Causes, prevention, and management of diabetes-related foot ulcers

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In this Review, we aim to complement the 2023 update of the guidelines of the International Working Group on the Diabetic Foot. We highlight the complexity of the pathological processes that underlie diabetes-related foot ulceration (DFU) and draw attention to the potential implications for clinical management and outcome. Variation observed in the incidence and outcome of DFUs in different communities might result from differences in study populations and the accessibility of care. Comparing differences in incidence, management, and outcome of DFUs in different communities is an essential component of the quality of disease care. Additionally, these comparisons can also highlight the relationship between DFU incidence, management, and outcome and the structure of local clinical services and the availability of staff with the necessary skills. The clinical outcome is, however, also dependent on the availability of multidisciplinary care and the ability of people with DFUs to gain access to that care.

Introduction

The term diabetes-related foot ulcer (DFU) has been defined as a break in the skin of the foot of a person with diabetes, which penetrates as a minimum to the epidermis and part of the dermis.[1] An ulcer might be triggered by trauma—whether from an accident or from the effect of excessive local forces—or its precipitating cause might not be clear. For the purposes of research and comparison, it is now usual to limit the use of the term DFU to wounds that occur below the malleoli to distinguish them from leg ulcers arising from causes other than diabetes.

A 2002 prospective assessment from the UK reported the average annual DFU incidence to be 2·2% in people with known diabetes.[2] Since this assessment, there has been an increase in publications reporting epidemiological studies of DFUs undertaken in different countries and communities. Most describe an annual incidence of 1% or less,[3] with the exception of one meta-analysis that reported a cumulative DFU incidence of 6%,[4] although the timeframe over which these occurred was not defined. 1-year rates of ulcer recurrence were, however, higher and ranged from 7·7% to 44%.[5–9]

More recent studies suggest a lower incidence of foot ulceration compared with previous studies and there might be many reasons for this.[3] One reason might be due to the advances made in the overall quality of diabetes care. Another might, however, reflect the fact that screening for diabetes is now part of routine clinical practice in many countries and, as a consequence, people with previously undetected diabetes might now be diagnosed at an earlier stage of disease. This conclusion is supported by a decline in the proportion of people with undiagnosed diabetes from 1988 to 2020 in the USA.[10] As many of these people diagnosed earlier will be free from overt complications due to lesser cumulative exposure to hyperglycaemia, it follows that the new, increased, population with diabetes might have a lower overall incidence and prevalence of new DFUs. Unless care is taken to address such changes, it might be incorrectly concluded that the lower incidence (or prevalence) of DFUs in those diagnosed earlier was the result of some other aspect of management.

Despite the differing quantity and quality of the reports of lower incidence of DFU, it is notable that there is also quite wide variation in some of the findings. Interpretation of these findings requires considerable care if underlying causes are to be identified with confidence; while there might be major differences (in incidence, recurrence, prevalence, outcome, etc), it is essential that there is greater standardisation of the criteria used to characterise populations in such studies.

Among the aims of epidemiological studies in the field of DFUs, is the demonstration of the factors that contribute to their occurrence, persistence, and recurrence, and to help define the components of prevention and optimal care for any population. Only when the potential impact of contributory factors is established in different study populations will it be possible to define how best to improve the details of overall care delivery. Recording the incidences and outcomes of ulceration, or of amputation, in different populations is insufficient to improve outcomes for people with DFUs. In this Review, we consider the multiple factors involved in the assessment and management of individuals at risk of, or presenting with, DFUs.

Factors contributing to foot ulceration

The factors contributing to the development and continued morbidity of DFUs can be considered under three headings: predisposition, precipitation, and perpetuation. Multiple processes can predispose to the potential of the skin to breakdown, which precedes the onset of ulceration, but the processes that dominate are linked to either neuropathies or peripheral artery disease, both of which occur more frequently in people with diabetes, compared with people who do not have diabetes (figure 1).

Distal neuropathies are estimated to affect 30–50% of all people with diabetes and their impact depends on the types of nerve affected and the extent of the nerve damage.[11,12] The effects of distal neuropathy on people with diabetes include motor neuropathies, which can cause a change in gait and abnormalities of loading on the foot during day-to-day activity (or inactivity), and sensory

neuropathies, which might lead to reduced awareness of trauma. Loss of sweating caused by autonomic neuropathy could also predispose individuals to skin damage. Peripheral artery disease can be defined as a stenosis or occlusion of an artery (or arteries) from the aorta to the foot associated with a reduction of blood flow to one or both feet. Peripheral artery disease frequently involves the below-knee arteries in diabetes, and these arteries are also frequently affected by medial artery calcification (Mönckeberg's sclerosis). The presence of medial artery calcification is associated with increased mortality and risk of limb loss.[13] Other factors that might contribute to new ulcer onset include personal or cultural attitudes and behaviour, education, comorbidity, and difficulty accessing medical assessment and care.

Ulceration will be precipitated if a foot is predisposed by one or more of the aforementioned processes—whether or not the skin is broken by a single episode of accidental trauma or by repeated or sustained increases in local forces—especially when there is an associated loss of protective sensation. In a large, UK-based study,[2] it was estimated that, in just over half of new ulcers identified over a 2-year period, the precipitating factor was trauma from inappropriate footwear, and a further 6% of new ulcers were the result of self-treatment injury, such as nail cutting or removing callus. Trauma is more likely in communities where footwear is simple or even non-existent, than in communities where footwear is more available.

Impairment of wound healing exists in DFUs, with the median time to re-epithelialisation ranging from 147 days to 237 days depending on ulcer location in the EURODIALE study.[14] Wound healing is a coordinated process that can be divided into four overlapping phases:[15] haemostasis; inflammation, initially involving pro-inflammatory (M1) macrophages transitioning to an anti-inflammatory, healing phenotype (M2); proliferation (re-epithelialisation, matrix deposition, and angiogenesis); and remodelling of collagen into a mature scar. When wound healing is defective in diabetes, it is often characterised by persistent unresolved inflammation, decreased angiogenesis, biofilm involvement, and non-migratory endothelialisation.[16]

Several mechanisms also exist by which distal neuropathy can impair healing of DFUs. The best recognised mechanism is the loss of protective sensation, which will encourage a person to continue with any adverse foot protection behaviours (eg, ill-fitting footwear or self-treatment) that might have precipitated the lesion in the first place. Neuropathies can, however, be associated with a disordered inflammatory response to injury and this can delay wound healing.[17,18] The presence of wound biofilms and underlying infection (including osteomyelitis) can also delay wound healing.[19]

Early assessment and initial management of DFUs

Early expert assessment of either incipient or active ulceration is key to optimal DFU outcomes. Data from the

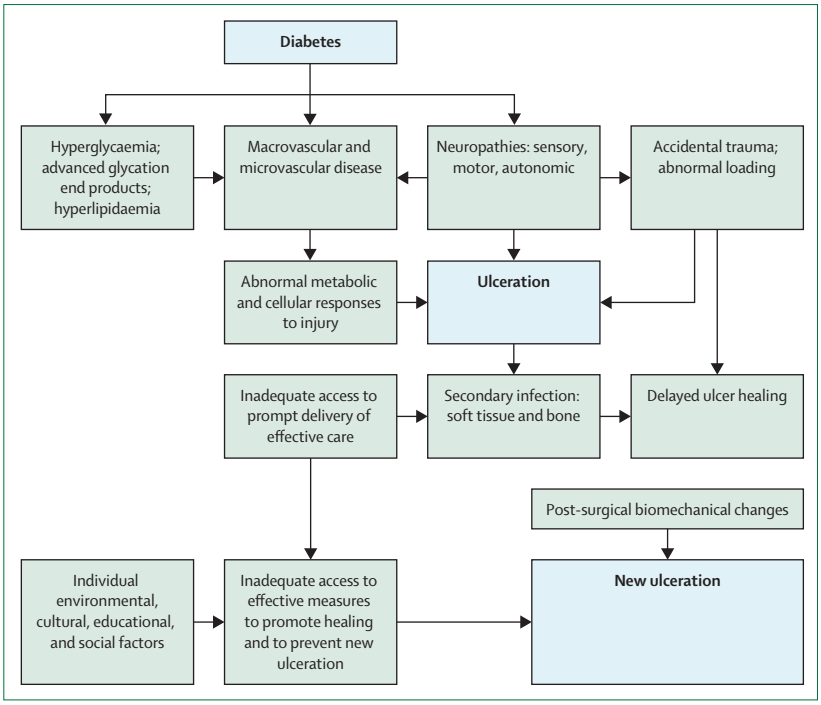

Figure 1: **Pathogenesis of the onset, persistence, and perpetuation of foot ulcers in diabetes**

National Diabetes Foot Care Audit of England and Wales[20] reported the outcome of over 100 000 new ulcer episodes between 2014 and 2021 and showed that there is a statistically significant link between outcome and time from first presentation of a new ulcer episode to first assessment by a member of a specialist multidisciplinary team. Management by multidisciplinary teams has been statistically shown to be associated with fewer major amputations for people with DFU, than when an individual is not assessed by a multidisciplinary team.[21] As a result, the National Diabetes Foot Care Audit suggested that all DFUs should ideally be assessed by an expert in the field within 14 days of presentation.

The principal objective of the first expert assessment of a DFU is to determine whether or not there is infection or limb-threatening peripheral artery disease present, or both, or other threats from disabilities and comorbidities that require specific intervention.[22]

Assessment of peripheral artery disease

Not every person with a DFU and peripheral artery disease has a history of claudication or rest pain. Moreover, the presence of autonomic neuropathy might give the clinical impression of a warm, well-perfused foot and might delay diagnosis of peripheral artery disease.[23] Palpation of foot pulses should be performed at every clinical assessment of the feet. The presence of palpable foot pulses is reassuring, but the diagnostic accuracy of pedal pulse palpation in people with a DFU is low and thus ankle to brachial index, toe to brachial index, toe pressures, and pedal doppler waveforms should ideally

be measured to diagnose or exclude peripheral artery disease and to assess the adequacy of foot perfusion.[24]

Assessment of peripheral artery disease can also be complicated in people with diabetes if the calf arteries have been rendered relatively incompressible by medial artery calcification, meaning that the results of standard tests such as the ankle to brachial index might be uninterpretable, with results that are artifactually high. Using the toe to brachial index for peripheral artery disease diagnosis is preferable as the toe pressures are less likely to be affected by medial artery calcification than when other standard tests are done.[24]

Chronic limb-threatening ischaemia defines advanced peripheral artery disease in people with and without diabetes who have either ischaemic rest pain or tissue loss (ulceration or gangrene) and in whom the perfusion deficit contributes to delayed wound healing and increased risk of amputation.[25] The WIfI classification system is widely used to stage DFUs where vascular surgery expertise is available. This system grades the wound characteristics (W), presence and severity of ischaemia (I), and presence and severity of foot infection (fI) from 0 to 3, which is then used to stage the limb in terms of risk of major amputation and likely benefit from revascularisation.[26] Grade 3 ischaemia in WIfI (toe pressure <30 mm Hg; ankle to brachial index <0·4 or ankle pressure <50 mm Hg, or both) indicates individuals who should be considered for urgent vascular assessment.[24] Less severe limb perfusion deficits are also associated with compromised wound healing and risk of limb loss and should be considered for revascularisation should the wound fail to heal promptly with best-practice care.

When revascularisation is considered for the management of ulceration or gangrene in DFUs, it is important to achieve inline flow from the aorta into the foot to optimise the chance of wound healing. Non-invasive arterial imaging (arterial duplex scan, CT angiography, or magnetic resonance angiography) is performed, depending on local expertise and facilities, for planning revascularisation. Diagnostic angiography might be performed for diagnosis of occlusive lesions and distal vessel patency but is usually done as part of a revascularisation procedure if revascularisation is possible.

Advances in endovascular technologies have enabled vascular specialists to treat long-segment arterial occlusions including those of the tibial and foot arteries, which until recently were only treatable with bypass surgery (or were deemed unreconstructable). Two recent multicentre, randomised controlled trials of patients with chronic limb-threatening ischaemia (rest pain or tissue loss) who required revascularisation for infrainguinal disease and were considered suitable for either a surgical or endovascular approach (ie, in clinical equipoise) have been published.[27,28] The BEST-CLI trial found that in patients with an adequate single segment of great saphenous vein, the outcomes for bypass surgery, in terms of major adverse limb events (major limb reintervention or amputation above the ankle) and death, were superior to the outcomes of endovascular surgery.[27] In the cohort of patients who did not have a single segment of suitable saphenous vein to use as a bypass conduit, the results of bypass surgery and endovascular therapy were not significantly different.[27] The BASIL-2 trial recruited patients (68% of whom had diabetes and 88% had tissue loss) who required infrapopliteal revascularisation (tibioperoneal trunk or tibial arteries, or both) with or without proximal infrainguinal revascularisation to treat limb ischaemia.[28] Patients were randomly allocated to vein bypass treatment or best endovascular treatment. Major amputation or death occurred in 63% of the bypass group versus 53% of the best endovascular therapy group.[28]

The findings of both trials showed that patient mortality was over 10% per year, reflecting the comorbidities that affect these patients, and that the endovascular cohorts required high rates of reintervention (repeat endovascular or open surgery) during follow-up. Patients enrolled in the BASIL-2 trial were older and more frail than those in the BEST-CLI trial.[27,28] All patients in the BASIL-2 trial required infrapopliteal revascularisation, which is a more challenging open or endovascular procedure than above-knee revascularisation, whereas patients from the BEST-CLI trial did not all require distal revascularisation. Only a small proportion of patients with tissue loss were suitable for recruitment to these trials.[29]

These studies support the concept that there is an important role for both endovascular and open revascularisation (and frequently both techniques), and that revascularisation strategies should be based on an assessment of patient fitness, the severity or staging of the foot pathology, the anatomical distribution of arterial disease, the availability of usable autogenous veins, and patient preference.[25] It follows that clinicians managing people with DFUs need to work closely with colleagues who can assess the severity of any peripheral arterial disease present and who can undertake both open and endovascular procedures.[24]

Assessment and management of soft tissue infection complicating ulceration

Infection complicates the management of DFUs as it might impair wound healing and can lead to tissue loss, sepsis, and osteomyelitis. Diabetes-related foot infections (DFIs) are traditionally defined by the multiplication of microorganisms with tissue invasion in DFUs. Although the process is not fully understood, the immunological dysfunction associated with diabetes might contribute to the occurrence of infection.[30–34]

DFUs are colonised by a diverse range of microorganisms, including commensal and pathogenic bacteria, fungi, and viruses.[35] *Staphylococcus aureus* is by far the most prevalent microorganism identified in DFUs in temperate climates, (where the mean annual temperature is above –3°C and below 18°C), whereas Gram-negative bacilli (and especially

Pseudomonas species) dominate in countries with warm climates (mean temperature each month above 18°C).[33,36] Pathogenic bacteria (such as *S aureus* and *Streptococcus agalactiae*) and commensal bacteria (such as *Staphylococcus epidermidis* and *Corynebacterium* species) also coexist with anaerobic bacteria, including, in particular, *Peptostreptococcus* spp. It has been suggested that bacterial communities are organised in functionally equivalent pathogroups.[35] Bacterial competition and cooperation via diffusible molecules modulate bacterial virulence. For instance, *Pseudomonas aeruginosa* enhances the virulence of *S aureus*, whereas *Helcococcus kunzii* reduces the pathogenicity of *S aureus*.[37]

Biofilms contain planktonic and sessile bacteria, including those referred to as persisters, which exhibit resistance to almost all antibiotics. The high level of intercellular transfer of resistance genes could contribute to reducing antibiotic activity on bacteria that remain metabolically active within the biofilm.[38] Such biofilms have been identified in 60–80% of chronic (non-healing) wounds, in contrast to a prevalence of only 6% observed in acute wounds.[39] The natural cellular and non-cellular defences of the host are ineffective in combating mature biofilms, which can lead to chronic inflammation[40] (sometimes referred to as chronic biofilm infection or local infection), which delays ulcer healing.[41] Another effect arising from biofilms is to encourage colonisation by other micro-organisms,[42] but it is not clear to what extent biofilms are either the cause or the consequence of non-healing DFUs.

An alternative approach to reducing biofilm formation is the use of sharp or other physical debridement of the wound, with or without irrigation and regular repetition.[43] Some new techniques have been described for the identification and treatment of DFU-associated biofilms.[44,45] Other options suggested for the reduction of biofilms have included phage therapy, molecules mimicking antimicrobial peptides, and silver nanoparticles.[46,47] Biofilm disruptors with antimicrobial activity, such as topical cadexomer iodine, have also been reported to have some efficacy in the treatment of chronic wounds.[48–50] However, evidence of in-vivo effectiveness for these new approaches remains scarce and the benefit of adoption has not been proven.

The diagnosis of DFU infection is clinical, whereby microbiological assessment is an essential step for introducing appropriate treatments. The clinical features that might suggest infection of a DFU are two or more of the local classic signs of inflammation (local swelling or induration, erythema around wound, local tenderness or pain, local increased warmth, and purulent discharge). Once a DFI is suspected, a microbiological assessment is required to determine the most appropriate antimicrobial therapy and this should be done using tissue samples, such as curettage-biopsy, tru-cut biopsy, and needle aspiration in the case of a subcutaneous abscess.[36] Simple wound swabs can be taken, although it should be noted that swabs do not allow reliable differentiation between pathogens and colonisers,[51] and the quality of the sample sent to the laboratory is key to the differentiation of pathogenic microorganisms from non-pathogenic microorganisms.[36] The aim of microbiological sampling is to identify the microorganisms responsible for the infection. Taking tissue samples rather than superficial swabs, with proper precautions to avoid the contamination of the sample, provides more useful information to help guide the antibiotic treatment. This strategy is in accordance with the International Working Group on the Diabetic Foot (IWDGF) and Infectious Disease Society of America guidelines.[52] The use of inflammatory markers should be considered in situations where clinical examination is diagnostically equivocal or uninterpretable.[52]

Molecular methods cannot usually differentiate living microorganisms from dead microorganisms and do not provide full data about the antibiotic sensitivities of any bacteria that are identified. Therefore, these methods do not yet have a place in the routine care of people with DFIs. One exception is the detection by direct PCR of nasal carriage of meticillin-resistant *S aureus*, which has been shown to be a valid indicator of methicillin-resistant *S aureus* involvement in any associated DFIs and could therefore guide antibiotic choice.[53,54]

	Usual pathogens	Potential empirical regimens
No complicating features	GPC	Cephalexin, clindamycin, or doxycycline
β-lactam allergy or intolerance	GPC	Clindamycin or doxycycline
Recent antibiotic exposure	GPC plus GNB	Amoxicillin–clavulanate, trimethoprim–sulfamethoxazole, or group one carbapenem
High risk for meticillin-resistant *S aureus*	Meticillin-resistant *S aureus*	Linezolid or tedizolid, clindamycin, or trimethoprim–sulfamethoxazole doxycycline
Macerated ulcer or warm climate	GNB including *P aeruginosa*	Piperacillin–tazobactam or group two carbapenem*
Ischaemic limb or necrosis	GPC plus GNB plus strict anaerobic bacteria	Piperacillin–tazobactam, second-generation or third-generation cephalosporin plus clindamycin or metronidazole

GPC=Gram-positive cocci. GNB=Gram-negative bacilli. *P aeruginosa=Pseudomonas aeruginosa*. *S aureus=Staphylococcus aureus*. *An oral antibiotic treatment for *P aeruginosa* is feasible in the outpatient setting with ciprofloxacin in cases of moderate diabetes-related foot infections when these bacteria are highly suspected to play a pathogenic role.

Table: **Empirical antibiotic therapy for soft tissue infection of diabetes-related foot ulcers**

Management of soft tissue infection

Current guidelines recommend initiating treatment as soon as the diagnosis of infection is established to minimise the risk of the spread of infection to deep structures and the bloodstream (table).[52] People with infected non-necrotic acute wounds who have not been treated within 4 weeks with antibiotics are likely to be infected with *S aureus* or β-haemolytic streptococci, or both. In countries with warm climates, the higher prevalence of Gram-negative bacteria might justify the use of broader-spectrum antibiotics. Obligate anaerobes (ie, bacteria that can only survive in oxygen-free

environments) involved in necrotic DFIs are generally susceptible to the antibiotics recommended as first-line choice (table), except for *Bacteroides* spp. Scarcity of data regarding the local microbiological ecology is likely to result in overprescription of empirical broad-spectrum antibiotics.

Parenteral antibiotic therapy is indicated initially in some moderate DFIs and all severe DFIs, but a switch to oral therapy should be considered as soon as a patient is clinically improving and provided there are no contraindications to oral therapy. The duration of antibiotic therapy for DFIs is a matter of debate. Nevertheless, the tendency over recent decades has been to continue antibiotics for only 1–2 weeks for skin and soft-tissue DFIs. An end date should be specified when prescribing antibiotics to reduce the risk that the treatment is continued longer than necessary. Surgery is recommended for the removal of any necrotic material and for draining purulent collections, and should be considered in any moderate or severe DFI (figure 2).[55]

Osteomyelitis

Diabetes-related foot osteomyelitis is a consequence of the spread of microbes from the ulcer to the underlying osteoarticular tissues and can be detected in patients with non-infected DFUs. Certain clinical and biological signs are suggestive of diabetes-related foot osteomyelitis, including an ulcer surface area of more than 2 cm², ulcer depth of more than 3 mm, and an inflamed toe featuring the classic so-called sausage toe appearance.[36] Exploration of the wound using a sterile metal probe to detect hard and gritty contact is known as the probe to bone test; this test is widely used even though the limitations of the available evidence have been emphasised and it is not 100% accurate.[56] A plain x-ray scan of the foot is the standard first test to use when diabetes-related foot osteomyelitis is suspected, given its widespread availability. Sensitivity of x-ray is relatively low, but this can be offset by repeat imaging after 2–3 weeks.

Although bone pathogens can be derived from the DFU microbiota, the concordance of bone versus non-bone specimens is low.[57,58] Nevertheless, bone samples can be obtained either percutaneously or through seemingly healthy overlying skin including at the bedside or perioperatively.[59]

Although surgical resection of infected bone has traditionally been promoted as a treatment for osteomyelitis of the foot in people with diabetes, there is evidence that it is only required in a minority of cases. Primary excision of infected bone was undertaken in only 34 (23%) of 147 patients in a single-centre series managed over a 5-year period. 113 patients were managed without bone resection and 93 (82%) patients in this group remained disease-free for the 2-year duration of follow-up, with only a very small minority (eight [7%]) of patients initially treated with antibiotics only requiring resection after relapse.[60] The decision to reserve bone resection for the minority in whom it was necessary has been reinforced by other studies.[61,62]

Recommendations for the duration of antibiotic therapy for diabetes-related foot osteomyelitis have tended to decrease in recent years and now range from 5 days (post amputation) to a maximum of 6 weeks when no bone resection has been performed, or to 3 weeks after resection of all visibly infected bone but with positive proximal bone margins on culture.[52] The dogma of intravenous antibiotic treatment has been questioned by some experts who have argued that antibiotics with a high bone to blood ratio might justify the choice of oral administration.[63]

Offloading in the management of DFUs

To date, there are no specific therapies that can reverse the loss of either motor or sensory sensation, and therefore people with DFUs are likely to continue applying inappropriate mechanical stress to an area of damaged tissue, most often by walking on it. Therefore, the use of devices is required to reduce the pressure on the affected area (by offloading). This intervention is arguably one of the most important available to promote healing of a DFU. The application of good offloading with total contact casting for 20 days was shown in one outcome-blinded study to shift the inflammatory pathology seen on histological examination of ulcer biopsy samples from one marked by inflammatory elements, matrix alterations, vessel disruption, and debris to a picture of repair with newly formed capillaries and fibroblast proliferation.[64]

Several good-quality randomised controlled trials and meta-analyses have shown the benefit of offloading devices to improve the healing of DFUs.[65] All of these studies found that healing outcomes were substantially improved when below-knee devices were made non-removable—whether as total contact castings or prefabricated knee-high walkers. Total contact castings are custom made at each clinic visit and are thus labour intensive and require a highly skilled workforce in contrast to prefabricated walkers, which can be reused and rendered irremovable at each visit with a layer of casting tape or an irremovable tie. However, an appropriate foot device interface (eg, total contact insole) is required to ensure axial offloading and appropriate pressure redistribution.

Irremovable devices have been shown to be more effective than removable devices with the same offloading potential—healing of DFUs was 17–43% more likely and time to healing was reduced by 8–12 days compared with removeable devices.[66] Nevertheless, below-knee devices are not always well tolerated (particularly in older people with increased risk of falls), and there is a risk of new ulceration resulting from poorly fitting devices or from changes in leg size. Moreover, even in people of working age, tolerance for using below-knee devices is often poor, as the devices limit activities of daily living including driving. Despite these limitations, current IWGDF guidance is that the benefits of using irremovable devices outweigh any potential harm.[67]

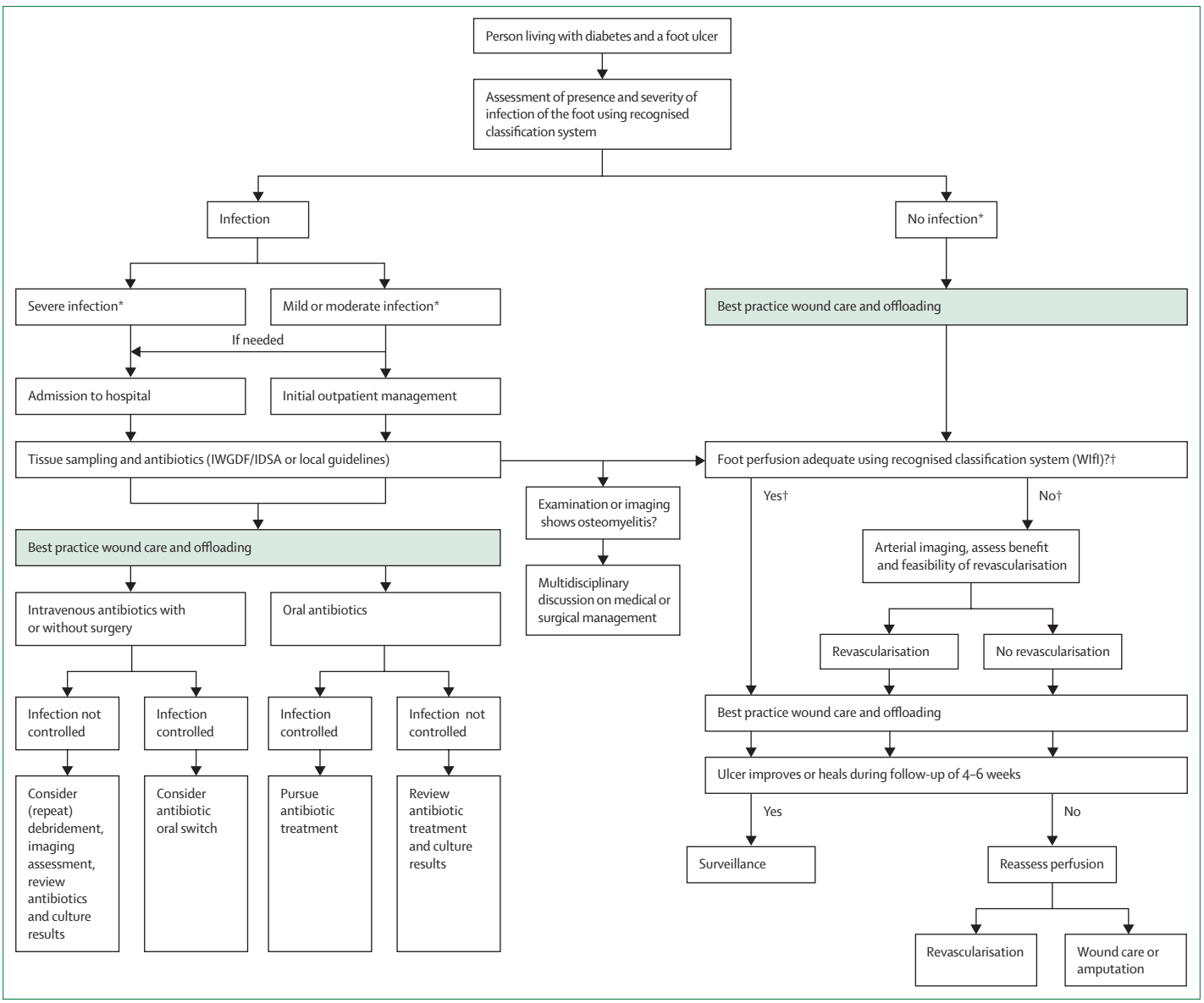

Figure 2: **Initial assessment and treatment of a person with diabetes and a foot ulcer**
IWGDF/IDSA=International Working Group on the Diabetic Foot and Infectious Diseases Society of America. WIfI=wound, ischaemia, and foot infection classification system. *IWGDF/IDSA; Senneville and colleagues.[36] †Using WIfI classification system; the likely benefit or need for revascularisation (table 4; Mills and colleagues[26]).

Other wound healing interventions

As more than 80% of lower limb amputations in people with diabetes are preceded by a foot ulcer, it stands to reason that healing of an ulcer is of fundamental importance in reducing the risk of amputation, and hence the financial burden on society and health-care systems. However, most DFUs will eventually heal with best standard of care treatment of any tissue infection, offloading, and revascularisation where necessary and possible. Many interventions (whether topical or systemic) are available to improve the healing of DFUs but few interventions have any high-quality evidence to support their use, and fewer still have any evidence of cost effectiveness.[68] The IWGDF recently reviewed this subject and made few positive recommendations in their guidelines, despite reviewing over 400 randomised controlled trials of interventions to enhance wound healing of DFUs.[68]

The use of a sucrose octasulfate-impregnated dressing was one of the recommendations made by the IWGDF. In one 2018 randomised controlled trial, participants with hard-to-heal, non-infected, neuro-ischaemic foot ulcers who were treated with the impregnated dressing showed a significant improvement in complete wound healing at week 20, a significantly faster estimated time to heal, and an increased percentage area reduction compared with the

placebo dressing.[69] The sucrose octasulfate within the dressing inhibits protease activity, specifically matrix metalloproteinases, and this is thought to be the mechanism by which accelerated healing takes place.

Similarly, the use of an autologous leukocyte, fibrin, and platelet patch made from 18–36 mL of the patient's own venous blood was reported in a multicentre outcome-blind study. Weekly treatments led to significant improvements in healing, time to healing, and wound area reduction at 20 weeks in patients with hard-to-heal ulcers compared with standard dressings, when used in addition to best standard of care.[70] Although weekly venesection requires skilled personnel and resources, this intervention was recommended for use in the IWGDF guidelines.[68]

Another recommendation was the use of placental-derived products, including amniotic membranes (dried and cryopreserved) and umbilical cord-derived products. All ten trials reviewed by the IWGDF showed positive improvements in absolute healing and time to healing at specific timepoints between 4 weeks and 12 weeks when the intervention was used in addition to standard of care, although only three trials were assessed to be at low risk of bias,[68] and it is acknowledged in these studies that placental-derived products are expensive and cost effectiveness has yet to be ascertained in most health economies.

Oxygen is a critical element in key processes of wound healing, including angiogenesis, collagen deposition, and epithelialisation. In the context of an intervention to enhance wound healing, oxygen can be delivered in two ways. Hyperbaric oxygen therapy involves the patient breathing 100% oxygen at a pressure of two atmospheres or above, which increases the partial pressure of oxygen in hypoxic or ischaemic tissues. Alternatively, topical oxygen, for which several different delivery devices are available, delivers oxygen directly to the wound surface by continuous diffusion or by pressurised systems by use of mechanical devices. Both interventions were given cautious approval in the recent IWGDF guidelines,[68] although high-quality studies are required to determine the cost effectiveness, as both interventions require considerable health-care resources, and it is not clear which types of ulcer will benefit the most.

Amputation

Amputation (minor or major) is one of the complications of diabetes most feared by many people with diabetes, particularly those with foot ulcers,[71] even though the disabilities resulting from major and minor amputation are very different. The incidence of amputation has also become the most widely used measure of ulcer outcome, primarily because data are consistently recorded by most institutions, communities, and countries. However, an amputation is a treatment and not strictly an outcome of disease. As a treatment, amputation will be selected on the basis of clinical circumstances, the attitudes and training of the health-care professionals involved, and the wishes of the patient.

Diabetes is implicated in 61–92% of all major (above ankle) non-traumatic amputations and in 79–89% of minor amputations in all contemporary large national series.[72,73] In several national datasets, the risk of major amputation is from 9·5 times to more than 30 times higher in those with diabetes compared with those without diabetes.[72,73] Although the number of major amputations has generally been reported to be either stable or decreasing in many countries, the number of minor amputations (which account for 70–80% of all amputations) has tended to be either stable or increasing.[72–77]

However, these observations are not universal. Several studies have noted that while the incidences of major and minor amputation would generally be expected to have opposite trends—with major amputation falling while minor amputation rises and vice versa—there are exceptions. Data from the UK have shown that the changes in incidence of major and minor surgery might not be counterposed but could actually be similar, with the incidences of both major and minor amputations being higher in some localities and being lower in others.[78–80] The result is that the incidence of both major and minor amputation varied from 0·64 to 5·25 per 1000 person-years across primary care trusts in England. These studies also observed that similar variation in surgery incidence might be observed in populations both with and without diabetes.

Similarly, Margolis and colleagues[78] reported geographical clustering in the incidence of major amputations in different localities in the USA and suggested that this might be the result of clustering of surgical training and of the resulting surgical treatment preferences regarding clinical care.[81] These findings suggest that different health-care centres might have different thresholds for undertaking amputations, whether from aspects of professional training or from other undefined causes. However, the phenomenon of such regional variation is not unique to amputation in diabetes but is also seen, for example, in operative procedures to treat orthopaedic, vascular, and neoplastic conditions.[74,82] It follows that interpretation of apparent differences in incidence of major and minor amputation requires great care.[83,84]

Other important aspects relating to prevention of DFUs

Prediction of ulcer onset

Most national diabetes guidelines suggest annual screening to identify people with diabetes at risk of later ulceration, even though these recommendations have been mainly based on expert opinion. However, a systematic review that used an international dataset from over 16 000 individuals with diabetes identified from ten cohort studies[85,86] found that those at significantly

increased risk of future ulceration could be identified using just three criteria: a history of foot ulceration, an inability to feel a 10-g monofilament applied to the foot, and at least one absent pedal pulse. By far the greatest risk for the development of new ulceration exists in people with diabetes who have had a previous ulcer (odds ratio 6·589, 95% CI 2·488–17·45).[85]

Recurrence of foot ulceration

The risk of recurrent ulceration after DFU healing is accepted to be approximately 40% at 12 months after first occurrence of DFU.[87] If the cause for ulcer onset and ulcer recurrence can be identified in an individual, it should be possible to explore interventions that might prevent recurrent ulceration. The causes of ulcer recurrence are likely to include factors associated with an earlier episode, including peripheral arterial disease, neuropathy, and comorbidities.

Contribution of social and behavioural factors

A systematic review[88] explored the psychological and behavioural influences on DFU outcomes and suggested that moderate and regular physical activity might protect against new and recurrent ulceration, whereas physical inactivity, non-adherence with recommended footwear, social isolation, and depression increased the risk of recurrent ulceration. Several risk factors for DFU occurrence have been shown to be associated with delayed ulcer healing—including depression, delayed help-seeking, unhelpful cognitions, and non-adherence with pressure-relieving treatments.[88]

Contribution of educational programmes

When an individual or population is identified to be at high risk of ulceration the use of evidence-based preventive strategies could be both effective and cost-effective. Patient education is considered important by most clinicians and improving knowledge about foot care would seem to be important for an individual to reduce future damage. However, the results of education programmes have been disappointing to date and successive systematic reviews have been unable to show any patient outcome benefits from their use.[89] Given the myriad psychological factors associated with delayed ulcer healing, however, it is essential that future DFU research includes an assessment of psychological and behavioural interventions in any suggested preventive programme.

Routine monitoring of the outcomes of care of DFUs

A detail of DFU management that needs particular emphasis is the need for all specialist care units to maintain records of clinical outcomes, and hence obtain evidence of the overall effectiveness of the management of DFUs. This record-keeping should enable all services to deliver care of equivalent quality, and such monitoring of outcomes should be part of accepted good practice. When aiming to undertake a prospective audit of routine clinical practice, specialist care units should work together to agree which DFU outcome measures should be chosen to compare optimal outcome performance between populations. The total number of chosen measures should be reduced to a minimum to ensure the records are not too complicated or time-consuming for medical practitioners to complete. Although research based on electronic health records has become increasingly common in medical research, it is unlikely that it will replace prospective audits of quality of care for DFUs due to insufficient data granularity.

Conclusion

DFUs continue to inflict a harmful toll on people with diabetes due to the medical treatments and lifestyle changes needed to heal these lesions or, in the case of healing failure, limb loss through amputation. Multiple predisposing factors have been identified but educational programmes aimed at preventing DFUs that have used this information have been disappointing. Perpetuation of DFUs might be due to peripheral artery disease, infection or biofilms, and abnormal pressure, all of which could in part be treated effectively with revascularisation with suitable anatomy, antibiotics or debridement, or both, and offloading. In addition, topical treatments such as the leukocyte, fibrin, and platelet patch or sucrose octasulfate-impregnated dressing might increase the rate of healing. The non-healing DFU, which becomes complicated by severe infection or gangrene that is not responsive to limb-sparing interventions, has been shown to be the primary antecedent to lower limb amputation. First assessment by clinicians with expertise in the care of DFUs within 14 days of initial presentation to a health professional has been shown to be associated with improved outcomes. Although DFU incidence has been shown to be declining in some, but not all, studies, several reports have shown an increase in lower limb amputation incidence in people with diabetes. It follows that it is necessary to adopt DFU management strategies to maximise the incidence of wound healing and prevention of ulcer recurrence. Ongoing practice, review, and further research into the prevention and treatment of DFUs is essential.

Search strategy and selection criteria

We identified references for this Review through searches of PubMed for articles published from Jan 1, 1976 to April 5, 2024, using the terms "foot ulceration", "foot infection", "peripheral artery disease", "wound healing", "ulcer prevention", and "amputation" in combination with "diabetes". Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

Contributors

WJ, ES, EJB, FG, and RF were involved in literature search, writing, review and editing, and final approval of the Review. PC assisted the literature search and was involved in review and editing for the review, preparation of the figures and tables, curating endnote library and formatting references, project administration, and had a major role in writing the response to reviewers document.

Declaration of interests

ES has received payment or honoraria for lectures from AdvanzPharma, Merck Sharp and Dohme, Pfizer, Shionogi, Menarini, and BioMérieux; has received support for attending meetings or travel from AdvanzPharma, Merck Sharp and Dohme, Pfizer, Shionogi, Menarini, and BioMérieux; has participated on the data safety monitoring board or advisory board for AdvanzPharma, Debiopharm, and MicuRx; is an editorial board member for IWGDF; and is chair of the National Diabetes Foot Audit England and Wales. EJB reports grant funding from the National Institutes of Health and US Department of Veterans Affairs; payment or honoraria for lectures, presentations, speakers bureaus, or educational events; support for attending meetings or travel from the Korean Diabetes Association, International Society for the Diabetic Foot Diabetes Association of the ROC (Taiwan), and the American Diabetes Association. FG has received grant funding from the National Institute for Healthcare Research; is an editorial board member of the IWGDF; and is chair for the National Diabetes Foot Audit England and Wales. RF is co-chair for the peripheral artery disease working group of the IWGDF. All other authors declare no competing interests.

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