the clinic or at the bedside, or a more thorough surgical procedure carried out in the operating theatre.
- Other surgical procedures that also need to be be considered include *incision and drainage, minor amputations* (Tan et al, 1996), *bone resections*, and *revascularisation* (Gibbons and Habershaw, 1995).
- Finally, any *metabolic abnormalities must be corrected* and *glycaemic control optimised.*

Selection of an appropriate antibiotic

When all of the above issues have been addressed, attention can turn to selecting appropriate antibiotic therapy.

Two decades ago the standard recommendations for the treatment of diabetic foot infections included hospitalisation of virtually all patients, and the prescription of broad-spectrum parenteral therapy. Since then, several studies of antibiotic therapy of diabetic foot infections have generated data upon which evidence-based choices can be made.

We now know that most patients with mild to moderate infection (i.e. those without deep tissue involvement or evidence of systemic toxicity or metabolic instability) can be treated with oral agents as out-patients (Lipsky et al, 1990a). The expanded menu of broad-spectrum, highly bioavailable, and infrequently dosed, oral antibiotics, especially fluoroquinolones (Kuck et al, 1998), have made this an option in most cases.

Furthermore, the microbiology of diabetic foot infections has been better defined, allowing more targeted therapy (Lipsky et al, 1990b). Studies have shown that infections that are serious, or occur in patients who have recently received antibiotic therapy, are often polymicrobial. Mild infections in antibiotic-naïve patients, however, are usually caused by only one or two organisms, most often aerobic Gram-positive cocci.

The specific agents recommended for treating infections will constantly change

as new data on their efficacy and evolving antibiotic resistance patterns become available, and as new agents are introduced. Thus, an understanding of the principles of antibiotic therapy will prove more valuable than memorising the currently preferred regimens.

What's new?

This series of articles in *The Diabetic Foot* aims to provide an up-to-date overview of the important principles needed for successful therapy of these common, complex and serious infections.

In addition to this introductory paper, the editors have commissioned articles by several leading international experts in diabetic foot infections. In the coming months we plan to present thoughtful, evidence-based, and perhaps controversial, comments on the topics outlined below.

Antimicrobial therapy of clinically uninfected ulcers — is it indicated?

While no-one would argue with the need for antibiotic therapy of an infected lesion in the foot of a diabetic patient, most would agree that it is not required for uninfected lesions (Chantelau et al, 1996).

A recent abstract of a small prospective randomised study has suggested, however, that this approach can significantly reduce the incidence of adverse outcomes (Foster et al, 1999). If true, this is an important finding, which could result in prolonged antibiotic therapy for many patients who would otherwise not have received it.

In light of the substantial financial costs, possible drug-related adverse effects, and potential threat to the patient's and world's microbial ecology associated with this approach, careful consideration of this topic is warranted. We have therefore invited two noted experts to debate the issue.

Topical antimicrobial therapy of infected ulcers: whether, when, which?

Just 15 years ago, published recommendations for treating diabetic foot infections generally called for parenteral therapy. Studies have since shown that oral therapy is safe and effective in treating mild to moderate infections (Lipsky et al, 1990a).

The next logical step in the evolution of treatment for these non-limb-threatening infections may be topical therapy. Whereas topical antiseptic agents appear to be harmful to host cells, antibiotics may prove to be safer.

Potential advantages of this approach include:

- Avoiding excessive use of systemic antibiotic agents
- Having access to new antimicrobials not available for systemic use
- Possibly improved outcomes with infected wounds.

If appropriate agents are available and are found to be safe and effective, this could be a substantial advance in therapy. One topical peptide antibiotic, pexiganin acetate, has demonstrated near equivalence to oral ofloxacin in treating mildly infected diabetic foot ulcers in two large randomised controlled trials (Lipsky et al, 1997).

What is the appropriate duration of antibiotic therapy for various types of diabetic foot infection?

The optimal treatment duration for most infectious diseases has not been defined, and this is largely true for diabetic foot infections. The goal is to treat long enough to ensure a good clinical outcome and avoid recurrence. Balanced against this need is the desire to treat no longer than is necessary, to avoid the financial, toxic and ecological problems associated with over-use of antibiotics.

This paper will explore what constitutes sufficient therapy for different types of lesions, and how the duration may be modified by a variety of factors.

How should bone infection of the foot in diabetic patients be treated?

Few areas in this field are more controversial than the treatment of osteomyelitis (except, perhaps, its diagnosis — but that would need to be addressed in another symposium) (Lipsky, 1997).

Therapeutic recommendations for diabetic foot osteomyelitis are largely based on information gathered from studies of haematogenous osteomyelitis. Obviously, differences in the pathophysiology of

PAGE POINTS

1 Understanding the principles of antibiotic therapy is more valuable than memorising currently recommended regimens.

2 Recent evidence suggests that antibiotic therapy for non-infected diabetic ulcers may significantly reduce the incidence of adverse outcomes.

3 Oral antibiotic therapy is now recommended for mild to moderate diabetic foot infections.

4 Topical therapy is also showing promise in the form of peptide antibiotic, pexiganin acetate, which has shown near equivalence to oral ofloxacin in treatment of mildly infected diabetic foot ulcers in two large RCTs.

PAGE POINTS

1 Issues around the therapy of infected diabetic foot lesions can best be addressed by prospective RCTs.

2 Ideally, such studies would stratify patients by the severity of their infection.

3 The large number of subjects that would need to be enrolled in such trials means that collaborative groups and multicentre protocols are probably required.

4 A team approach to the treatment of these multifaceted infections has been shown to markedly improve the outcome.

5 Adding the infectious diseases clinician to the foot care team should help to improve antimicrobial choices for diabetic foot infections.

these two types of bone infection call into question the applicability of these data.

Traditional teaching that chronic osteomyelitis, especially when due to contiguous spread of infection and involving a relatively ischaemic site, cannot be cured by antibiotic therapy alone has recently been challenged by two retrospective studies showing the efficacy of antibiotic therapy alone (Venkatesan et al, 1997; Pittet et al, 1999). Issues that need to be addressed include:

- What is the appropriate duration of therapy for osteomyelitis?
- Can bone penetration of antibiotics be accurately measured, and how important is it?
- Is parenteral therapy required, and if so for how long?
- When is surgical resection needed?
- How does a bone resection change the duration of antibiotic therapy?
- Are there adjunctive measures worth considering for treating this infection?

All of these issues will be explored in a future paper.

Specific antibiotic regimens: which ones for which patients?

At some point the clinician will need to select an antibiotic regimen. Usually this is an empirical choice at first.

Issues around this topic that need to be explored include:

- What clinical features or laboratory tests can help in choosing the appropriate regimen?
- How should that choice later be modified, based on the clinical response and the wound culture and sensitivity results?
- How should local antibiotic sensitivity data be incorporated into empirical antibiotic regimens?
- Which antibiotics have been shown to be effective in clinical trials of diabetic foot infections?
- Are there data on cost-effectiveness of various regimens? To my knowledge only one paper has analysed this issue (McKinnon et al, 1997), which is crucial in modern healthcare systems.

Selection of topics for exploration

In light of the great progress that has been made in various aspects of the treatment of diabetic foot infections, the issues that will be explored in these articles are those in most need of further inquiry.

They can best be addressed by prospective randomised controlled trials, which would ideally stratify patients by the severity of their infection. The large number of subjects that would need to be enrolled

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Evidence-based antibiotic therapy for infected diabetic foot lesions should help to reduce amputation rates in the diabetic population

in such trials means that collaborative groups and multicentre protocols are probably required.

Fortunately, clinicians interested in the problems of the diabetic foot can now connect with one another through several established forums, including:

- The foot councils of the American Diabetes Association (1999)
- The British Diabetic Association
- The International Diabetes Federation
- The International Working Group on the Diabetic Foot (1999)
- The guidelines committees of the Infectious Diseases Society of America and the Canadian Committee on Antimicrobial Agents (1996).

Role of the infectious diseases clinician

The treatment of infectious problems of the diabetic foot involves many specialists, such as endocrinologists and diabetologists, podiatrists, orthopaedists, vascular and plastic surgeons, and wound care nurses.

A team approach to the treatment of these multifaceted infections has been shown to markedly improve the outcome (Holstein and Sorensen, 1999). Adding the infectious diseases clinician to the foot care team should help to improve antimicrobial choices for diabetic foot infections.

We hope that you will find this series on antibiotic therapy of diabetic foot infections enlightening, clinically helpful, and perhaps even entertaining. We encourage and eagerly await your feedback. ■

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