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Diabetic Foot Ulcers

Practical Treatment Recommendations

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Contents

Abstract

When treating diabetic foot ulcers it is important to be aware of the natural history of the diabetic foot, which can be divided into five stages: stage 1, a normal foot; stage 2, a high risk foot; stage 3, an ulcerated foot; stage 4, an infected foot; and stage 5, a necrotic foot. This covers the entire spectrum of foot disease but emphasises the development of the foot ulcer as a pivotal event in stage 3, which demands urgent and aggressive management. Diabetic foot care in all stages needs multidisciplinary management to control mechanical, wound, microbiological, vascular, metabolic and educational aspects. Achieving good metabolic control of blood glucose, lipids and blood pressure is important in each stage, as is education to teach proper foot care appropriate for each stage.

Ideally, it is important to prevent the development of ulcers in stages 1 and 2. In stage 1, the normal foot, it is important to encourage the use of suitable footwear, and to educate the patient to promote healthy foot care and footwear habits. In stage 2, the foot has developed one or more of the following risk factors for ulceration: neuropathy, ischaemia, deformity, swelling and callus. The majority of deformities can be accommodated in special footwear and as callus is an important precursor of ulceration it should be treated aggressively, especially in the neuropathic foot. In stage 3, ulcers can be divided into two distinct entities: those in the neuropathic foot and those in the neuroischaemic foot. In the neuropathic foot, ulcers commonly develop on the plantar surface of the foot and the toes, and are associated with neglected callus and high plantar pressures. In the neuroischaemic foot, ulcers are commonly seen around the edges of the foot, including the apices of the toes and back of the heel, and are associated with trauma or wearing unsuitable shoes. Ulcers in stage 3 need relief of pressure (mechanical control), sharp debridement and dressings (wound control), and neuroischaemic foot ulcers may need vascular intervention (vascular control). In stage 4, microbiological control is crucial and severe infections need intravenous antibacterial therapy, and urgent assessment of the need for surgical drainage and debridement. Without urgent treatment, severe infections will progress to necrosis. In stage 5, necrosis can be divided into wet and dry necrosis. Wet necrosis in neuropathic feet requires intravenous antibacterials and surgical debridement, and wet necrosis in neuroischaemic feet also needs vascular reconstruction. Aggressive management of diabetic foot ulceration will reduce the number of feet proceeding to infection and necrosis, and thus reduce the number of major amputations in diabetic patients.

At some time in their life, 15% of people with diabetes mellitus develop foot ulcers that are highly susceptible to infection.[1] This may spread rapidly leading to overwhelming tissue destruction and amputation. Indeed, 85% of amputations are preceded by an ulcer[2] and there is an amputation every 30 seconds throughout the world.[3] However, major advances have taken place. Diabetic foot programmes that have enthusiastically promoted a multidisciplinary approach to heal foot ulcers with aggressive management of infection and ischaemia have achieved a substantial decrease in amputation

rates,[4,5] and a prospective intervention in a US population of Native Americans has substantially lowered rates of amputation.[6,7] Furthermore, a reduction in amputations has been reported nationwide in The Netherlands.[8]

Systematic reviews on prevention[9] and treatment have been carried out,[10-13] and national guidelines have recently been formulated,[14-16] as well as the creation of an International Consensus[17] to which has been added a recent supplement on Diagnosing and Treating the Infected Diabetic Foot.[18] Guidelines have also been issued by the Infectious Disease Society of America on the Diagnosis and Treatment of Diabetic Foot Infections.[19]

The aim of this article is to help practitioners treat diabetic foot ulcers by developing a clear understanding of the overall natural history of the diabetic foot and by recognising a definite framework of crucial stages or milestones that demand appropriate treatment. Sources for this article include recently published literature, but the evidence base is somewhat limited. Furthermore, the existing literature often examines the effect of single interventions.[20] However, in the 'real world', all aspects of care need to be integrated into a multidisciplinary approach. For these reasons, this article also reflects the personal opinions of the author acquired from working in the Diabetic Foot Clinic at King's College Hospital, London, UK for 25 years.

1. The Natural History of the Diabetic Foot

The natural history of the diabetic foot[21] can be divided into the following stages (see table I):

1. The foot is normal and does not have the risk factors of ulceration namely neuropathy, ischaemia, deformity, callus and oedema.

2. At-risk foot. The patient has developed one or more of the risk factors listed in 1.

3. Foot with ulcer. There are two main types of diabetic foot that have characteristic ulceration. Ulceration in the neuropathic foot develops at the sites of high mechanical pressure on the plantar surface. In contrast, ulcers in the foot with both neuropathy and ischaemia (neuroischaemic foot) occur on the margins of the foot and toes, at sites of pressure from poorly fitting shoes.

4. Foot with cellulitis. The ulcer has developed infection with the presence of cellulitis, which can complicate both the neuropathic and neuroischaemic foot.

5. Foot with necrosis. In the neuropathic foot, infection is usually the cause; in the neuroischaemic foot, experience at King's College Hospital indicates that infection is still the most common reason for tissue destruction, although ischaemia contributes.[21]

The foot with extensive necrosis cannot be saved and results in major amputation.

Every diabetic patient can be placed into one of these stages, which all demand appropriate multidisciplinary management to address various aspects of wound, microbiological, mechanical, vascular, metabolic and educational care (table II). Metabolic management is similar for all stages. Thus, tight control of blood glucose is extremely important to preserve neurological function, and treatment of high blood pressure and lipids to maintain cardiovascular function. Advice should be given to smokers to stop.

Table I. Staging of the diabetic foot

Stage 1	Normal foot	Absence of neuropathy, ischaemia, deformity, callus and oedema
Stage 2	At risk foot	Presence of neuropathy, ischaemia, deformity, callus and oedema
Stage 3	Ulcerated foot	Neuropathic ulcer on plantar surface; neuroischaemic ulcer on margins
Stage 4	Infected foot	Local ulcer infection, cellulitis, lymphangitis, osteomyelitis
Stage 5	Necrotic foot	Wet necrosis in the neuropathic foot, secondary to infection; dry necrosis in the neuroischaemic foot, secondary to large artery occlusion

Table II. Multidisciplinary management of stages 1–5

Stage	Mechanical control	Wound control	Microbiological control	Vascular control	Metabolic control	Education
1: Normal foot	Encourage suitable footwear				Control glucose, blood pressure, lipids	Teach patient how to look after feet
2: At-risk foot	Accommodate deformity Remove callus			Statins and antiplatelet agents	Stop smoking	Teach signs of early tissue loss
3: Ulcerated foot	Off-load ulcers	Debridement dressings; wound stimulation	Assessment for early signs of infection Antibacterials: oral/ topical	Revascularise: angioplasty/bypass	Treat impaired renal and cardiac function	Teach ulcer care and early signs of infection
4: Infected foot	Acute stage: bed rest Chronic stage: casts to offload the foot	Surgical debridement VAC pump	Antibacterials: intravenous/ intramuscular	Revascularise: angioplasty/bypass	Control blood glucose with intravenous insulin Optimise cardiac and renal function	Teach patients to observe for signs of infection
5: Necrotic foot	Acute stage: bed rest Chronic stage: casts to offload the foot	Surgical debridement VAC pump	Antibacterials: intravenous	Revascularise: angioplasty/bypass	Control blood glucose with intravenous insulin Optimise cardiac and renal function	Teach patients care of necrotic toes and to look for signs of infection

VAC = vacuum-assisted closure.

2. Stage 1: Normal Foot

2.1 Diagnosis

All diabetic patients should be screened annually to detect risk factors for foot ulcers, namely neuropathy, ischaemia, deformity, callus and swelling. Their absence confirms a normal foot and their presence confirms a foot that is at risk.

2.1.1 Neuropathy

A simple technique to assess pressure sensation is to use a nylon monofilament, which, when applied perpendicular to the foot, buckles at a given force of 10g. If the patient does not detect the filament, then protective pain sensation is lost.[22] The recommended sites to use are the plantar aspects of great toe, heel and five metatarsal heads. After using monofilaments on ten consecutive patients there should be a recovery time of 24 hours before further usage.

Alternatively, vibration perception threshold can be measured using a neurothesiometer, although this is more suitable for research purposes. It assesses large fibre function. A vibration threshold >25 volts is strongly predictive of foot ulceration.[23] Recently, the vibration perception threshold has been shown to be more sensitive than the 10g monofilament for the assessment of individuals at risk for foot ulcers.[24]

2.1.2 Ischaemia

If either dorsalis pedis or posterior tibial pulse can be felt, then it is highly unlikely that there is significant ischaemia. However, failure to palpate the posterior tibial may possibly indicate occlusive disease in the plantar arcade,[25] but if the dorsalis pulse is palpable further investigation is not usually indicated. Brachial systolic pressure and ankle systolic pressure can be measured using a hand-held Doppler, and the pressure index, which is the ratio of ankle systolic pressure to brachial systolic pressure, can be calculated. In healthy individuals, the pressure index is usually >1 but in the presence of ischaemia it is <1. Thus, absence of pulses and a pressure index of <1 confirms ischaemia. A pressure

index <0.5 indicates severe ischaemia. The presence of pulses and a pressure index of >1 rules out ischaemia and further vascular investigations are not necessary.

Many diabetic patients have medial arterial calcification, giving an artificially elevated systolic pressure even in the presence of ischaemia. When the pulses are not palpable and the pressure index is >1, a reduced Doppler arterial waveform usually indicates ischaemia. The value of performing Doppler pressures on asymptomatic patients has been questioned. However, the American Diabetes Association has recommended that the ankle-brachial pressure should be measured in all diabetic patients >50 years of age.[26] Indeed, a recent study showed a prevalence of peripheral arterial disease in 21% of newly diagnosed diabetic patients.[27]

2.1.3 Deformity

Deformity often leads to bony prominences, which are associated with high mechanical pressures on the overlying skin. This leads to ulceration, particularly in the absence of protective pain sensation and when shoes are unsuitable. Common deformities that should be noted include claw toes, pes cavus, hallux valgus, hallux rigidus, hammer toe, Charcot foot (see section 3.2.2) and nail deformities.

2.1.4 Callus

A callus is a thickened area of epidermis which develops at sites of high pressure and friction. It should not be allowed to become excessive, as this can be a forerunner of ulceration (usually in the presence of neuropathy).

2.1.5 Oedema

Oedema is a major factor predisposing to ulceration and often exacerbates a tight fit inside poorly fitting shoes. It also impedes healing of established ulcers.

2.2 Management

Advice on basic foot care including nail cutting techniques, the treatment of minor injuries and the purchase of shoes should be given to the patient and caregivers. Nails should be cut after a bath or shower when they are softer. It is unwise to try to cut the whole nail in one piece. Nails should not be cut too short or left thrusting beyond the end of the toe. The patient should never try to cut out the corner of the nail or dig down the sides. Sensible shoes should be made of soft leather and have broad rounded or squared toes, with a high toe box. The heels should be low to avoid excessive toe pressure on the forefoot and they should be either fitted with laces, Velcro® [1] or buckle straps to prevent movement within the shoe.

3. Stage 2: At-Risk Foot

3.1 Diagnosis

If, on annual review, one or more risk factors for ulceration are detected, then the patient enters stage 2. One of the most important deformities to diagnose is Charcot foot (see section 3.2.2).

3.2 Management

3.2.1 Dry Skin and Fissures

Dry skin should be treated with an emollient such as E45 cream or Calmurid® cream.

3.2.2 Deformity (Including Charcot Foot)

Ideally, deformity should be recognised early and accommodated in properly fitting shoes before ulceration occurs. Footwear can be divided into three broad types:

- sensible shoes (from high street shops) for patients with only minimal sensory loss;
- ready-made stock (off the shelf) shoes, suitable for neuroischaemic feet that need protection along the margins of the foot but that are not greatly deformed;
- customised or bespoke (made to measure) shoes containing cushioned insoles that redistribute areas of high plantar pressure.

Charcot foot refers to bone and joint destruction that occurs in the neuropathic foot.[28] It is important to diagnose it early so as to prevent severe deformi-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ty. The foot presents with unilateral erythema, warmth and oedema. There may be a history of minor trauma. Approximately 30% of patients complain of pain or discomfort. A radiograph at this time may be normal. However, a technetium-99m diphosphonate bone scan will detect early evidence of bony destruction, which in this particular situation is indicative of a Charcot foot. Early diagnosis is essential. Cellulitis, gout and deep vein thrombosis may masquerade as a Charcot foot.

Initially, the foot is immobilised in a cast to prevent bone destruction and deformity that radiographically is shown as fragmentation, fracture, new bone formation, subluxation and dislocation. Immobilisation is continued until there is no longer radiographic evidence of continuing bone destruction and the foot temperature is within 2°C of the contralateral foot.[28] The patient can now progress from a cast to an orthotic walker that is fitted with cradled moulded insoles. Bisphosphonates may be helpful in the treatment of Charcot foot but are not yet fully established therapy.[29] In 30% of patients, Charcot osteoarthropathy subsequently develops in the contralateral foot.[28]

3.2.3 Callus

Patients should never cut their callus off or use callus removers. Instead, the callus should be removed regularly by the podiatrist to prevent ulceration.

3.2.4 Ischaemia

Patients with absent foot pulses should have the pressure index measured to confirm ischaemia and to provide a baseline, so that subsequent deterioration can be detected. If the patient has rest pain or disabling claudication, or the pressure index is <0.5, referral for a vascular opinion should be made. All diabetic patients with evidence of peripheral vascular disease may benefit from antiplatelet agents.

3.2.5 Evidence-Based Management in Stage 2

Recent studies have demonstrated the value of foot protection programmes, education and footwear intervention. A large randomised controlled trial (RCT) demonstrated that amputation rates among people at high risk of ulcers could be significantly reduced by a foot protection programme and it is cost effective.[30] Patients with foot deformities, a history of foot ulceration, and significant vascular or neuropathic disease were randomised to the intervention, which consisted of weekly clinics providing chiropody hygiene, hosiery, protective shoes and education, or to usual care. At 2 years, the ulcer rate in the intervention group was non-significantly reduced to 2.4% compared with 3.5% in the usual care group ($p = 0.14$). However, amputations were reduced 3-fold, with 7 in the intervention group and 23 among the controls ($p < 0.04$).

Education and podiatry may improve knowledge of foot care and in some studies have led to improvements in foot condition.[31] A recent review of the role of patient education in preventing diabetic foot ulceration concluded that there was poor methodology and conflicting results.[32] However, weak evidence suggests that education may have positive but short-lived effects on foot care and short-term effects on the knowledge and behaviour of patients. Malone et al.[33] reported significantly reduced ulcer rates in high-risk patients. Patients who had ulcers or who had undergone amputation were randomised to a one-off, hour-long class (intervention group n = 103 or usual care control n = 100). The intervention group were shown slides of infected feet and amputations, and given a simple checklist of foot care instructions. After 1 year, there were 8 ulcers and 7 amputations in the intervention group compared with 26 ulcers and 21 amputations among the controls ($p = 0.005$ and $p = 0.025$ for each outcome, respectively).

A very small trial (n = 20) found that orthoses without special shoes reduced callus over a year, but the benefit was not significantly greater than that of podiatry.[34] With regard to the prevention of ulcers, most studies have examined the effect of therapeutic shoes on ulcer recurrence. The majority, but not all, have been positive. In a recent review of studies assessing the association between therapeutic footwear and re-ulceration, risk ratios in all of them were <1.0, suggesting some protective footwear benefit.[35] One study (n = 69) found that therapeutic shoes with custom-made insoles could reduce ulcers

in people at high risk.[36] The relapse or new ulcer rate at 1 year was 28% in the intervention group compared with 58% among those who continued to wear their own shoes ($p < 0.01$). However, in the most rigorous experimental study, no statistically significant benefit was observed between control patients wearing their own footwear and intervention patients wearing study footwear.[37] However, in patients with severe foot deformity or prior toe or ray amputation, observational studies suggested a significant protective benefit from therapeutic shoes. However, this issue remains equivocal.[38]

3.2.6 Risk Stratification

All patients in stage 2 are at risk, but national guidelines stratify patients so that limited resources can be channelled to appropriate patients.[14] Patients at high risk with deformity (as well as neuropathy or ischaemia), or with a history of ulceration should have frequent review (1–3 monthly) from a specialised podiatry/foot care team, who should provide intensified foot care, education, and specialised footwear and insoles. Patients at risk with neuropathy or absent pulses should receive enhanced foot care education, inspection of the feet every 3–6 months, and advice on appropriate footwear.

The foot risk classification system of the International Working Group divided patients into four groups: (i) individuals without neuropathy; (ii) patients with neuropathy, but without deformity or peripheral vascular disease; (iii) patients with neuropathy and deformity or peripheral vascular disease; and (iv) patients with a history of foot ulceration or a lower extremity amputation. This system has recently been shown to be effective in predicting clinical outcomes of ulceration and amputation.[39]

4. Stage 3: The Ulcerated Foot

4.1 Diagnosis

Ulceration in the neuropathic foot develops at the sites of high mechanical pressure and shear forces on the plantar surface of the toes.[40] In contrast, neuroischaemic ulcers develop on the margins of the foot and apices of the toes, on sites that are vulnerable to trauma and pressure from poorly fitting shoes.

4.2 Management

Multidisciplinary management is urgently required from a foot ulcer care team with specialised control of mechanical, wound, microbiological, vascular and educational aspects.

4.2.1 Mechanical Control

In the neuropathic foot, the ulcer is managed by off-loading, which means that there is a redistribution of load bearing on the plantar surface of the foot. The most efficient way is by the immediate application of some form of cast, including the removable cast walker such as the Aircast Walker™, the Scotchcast™ boot and the total contact cast.[21] The Aircast is a removable bi-valved cast. It is lined with four air cells, which can be inflated with a hand pump to ensure a close fit. The Scotchcast boot is a simple removable boot made of stockinet, felt and fibreglass tape. The total contact cast is a close fitting plaster of Paris and fibreglass cast applied over minimum padding. It should be reserved for plantar ulcers that have not responded to other casting treatments.[41] It is also useful in patients with recurrent foot ulceration.[42] Non-removable fibreglass casts have also been used.[43]

Recently, standard removable cast walkers have been modified by wrapping plaster around them to make them non-removable and to increase patient compliance. This is just as successful in healing diabetic foot ulcers as the total contact cast.[44] If casting techniques are not available, accommodative sandals such as half shoes can off-load the site of ulceration. However, a comparative study showed that total contact casts healed a higher proportion of wounds in a shorter time than the removable cast and the half shoe.[45]

In the neuroischaemic foot, a high street shoe that is sufficiently long, broad and deep, and fastens with a lace or strap high on the foot to reduce frictional forces on the vulnerable margins of the foot may be sufficient. Alternatively, a ready-made stock shoe, which is wide fitting, may be suitable.

Heel ulcers can be off-loaded by a foam wedge or pressure relief ankle-foot orthosis (PRAFO), which suspends the heel to protect against further breakdown and allow the ulcer to drain. The PRAFO has a washable fleece liner with an aluminium and polypropylene adjustable frame and a non-slip walking neoprene base.[46]

4.2.2 Wound Control

Wound control includes debridement, dressings, stimulation of wound healing, vacuum-assisted closure, hyperbaric oxygen and skin grafting.

Debridement

Debridement is the most important part of wound control and is best carried out with a scalpel. It allows removal of callus and devitalised tissue, and enables the true dimensions of the ulcer to be perceived. It reduces the bacterial load of the ulcer even in the absence of overt infection, restores chronic wounds to acute wounds and releases growth factors to aid the healing process.[47] It also enables a deep swab to be taken for culture. The larvae of the green bottle fly are sometimes used to debride ulcers,[48] especially in the neuroischaemic foot.[49] Maggot debridement therapy has recently been shown to reduce short-term morbidity in non-ambulatory patients with diabetic foot wounds, thus decreasing antibacterial use and risk of amputation.[50]

Dressings

Although moist wound healing is generally carried out in the management of chronic wounds, the situation with diabetic foot ulcers is more complex.[51] Indeed, a fine balance is needed to avoid maceration of tissues while, on the other hand, encouraging conditions that prevent eschar formation and assist cell migration within the wound.[52]

There is no firm evidence that any dressing is better or worse than any other. A review that assessed ten randomised trials and two controlled trials concluded that there was no evidence to support the effectiveness of any one type of protective dressing over any other for treating diabetic foot ulcers.[10] Sterile, non-adherent dressings should cover all ulcers to protect them from trauma, absorb exudate, reduce infection and promote healing. Wounds should be inspected frequently to ensure that problems or complications are detected quickly, especially in patients who lack protective pain sensation.

The following dressing properties are essential for the diabetic foot: ease and speed of lifting, the ability to be walked on without the experiencing disintegration and good exudate control. Dressings should be lifted every day to ensure that problems or complications are detected quickly, especially in patients who lack protective pain sensation.

Stimulation of Wound Healing

When ulcers do not respond to basic treatment, techniques to stimulate wound healing may have to be put into practice. These include Regranex® (platelet-derived growth factor [PDGF]), Dermagraft®, Apligraf® and Hyaff®, and they have been investigated in studies of clean, non-necrotic ulcers. These are expensive treatments and should only be used when basic treatments have failed. Clinical decisions about when to use advanced or more experimental therapies may be based on healing rates. Studies in venous and diabetic ulcers suggest that advancement of >0.7mm per week is 80% sensitive and specific for eventual wound closure.[53]

PDGF (Regranex®) stimulates fibroblasts and other connective tissue cells located in the skin, and is beneficial in enhancing wound healing processes of cell growth and repair. Four placebo-controlled trials of PDGF-BB in neuropathic ulcers have been carried out. The pivotal study of 382 patients demonstrated that Regranex® gel (100 μg/g) healed 50% of chronic diabetic ulcers, which was significantly greater than the 35% healed with a placebo gel.[54]

Two main types of living bioengineered skin have been tested and proven to be effective in diabetic neuropathic foot ulcers. Dermagraft® is an artificial human dermis manufactured through the process of tissue engineering. Human fibroblast cells obtained from neonatal foreskin are cultivated on a three-dimensional polyglactin scaffold. This results in a metabolically active dermal tissue with the structure of a papillary dermis of newborn skin. A randomised controlled multicentre study of 281

patients with neuropathic foot ulcers demonstrated that at 12 weeks 50.8% of the Dermagraft® group experienced complete wound closure, which was significantly greater than in the controls, of whom 31.7% healed ($p < 0.05$).[55] In another 12-week randomised study with living foreskin fibroblasts in a Vicryl® mesh, incidence of complete wound closure of neuropathic foot ulcers was 30% in the active group and 18% in the control group ($p = 0.023$).[56]

Apligraf® consists of a collagen gel seeded with fibroblasts and covered by a surface layer of keratinocytes.[57] In a randomised 12-week trial of 208 patients with neuropathic ulcers, the bilayered construct, Apligraf®, led to complete wound closure in 56% of patients, compared with 38% in controls ($p = 0.0042$). There was a reduced time to complete closure (65 days vs 90 days; $p = 0.0026$).

In addition to the use of growth factors, there has also been considerable interest in the application of extracellular matrix proteins to accelerate healing of diabetic foot ulcers, including collagen and hyaluronic acid.

Hyaff® is an ester of hyaluronic acid, which is a major component of the extra cellular matrix. Hyaluronic acid is a polysaccharide that facilitates growth and movement of fibroblasts, but is unstable when applied to tissues. When it is esterified, it becomes more stable and when in contact with wound exudate produces a hydrophilic gel that covers the wound. This creates a hyaluronic acid-rich tissue interface that promotes granulation and healing.[58]

Some preliminary work suggests that topically applied autologous bone marrow cultured cells can heal human chronic wounds that are recalcitrant to other treatments, including growth factors and bioengineered skin.[59] Promogran™ is a protease inhibitor which consists of oxidised regenerated cellulose and collagen. It inhibits proteases in the wound and protects endogenous growth factor. In a 12-week study of 184 patients, 37% of Promogran™-treated ulcers healed compared with 28% of saline gauze-treated ulcers, which is a non-significant difference.[60]

Vacuum-Assisted Closure

In this technique, the vacuum-assisted closure (VAC) pump applies gentle negative pressure to the ulcer through a tube and foam sponge that are applied to the ulcer over a dressing and sealed in place with a plastic film to create a vacuum. Exudate from the wound is sucked along the tube to a disposable collecting chamber. The negative pressure improves the vascularity and stimulates granulation of the wound. In a recent study, 162 patients with postoperative wounds following partial foot amputation were enrolled into a 16-week, 18-centre, randomised clinical trial in the US. More patients were healed in the VAC pump group than in the control group (43 [56%] vs 33 [39%]; $p = 0.040$). The rate of wound healing, based on the time to complete closure, was faster in the VAC pump group than in controls ($p = 0.005$).[61]

Hyperbaric Oxygen

Adjunctive systemic hyperbaric oxygen therapy has been shown to reduce the number of major amputations in ischaemic diabetic feet.[62] Studies involving relatively small groups of patients have shown that hyperbaric oxygen accelerates the healing of ischaemic diabetic foot ulcers. It is reasonable to use hyperbaric oxygen as an adjunctive in severe or life-threatening wounds.[63]

Skin Grafting

To speed the healing of ulcers that have a clean granulating wound bed, a split skin graft may be harvested and applied to the ulcer. If chosen from within the distribution of sensory neuropathy, the donor site will be less painful.

4.2.3 Microbiological Control

When the skin of the foot is broken, the patient is at great risk of infection as there is a clear portal of entry for invading bacteria. At every patient visit, the foot should be examined for local signs of infection, cellulitis or osteomyelitis. If these are found, antibacterial therapy is indicated. In the presence of neuropathy and ischaemia, the inflammatory response is impaired. The patient lacks protective pain sensation, which would otherwise automatically force them to rest. Furthermore, there may be a

failure of vasodilation as a result of an impaired axon reflex.[64]

Topical antibacterials may be used.[65] Iodine is effective against a wide spectrum of organisms. At high concentrations, it can be toxic to human cells but bacteria are more sensitive to these effects than human cells such as the fibroblast. Povidone-iodine is effective in antibacterial prophylaxis in burn patients. Cadexomer-iodine consists of microspheres formed from a 3-dimensional lattice of cross-linked starch chains and has been used with success in diabetic foot ulcers. Silver compounds are also widely used in antibacterial prophylaxis.[66] Mupirocin is active against Gram-positive bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA).

Uniform agreed practice on the place of antibacterials in the clinically non-infected ulcer has not been established, but is important to maintain close surveillance of the ulcer to detect the signs of infection that would be an indication for antibacterial therapy. A controlled trial was conducted in patients with neuropathic ulcers who were randomised to oral amoxicillin/clavulanic acid or matched placebo. At 20 days' follow-up, there was no significant difference in outcome.[67] In a small RCT, antibacterial therapy of uninfected ulcers reduced the incidence of clinical infection, hospital admission and amputation, and increased the prospects of healing.[64] In this study, 32 patients with new foot ulcers were treated with oral antibacterials and 32 patients without antibacterials. In the group with no antibacterials, 15 patients developed clinical infection compared with none in the antibacterial group ($p < 0.001$). Seven patients in the non-antibacterial group needed hospital admission and amputation was required in three patients (one major and two minor). The ulcers healed in 17 patients in the non-antibacterial group compared with 27 in the antibacterial group ($p < 0.02$). When the 15 patients who developed clinical infection were compared with 17 patients who did not, there were significantly more patients with ischaemia in the infected group. Furthermore, of the 15 patients who became clinically infected, 11 had positive ulcer swabs at the start of the study compared with only 1 patient of 17 in the non-infected group ($p < 0.01$). From this study, it was concluded that diabetic patients with clean ulcers associated with peripheral vascular disease and positive ulcer swabs should be considered for early antibacterial treatment.

Thus, the following recommendations may be made according to the author's clinical practice and based on extensive personal experience. With regard to the neuropathic ulcer, at the first visit if there is no cellulitis, discharge or probing to bone (indicative of osteomyelitis), then debridement, cleansing with saline, application of dressing, daily inspections and off-loading should suffice. However, for the neuroischaemic ulcer, at the initial visit if the ulcer is superficial, oral amoxicillin 500mg three times daily and flucloxacillin 500mg four times daily may be prescribed. If the patient is allergic to penicillin, erythromycin 500mg four times daily or cefadroxil 1g twice a day may be prescribed. If the ulcer is deep, extending to the subcutaneous tissue, trimethoprim 200mg twice a day and metronidazole 400mg three times daily may be added to cover possible Gram-negative bacteria or anaerobes.[46] The patient is reviewed preferably at 1 week, together with the result of the ulcer swab. If the ulcer shows no sign of infection and the swab is negative, treatment is continued without antibacterials. However, in patients with severe ischaemia (pressure index <0.5), antibacterials may be prescribed until the ulcer is healed. If either the neuropathic or neuroischaemic ulcer has a positive swab, the patient may be treated with the appropriate antibacterial according to sensitivities until the repeat swab, taken at weekly intervals, is negative.

4.2.4 Vascular Control

If an ulcer has not responded to optimum treatment within 2 weeks, ankle brachial pressure index is <0.5 and the Doppler waveform is damped, then angiography should ideally be carried out. Severe ischaemia can also be confirmed by a transcutaneous oxygen on the dorsum of the foot of <30mm Hg or a toe pressure of <30mm Hg. Angiography can be performed by a Duplex examination, which combines the features of Doppler waveform analysis

with ultrasound imaging to produce a picture of arterial flow dynamics and morphology. Alternatively, magnetic resonance imaging (MRI)-assisted angiography can be carried out. In contrast to conventional arteriography, this can be performed without the need for intra-arterial catheter and potentially nephrotoxic contrast.

Angioplasty is a valuable treatment to improve arterial flow in the presence of ischaemic ulcers, and is indicated for the treatment of isolated or multiple stenoses as well as short segment occlusions <10cm in length.[68] If lesions are too widespread for angioplasty, then arterial bypass may be considered. However, this is a major and sometimes lengthy operation, which is not without risk and is more commonly reserved to treat the foot with severe tissue destruction that cannot be managed without the restoration of pulsatile blood flow.[65,69]

4.2.5 Education

Patients should be instructed on the principles of ulcer care, stressing the importance of rest, footwear, regular dressings and frequent observation for signs of infection.

5. Stage 4: The Infected Foot

5.1 Diagnosis

Ulcers are often complicated by infection caused by organisms from the surrounding skin. The following signs indicate that an ulcer has become infected: (i) the base of the ulcer changes from healthy pink granulations to yellowish or grey tissue; (ii) a purulent discharge; (iii) an unpleasant smell; (iv) sinuses develop in an ulcer; (v) the edges may become undermined; and (vi) bone or tendon becomes exposed.

Cellulitis presents as localised erythema, warmth and swelling. In severe infection, there is an intense widespread erythema and swelling. Lymphangitis, regional lymphadenitis, malaise, 'flu-like' symptoms, fever and rigors may be present. Often, there is a generalised sloughing of subcutaneous tissues, which eventually liquefy and disintegrate. Infection can also present as a blue/purple discoloration when there is an inadequate supply of oxygen to the soft tissues. In severe infection, blue discoloration can occur in neuroischaemic foot, particularly in the toes, and must not be automatically attributed to worsening ischaemia. It is important to remember that classical signs of infection may not be present because of neuropathy and ischaemia. Only 50% of episodes of severe cellulitis will provoke a fever or leukocytosis.[70]

Osteomyelitis is usually associated with ulceration and cellulitis. In the initial stages, radiographs may be normal but MRI can detect early changes.[71] Clinically, it can be diagnosed if a sterile probe inserted into the ulcer penetrates to bone. This test has a sensitivity of 66%, specificity of 85% and positive predictive value of 89%.[72]

The microbiology of diabetic foot infections is unique, Gram-positive, Gram-negative and anaerobes can be responsible. Staphylococci and streptococci are the most common pathogens. However, infection due to Gram-negative and anaerobic organisms occurs in approximately 50% of patients and often infection is polymicrobial. *S. aureus* is the most common organism, although MRSA is increasingly found in infected ulcers.[73] There is a poor immune response of the diabetic patient to sepsis, and even bacteria regarded as skin commensals may cause severe tissue damage. These include Gram-negative organisms such as *Citrobacter*, *Serratia*, *Pseudomonas* and *Acinetobacter* spp. It is advisable to send swabs or tissue for culture after initial debridement in all stage 4 patients.[74,75] In osteomyelitis, superficial swab cultures do not reliably identify bone bacteria, but percutaneous bone biopsy seems to be safe for patients with diabetic foot osteomyelitis.[76]

5.2 Management

The development of cellulitis and discoloration constitutes a foot care emergency, which requires referral to a specialised foot care team within 24 hours.[14] The underlying principle is to detect the bacteria responsible and treat aggressively.

5.2.1 Microbiological Control

Mild Infections

Mild infections with limited cellulitis can generally be treated with oral antibacterials on an outpatient basis. Several antibacterials have been shown to be effective in clinical trials including cefalexin, clindamycin, ciprofloxacin, ofloxacin, levofloxacin, clindamycin, pexiganan and linezolid.[19] However, no single drug or combination of agents appears to be better than others. Antibacterials used should be consistent with local antibacterial policies, and initially commonly used first-line antibacterials should be prescribed with new broad spectrum antibacterials reserved for later use if resistant organisms are isolated.

On a practical level, the following regimen has been developed for when there are local signs of infection in the ulcer or mild cellulitis, and is based on many years of treating the diabetic foot and significantly reducing amputations.[21] It uses an initial empirical regimen followed by appropriate antibacterials once the results of cultures and sensitivities are available. As initial treatment, amoxicillin, flucloxacillin, metronidazole and trimethoprim should be given orally. If the patient is allergic to penicillin, erythromycin can be substituted for flucloxacillin. On follow-up, if there are no longer signs of infection and no organisms are isolated, antibacterial therapy may be stopped, but if the foot is severely ischaemic with a pressure index <0.5, antibacterials may need to be continued until healing. If no signs of infection are present but organisms are isolated, appropriate antibacterials should be given, and reviewed in 1 week. If signs of infection are present but no organisms are isolated, the original empirical regimen should be continued until there are no signs of infection. If signs of infection are still present and organisms are isolated, the antibacterial regimen should be tailored according to sensitivities. If MRSA is grown, but there are no local or systemic signs of infection, topical mupirocin 2% ointment (if sensitive) may be used. If MRSA is grown and accompanied by local signs of infection, oral therapy with two of the following should be considered: sodium fusidate, rifampicin, trimethoprim and doxycycline, according to sensitivities, together with topical mupirocin 2% ointment.

Severe Infections

Severe deep infections need urgent admission to hospital for broad-spectrum intravenous antibacterials. Infected tissue should be sent for culture after debridement. Clinical and microbiological response rates have been similar in trials of various antibacterials and no single agent or combination has emerged as the most effective.[19] Recently, clinical and microbiological outcomes for patients treated with ertapenem were equivalent to those for patients treated with piperacillin/tazobactam in a randomised, double-blinded, multicentre trial in adults (n = 586) with diabetes and a foot infection classified as moderate to severe and requiring intravenous antibacterials.[77]

In an open-label, randomised study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam, clinical efficacy rates (cure or improvement) were statistically equivalent overall (81% for piperacillin/tazobactam vs 83.1% for ampicillin/sulbactam), and median duration of treatment was similar in the clinically evaluable populations (9 days for piperacillin/tazobactam, 10 days for ampicillin/sulbactam).[78]

It is important to have a practical approach to the treatment of severe infections, reserving complex new antibacterials for resistant organisms, as described in the approach to mild infections. Ideally, the diabetic patient with severe cellulitis needs admission for intravenous antibacterials. If admission is not possible, then ceftriaxone may be given intramuscularly together with metronidazole given orally. Ceftriaxone has been demonstrated to be just as efficacious as ticarcillin/clavulanic acid.[79] On review as an outpatient, if cellulitis is controlled, ceftriaxone intra-muscularly and metronidazole orally should be continued and the patient reviewed 1 week later.

If cellulitis is increasing, then the patient should be admitted for intravenous antibacterials. Quadruple therapy with amoxicillin, flucloxacillin, metronidazole and ceftazidime is indicated. If the pa-

tient is allergic to penicillin, amoxicillin and flucloxacillin should be replaced with erythromycin or vancomycin (with dosages adjusted according to serum concentrations). On follow-up, the infected foot should be inspected daily to gauge the initial response to antibacterial therapy. Appropriate antibacterials should be selected when sensitivities are available. If an infection responds well to the initial antibacterial regimen but the swabs suggest that the isolated organisms are resistant to these antibacterials, it is best to change the antibacterial regimen according to sensitivities, although this is not universal practice.

If no organisms are isolated and yet severe cellulitis of the foot remains, then a repeat tissue sample should be taken, but the quadruple antibacterial therapy, as described previously, should be continued. If MRSA is isolated, then vancomycin (dosage to be adjusted according to serum concentrations) or teicoplanin should be given. These antibacterials may need to be accompanied by a further appropriate oral antibacterial such as sodium fusidate or rifampicin. When the signs of cellulitis have resolved, intravenous antibacterial therapy can be changed to the appropriate oral therapy to include two of the following - sodium fusidate, rifampicin, trimethoprim or doxycycline.

Osteomyelitis

Classically, the treatment of osteomyelitis is surgical removal of bone, but long-term suppressive antibacterial therapy is also used. As osteomyelitis is usually associated with an infected ulcer and cellulitis, broad-spectrum antibacterials should be given initially. On review, antibacterial selection is guided by the results of cultures. Ideally, percutaneous bone biopsy should be carried out,[76] but this is not always practical, especially in ischaemic feet. Bone fragments removed from the base of the wound should then be sent for culture. It is useful to choose antibacterials with good bone penetration, such as sodium fusidate, rifampicin, clindamycin and ciprofloxacin. Antibacterials should be given for at least 12 weeks. Such therapy is often successful, with resolution of cellulitis and healing of the ulcer.[80] However, if after 3–6 months' treatment it is still possible to probe to bone, then operative resection may be necessary.

At first, antibacterials should be given for the associated infected ulcer and cellulitis as described previously. On review, antibacterial selection is guided by the results of deep swabs or tissue. Such conservative therapy is often successful, and is associated with resolution of cellulitis and healing of the ulcer. However, if after 3 months' treatment the ulcer persists, with continued probing to bone (which is fragmented on radiograph), then the neuropathic foot resection of the underlying bone is probably indicated.

When prescribing antibacterials, it is important to keep a very close surveillance for adverse effects, particularly vomiting and diarrhoea. If this does occur, it is advisable to stop the antibacterials, at least for a short period, to prevent the development of *Clostridium difficile* colitis. Abdominal pain associated with diarrhoea and a raised white blood cell count and fever suggests *C. difficile* infection. Stools should be sent for investigation but therapy should be started immediately with either oral vancomycin 125mg four times daily (intravenous vancomycin does not treat *C. difficile*) or metronidazole 400mg three times daily orally. Acidophilus tablets can also be given to restore the intestinal bacterial flora. Patients should be advised to eat live yoghurt when taking antibacterials. In severe cases of diarrhoea, patients may need hospitalisation and intravenous fluids. A useful diagnostic investigation for *C. difficile* colitis is an abdominal CT scan, which will reveal loops of oedematous large bowel.

5.2.2 Vascular Control

It is important to explore the possibility of revascularisation of the infected neuroischaemic foot as improvement of perfusion will help to control infection as well as to promote healing of the ulcer and wounds if operative debridement is carried out. Revascularisation may be carried out by angioplasty or arterial bypass. When there is considerable tissue destruction, it is necessary to restore pulsatile blood flow and this is best carried out by distal bypass.[81]

5.2.3 Wound Control

On admission, the foot should be urgently assessed as to the need for surgical debridement. Indications for urgent surgical intervention are infected sloughy tissue, localised fluctuance and expression of pus, crepitus with gas in the soft tissues on radiograph and purplish discoloration of the skin indicating subcutaneous necrosis. The VAC pump is useful in healing postoperative wounds, especially in neuroischaemic feet.

5.2.4 Education

It is important for the patient to know the warning signs of infection and to understand what they have to do, once they have developed the infection.

6. Stage 5: The Necrotic Foot

6.1 Diagnosis

Necrosis has very grave implications, which threaten the loss of the limb, and is caused by infection or ischaemia or by both together. It is classified as either wet or dry, each with its specific management. In the neuropathic foot, necrosis is invariably wet initially and is nearly always due to a septic arteritis secondary to soft tissue infection complicating a digital or metatarsal ulcer. The arterial lumen is often occluded by a septic thrombus.[21] Both wet and dry necrosis can occur in the neuroischaemic foot. The commonest cause of a black toe is again septic arteritis, exacerbated by large vessel disease in the leg. Dry necrosis can also develop in the neuroischaemic foot and is secondary to a severe reduction in arterial perfusion.

6.2 Management

6.2.1 Wound Control

The practical approach as carried out at Kings College Hospital is described.[46] In the neuropathic foot, operative debridement is nearly always indicated for wet necrosis. There is a good arterial circulation and the wound usually heals as long as infection is controlled. In the neuroischaemic foot, wet necrosis should also be removed when it is associated with severe spreading sepsis. This should be done whether pus is present or not.[21] The VAC pump is useful in healing postoperative wounds, especially in neuroischaemic feet.

In patients where the limb is not immediately threatened and the necrosis is limited to one or two toes, it may be possible to control infection with intravenous antibacterials and proceed to urgent revascularisation and at the same operation perform digital or ray amputation, which should subsequently heal. Some patients may not be suitable for revascularisation. Wet necrosis should be allowed to convert to dry necrosis with the use of antibacterials and then left to auto-amputate.

6.2.2 Microbiological Control

The microbiological principles of managing wet necrosis are similar to that of the management of infection in stage 4. When the patient presents, deep wound swabs and tissue should be sent for culture, and broad-spectrum antibacterial therapy commenced to be adjusted when results of cultures are available. In cases of auto-amputation, antibacterials should only be stopped if the necrosis is dry and mummified, the foot is entirely pain free, and there is no discharge exuding from the demarcation line.

6.2.3 Vascular Control

When necrosis occurs in the background of severe arterial disease, revascularisation is usually necessary to maintain the viability of the limb. In some patients, increased perfusion following angioplasty may be useful, but many patients with necrosis will need arterial bypass to restore pulsatile blood flow to the foot. After operative debridement of wet necrosis, revascularisation is necessary to heal the tissue deficit. Distal bypass is now established as successful treatment in the diabetic lower limb.[82,83]

6.2.4 Mechanical Control

During the peri- and postoperative period, bed rest is essential with elevation of the limb to relieve oedema, but heels must be protected. After operative debridement in the neuroischaemic foot, especially when revascularisation has not been possible, non-weight bearing is advised until the wound is healed. In the neuropathic foot, non-weight bearing is advis-

able initially and then off-loading of the healing postoperative wound may be achieved by casting techniques.

6.2.5 Education

Patients need to understand why they have developed necrosis and be reassured that much can be done to help them. They should be taught how to care for dry necrotic toes and look for signs of infection.

7. Conclusion

In this article, practical treatment recommendations for the diabetic foot ulcers are described within the context of a simple staging system that is based upon the natural history of the diabetic foot. This has been developed to provide a framework for diagnosis and management, and defines five specific stages. In stages 1 and 2, the emphasis is on prevention of ulceration. Stage 3 describes the management of foot ulceration. Finally, stages 4 and 5 deal with the complications of foot ulceration, namely, cellulitis and necrosis. The system has depicted a simple plan of management for each stage, which requires a well organised multidisciplinary approach that should be available to all diabetic patients.

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