Opinions on antibiotic therapy for the infected diabetic foot

Antibiotic therapy for the treatment of the infected diabetic foot has been, and remains, a topic of much debate among diabetic foot care, and infection control, specialists. In the Summer edition of *The Diabetic Foot Journal*, The Scottish Diabetes Group and the Scottish Infectious Diseases Society presented guidance for antibiotic therapy in the infected diabetic foot. Here, Michael Edmonds and Melanie Doxford (pages 112–14), followed by Magnus Löndahl and Jan Apelqvist (pages 114–16), provide two opinions on the guidance. Graham Leese and Dilip Nathwani, lead authors of the guidance, reply to these opinions on pages 116–18.

Michael Edmonds

Melanie Doxford

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We congratulate the Scottish Diabetes Group and the Scottish Infectious Diseases Society on the production of the important document "Use of antibiotics in people with diabetic foot disease: A consensus statement" (Leese et al, 2009). Scotland is at the forefront of diabetes care, and this document will continue to improve diabetic foot care in Scotland and much further afield.

Management of the infected diabetic foot is a difficult, controversial and evolving discipline, especially in the context of the rise of the modern "super bugs". We very much respect all the authors who contributed to this document, all of whom are well known in the diabetic foot, and infection control, fields. We are honoured to have been asked to write this commentary. We hope our comments will be received as positive, constructive contributions to the overall debate. Here, we discuss three practical points, arising from the consensus statement, that are primarily concerned with the clinical approach to the infected diabetic foot.

First, we are uneasy about the "moderate" and "severe" classifications for diabetic foot infections. While infection classification was not the aim of this article, decisions about antibiotic use follow on from the specific grading of the infection, making the grading system central to treatment choices. Under the system used by Leese et al (2009), a foot with extensive, deep soft tissue infection and cellulitis >2 cm is regarded as being only "moderately" infected, though it may be limb-threatening. To acquire the designation of "severe", a person would need to display symptoms of systemic toxicity. However, symptoms of systemic toxicity are notoriously absent – or appear very late in the course of the infection – in the diabetic foot, often being masked by neuropathy.

Second, the consensus statement reads: "An acutely infected wound of mild or moderate severity in a person who has not been recently treated with antibiotics does not need to be cultured" (Leese et al, 2009). Infection is a highly significant development on the road to amputation (Prompers et al, 2007) and, in view of the possibility of such a disastrous outcome, we regard diabetic foot infections as medical emergencies. We believe that adopting a "guess the infecting organism" or "wait and see" approach is not ideal practice in the management of diabetic foot infections, nor is such a practice in keeping with the concept of the infected diabetic foot as medical emergency.

All diabetic foot ulcers demonstrating any level of clinical infection should be cultured on presentation to identify the infecting organism, select the correct agent for treatment, and eradicate the infection in the first instance. Diabetic foot infections can deteriorate so rapidly that the foot may be irretrievably damaged if initial antibiotic treatment – carried out blindly, and without microbiological information – fails. We accept that the most likely organisms in a person who has not been recently treated with antibiotics will be a *Staphylococcus* or a *Streptococcus*, but within the *Staphylococcus*-infected population, we are increasingly seeing meticillin-resistant *Staphylococcus aureus* infections directly from the community that could not be diagnosed without microbiological investigation.

Third, we are concerned by the approach to the ischaemic diabetic foot that is infected. We strongly agree that the presence of critical ischaemia may make the infection severe. However, for the clinician at the bedside, the concept of critical ischaemia in the diabetic foot is a difficult one; true "critical" ischaemia is not easy to diagnose, with neuropathy often masking resting pain. We believe that there should be tailored advice for the treatment of the ischaemic, as opposed to the neuropathic, diabetic foot that is infected. The consensus statement makes little differentiation between the treatment of diabetic foot infection in the reasonably healthy, neuropathic person at one end of the spectrum, and the medically fragile, ischaemic, renal person at the other. As Louis Pasteur put it: "The germ is nothing, it is the terrain in which it grows that is everything."

In conclusion, this is a thought-provoking document on a subject that is continually developing and is always in need of healthy debate. But ultimately, all healthcare professionals working with the infected diabetic foot have the same aim: the rapid successful diagnosis, treatment and resolution of diabetic foot infections, and thereby the prevention of amputations. ■

Michael Edmonds and Melanie Doxford

Magnus Löndahl

Jan Apelqvist

Infection plays a major role in diabetic foot disease. The Eurodiale study (Prompers et al, 2007) reported that 58% of all ulcers were infected at the time of referral to a diabetic foot clinic, and signs of infection were present in >80% of people admitted to hospital for diabetic foot care. Furthermore, amputation is preceded by infection in the majority of cases (Lavery et al, 2006).

Antimicrobial treatment is one of the cornerstones in the clinical management of the diabetic foot. However, incorrect and over-use of antibiotics has resulted in clinically significant rises in antibiotic-resistant microbes (Rossolini and Mantengoli, 2008). The need for more selective and efficient antimicrobial therapy is widely advocated, but given that initial treatment is usually empirical, and that use of narrow-spectrum antibiotic therapy requires more detailed pathogen knowledge than for broad-spectrum antibiotics, there is a need for easily applicable clinical guidance.

In this vein, the authors of "Use of antibiotics in people with diabetic foot disease: A consensus statement" (Leese et al, 2009) have succeeded in providing broad, practical guidance on the use of antibiotics in people with diabetic foot disease complicated by infection. The authors have contributed an impressive and concise document, based on the trial evidence available, existing guidelines and expert opinion.

Recommendations for bacterial culture and evaluation of the clinical signs of infection are specified, and the importance of classifying the presence and severity of infection to determine clinical choices is discussed. The authors stress the importance of local microbiological epidemiology and susceptibility patterns, and the consideration of these factors when making treatment choices. Finally, the guidance gives clinicians an easily understandable summary of recommendations for antibiotic therapy according to the level of infection.

The authors also highlight the lack of robust knowledge of the causative microbes in chronic diabetic foot ulcer infection, as almost all research looks at acute wounds or skin infections. A need persists for randomised clinical trials that evaluate the effects of various antibiotic therapies in deep tissue infections, as well as in chronic ulcers of the diabetic foot.

Several unresolved questions about the use of antimicrobials in the diabetic foot remain: when should we start, and when should we stop, antimicrobial treatment? Are the classical signs and symptoms of infection trustworthy in the person with diabetes? How do we know if healing of a chronic ulcer – to the eye uninfected – is being stalled by microbial activity? Do biofilms affect the healing process, and if so, how should this be managed? We needed more robust markers than our eyes and noses for evaluating when microbes are preventing healing and when they are causing infection, and for determining when it is resolved.

Given the prevalence of antibiotic resistant microbes, we should be seeking other ways of treating infections in the diabetic foot, especially for superficial or local infections. Robust trials evaluating the effects on microbial activity of treatment modalities (e.g. negative pressure therapy and hyperbaric oxygen therapy) should be pursued. Furthermore, the clinical usefulness of topical antimicrobials (e.g. therapeutic polypeptides and silver ions) needs to be further evaluated. Where proven appropriate, these auxiliary antimicrobial modalities should be brought into clinical practice.

To develop structured programmes and protocols, based on the evidence of large-scale randomised clinical trials into all aspects of the treatment of the infected diabetic foot, will require cooperation between diabetic foot clinics, and across national boarders. Until then, clinical practice must be continuously debated to ensure that people are receiving the best care possible. The document provided by the Scottish Diabetes Group and the Scottish Infectious Diseases Society (Leese et al, 2009) is an excellent example of converting the best available knowledge into practical guidance for the clinician. ■

Magnus Löndahl and Jan Apelqvist

Graham Leese

Dilip Nathwani

The comments from Edmonds and Doxford, and from Löndahl and Apelqvist, are extremely helpful and constructive, and we hope may help us move towards a wider consensus on the use of antibiotics for the treatment of the infected diabetic foot.

The first issue raised by Edmonds and Doxford is one of terminology. We agree that a potentially limb-threatening infection classified as "moderate" could be misconstrued as being less serious than it actually is. However, we based our guidance (Leese et al, 2009) on the classification of infection provided by the Infectious Diseases Society of America (Lipsky et al, 2004), a recognised and clinically useful classification system used in many centres. The PEDIS (perfusion, extent/size, depth/tissue loss, infection, sensation) score for infection is similar, and classifies infection as grades 1–4 (Schaper, 2004). The PEDIS score has an advantage in that the terminology is less pejorative.

The question of when to culture a diabetic foot wound proved to be hugely controversial, even within the consensus group. In general, as infecting organisms become

more variable, and less predictable, early culture becomes increasingly important. The guidance we have produced is primarily aimed at the assessment of infection, its severity and antibiotic therapy. It is meant to offer pragmatic advice for clinicians in both primary and secondary care.

In acute mild to moderate infections, the clinical benefit and cost-effectiveness of a routine swab has not been proven, nor has the predictive value of a swab culture been confirmed in the literature. Many times, especially in older people, the growth of contaminants on these swabs may be interpreted as the causative pathogen(s), leading to the prescription of unnecessary antibiotics.

Generally, in antibiotic-naïve patients without frequent healthcare setting exposure, the likelihood of unusual pathogens is rare in Scotland. However, we accept that when there are adequate local resources and confidence in the quality of its results, then obtaining swab cultures would be a reasonable strategy for these types of infection. If there has been previous exposure to healthcare settings or antibiotics, then cultures should definitely be taken. When in doubt, it is better to take cultures. The guideline we produced could, and possibly should, have expanded on this section to make these points clearer, as this is a very important debate.

The third issue regarding the ischaemic foot is well made. Our guideline was aimed very specifically at the use of antibiotics in the infected diabetic foot, while the issues surrounding the management of the ischaemic foot are more in the domain of general diabetic foot care. We are unaware of any evidence that suggests some antibiotics should be used instead of others if a diagnosis of ischaemia is made concomitantly to foot infection. We do

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suggest that the duration of antibiotic treatment may be prolonged in a slowly healing ischaemic wound. Certainly in any diabetic foot ulcer, whether infected or not, a full assessment of the vascular supply needs to be made. We agree that some comment on vascular assessment could have usefully been made, but we consider that any detailed discourse on this subject was beyond the remit of this guideline.

The guideline was launched at the Scottish Diabetes Group and *The Diabetes Foot Journal* Conference in Edinburgh in June, 2009. The immediate feedback was positive, and podiatrists and doctors have indicated that the guideline has been useful. Clearly, as microbial sensitivities change, the guideline will need to be updated. We agree with Löndahl and Apelqvist that there is a need for randomised controlled trials that assess the use of antibiotics, and dressings, in the diabetic foot ulcers. We are grateful for the comments provided and hope that we can expand evidence-based management to all aspects of diabetic foot care. ■

Graham Leese and Dilip Nathwani

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Letter to the Editors

Sirs,

In a recent article (*The Diabetic Foot Journal* **12**: 39–43), Martin Turns provided an interesting case report in which healing of a diabetic foot ulcer occurred concurrent to the use of glucose oxidase dressings.

In the background to the report, and in justification of the use of this dressing, the author reported the results obtained with the dressing in three observational studies, called trials.

I am concerned that the numbers of people with diabetes and foot ulcers are so small in the combined studies that they provide no clear justification for the use of this dressing. The combined number of cases reported were 19: in one case the ulcer worsened, in three cases we are given no further information, and in 15 cases the wound improved or healed. Indeed, the occurrence of an adverse event in one of the studies may rather be a reason not to use the dressing. What is surely needed for any new dressing is a randomised controlled trial with a large number of participants.

In an individual case report, such as reported by Turns, assuming ethical permission, what would help is an *n*=1 study. In this, the healing rate is assessed for 1 week on the standard therapy and the healing rate measured, then the treatment is changed to the trial dressing for 1 week and the healing rate is measured again. The treatment is again changed to standard for the next week and further measurement taken, with the sequence continuing until the wound is healed. By comparing the healing rates between the two dressings, the hypothesis that the new dressing is superior to the standard therapy can be tested. This would also allow for a power calculation for a formal randomised controlled trial.

Yours sincerely,

AC Felix Burden,
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