Managing infection in the diabetic foot

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The prevalence of diabetes is rising around the world. Alongside this is a continued rise in the number of people with diabetic foot ulceration and, in most countries, an absence of a reduction in the number of amputations for diabetes performed (IDF, 2005). The two main reasons for the failure of diabetic foot services to halt the rise in amputations is the number of people with type 2 diabetes who have dysvascular feet with limited salvage options and infection due to resistant organisms or deep-seated infections (Young, 2003). This article will concentrate on infection and explore the role of antibiotics as an integral part of infection management in the diabetic foot.

Article points

1. The core tenets of diabetic foot care are the annual screening of low-risk people with diabetes, the care of individuals with identified risk factors before they develop an ulcer, the care of the ulcerated patient and aftercare following ulcer healing or amputation.

2. The emphasis on dressings and bandages by non-specialist teams is a common reason for delayed healing of foot ulcers.

3. The author's clinic advocates vancomycin as the first-line intravenous therapy for MRSA. If this fails or there are reasons not to use it then daptomycin, teicoplanin or linezolid should be used.

Key words

- Ulcer
- Bacterial infection
- Antibiotic treatment
- MRSA

Last year was designated the year of the diabetic foot by the International Diabetes Federation (IDF). A number of events and articles looked at the prevalence of foot ulceration around the world and these were detailed in various publications (Diabetes UK, 2004; IDF Consultative Section and International Working Group on the Diabetic Foot, 2005). There are few accurate figures available, but *Table 1* shows some estimates.

Diabetic foot ulceration remains the most common serious long-term diabetes complication, being more prevalent than blindness or renal failure and just as disabling for many individuals (Young, 2003). Diabetes is also the most common cause of non-traumatic lower limb amputation in the world and, as mentioned in the introduction, these numbers are not declining (IDF Consultative Section and International Working Group on the Diabetic Foot, 2005).

Pathophysiology of the diabetic foot

A recent consensus meeting of leading foot care practitioners in the UK was unable to decide on a single definition of a diabetic foot ulcer: the formation of blisters, gangrene without ulceration and minor abrasions were the main points of disagreement (Roundtable Discussion, 2006b). However, it was agreed that all present could identify an ulcer in clinical circumstances.

The diabetic foot syndrome comprises the spectrum of disease from the presence of risk factors for ulceration through to limb amputation. Ultimately, everyone with diabetes is at increased risk of lower limb amputation compared to the general population without diabetes. However, the presence of additional characteristics has a cumulative effect on the risk of the type of ulceration that, in turn, leads on to 95% of the amputations associated with diabetes (Scottish Intercollegiate Guidelines Network [SIGN], 2001). These additional risk factors are detailed in *Table 2*.

In point prevalence surveys, around a third of the population with diabetes also has significant predisposing factors for ulceration (Young et al, 1994). Despite this, only around 5–10% of this group develop ulcerations each year (Reiber, 1996).

The impact of environmental factors, such as shoes and walking, cannot be underestimated, but there must also be other factors. The author

Table 1. Epidemiology of the diabetic foot. Adapted from *Diabetes and Foot Care: A Time to Act* (IDF Consultative Section and International Working Group on the Diabetic Foot, 2005).

- The prevalence of diabetes is rising around the world.
- At least a third of all people with diabetes have sufficient neuropathy or peripheral vascular disease to make them at increased risk of foot ulceration.
- Around 1 in 6 people with diabetes will develop a foot ulcer at some time in their life.
- Foot ulceration is the most common serious long-term diabetes complication.
- Amputations are preceded by foot ulcers in 95% of cases.
- Infection and failure to heal are the main reasons for amputation in people with diabetes.
- Diabetes is the single most common predisposing factor for amputation worldwide.
- Half of all non-traumatic amputations are in people with diabetes.
- Every 30 seconds, a limb is lost to diabetes somewhere in the world.

Table 2. Proven risk factors for predicting future foot ulceration. Adapted from SIGN (2001) and Game et al (2006).

- Peripheral neuropathy
  – absent 10 g monofilament sensation.
  – VPT > 25 volts.
  – neuropathy disability score > 6.
- Peripheral vascular disease
  – Absence of two or more foot pulses.
- Diabetic nephropathy with established renal failure.

the diabetic foot that will be completed in the summer of 2007.

Essentially, the core tenets of diabetic foot care are the annual screening of low risk people with diabetes, the care of pre-ulcer individuals with identified risk factors, the care of the ulcerated patient and aftercare following amputation (Roundtable Discussion, 2006a).

Once one or more of the risk factors from *Table 2* are identified the individual should be considered at significantly increased risk of ulceration. At this stage they require additional podiatric input and open access to services if an ulcer develops. The risk of ulceration is around 10% per year for this group, but the expected beneficial effects of structured care for this group remain more theoretical than evidence-based.

Once a foot has an ulcer, or there is established peripheral arterial disease leading to tissue necrosis, then the only intervention that is proven to reduce amputation is specialised multidisciplinary care in a hospital setting (SIGN, 2001). Appropriate debridement, pressure relief and infection control are the three main pillars of diabetic foot care. These are augmented by revascularisation in the ischaemic limb. The individual will require the input of a multidisciplinary team including podiatrists, diabetologists, diabetes specialist nurses, orthotists, surgeons and vascular specialists. Additional support should come from interventional radiologists and diagnostic services such as radiology and microbiology. A close-knit team can work consistently and therefore improve outcomes. They can also apply the latest knowledge and use their extensive experience to

believes that a neurobehavioural factor has yet to be identified (discussed by Vileikyte et al, 2004). Why else is it that once a person with diabetes develops an ulcer their chance of being ulcer free is less than 50% over the next year? (Jeffcoate et al, 2006.)

Management pathways for diabetic feet

Despite a wealth of national and international guidelines for the management of the diabetic foot there are few, if any, clear clinical pathways that can be practically used to drive a service model for diabetic foot care (Apelqvist et al, 1999; SIGN, 2001; National Collaborating Centre for Primary Care, 2004). The recent UK foot care competencies, developed by the Foot in Diabetes UK group (FDUK et al, 2006) and widely adopted, are based more around the skills of the practitioner. *The Diabetic Foot Journal* is developing a clinical pathway for managing

develop strategies for clinical areas lacking a firm evidence base.

The emphasis on dressings and bandages without the core pillars of care by non-specialist teams is a common reason for delayed healing (Young MJ, personal observation). Many people referred to specialist clinics are still wearing the shoes that contributed to the original ulcer. Neuropathic ulcers are often surrounded by a thick rim of callus despite being seen in a podiatry clinic elsewhere. Surgical debridement in specialist clinics is more extensive than many would practice, augmented by larval debridement and even the use of the Versajet system (Smith & Nephew, Hull) when required (McCardle, 2006).

Off-loading is frequently via the use of temporary sandals with off-loading inserts. Specialist clinics will also put people into casts if they do not respond to standardised off-loading.

Treatment of infection

One of the major areas of contention in the management of the diabetic foot remains the treatment of infection. Whether it is a lack of awareness of the rapidity with which infection can spread, a growing alarm over the use of inappropriate antibiotics or pressure to reduce prescribing costs, the use of antibiotics is probably the most frequent reason for GPs to contact the author at his hospital.

So what is the evidence? The choice of antibiotics is frequently guided by either local microbiologists or prescribing advisors who might not be experts in this area. There are no studies with adequate design or power to guide the use of antibiotics in the management of the diabetic foot (Nelson et al, 2006). Similarly, despite the rise in availability and use of dressings containing topical antimicrobials – particularly silver – there are no studies that conclusively prove that these influence healing. However, a few principles can be used for devising a policy.

The signs of infection are often muted in the diabetic foot due, at least in part, to a limited hyperaemic response in the neuropathic or ischaemic foot and the immunosuppressive effects of hyperglycaemia. Therefore a foot which might not clinically appear badly infected may be destroyed by sepsis in a day.

In addition, the use of routine surface swabs has been repeatedly demonstrated as being inadequate to determine the main pathogen within the polymicrobial colonisation of a typical foot ulcer (O'Meara et al, 2006). This is even more relevant if the ulcer has been present for more than 6 weeks – as is often the case. It is for this reason that most diabetic foot teams use antibiotics at the earliest signs of infection and prefer an aggressive approach which can be extended over a long time period (Jude and Unsworth, 2004). This raises the possibility that it may be theoretically likely that short courses of narrow spectrum antibiotics might predispose to the selection of MRSA rather than prolonged broad spectrum effective antibiotic use (Tenover, 2001; Tentolouris et al, 1999).

The author's clinic uses three routine antibiotics, discussed below. While this is supported by limited trial evidence, it is based on 16 years of experience working with the diabetic foot and is in keeping with national and international guidelines (Lipsky et al, 2004).

Co-amoxiclav

This drug is the first line choice oral antibiotic for most superficial infections. It can treat most staphylococci and streptococci infections together with the gut flora which are invariably present and the cause of most infections in Texas grades 1 and 2 ulcers. This is also the most frequently selected antibiotic for foot ulcers in the US and Canada (Lipsky et al, 2004; Embil, 2000). In our practice the 375 mg tablet three times per day has proved effective while the 625 mg seems to offer few advantages but more side effects, particularly nausea. A dose reduction to twice daily is required in patients with moderate to severe renal impairment to prevent excess clavulanate accumulation (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2006)

Clindamycin and ciprofloxacin

Clindamycin is used in our practice for those with penicillin allergies or where the infection is deeper, particularly where there is osteomyelitis (Embil, 2000; Sesin et al, 1990). A previous clinical audit has shown that up to 20 % of patients in the foot

clinic of the Royal Infirmary of Edinburgh have evidence of osteomyelitis and around 90% have evidence of clinical infection (McCormick and Young, 1999). These are similar figures to those published elsewhere. The usual dose range is 150–300 mg four times a day. In nearly 20 years of using this antibiotic in outpatients with diabetic foot ulcers the author has had no major episodes of clostridium difficile despite many weeks of treatment.

Ciprofloxacin is used with clindamycin in serious infections as a last resort before admission. The usual dose range is 250 mg twice daily to 500 mg twice daily (Sesin et al, 1990).

MRSA

The only exceptions to the use of the antibiotics described above would be in people with MRSA where the MRSA is either causing significant infection, osteomyelitis, cellulitis or the ulcer is failing to heal. If an ulcer is healing adequately with MRSA colonisation the author's team would not usually treat the infection. If the individual was already on antibiotics for other infections we would usually leave these unchanged. In this respect we have similar outcomes to the Nottingham diabetic foot group (Game et al, 2003) where the presence of MRSA does not appear to cause significant delay in healing foot ulceration in the absence of invasive infection.

MRSA antibiotics vary according to the sensitivity patterns of the infecting organism Tenover, 2001; Tentolouris et al, 1999). At the Royal Infirmary of Edinburgh these are usually a combination of two from clindamycin, doxycycline, rifampicin or trimethoprim. Although the microbiologists regularly recommend treatment of MRSA with fusidic acid, in the author's experience it is usually poorly tolerated. In the Royal Infirmary of Edinburgh, although the use of linezolid is growing, it has been limited by the high cost and the frequency of blood dyscrasias which approach those seen by Bishop et al (2006).

Inpatient treatment of infection

While oral antibiotics suffice for the majority of individuals there will usually be one or two who need to be hospitalised. The principle reason for this is further infection control. Only rarely in the modern era are people with diabetic foot complications admitted solely for bed rest or metabolic control.

The principle antibiotic regimen for inpatient care in Royal Infirmary of Edinburgh is intravenous vancomycin plus oral ciprofloxacin. This is based upon the high levels of MRSA, the local formulary and microbiological advice.

Vancomycin

Use of vancomycin is limited if the individual has renal impairment – a common co-morbidity in people with diabetic foot complications – or develops side effects. In this case the second choice is teicoplanin and then linezolid. However, because this group often requires lengthy courses of treatment to achieve clinical and microbiological resolution, the numbers of individuals with resistance, blood count abnormalities or other adverse reactions with these treatments is high. These treatments are also more expensive.

Daptomycin

Daptomycin is the first in a new class of antibiotics called cyclic lipopeptides. It is bactericidal against Gram-positive bacteria and is indicated for the treatment of complicated skin and soft tissue infections in adults (European Medicines Agency [EMEA], 2006). This antibiotic has been shown to kill 99.9% of both MRSA and methicillin-susceptible *Staphyloccus aureus* (MSSA) one hour after dosing (Arbeit, 2004). It is administered intravenously at 4 mg/kg over 30 minutes every 24 hours. The dose can be reduced to once every 48 hours if there is a creatinine clearance of less than 30 ml/min. Monitoring is limited to weekly creatine phosphokinase (CPK) level. Elevated levels of CPK are seen in a minority of patients and are reversible.

The trials of daptomycin have so far contained around 200 diabetic foot ulcer cases of serious skin and soft tissue infections, of which half were randomised to receive daptomycin and the rest to standard care including vancomycin and teicoplanin (LaPlante and Rybak, 2004; Arbeit et al, 2004). In these studies, ulcer outcomes were comparable to the standard therapies outlined

above and suggest that daptomycin is as effective as current therapy – with some theoretical advantages in resistant organisms or where there are adverse reactions to conventional therapy.

Conclusion

Diabetic foot ulceration does not appear to be declining and, with increasing numbers of people suffering from diabetes, is likely to remain a growing problem for diabetes teams for many years to come. Managing the diabetic foot is a multifactorial team based process requiring cooperation across specialty and clinical care settings. Along with debridement and off-loading, one of the most important aspects of this is managing the infected foot, the major destroyer of tissue and cause of amputations in diabetic patients. Increasing patterns of antibiotic resistance are making this task more difficult. In the continuing efforts to try and reduce morbidity from the diabetic foot and particularly to prevent spreading infection in patients requiring intravenous therapy or with resistant organisms, newer antibiotics, including daptomycin, will be required. ∎

Conflicting interests

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