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DERMATOLOGY AND WOUND CARE (M REDDY, SECTION EDITOR)

Management of Diabetic Foot Ulcers

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Abstract Diabetes is an increasing urgent global health issue, with an increasing prevalence in those aged 65 or over. Diabetic foot ulcers (DFUs) are a common complication, affecting up to 15 % of those diagnosed with diabetes; they can result in loss of employment, have a significant decrease on quality of life, may lead to limb loss and are costly to healthcare systems. In this paper, we discuss the recent advances in the various management options for diabetic foot ulcers.

Keywords Diabetic foot ulcers · Wound healing · Diabetic foot infection · Wound dressings · Pressure-relieving devices · Diabetic foot surgery · Diabetes

Introduction

Diabetes is an increasing urgent global health issue, with an estimated prevalence of roughly 370 million people worldwide [1•]. In 2014, 6.0 and 9.3 % of the UK and USA population, respectively, were reportedly affected with diabetes [2, 3], with a prevalence of 25.9 % in those aged 65 or over [3].

The combination of peripheral neuropathy, peripheral arterial disease, trauma and/or infection contributes to the development of foot ulceration. Diabetic foot ulcers (DFUs) are a common complication, affecting up to 15 % of those diagnosed with diabetes [4]; they can result in loss of employment, have a significant decrease on quality of life and may lead to limb loss. In 2010 in the USA, 73,000 lower-limb amputations were performed in adults with diabetes, accounting for 60 % of all non-traumatic lower-limb amputations [3], and have reported 5-year mortality rates are as high as 80 % [5]. Lower-limb amputations for diabetic complications are costly, with the UK National Health Service spending over £252 million each year [2]; however, these costings do not take into account the personal costs to the patient such as a reduction in a patient's ability to work. Huge reductions in amputation rates (>50 %) have been demonstrated with increased access to footcare services and introduction of multidisciplinary foot care [6]. In patients with DFUs, a full medical history is essential, which includes history of the wound, previous DFUs or amputations, symptoms suggestive of neuropathy or peripheral arterial disease (PAD), diabetic status, comorbidities and medications. Physical examination should encompass general condition of the extremity including vascular examination and assessment of neuropathy, as well as examination of the ulcer. Examination of the ulcer should assess the conditions of the wound bed, size, depth, location, involvement of bone and presence of exudate. Blood tests including full blood count; serum glucose, urea, and electrolytes; and HbA1C should be performed. In this paper, we discuss the recent advances in the various management options for DFUs.

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Devices and Adjuncts

Pressure-Relieving Devices

Pressure-relieving devices can be classified as non-removable or removable and aim to support the lower leg, off-load affected areas and redistribute pressures across the foot. Non-removable includes the total contact cast, which can be fitted with a heel or 'rocker' to allow the patient to walk. Removable devices are not custom made but are easily removed for reviews and dressing changes and allows the patient to walk with them on (Figs. 1 and 2). Surgical footwear with insoles is often used as are widely available and have high patient acceptance. Padding can also be applied as a temporary pressure relief. The total contact cast (a fibreglass shell that fits around the leg and has a bar on the bottom with a layer of foam around the ulcer) is considered the gold standard therapy in off-loading for DFUs, as compliance can be poor in patients with removable devices (Fig. 3) [7]. The total contact cast is suitable for those with forefoot ulcers, but should be avoided in those with ischaemia or infection. Ulcers on the heel can be managed with pressure relief ankle foot orthoses, a ready-made device used to relieve pressure over the heel and maintain the ankle joint in a suitable position. It is advised to limit standing and walking and to rest with the foot elevated [1•].

Two randomised controlled trials (RCTs) comparing non-removable devices versus no pressure relief reported the number of healed DFUs in a total of 40 participants with 40 ulcers at 92 days [8] (risk ratio (RR) 2.87, 95 % confidence interval (95 % CI) 1.46 to 5.63) and 58 participants with 75 ulcers at 6 months [9] (RR 1.3, 95 % CI 1.05 to 1.68). Both trials reported that significantly more ulcers healed in the non-removable pressure relief group.

Fig. 1 Orthowedge forefoot off-loading shoe to redistribute pressure from plantar forefoot ulcers or following forefoot amputations

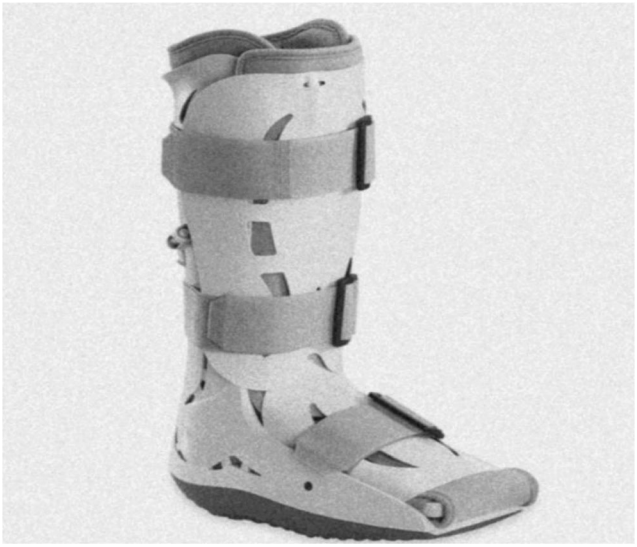

Fig. 2 Pneumatic walker used to off-load plantar ulcers or Charcot-related rocker bottom deformities

Five RCTs with 230 patients were analysed comparing a non-removable total contact device with a removable device [10–14]. A Cochrane review [15] performed a meta-analysis of these five RCTs and showed that DFU healing rates at 12 weeks showed significantly more DFUs healed in the non-removable device group (RR 1.17, 95 % CI 1.01 to 1.36).

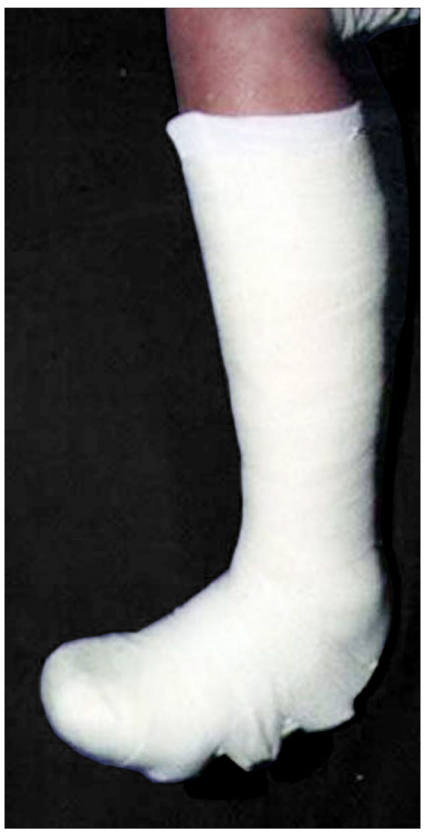

Fig. 3 Total contact cast used to off-load forefoot ulcers

Negative-Pressure Therapy

Negative pressure wound therapy (NPWT) is a technology that is currently used widely in wound care and is promoted as an adjunct therapy to standard care, yet there is limited evidence to support its use. NPWT involves the application of a wound dressing through which a negative pressure (or vacuum) is applied, with wound and tissue fluid being collected into a canister. NPWT is thought to work in a number of ways: collecting wound exudate, keeping the wound clean, increasing perfusion, drawing the wound edges together, off-loading and reduced dressing changes. However, NPWT may be inconvenient for the patient (due to pump noise and lack of portability) and can be associated with high costs.

A systematic review by Ubbink et al. [16] found three RCTs comparing NPWT in DFUs. They reported a shortened wound healing time and increased mean reduction in wound surface area with NPWT when compared to moistened gauze (plus the use of hydrogel in one study); however, they concluded that the studies were methodologically flawed.

A further two RCTs have randomised patients with DFUs to receive either NPWY or advanced moist wound therapy dressings. Blume et al. [17] found a statistically significant increase in the number of wounds healed in the NWPT group (73/172; 42 %) compared with the moist dressing group (48/169, 28 %) (RR 1.49, 95 % CI 1.11 to 2.01) at a 16-week follow-up. Novinsack et al. [18] reported that 90 % of the 19 participants treated in the NPWT group (n=7) had a healed wound compared with 75 % in the moist dressing group (n=12, at a 2-month follow-up).

Two RCTs compared NPWT with gauze dressing for DFUs. Karatepe [19] randomised 67 patients and reported median time to healing was 3.9 weeks in the NPWT group compared with 4.4 weeks in the gauze-dressing group. Mody et al. [20] randomised 48 patients, and results showed that 1/6 (16.6 %) participants allocated to NPWT had healed compared with 4/9 (44.4 %) allocated to dressings (RR 0.38, 95 % CI 0.05 to 2.59).

Trials involving NPWT are frequently sponsored by manufacturers and often have methodological flaws. NPWT may hasten wound healing, but the efficacy and cost-effectiveness have yet to be established.

Hyperbaric Oxygen

Hyperbaric oxygen therapy (HBOT) is the short-term, high-dose oxygen inhalation and diffusion, achieved by breathing concentrated oxygen at a pressure higher than at sea level in hyperbaric chambers [21]. It has been suggested in the management of chronic wounds, in order to increase supply of oxygen to the wound; however, it has limited availability in many countries, requires frequent visits and often cannot be tolerated in a certain patient group such as the elderly.

A Cochrane review analysed pooled data from three randomised controlled trials, looking at 140 patients with DFUs [22]. There was an increase in the rate of ulcer healing with HBOT when compared to standard care at 6 weeks (RR 5.20, 95 % CI 1.25 to 21.66; p=0.02); however, this benefit was no longer evident at longer follow-up. A further RCT [23] randomised 36 patients with DFUs to either HBOT versus control. Results demonstrated a mean increased reduction in ulcer size in the HBOT group 42.4 % compared to the control group 18.1 % (p<0.05); however, they observed an oxidation stress in local ulcer tissue that may offset the effect long term. These findings were confirmed in two further systematic reviews, and concluded that it was not possible to establish the benefits in treating DFUs, including cost-effectiveness [24, 25].

Surgery

Debridement

Debridement is an important component of DFU management, if there is adequate arterial flow. (How to determine arterial sufficiency is detailed further in this paper). Benefits of debridement include removal of necrotic tissue, reduction of pressure, inspection of underlying tissue, drainage of pus, optimisation of topical preparations and stimulation of healing [26]. Debridement can consist of either sharp (surgical), larval, autolytic, mechanical, hydrosurgery or ultrasonic methods.

Sharp (surgical) debridement is an invasive technique involving removal of callus (non-viable, hyperkeratotic tissue), devitalised tissue and foreign bodies as well as debriding wound edges and base down to healthy bleeding tissue using either a curette and/or scalpel. Traditionally, sharp debridement is the gold standard form of debridement, in those with neuropathy allowing procedure without anaesthesia; however, to date, no form of debridement has been proven superior over another as there is insufficient evidence from randomised controlled trials [27].

Mechanical debridement, traditionally involved using wet to dry gauze that dries and adheres to the top layer of the wound bed, and therefore debridement takes place on removal of the dressing. Debridement pads have recently been introduced which comprise a fleece-like contact layer, which is used to remove debris, slough, exudate and necrotic tissue [28].

Hydrosurgery and ultrasonic systems combine lavage or ultrasound (respectively) with sharp debridement in order to removal devitalised tissue. It is a relatively painless procedure and has been shown to reduce bioburden [29].

Larval therapy is a form of atraumatic removal of moist slough using larvae from the greenbottle fly (*Lucilia sericata*); they can ingest pathogenic organisms but cannot remove callus [30]. Larval therapy should be combined with off-loading to avoid crushing the larvae during weight bearing.

Jenson [31] compared hydrogel with wet to moist saline gauze (mechanical) debridement in 31 patients with DFUs. In the hydrogel group, 12/14 (86 %) of patients healed completely compared with 6/17 (46 %) in the control group, (RR 2.43, 95 % CI 1.23 to 4.79) (a statistically significant difference in favour of hydrogel). D'Hemecourt [32] compared hydrogel with standard care in 172 patients with DFUs. Within a 20-week study period, 15/68 (22 %) of patients healed with good wound care alone (daily dressing changes, sharp debridement of ulcer, systemic control of any present infection, off-loading of pressure) compared with 25/70 (36 %) of patients healed with hydrogel, (RR 1.62, 95 % CI 0.94 to 2.80) (no statistically significant difference).

Vascular Disease

Patients with diabetes are twice as likely to have peripheral arterial disease (PAD) compared to those without diabetes [33], and 5-year mortality rates of patients with both DFU and PAD are 50 % [34]. Clinical manifestations of PAD range from mild claudication to limb-threatening ischaemia. However, typical symptoms of PAD in diabetic patients maybe absent, due to underlying neuropathy; therefore, all diabetics over the age of 50 should be regularly assessed with ankle-brachial pressure index (ABPI) [35]. Guidelines recommend that an ABPI value <0.90 should be diagnostic for PAD [36]. It is also important to note that diabetics tend to get earlier arterial wall calcification, resultant in ABPI readings >1.30. These patients with ABPI readings <0.90 and >1.30 should be further assessed with non-invasive imaging including ultrasound, computed tomography angiography, or magnetic resonance angiography, or invasive imaging, including digital subtraction angiography [36]. Choice will depend on cost, local resources and attempt at keeping radiation exposure to a minimum.

Percutaneous transluminal angioplasty (PTA) is a minimally invasive therapeutic procedure widely accepted for the first-line treatment of critical limb ischaemia to prevent limb loss, relieve rest pain and heal ischaemic ulcers [36]. The advantages are avoidance of a general anaesthetic, reduced hospital length of stay, less pain, reduced surgical stress and can be repeated as required, when compared to open bypass surgery. Five-year limb salvage rate following PTA in patients with diabetes is 88 % [37]. There is increasing interest in the use of angiosomal revascularisation, i.e. targeting the direct 'feeding' artery to an area of tissue loss, in order for reperfusion to be directed [38].

Vogel [39] found that mortality rates after endovascular procedures were lower when compared to surgical procedures; however, the difference was only 1 %. There is little robust evidence to support endovascular therapies being superior to surgical procedures. The BASIL Trial [40] is the largest RCT to date, but they did not perform sub-group analysis outcomes in those with diabetes. Neville et al. [41] suggested that patients with DFU and PAD would achieve complete and faster healing from open bypass surgery, compared to endovascular techniques; however, in practice, there is a tendency to attempt endovascular procedures first. TransAtlantic interSocietal Consensus recommends attempt of angioplasty if the short- and long-term benefits to the patient, in terms of symptom improvement, is equivalent to open bypass surgery [36] (Table 1).

Non-vascular Foot Surgery

Debridement and joint resections are often used in the treatment of osteomyelitis that has failed prolonged antibiotic therapy. Piaggesi et al. [42] randomised 42 patients with non-infected DFUs to either surgical excision and/or bone segment removal versus non-surgical treatment and showed an improved ulcer healing rate of 95 % versus 79 %, respectively, at a 6-month follow-up; however, this was not statistically significant.

Lengthening of the Achilles tendon can reduce pressure under the forefoot and has been used in the treatment of diabetic patients who mobilise in the equinus position due to shortening of the gastrocnemius complex. Mueller et al. [43] performed a RCT comparing percutaneous Achilles tendon lengthening and total contact cast versus total contact cast alone in a total of 64 diabetic patients with recurrent or non-healing forefoot ulcers; they demonstrated a lower ulcer recurrence rate of 38 % versus 81 %, respectively, at a 2-year follow-up (p=0.004).

Dorsiflexion osteotomy of the metatarsals is advocated for patients with toe misalignment and provides pressure reduction under the respective metatarsal heads and redistributes the pressure towards the remaining ones [44]. Exostosectomy is performed for removing pseudoexostoses (bony prominences surgically removed) in Charcot foot deformities. External off-loading with an external fixator or Ilizarov frame has the advantage of aligning the limb and compressing the joint and providing a tight pseudoarthrosis [45].

Armstrong et al. [46] performed a retrospective cohort study comparing diabetic patients with hallux interphalangeal joint wounds who either underwent first metarsophalangeal joint arthroplasties versus non-surgical treatment. Faster healing times were achieved in the surgical group, 24.2 versus 67.1 days (p<0.001)

Wound Dressings

The choice of appropriate dressing in the management of DFUs is dependant on a number of factors, including severity and position of wound, and stage of healing, as well as wound bed characteristics such as the need for control of

Table 1 Classification of femoropopliteal lesions according to TASC 2007 Guidelines [36]

Type A single stenosis >10 cm in length, single occlusion >5 cm in length	PTA first choice
Type B multiple stenosis or occlusions, each >5 cm; single stenosis or occlusion >5 cm not involving the infrageniculate popliteal artery; single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass; heavily calcified occlusion >5 cm in length; single popliteal stenosis	PTA first choice
Type C multiple stenosis or occlusions totalling >15 cm with or without heavy calcification or recurrent stenosis or occlusions that need treatment after two endovascular interventions	Stenosis or occlusion >15 cm: surgery preferred
Type D chronic total occlusion of the superficial femoral artery >20 cm. Chronic total occlusion of popliteal artery and proximal trifurcation vessels	Occlusion >20 cm: surgery first choice

microorganisms, exudate absorption, debridement, pain control and atraumatic dressing removal (Table 2).

The ideal dressing for DFUs has been described as one that does not take up too much room in the shoe, performs well in an enclosed environment, can withstand shear forces, absorbs exudate and allows drainage, does not increase the risk of infection and can be changed often and easily [47]. There is little evidence to suggest that one dressing is superior to another, but rather clinical judgement at repeated assessment should be used to select the most appropriate dressing choice [1].

Low-Adherent Dressings

Low-adherent dressings (e.g. Atrauman®, NA dressing®) are cheap, widely available, and useful as a primary dressing in lightly exuding or granulating wounds or in those with sensitive surrounding skin. There has been no statistical difference demonstrated when comparing low-adherent dressings with iodine-impregnated dressing or a modern fluid handling dressing [48].

Semipermeable Films

Semipermeable dressings (e.g. Tegaderm™, Opsite®, Mepore®) are sterile transparent plastic sheeting made from polyurethane coated with hypoallergenic acrylic adhesive, which are permeable to air and water vapour but not fluids and bacteria.

Foam Dressings

Foam dressings (e.g. Allevyn®, Biatain®) normally contain hydrophilic polyurethane or silicone foam and are designed to absorb wound exudate, maintain a moist wound surface and are easy to apply as conform to body contours and have a cushioning affect. No statistically significant difference has been found in the number of DFUs healed when foam dressings were compared to hydrocolloid dressings [49], alginate dressings [47] and basic wound contact dressings [50].

Table 2 Suggested criteria for determining dressing choice in DFUs

Wound attributes	Choice of dressing	Reason for choice of dressing
Necrosis and/or slough	Hydrogel	Donate liquid
	Hydrocolloid	Promote autolysis and debridement
Dry gangrene	Low adherent	Prevent formation of wet gangrene
Wet gangrene	Antimicrobial	Bacterial control
Infection	Antimicrobial	Bacterial control
Low exudate	Hydrocolloid Semipermeable film hydrogel	Maintain a moist wound environment
High exudate	Alginate	Prevent maceration
		High absorbent qualities
Flat/shallow	Hydrogel Foams	Promote a moist wound environment
		Allow visual check
Cavity with sinus	Alginate Hydrogel	Fill the cavity
Cavity with no sinus	Foams Hydrocolloid	Maintain a moist wound environment
	Hydrogel	
	Alginate	

Alginate Dressings

Alginate dressings (e.g. Aquacel®, Sorbsan®, Kaltostat®) are produced from naturally occurring calcium and sodium salts of alginic acid found in a family of brown seaweed. Alginate dressings are highly absorbent and form a hydrophilic gel when in contact with the wound surface, due to the exchange of sodium ions in the wound fluid for calcium ions in the dressing. Evidence from RCTs has demonstrated no statistically significant difference when comparing alginate dressings with low-adherent dressings [51–53] or an antimicrobial (silver) hydrocolloid dressing [54].

Antimicrobial Dressings

There has been popularity of antimicrobial dressing usage, with an increasing awareness of antibiotic resistance. Iodine can be used as either povidone-iodine (impregnated dressing) or cadexomer iodine (ointment, beads or impregnated dressing). Iodine is slowly released, as exudate is absorbed, with resultant reduction in bacterial load. There is potential for systemic uptake of iodine, and therefore thyroid function should be monitored in patients on long-term iodine dressings with large wounds [55].

Silver has been used as an antibacterial agent, in the form of silver sulfadiazine cream or silver impregnated (elemental, inorganic compound or organic complex) in dressings. A RCT comparing silver dressings versus non-silver dressings found difference in healing in venous leg ulcers [56].

PHMB (polyhexamethylene biguanide) is advocated to reduce wound bioburden and has been shown to interact with acidic phosphatidylglycerol, a component of bacterial membranes [57]. It is available as a wound cleanser solution (which is a Has surfactant designed to disrupt biofilms), gel or impregnated wound dressing.

Honey is used as an antimicrobial agent for infected wounds as gel, ointment or impregnated dressing and performs autolytic debridement, stimulates granulation tissue formation and reduces pain and oedema due to anti-inflammatory properties [58]. Honey should be of medical grade, due to the problematic impurities found in natural honey. A Cochrane review concluded there was low-grade evidence to support the use of honey dressings for DFUs [59].

Hydrocolloids

Hydrocolloids (e.g. DuoDERM®, Comfeel®, Granuflex®) are comprised of carboxymethyl cellulose, pectin, gelatin, elastomers and adhesives, on foam or semipermeable film dressings, which form a gel on the wound bed. They provide a moist environment and autolytic debridement and are suitable for wounds with low exudate. A Cochrane review concluded that there was no difference between hydrocolloids and other dressings for healing of DFUs [60].

Hydrogels

Hydrogels (e.g. IntraSite®, Cutimed®) are composed of insoluble polymers with up to 96 % water content and are therefore advocated to maintain a moist environment, as well as autolytic debridement. They should be changed frequently to avoid maceration of the skin edges. The most commonly used are amorphous hydrogels, which come in a viscous gel formation [61]. Evidence suggests there was no difference between hydrogels and other dressings for DFU healing [62].

There is a large amount of different dressings available, and a number of clinical trials involving dressings may have a conflict of interest and do not compare difference dressings with each other. Varying dressing types rarely affect DFU healing rates, but may increase acceptability by patients, and where frequent dressing changes are required, they may be cost-effective.

Biologicals

Tissue-Engineered Products

The advances in the understanding of chronic wound biology have led to the development of tissue-engineered products that can be applied to the wound bed, which contain a collagen matrix, scaffold or dressing that replaces or stimulates the extracellular matrix by facilitating attachment, migration, proliferation, differentiation and three-dimensional spatial organisation of the cell population required for tissue regeneration [63]. These tissue-engineered products can be either acellular (biologically inert and devoid of living cells) or cellular (containing living cells) and can be derived from either biological tissue (animal or human), synthetic or composite.

There have been four RCTs evaluating DFU healing rates with acellular dermal matrix compared to standard care and found increased rates of ulcer healing at 12–16-week follow-up in favour of the acellular dermal matrix [64–67]. Human fibroblast-derived dermal matrix use has been evaluated in four RCTs. All reported increased rates of DFU healing with the cellular matrix compared to standard care at 6–12-week follow-up [68–71]. To date, there has been no RCT comparing the use of acellular with cellular dermal matrix use in DFUs; however, a RCT is currently in progress [72].

Protease-Modulating Dressings

Chronic wounds exhibit increased levels of tissue-degrading enzymes and matrix metalloproteases (MMPs), which subsequently denature growth factors and the extracellular matrix

[73]. Development of dressings has been focused on reducing levels of MMPs by absorbing wound exudate and holding proteases within the dressing structure and inactivating the excess MMPs [74]. A RCT compared Promogran® versus standard of care (moistened gauze and a secondary dressing) in DFUs showed increased healing rates with Promogran® [75].

Growth Factors

Growth factors are secreted regulatory proteins, which can control functions of tissue cells including survival, growth and differentiation. Recombinant human platelet-derived growth factor-BB (PDGF-BB), basic fibroblast growth factor (bFGF) recombinant human epidermal growth factor (rhEGF) and granulocyte macrophage colony-stimulating factor (GM-CSF) are growth factors currently suggested for use in the treatment of wounds [76, 77]. It has been suggested to limit lifetime use due to anxieties over tumourigenesis [78].

PDGF-BB (Becaplermin) is the only growth factor product licensed for use to date and has been proven to be safe for use in DFUs [79, 80]. Regranex gel use in DFUs has been evaluated in three RCTs: No difference was found when used combined with Theragauze when compared to Theragauze alone [81]. It was found to be inferior to an acellular wound matrix use [65], but superior to placebo gel [82].

A RCT evaluated the infiltration of rhEGF in DFUs versus placebo and concluded that it offered a favourable risk-benefit balance in patients with advanced DFU [83]. Topical rhEFG gel has been investigated with two RCTs, both of which reported increased DFU healing compared to placebo [84, 85]. bFGF was found to accelerate DFU healing rates when compared to placebo in a RCT [86]. GM-CSF has been evaluated in a RCT for treating infected foot ulcers in diabetic patients and was associated with more rapid resolution of cellulitis and decreased antibiotic requirements [87].

Stem Cells

Stem cells are thought to migrate to wounded tissue and secrete chemokines and growth factors in order to promote angiogenesis and ECM remodelling [88]. They can be categorised into allogenic and autologous stem cells, based on their source. Allogenic stem cells include placental or amnion-derived mesenchymal and embryonic stem cells. Autologous stem cells include bone marrow-derived endothelial progenitor cells and bone marrow-derived mesenchymal, haematopoietic and adipose-derived stem cells.

Although the use of stem cells is promising from animal studies, only one RCT has investigated the use of stem cells in DFUs. Lu [89] compared bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for the treatment of DFUs and found the healing rate was significantly less with the bone marrow mesenchymal stem cells. Further work is required to determine the use in human subjects.

Platelet-Rich Plasma

There has been recent development of autologous platelet-rich plasma (blood plasma which has been enriched with platelets) [90]. Evidence is currently lacking to determine its efficacy and safety for use in DFUs.

The development of biologicals certainly shows much promise; however, there is only evidence to support the licensed use of acellular and cellular dermal matrix, protease-modulating dressings and PDGF-BB growth factor in humans for DFUs.

Drugs

Antibiotics

Evidence suggests that 56–58 % of patients attending a foot clinic with DFUs are clinically infected [91, 92]. Diabetic patients may not present with classical signs of infection due to underlying immunocompromisation, loss of pain sensation or arterial insufficiency [93••]. It is therefore important to assess for friable granulation tissue, wound undermining, malodour or wound exudate as well as the classic signs of redness, heat and swelling [94]. When clinical infection is suspected in DFUs, cultures should be taken for microbiology. Superficial swabs can be inaccurate due to surface contaminants; therefore, cultures of soft tissue (or bone if osteomyelitis is suspected) or aspiration of pus has a higher yield of the true infective pathogen [93••].

The International Working Group (2011) on the Diabetic Foot [1•] define

- Superficial infection as infection of the skin and soft tissues that does not extend to any structure below the dermis
- Deep infection as infection involving tissues deeper than the dermis, including abscess, septic arthritis, osteomyelitis, septic tenosynovitis and necrotizing fasciitis

Infectious Disease Society of America (IDSA) recommended classifying DFUs by severity and use appropriate antibiotic therapy (Table 3) [93••].

Superficial (or mild) DFUs with skin infections in those who have not previously received antibiotic treatment should be commenced on empirical oral antibiotic therapy to cover Gram-positive cocci (*staphylococcus aureus*, *β-haemolytic streptococci*), unless cultures indicate another antibiotic choice [95]. Treatment with a semisynthetic penicillin with antistaphylococcal activity or a first-generation cephalosporin

Table 3 IDSA classifications of diabetic foot infection [93••]

IDSA infection severity	Clinical manifestation of infection
Uninfected	No symptoms or signs of infection
Mild	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic inflammatory response signs)
	If erythema, must be >0.5 cm to <2 cm around the ulcer
	Exclude the other causes of an inflammatory response of the skin (e.g. Trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
Moderate	Local infection (as described above) with erythema >2 cm or involving structures deeper than skin and subcutaneous tissues (e.g. abscess, osteomyelitis, septic arthritis, fasciitis) and no systemic inflammatory response signs
Severe	Local infection (as described above) with the signs of systemic inflammatory response signs

Infection present, as defined by the presence of at least two of the following criteria:

- Local swelling or induration
- Erythema
- Local tenderness or pain
- Local warmth
- Purulent discharge

Systemic inflammatory response signs, as described by at least two of the following criteria:

- Temperature >38 or <36 °C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg
- White blood cell count >12,000 or <4000 cells μL or >10 % immature (band) forms

for a duration of 1–2 weeks is recommended in mild infections.

Moderate to severe infections tend to be caused by mixed Gram-positive cocci and Gram-negative rods (*Escherichia coli*, *Proteus*, *Klebsiella*) and less so non-fermentative Gram-negative rods (*Pseudomonas*). Obligate anaerobes (*Bacteroides*, *Petostreptococcus*) tend to only be encountered in the presence of ischaemia or necrosis [93••, 95]. Combinations of a fluoroquinolone or a β-lactam antibiotic with anti-β-lactamase activity for up to 4 weeks are recommended in moderate infections. Severe infections should be treated initially with intravenous antibiotics, as the pathogen load is high and adequate serum levels need to be ensured [93••].

Evidence from systematic reviews has shown no single antibiotic regime to be superior over another in the treatment of diabetic foot infections [96–99]. Antibiotic therapy should always be used in combination with other measures such as debridement, off-loading, and surgical procedures as appropriate, in the treatment of DFU infections.

Vasodilators

Nitric oxide is a critical molecular signal and mediator for normal wound healing, and its deficiency has been established as an important mechanism responsible for poor healing in diabetic foot ulcer (DFU) patients [100]. Vasodilators are not commonly used in clinical practice; topical nitroglycerine has been proposed as a treatment for DFUs [101]; however, further work needs to be undertaken.

Prostaglandins have been shown to increase the skin blood flow in the feet of type 2 diabetics [102], and prostacyclin analogues (Iloprost) have been shown to improve limb perfusion in diabetic patients with foot ulcers [103]; however, this has not been formally assessed with high-level evidence, and therefore, vascular intervention should always be considered first line.

Lipid-Lowering Medications

Aggressive cardiovascular risk management has been shown to reduce mortality associated with DFUs by preventing macrovascular disease [104], and it is suggested that statins may be able to slow the progression of microvascular disease [105]. Johansen et al. [106] reported a pilot trial evaluating 6-month atorvastatin use (10 versus 80 mg) in DFUs; they observed a possible beneficial effect of DFU healing with the high-dose statin use. Topical statin use in animal models has demonstrated some benefit in diabetic wound healing [107].

Glycaemic Control

As with all diabetic complications, there is evidence to suggest that wound healing is adversely affected by hyperglycaemia [108]. The American Diabetes Association therefore

recommends maintaining an HbA1C <7 % in order to promote DFU healing [109], whereas in the UK, an HbA1C of <6.5 % is recommended [110]. However, there is a reported risk of traumatic falls associated with hypoglycaemia; thus, the target HbA1C should be higher (≤8.0 %) in frail elderly adults with medical and functional comorbidities and in those whose life expectancy is less than 10 years [111].

Conclusions

Diabetic foot ulcer disease is complex and associated with high morbidity and mortality. The interventions are many and varied and should be tailored to individual patients based on factors related to both wound and patient. There is limited evidence base to date to show value for many of these interventions. The measure of success in much of the evidence is presence or rate of wound healing, however, should patient acceptance, ease of use and/or cost be measures of success in healing of DFUs.

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Compliance with Ethics Guidelines

Conflict of Interest Rhiannon L. Harries and Keith G. Harding declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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