2019

IWGDF Guidelines on the prevention and management of diabetic foot disease

Practical Guidelines

6 Guideline Chapters

Development and methodology

IWGDF Guidelines

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IWGDF Practical guidelines on the prevention and management of diabetic foot disease

Part of the 2019 IWGDF Guidelines on the Prevention and Management of Diabetic Foot Disease

IWGDF Guidelines

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ABSTRACT

Diabetic foot disease results in a major global burden for patients and the health care system. The International working Group on the Diabetic Foot (IWGDF) has been producing evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. In 2019, all IWGDF Guidelines have been updated, based on systematic reviews of the literature and formulation of recommendations by multidisciplinary experts from all over the world.

In this document, the IWGDF Practical Guidelines, we describe the basic principles of prevention, classification and treatment of diabetic foot disease, based on the six IWGDF Guideline chapters. We also describe the organizational levels to successfully prevent and treat diabetic foot disease according to these principles and provide addenda to assist with foot screening. The information in these practical guidelines is aimed at the global community of healthcare professionals who are involved in the care of persons with diabetes.

Many studies around the world support our belief that implementing these prevention and management principles is associated with a decrease in the frequency of diabetes-related lower-extremity amputations. We hope that these updated practical guidelines continue to serve as reference document to aid health care providers in reducing the global burden of diabetic foot disease.

INTRODUCTION

In these International Working Group on the Diabetic Foot (IWGDF) Practical Guidelines we describe the basic principles of prevention and management of diabetic foot disease. The Practical Guidelines are based on the IWGDF Guidelines 2019, consisting of evidence-based guideline chapters on:

- Prevention of foot ulcers in persons with diabetes (1)
- Offloading foot ulcers in persons with diabetes (2)
- Diagnosis, prognosis and management of peripheral artery disease in patients with a foot ulcer and diabetes (3)
- Diagnosis and treatment of foot infection in persons with diabetes (4)
- Interventions to enhance healing of foot ulcers in persons with diabetes (5)
- Classification of diabetic foot ulcers (6)

The authors, as members of the Editorial Board of the IWGDF, have summarized the information from these six chapters, and also provide additional advice based on expert opinion in selected areas for which the guideline chapters were not able to provide evidence-based recommendations. We refer the reader for details and background to the six evidence-based guideline chapters (1-6) and our development and methodology document (7); should this summary text appear to differ from information of these chapters we suggest the reader defer to the specific guideline chapters (1-6). Because terminology in this multidisciplinary area can sometimes be unclear we have developed a separate IWGDF Definitions and Criteria document (8).

The information in these practical guidelines is aimed at the global community of healthcare professionals involved in the care of persons with diabetes. The principles outlined may have to be adapted or modified based on local circumstances, taking into account regional differences in the socio-economic situation, accessibility to and sophistication of healthcare resources, and various cultural factors.

Diabetic foot disease

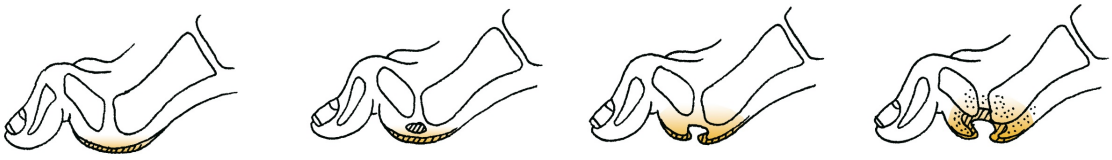
Diabetic foot disease is among the most serious complications of diabetes mellitus. It is a source of major suffering and financial costs for the patient, and also places a considerable burden on the patient's family, healthcare professionals and facilities and society in general. Strategies that include elements of prevention, patient and staff education, multi-disciplinary treatment, and close monitoring as described in this document can reduce the burden of diabetic foot disease.

Pathophysiology

Although both the prevalence and spectrum of diabetic foot disease vary in different regions of the world, the pathways to ulceration are similar in most patients. These ulcers frequently result from a person with diabetes simultaneously having two or more risk factors, with diabetic peripheral neuropathy and peripheral artery disease usually playing a central role. The neuropathy leads to an insensitive and sometimes deformed foot, often causing abnormal loading of the foot. In people with

neuropathy, minor trauma (e.g., from ill- fitting shoes, or an acute mechanical or thermal injury) can precipitate ulceration of the foot. Loss of protective sensation, foot deformities, and limited joint mobility can result in abnormal biomechanical loading of the foot. This produces high mechanical stress in some areas, the response to which is usually thickened skin (callus). The callus then leads to a further increase in the loading of the foot, often with subcutaneous haemorrhage and eventually skin ulceration. Whatever the primary cause of ulceration, continued walking on the insensitive foot impairs healing of the ulcer (see Figure 1).

Figure 1. Mechanism of ulcer developing from repetitive or excessive mechanical stress



Peripheral artery disease (PAD), generally caused by atherosclerosis, is present in up to 50% of patients with a diabetic foot ulcer. PAD is an important risk factor for impaired wound healing and lower extremity amputation. A small percentage of foot ulcers in patients with severe PAD are purely ischaemic; these are usually painful and may follow minor trauma. The majority of foot ulcers, however, are either purely neuropathic or neuro-ischaemic, i.e., caused by combined neuropathy and ischaemia. In patients with neuro-ischaemic ulcers, symptoms may be absent because of the neuropathy, despite severe pedal ischaemia. Recent studies suggest that diabetic microangiopathy (so-called "small vessel disease") does not appear to be the primary cause of either ulcers or of poor wound healing.

CORNERSTONES OF FOOT ULCER PREVENTION

There are five key elements that underpin efforts to prevent foot ulcers:

1. Identifying the at-risk foot
2. Regularly inspecting and examining the at-risk foot
3. Educating the patient, family and healthcare professionals
4. Ensuring routine wearing of appropriate footwear
5. Treating risk factors for ulceration

An appropriately trained team of healthcare professionals should address these five elements as part of integrated care for people at high risk of ulceration (IWGDF risk stratification 3).

1. Identifying the at-risk foot

The absence of symptoms in a person with diabetes does not exclude foot disease; they may have asymptomatic neuropathy, peripheral artery disease, pre-ulcerative signs, or even an ulcer. Examine a person with diabetes at very low risk of foot ulceration (IWGDF risk 0) annually for signs or symptoms

of loss of protective sensation and peripheral artery disease, to identify if they are at-risk for foot ulceration, including doing the following:

- History: Previous ulcer/lower extremity amputation, claudication
- Vascular status: palpation of pedal pulses
- Loss of protective sensation (LOPS): assess with one of the following techniques (see addendum for details):
    - Pressure perception: Semmes-Weinstein 10 gram monofilament
    - Vibration perception: 128 Hz tuning fork
    - When monofilament or tuning fork are not available test tactile sensation: lightly touch the tips of the toes of the patient with the tip of your index finger for 1–2 seconds

LOPS is usually caused by diabetic polyneuropathy. If present, it is usually necessary to elicit further history and conduct further examinations into its causes and consequences; these are outside the scope of this guideline.

2. Regularly inspecting and examining the at-risk foot (IWGDF risk 1 or higher)

In a person with diabetes with loss of protective sensation or peripheral artery disease (IWGDF risk 1-3) perform a more comprehensive examination, including the following:

- History: inquiring about previous ulcer/lower extremity amputation, end stage renal disease, previous foot education, social isolation, poor access to healthcare and financial constraints, foot pain (with walking or at rest) or numbness, claudication
- Vascular status: palpation of pedal pulses
- Skin: assessing for skin colour, temperature, presence of callus or oedema, pre-ulcerative signs
- Bone/joint: check for deformities (e.g., claw or hammer toes), abnormally large bony prominences, or limited joint mobility. Examine the feet with the patient both lying down and standing up
- Assessment for loss of protective sensation (LOPS), if on a previous examination protective sensation was intact
- Footwear: ill-fitting, inadequate, or lack of footwear.
- Poor foot hygiene, e.g. improperly cut toenails, unwashed feet, superficial fungal infection, or unclean socks
- Physical limitations that may hinder foot self-care (e.g. visual acuity, obesity)
- Foot care knowledge

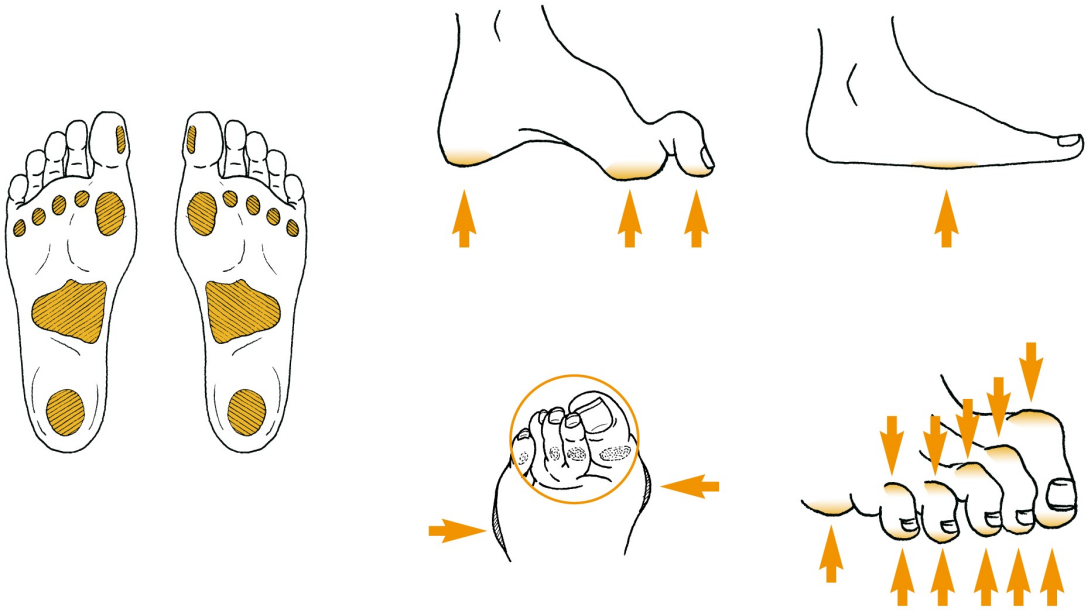
Following examination of the foot, stratify each patient using the IWGDF risk stratification category system shown in Table 1 to guide subsequent preventative screening frequencies and management. Areas of the foot most at-risk are shown in Figure 2. Any foot ulcer identified during screening should be treated according to the principles outlined below.

Table 1. The IWGDF 2019 Risk Stratification System and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Frequency*
0	Very low	No LOPS and No PAD	Once a year
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD, *or* LOPS + foot deformity *or* PAD + foot deformity	Once every 3-6 months
3	High	LOPS or PAD, *and* one or more of the following: - history of a foot ulcer - a lower-extremity amputation (minor or major) - end-stage renal disease	Once every 1-3 months

* Screening frequency is based on expert opinion, since there is no published evidence to support these intervals.

Figure 2. Areas of the foot at highest risk for ulceration

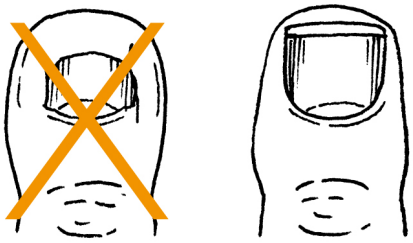


3. Educating patients, family and healthcare professionals about foot care

Education, presented in a structured, organized and repeated manner, is widely considered to play an important role in the prevention of diabetic foot ulcers. The aim is to improve a patient's foot self-care knowledge and self-protective behaviour, and to enhance their motivation and skills to facilitate adherence to this behaviour. People with diabetes, in particular those with IWGDF risk 1 or higher, should learn how to recognize foot ulcers and pre-ulcerative signs and be aware of the steps they need to take when problems arise. The educator should demonstrate specific skills to the patient, such as how to cut toe nails appropriately (Figure 3). A member of the healthcare team should provide structured education (see examples of instructions below) individually or in small groups of people, in

multiple sessions, with periodical reinforcement, and preferably using a mixture of methods. The structured education should be culturally appropriate, account for gender differences, and align with a patient's health literacy and personal circumstances. It is essential to assess whether the person with diabetes (and, optimally, any close family member or carer) has understood the messages, is motivated to act and adhere to the advice, to ensure sufficient self-care skills. Furthermore, healthcare professionals providing these instructions should receive periodic education to improve their own skills in the care for people at high-risk for foot ulceration.

Figure 3. The proper way to cut toe nails



Items to cover when educating the person at-risk for foot ulceration (IWGDF risk 1 or higher):

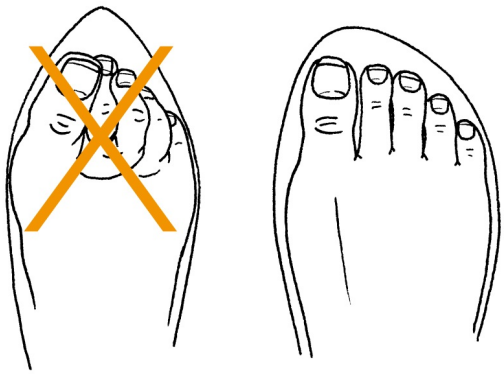
- Determine if the person is able to perform a foot inspection. If not, discuss who can assist the person in this task. Persons who have substantial visual impairment or physical inability to visualise their feet cannot adequately do the inspection
- Explain the need to perform daily foot inspection of the entire surface of both feet, including areas between the toes
- Ensure the patient knows how to notify the appropriate healthcare professional if measured foot temperature is perceptibly increased, or if a blister, cut, scratch or ulcer has developed
- Review the following practices with the patient:
  - Avoid walking barefoot, in socks without footwear, or in thin-soled slippers, whether at home or outside
  - Do not wear shoes that are too tight, have rough edges or uneven seams
  - Visually inspect and manually feel inside all shoes before you put them on
  - Wear socks/stocking without seams (or with the seams inside out); do not wear tight or knee-high socks (compressive stocking should only be prescribed in collaboration with the foot care team), and change socks daily
  - Wash feet daily (with water temperature always below 37°C), and dry them carefully, especially between the toes
  - Do not use any kind of heater or a hot-water bottle to warm feet
  - Do not use chemical agents or plasters to remove corns and calluses; see the appropriate healthcare professional for these problems
  - Use emollients to lubricate dry skin, but not between the toes
  - Cut toenails straight across (see Figure 3)
  - Have your feet examined regularly by a healthcare professional

4. Ensuring routine wearing of appropriate footwear

In persons with diabetes and insensate feet, wearing inappropriate footwear or walking barefoot are major causes of foot trauma leading to foot ulceration. Persons with loss of protective sensation (LOPS) must have (and may need financial assistance to acquire) and should be encouraged to wear, appropriate footwear at all times, both indoors and outdoors. All footwear should be adapted to conform to any alteration in foot structure or foot biomechanics affecting the person's foot. People without LOPS or PAD (IWGDF 0) can select properly fitting off-the-shelf footwear. People with LOPS or PAD (IWGDF 1-3) must take extra care when selecting, or being fitted with, footwear; this is most important when they also have foot deformities (IWGDF 2) or have a history of a previous ulcer/amputation (IWGDF 3).

The inside length of the shoe should be 1-2 cm longer than their foot and should not be either too tight or too loose (see Figure 4). The internal width should equal the width of the foot at the metatarsal phalangeal joints (or the widest part of the foot), and the height should allow enough room for all the toes. Evaluate the fit with the patient in the standing position, preferably later in the day (when they may have foot swelling). If there is no off-the-shelf footwear that can accommodate the foot (e.g., if the fit is poor due to foot deformity) or if there are signs of abnormal loading of the foot (e.g., hyperaemia, callus, ulceration), refer the patient for special footwear (advice and/or construction), possibly including extra-depth shoes, custom-made shoes, insoles, or orthoses.

Figure 4. Footwear should be sufficiently wide to accommodate the foot without excessive pressure on the skin



To prevent a recurrent plantar foot ulcer, ensure that a patient's therapeutic footwear has a demonstrated plantar pressure relieving effect during walking. When possible, demonstrate this plantar pressure relieving effect with appropriate equipment, as described elsewhere (1). Instruct the patient to never again wear the same shoe that has caused an ulcer.

5. Treating risk factors for ulceration

In a patient with diabetes treat any modifiable risk factor or pre-ulcerative sign on the foot. This includes: removing abundant callus; protecting blisters, or draining them if necessary; appropriately treating ingrown or thickened nails; and, prescribing antifungal treatment for fungal infections. This treatment should be repeated until these abnormalities resolve and do not recur over time, and should be performed by an appropriately trained healthcare professional. In patients with recurrent ulcers due to foot deformities that develop despite optimal preventive measures as described above, consider surgical intervention.

ASSESSMENT AND CLASSIFICATION OF FOOT ULCERS

Health care professionals should follow a standardized and consistent strategy for evaluating a foot ulcer, as this will guide further evaluation and therapy. The following items should be addressed:

Type

By history and clinical examination, classify the ulcer as neuropathic, neuro-ischaemic or ischaemic. LOPS is characteristic for a neuropathic ulcer. As a first step in seeking the presence of PAD, take a symptom-directed history and palpate the foot for pedal pulses. That said, there are no specific symptoms or signs of PAD that reliably predict healing of the ulcer. Therefore, examine the arterial pedal wave forms and measure the ankle pressure and ankle brachial index (ABI), using a Doppler instrument. The presence of an ABI 0.9-1.3 or a triphasic pedal pulse waveform largely excludes PAD, as does a toe brachial index (TBI) ≥0.75. However, ankle pressure and ABI can be falsely elevated due to calcification of the pedal arteries. In selected cases, other tests, such as measurements of toe pressure or transcutaneous pressure of oxygen ($TcpO_2$), are useful to assess the vascular status of the foot.

Cause

Wearing ill-fitting shoes and walking barefoot are practices that frequently lead to foot ulceration, even in patients with exclusively ischaemic ulcers. Therefore, meticulously examine shoes and footwear behaviour in every patient with a foot ulcer.

Site and depth

Neuropathic ulcers most frequently develop on the plantar surface of the foot, or in areas overlying a bony deformity. Ischemic and neuro-ischemic ulcers more commonly develop on the tips of the toes or the lateral borders of the foot.

Determining the depth of a foot ulcer can be difficult, especially in the presence of overlying callus or necrotic tissue. To aid assessment of the ulcer, debride any neuropathic or neuro-ischemic ulcers that is surrounded by callus or contains necrotic soft tissue at initial presentation, or as soon as possible. Do *not*, however, debride a non-infected ulcer that has signs of severe ischemia. Neuropathic ulcers can usually be debrided without the need for local anaesthesia.

Signs of infection

Infection of the foot in a person with diabetes presents a serious threat to the affected foot and limb and must be evaluated and treated promptly. Because all ulcers are colonised with potential pathogens, diagnose infection by the presence of at least two signs or symptoms of inflammation (redness, warmth, induration, pain/tenderness) or purulent secretions. Unfortunately, these signs may be blunted by neuropathy or ischaemia, and systemic findings (e.g., pain, fever, leucocytosis) are often absent in mild and moderate infections. Infections should be classified using the IDSA/IWGDF scheme as mild (superficial with minimal cellulitis), moderate (deeper or more extensive) or severe (accompanied by systemic signs of sepsis), as well as whether or not they are accompanied by osteomyelitis (4).

If not properly treated, infection can spread contiguously to underlying tissues, including bone (osteomyelitis). Assess patients with a diabetic foot infection for the presence of osteomyelitis, especially if the ulcer is longstanding, deep, or located directly over a prominent bone. Examine the ulcer to determine if it is possible to visualise or touch bone with a sterile metal probe. In addition to the clinical evaluation, consider obtaining plain radiographs in most patients seeking evidence for osteomyelitis, tissue gas or foreign body. When more advanced imaging is needed consider magnetic resonance imaging, or for those in whom this is not possible, other techniques (e.g., radionuclide or PET scans).

For clinically infected wounds obtain a tissue specimen for culture (and Gram-stained smear, if available); avoid obtaining specimens for wound cultures with a swab. The causative pathogens of foot infection (and their antibiotic susceptibilities) vary by geographic, demographic and clinical situations, but *Staphylococcus aureus* (alone, or with other organisms) is the predominant pathogen in most cases. Chronic and more severe infections are often polymicrobial, with aerobic gram-negative rods and anaerobes accompanying the gram-positive cocci, especially in warmer climates.

Patient related factors

Apart from a systematic evaluation of the ulcer, the foot and the leg, also consider patient related factors that can affect wound healing, such as end-stage renal disease, oedema, malnutrition, poor metabolic control or psycho-social problems.

Ulcer classification

Assess the severity of infection using the IWGDF/ISDA classification criteria (4,6) and in patients with PAD we recommend using the WIfI (wound/ischaemia/infection) system to stratify amputation risk and revascularisation benefit (3,6). For communication among healthcare professionals we recommend the SINBAD system, which can also be used for audit of outcome of populations (6).

PRINCIPLES OF ULCER TREATMENT

Foot ulcers will heal in the majority of patients if the clinician bases treatment on the principles outlined below. However, even optimum wound care cannot compensate for continuing trauma to the wound bed, or for inadequately treated ischemia or infection. Patients with an ulcer deeper than the subcutaneous tissues often require intensive treatment, and, depending on their social situation, local resources and infrastructure, they may need to be hospitalised.

1. Pressure offloading and ulcer protection

Offloading is a cornerstone in treatment of ulcers that are caused by increased biomechanical stress:

- The preferred offloading treatment for a neuropathic plantar ulcer is a non-removable knee-high offloading device, i.e, either a total contact cast (TCC) or removable walker rendered (by the provider fitting it) irremovable
- When a non-removable knee-high offloading device is contraindicated or not tolerated by the patient, consider using a removable knee-high offloading device. If such a device is contraindicated or not tolerated, consider using an ankle-high offloading device. Always educate the patient on the benefits of adherence to wearing the removable device.
- If other forms of biomechanical relief are not available, consider using felted foam, but only in combination with appropriate footwear
- When infection or ischemia are present, offloading is still important, but be more cautious, as discussed in the IWGDF offloading guideline (2).
- For non-plantar ulcers, use a removable ankle-high offloading device, footwear modifications, toe spacers, or orthoses depending on the type and location of the foot ulcer.

2. Restoration of tissue perfusion

- In patients with either an ankle pressure <50mm Hg or an ABI <0.5 consider urgent vascular imaging and, when findings suggest it is appropriate, revascularisation. Also consider revascularisation if the toe pressure is <30mmHg or $TcpO_2$ is <25 mmHg. However, clinicians might consider revascularisation at higher pressure levels in patients with extensive tissue loss or infection, as discussed in more detail in the IWGDF PAD Guideline (3)
- When an ulcer fails to show signs of healing within 6 weeks, despite optimal management, consider revascularisation, irrespective of the results of the vascular diagnostic tests described above
- If contemplating a major (i.e., above the ankle) amputation, first consider the option of revascularization
- The aim of revascularisation is to restore direct flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the wound. But, avoid revascularisation in patients in whom, from the patient perspective, the risk–benefit ratio for the probability of success is unfavourable
- Select a revascularisation technique based on both individual factors (such as morphological distribution of PAD, availability of autogenous vein, patient co-morbidities) and local operator expertise

- After a revascularisation procedure, its effectiveness should be evaluated with an objective measurement of perfusion.
- Pharmacological treatments to improve perfusion have not been proven to be beneficial
- Emphasise efforts to reduce cardiovascular risk (cessation of smoking, control of hypertension and dyslipidaemia, use of anti-platelet drugs)

3. Treatment of infection

Superficial ulcer with limited soft tissue (mild) infection:

- Cleanse, debride all necrotic tissue and surrounding callus
- Start empiric oral antibiotic therapy targeted at *Staphylococcus aureus* and streptococci (unless there are reasons to consider other, or additional, likely pathogens)

Deep or extensive (potentially limb-threatening) infection (moderate or severe infection):

- Urgently evaluate for need for surgical intervention to remove necrotic tissue, including infected bone, release compartment pressure or drain abscesses
- Assess for PAD; if present consider urgent treatment, including revascularisation
- Initiate empiric, parenteral, broad-spectrum antibiotic therapy, aimed at common gram-positive and gram-negative bacteria, including obligate anaerobes
- Adjust (constrain and target, if possible) the antibiotic regimen based on both the clinical response to empirical therapy and culture and sensitivity results

4. Metabolic control and treatment of co-morbidities

- Optimise glycaemic control, if necessary with insulin
- Treat oedema or malnutrition, if present

5. Local ulcer care

- Regular inspection of the ulcer by a trained health care provider is essential, its frequency depends on the severity of the ulcer and underlying pathology, the presence of infection, the amount of exsudation and wound treatment provided
- Debride the ulcer and remove surrounding callus (preferably with sharp surgical instruments), and repeat as needed
- Select dressings to control excess exudation and maintain moist environment
- Do not soak the feet, as this may induce skin maceration.
- Consider negative pressure to help heal post-operative wounds

Consider one of the following adjunctive treatments in non-infected ulcers that fail to heal after 4-6 weeks despite optimal clinical care:

- A sucrose octasulfate impregnated dressing in neuro-ischemic ulcers (without severe ischemia)

- A multi-layered patch of autologous leucocytes, platelets and fibrin in ulcers with or without moderate ischemia
- Placental membrane allografts in ulcers with or without moderate ischemia
- Systemic oxygen therapy as an adjunctive treatment in ischaemic ulcers that do not heal despite revascularisation

The following treatments are not well-supported for routine ulcer management:

- Biologically active products (collagen, growth factors, bio- engineered tissue) in neuropathic ulcers
- Silver, or other antimicrobial agent, containing dressings or topical applications

6. Education for patient and relatives

- Instruct patients (and relatives or carers) on appropriate foot ulcer self-care and how to recognize and report signs and symptoms of new or worsening infection (e.g., onset of fever, changes in local wound conditions, worsening hyperglycaemia)
- During a period of enforced bed rest, instruct on how to prevent an ulcer on the contra- lateral foot

ORGANIZATION OF CARE FOR DIABETIC FOOT DISEASE

Successful efforts to prevent and treat diabetic foot disease depend upon a well-organised team, that uses a holistic approach in which the ulcer is seen as a sign of multi-organ disease, and that integrates the various disciplines involved. Effective organisation requires systems and guidelines for education, screening, risk reduction, treatment, and auditing. Local variations in resources and staffing often dictate how to provide care, but ideally a diabetic foot disease programme should provide the following:

- Education for people with diabetes and their carers, for healthcare staff in hospitals and for primary healthcare professionals
- Systems to detect all people who are at risk, including annual foot examination of all persons with diabetes
- Access to measures for reducing risk of foot ulceration, such as podiatric care and provision of appropriate footwear
- Ready access to prompt and effective treatment of any foot ulcer or infection
- Auditing of all aspects of the service to identify and address problems and ensure that local practice meets accepted standards of care
- An overall structure designed to meet the needs of patients requiring chronic care, rather than simply responding to acute problems when they occur.

In all countries, there should optimally be at least three levels of foot-care management with interdisciplinary specialists like those listed in Table 2.

Table 2. Levels of care for diabetic foot disease

Level of care	Interdisciplinary specialists involved
Level 1	General practitioner, podiatrist, and diabetes nurse
Level 2	Diabetologist, surgeon (general, orthopaedic, or foot), vascular specialist (endovascular and open revascularisation), infectious disease specialist or clinical microbiologist, podiatrist and diabetes nurse, in collaboration with a shoe-technician, orthotist or prosthetist
Level 3	A level 2 foot centre that is specialized in diabetic foot care, with multiple experts from several disciplines each specialised in this area working together, and that acts as a tertiary reference centre

Studies around the world have shown that setting up an interdisciplinary foot care team and implementing prevention and management of diabetic foot disease according to the principles outlined in this guideline, is associated with a decrease in the frequency of diabetes related lower-extremity amputations. If it is not possible to create a full team from the outset, aim to build one step-by-step, introducing the various disciplines as possible. This team must first and foremost act with mutual respect and understanding, work in both primary and secondary care settings, and have at least one member available for consultation or patient assessment at all times. We hope that these updated practical guidelines and the underlying six evidence-based guideline chapters continue to serve as reference document to reduce the burden of diabetic foot disease.

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at:
www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published online, this current version will be replaced.

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ADDENDUM

Doing a sensory foot examination

Peripheral neuropathy can be detected using the 10g (5.07 Semmes-Weinstein) monofilament (detects loss of protective sensation) and a tuning fork (128 Hz, detects loss of vibratory sensation).

10g (5.07) Semmes-Weinstein monofilament (Figures 5 and 6)

- First apply the monofilament on the patient's hands (or elbow or forehead) to demonstrate what the sensation feels like.
- Test three different sites on both feet, selecting from those shown in Figure 5.
- Ensure the patient cannot see whether or where the examiner applies the filament.
- Apply the monofilament perpendicular to the skin surface (Figure 6a) with sufficient force to cause the filament to bend or buckle (Figure 6b).
- The total duration of the approach -> skin contact -> and removal of the filament should be approximately 2 seconds.
- Do not apply the filament directly on an ulcer, callus, scar or necrotic tissue.
- Do not allow the filament to slide across the skin or make repetitive contact at the test site.
- Press the filament to the skin and ask the patient whether they feel the pressure applied ('yes'/'no') and next where they feel the pressure (e.g., 'ball of left foot'/'right heel).
- Repeat this application twice at the same site, but alternate this with at least one 'mock' application in which no filament is applied (a total of three questions per site).
- Protective sensation is: present at each site if the patient correctly answers on two out of three applications; absent with two out of three incorrect answers.
- Encourage the patients during testing by giving positive feedback.

Monofilaments tend to lose buckling force temporarily after being used several times on the same day, or permanently after long duration use. Depending on the type of monofilament, we suggest not using the monofilament for the next 24 hours after assessing 10-15 patients and replacing it after using it on 70-90 patients.

Figure 5. Sites that should be tested for loss of protective sensation with the 10g Semmes-Weinstein monofilament

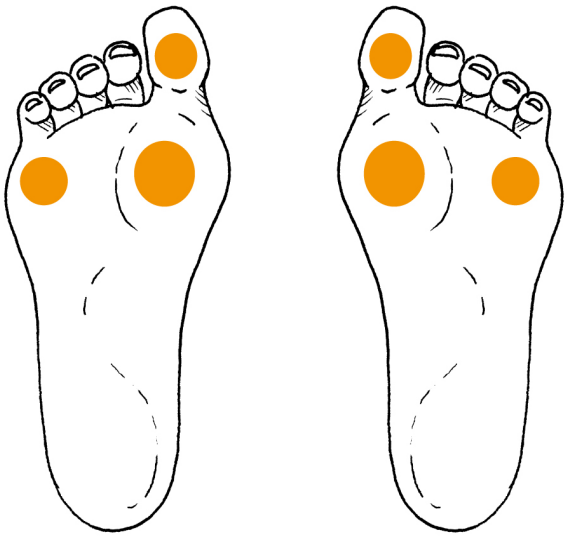
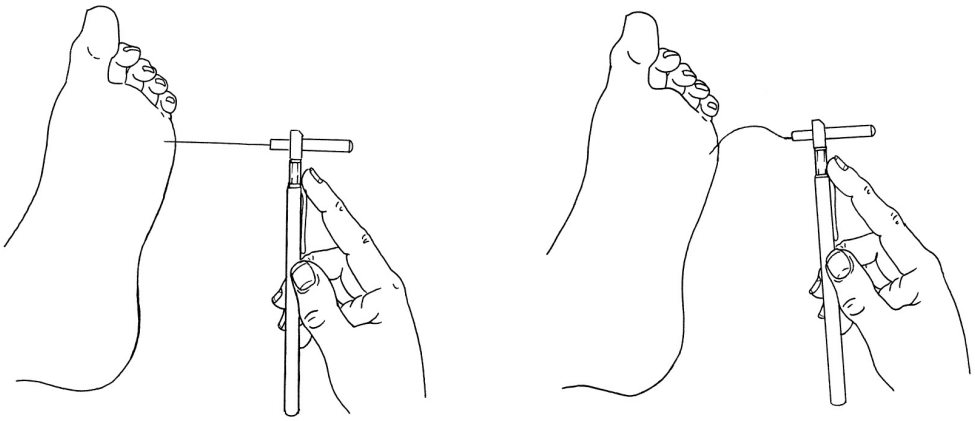


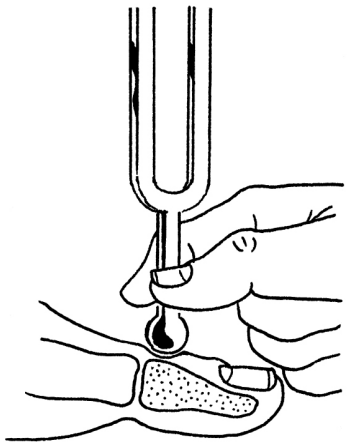
Figure 6. Proper method of using the 10g Semmes-Weinstein monofilament



128 Hz Tuning fork (Figure 7)

- First, apply the tuning fork on the patient's wrist (or elbow or clavicle) to demonstrate what the sensation feels like.
- Ensure the patient cannot see whether or where the examiner applies the tuning fork.
- Apply the tuning fork to a bony part on the dorsal side of the distal phalanx of the first toe (or another toe if the hallux is absent).
- Apply the tuning fork perpendicularly, with constant pressure (Figure 7).
- Repeat this application twice, but alternate this with at least one 'mock' application in which the tuning fork is not vibrating.
- The test is positive if the patient correctly answers at least two out of three applications, and negative if two out of three answers are incorrect.
- If the patient is unable to sense the vibrations on the toe, repeat the test more proximally (e.g., malleolus, tibial tuberosity).
- Encourage the patient during testing by giving positive feedback.

Figure 7. Proper method of using a 128 Hz tuning fork to check for vibratory sensation



Light touch test

This simple test (also called the Ipswich Touch test) can be used to screen for loss of protective sensation (LOPS), when the 10 gram monofilament or 128 HZ tuning fork is not available. The test has reasonable agreement with these tests to determine LOPS, but its accuracy in predicting foot ulcers has not been established.

- Explain the procedure and ensure that everything is understood
- Instruct the subject to close the eyes and to say yes when they feel the touch
- The examiner lightly sequentially touches with the tip of hers/his index finger the tips of the first, third, and fifth toes of both feet for 1–2 s
- When touching, do not push, tap, or poke
- LOPS is likely when light touch is not sensed in ≥ 2 sites

Foot screening sheet for clinical examination

Presence of a full thickness ulcer Risk factors for foot ulceration	Yes / No
Peripheral neuropathy (one or more of the following tests)	
- Protective sensation (monofilament) undetectable	Yes / No
- Vibration (128 Hz tuning fork) undetectable	Yes / No
- Light touch (Ipswich touch test) undetectable	Yes / No
Foot pulses	
- Posterior tibial artery absent	Yes / No
- Dorsal pedal artery absent	Yes / No
Other	
- Foot deformity or excessive bony prominences	Yes / No
- Limited joint mobility	Yes / No
- Signs of abnormal pressure, such as callus	Yes / No
- Ruddy discoloration on dependency	Yes / No
- Poor foot hygiene	Yes / No
- Inappropriate footwear	Yes / No
- Previous ulcer	Yes / No
- Lower extremity amputation	Yes / No

IWGDF Guideline on the prevention of foot ulcers in persons with diabetes

Part of the 2019 IWGDF Guidelines
on the Prevention and Management
of Diabetic Foot Disease

IWGDF
Guidelines

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KEYWORDS

diabetic foot; foot ulcer; guidelines; prevention; footwear; self-care; self-management; education

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This guideline is on the prevention of foot ulceration in persons with diabetes and updates the 2015 IWGDF prevention guideline.

We followed the GRADE methodology to devise clinical questions and critically important outcomes in the PICO format, to conduct a systematic review of the medical-scientific literature, and to write recommendations and their rationale. The recommendations are based on the quality of evidence found in the systematic review, expert opinion where evidence was not available, and a weighing of the benefits and harms, patient preferences, feasibility and applicability, and costs related to the intervention.

We recommend to screen a person at very low risk for ulceration annually for loss of protective sensation and peripheral artery disease, and persons at higher risk at higher frequencies for additional risk factors. For preventing a foot ulcer, educate the at-risk patient about appropriate foot self-care and treat any pre-ulcerative sign on the foot. Instruct moderate-to-high risk patients to wear accommodative properly fitting therapeutic footwear, and consider instructing them to monitor foot skin temperature. Prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking to prevent plantar foot ulcer recurrence. In patients that fail non-surgical treatment for an active or imminent ulcer, consider surgical intervention; we suggest not to use a nerve decompression procedure. Provide integrated foot care for high-risk patients to prevent ulcer recurrence.

Following these recommendations will help healthcare professionals to provide better care for persons with diabetes at risk of foot ulceration, to increase the number of ulcer-free days and reduce the patient and healthcare burden of diabetic foot disease.

LIST OF RECOMMENDATIONS

1. Examine a person with diabetes at very low risk of foot ulceration (IWGDF risk 0) annually for signs or symptoms of loss of protective sensation and peripheral artery disease, to determine if they are at increased risk for foot ulceration. (GRADE recommendation: Strong; Quality of evidence: High)
2. Screen a person with diabetes at risk of foot ulceration (IWGDF risk 1-3) for: a history of foot ulceration or lower-extremity amputation; diagnosis of end-stage renal disease; presence or progression of foot deformity; limited joint mobility; abundant callus; and any pre-ulcerative sign on the foot. Repeat this screening once every 6-12 months for those classified as IWGDF risk 1, once every 3-6 months for IWGDF risk 2, and once every 1-3 months for IWGDF risk 3. (Strong; High)
3. Instruct a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to protect their feet by not walking barefoot, in socks without shoes, or in thin-soled slippers, whether indoors or outdoors. (Strong; Low)
4. Instruct, and after that encourage and remind, a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to: inspect daily the entire surface of both feet and the inside of the shoes that will be worn; wash the feet daily (with careful drying, particularly between the toes); use emollients to lubricate dry skin; cut toe nails straight across; and, avoid using chemical agents or plasters or any other technique to remove callus or corns. (Strong; Low)
5. Provide structured education to a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) about appropriate foot self-care for preventing a foot ulcer. (Strong; Low)
6. Consider instructing a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) to self-monitor foot skin temperatures once per day to identify any early signs of foot inflammation and help prevent a first or recurrent plantar foot ulcer. If the temperature difference is above-threshold between similar regions in the two feet on two consecutive days, instruct the patient to reduce ambulatory activity and consult an adequately trained health care professional for further diagnosis and treatment. (Weak; Moderate)
7. Instruct a person with diabetes who is at moderate risk for foot ulceration (IWGDF risk 2) or who has healed from a non-plantar foot ulcer (IWGDF risk 3) to wear therapeutic footwear that accommodates the shape of the feet and that fits properly, to reduce plantar pressure and help prevent a foot ulcer. When a foot deformity or a pre-ulcerative sign is present, consider prescribing custom-made footwear, custom-made insoles, or toe orthoses. (Strong; Low)
8. Consider prescribing orthotic interventions, such as toe silicone or (semi-)rigid orthotic devices, to help reduce abundant callus in a person with diabetes who is at risk for foot ulceration (IWGDF risk 1-3). (Weak; Low)
9. In a person with diabetes who has a healed plantar foot ulcer (IWGDF risk 3), prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking, to help prevent a recurrent plantar foot ulcer; furthermore, encourage the patient to consistently wear this footwear. (Strong; Moderate).
10. Provide appropriate treatment for any pre-ulcerative sign or abundant callus on the foot, for ingrown toe nails, and for fungal infections on the foot, to help prevent a foot ulcer in a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3). (Strong; Low)

11. In a person with diabetes and abundant callus or an ulcer on the apex or distal part of a non-rigid hammertoe that has failed to heal with non-surgical treatment, consider digital flexor tendon tenotomy for preventing a first foot ulcer or recurrent foot ulcer once the active ulcer has healed (Weak; Low).
12. In a person with diabetes and a plantar forefoot ulcer that has failed to heal with non-surgical treatment, consider Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection, metatarsophalangeal joint arthroplasty or osteotomy, to help prevent a recurrent plantar forefoot ulcer once the active ulcer has healed. (Weak; Low)
13. We suggest not to use a nerve decompression procedure, in preference to accepted standards of good quality care, to help prevent a foot ulcer in a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) and who is experiencing neuropathic pain. (Weak; Low)
14. Consider advising a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) to perform foot and mobility-related exercises with the aim of reducing risk factors of ulceration, i.e., decreasing peak pressure and increasing foot and ankle range of motion, and with the aim of improving neuropathy symptoms. (Weak; Moderate)
15. Consider communicating to a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) that a moderate increase in the level of walking-related weight-bearing daily activity (i.e. an extra 1.000 steps/day) is likely to be safe. Advise this person to wear appropriate footwear when undertaking weight-bearing activities, and to frequently monitor the skin for pre-ulcerative signs or breakdown. (Weak; Low)
16. Provide integrated foot care for a person with diabetes who is at high risk of foot ulceration (IWGDF risk 3) to help prevent a recurrent foot ulcer. This integrated foot care includes professional foot care, adequate footwear and structured education about self-care. Repeat this foot care or re-evaluate the need for it once every one to three months, as necessary. (Strong; Low)

INTRODUCTION

Foot ulceration is a major complication of diabetes mellitus and is associated with high levels of morbidity and mortality, as well as significant financial costs (1-3). The lifetime incidence rate of diabetic foot ulceration is 19-34%, with a yearly incidence rate of 2% (4). After successful healing the recurrence rates of diabetic foot ulcers (DFU) are 40% within a year and 65% within 3 years (4). Therefore, the prevention of DFU is paramount to reduce the risks to the patient and the resultant economic burden to society.

Not all patients with diabetes are at-risk for ulceration. Key risk factors include: a loss of protective sensation (LOPS), peripheral artery disease (PAD) and foot deformity. Additionally, a history of foot ulceration and any level of lower extremity amputation further increase risk for ulceration (4-6). In general, patients without any of these risk factors do not appear to be at risk for ulceration. For the current guideline, we define the at-risk patient as one with diabetes who does not have an active foot ulcer, but who has at least LOPS or PAD. Table 1 shows the IWGDF system for stratifying risk for foot ulceration.

If patients have no risk factors, incidence of developing a foot ulcer is very low. Therefore, only interventions aimed specifically at the prevention of foot ulcers in at-risk patients are included in this guideline. Within this group, those patients with a history of DFU or amputation are considered at higher risk for ulceration when compared to those without these problems (6). Thus, we consider the first incidence of DFU and recurrent incidences of DFU separate outcomes of interest.

Various interventions for the prevention of foot ulcers are either used in clinical practice or have been studied in scientific research (7). We identify five key elements of prevention: 1) identifying the at-risk foot; 2) regularly inspecting and examining the at-risk foot; 3) Educating the patient, family and healthcare providers; 4) Ensuring routine wearing of appropriate footwear; 5) Treating risk factors for ulceration. Integrated foot care is a combination of these elements, and concerns the 6th element covered in this guideline.

The aim of this guideline is to provide evidence-based recommendations for the prevention of foot ulcers in people with diabetes and includes a rationale of how we came to each recommendation. This guideline is part of the IWGDF Guidelines on the prevention and management of diabetic foot disease (8-12), and updates our previous guideline (13). The rationale provided is based on a systematic review of the literature that underlies this guidance (14), together with a consideration of the benefits and harm, patients' values and preferences, and the costs related to the intervention. We also provide general considerations and propose an agenda for future research.

METHODS

In this guideline we have followed the GRADE methodology, which is structured around clinical questions in the PICO-format (Patient-Intervention-Comparison-Outcome), systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale (15,16).

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF editorial board. The members of the working group devised the clinical questions, which were revised after consultation with external experts from various geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and other health care professionals in providing useful information on the prevention of foot ulcers in at-risk people with diabetes. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate and colleagues (17) as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as 'high', 'moderate' or 'low'. The systematic reviews supporting this guideline are published separately (14,18).

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system we provided the rationale for how we arrived at each recommendation, based on the evidence from our systematic reviews (14,18), expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method (15,16). Based on these factors, we graded the strength of each recommendation as 'strong' or 'weak', and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

We refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (19).

1. IDENTIFYING THE AT-RISK FOOT

PICO: In people with diabetes, is structured annual screening for risk factors of foot ulceration, compared to less frequent or unstructured screening effective for preventing a first-ever or recurrent DFU?

Recommendation 1: Examine a person with diabetes at very low risk of foot ulceration (IWGDF risk 0) annually for signs or symptoms of loss of protective sensation and peripheral artery disease, to determine if they are at increased risk for foot ulceration. (GRADE recommendation: Strong; Quality of evidence: High).

Rationale: Targeting people with diabetes for foot ulcer prevention requires identification of those at-risk. We found no evidence in the literature on the effect of screening for preventing a DFU. However, we recommend an annual foot screening for all persons with diabetes with no additional risk factors (IWGDF risk 0). Foot screening identifies those at risk and should specifically include screening for LOPS caused by diabetic peripheral neuropathy, and for signs or symptoms of PAD. Foot screening should be performed by an adequately trained healthcare professional (see glossary for definition). LOPS can be assessed with a 10-gram Semmes Weinstein monofilament (20): a recent meta-analysis of individual patient data found consistent results using this assessment to predict risk of foot ulcer (6). If a 10-gram monofilament is unavailable use the Ipswich Touch Test (21). While outcomes of this test were not included in the aforementioned meta-analysis, the Ipswich Touch Test has shown results similar to testing with the 10-gram monofilament (22). Because limited vibratory sensation may also predict risk of foot ulceration (4) we suggest to screen for this with a tuning fork or biothesiometer/neurothesiometer, if outcomes from monofilament testing do not show LOPS. Screening for PAD is discussed in the IWGDF Guidelines on PAD (9). In short, this includes taking a cardiovascular history, palpating for foot pulses, obtaining pedal Doppler arterial waveforms and blood pressure measurements (9). Although evidence for a screening interval is non-existent, we recommend an annual screening for a person with diabetes in whom LOPS or PAD have not yet been identified.

Based on a meta-analysis (6) , the quality of the evidence that LOPS and PAD are predictive of foot ulceration is high. We suggest there are no harms associated with yearly foot screenings, the benefits of foot screening outweigh the harms. We also suggest positive value to persons with diabetes of such yearly screenings as part of their regular diabetes check-ups. While foot screening is generally feasible, acceptable and inexpensive on the individual level, it can be more complex and costly to organize on the societal level, given the growing number of people with diabetes and the limited time allotted for primary care visits. However, early identifying persons at risk of foot ulceration is highly important and is needed to target those who require preventative treatment. Therefore, the recommendation for annual foot screening is strong.

2. REGULARLY INSPECTING AND EXAMINING THE AT-RISK FOOT

PICO: In people with diabetes at-risk for foot ulceration, what are the risk factors that should be screened for, for preventing a first-ever or recurrent DFU?

Recommendation 2: Screen a person with diabetes at risk of foot ulceration (IWGDF risk 1-3) for: a history of foot ulceration or lower-extremity amputation; diagnosis of end-stage renal disease; presence or progression of foot deformity; limited joint mobility; abundant callus; and any pre-ulcerative sign on the foot. Repeat this screening once every 6-12 months for those classified as IWGDF risk 1, once every 3-6 months for IWGDF risk 2, and once every 1-3 months for IWGDF risk 3. (Strong; High)

Rationale: When either LOPS or PAD is identified in a person with diabetes, more extensive and more frequent foot examination is needed, as the ulcer risk is higher (4,6). For these patients, this examination should consist of taking a detailed history of foot ulceration, lower-extremity amputation, and determining a diagnosis of end-stage renal disease. Physically examine the foot for presence of deformities of progression thereof; abundant callus and pre-ulcerative signs, such as blisters, fissures and haemorrhage; and limited joint mobility (5,6). A history of a previous foot ulcer or amputation are important predictive factors for a new ulceration, as identified in a meta-analysis of individual patient data (6). Foot deformities, abundant callus, pre-ulcerative signs, and limited joint mobility may increase the risk of foot ulceration (4,23), and are important determinants of treatment in people with LOPS or PAD.

Notwithstanding the lack of evidence, other factors that we suggest taking a history of are: presence of social isolation, poor access to healthcare and financial constraints; foot pain (with walking or at rest); and numbness or claudication. We also suggest examining the presence of ill-fitting, inadequate, or lack of footwear; abnormal skin colour, temperature or oedema; poor foot hygiene, e.g., improperly cut toenails, unwashed feet, superficial fungal infection, or unclean socks; physical limitations that may hinder foot self-care (e.g. visual acuity, obesity); and foot care knowledge (23-26). Lacking footwear, or having Ill-fitting or inadequate footwear can be a cause of ulceration (24), and poor hygiene may be reflective of poor self-care. Appropriate interventions can potentially improve these modifiable risk factors when they are identified.

Any foot ulcer identified during screening should be treated according to the principles outlined in the other IWGDF guidelines (8-12).

IWGDF Risk Stratification

Based on the findings of the screening, patients can be stratified according to their risk for foot ulceration (Table 1). The risk categories defined are based on a meta-analysis and a systematic review of prospective risk factor studies on foot ulceration (6).

Table 1. The IWGDF Risk Stratification System and corresponding foot screening and examination frequency

Category	Ulcer risk	Characteristics	Frequency*
0	Very low	No LOPS and No PAD	Once a year
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD *or* LOPS + foot deformity *or* PAD + foot deformity	Once every 3-6 months
3	High	LOPS or PAD, *and* one or more of the following: ▪ history of a foot ulcer ▪ a lower-extremity amputation (minor or major) ▪ end-stage renal disease	Once every 1-3 months

Note: LOPS = Loss of protective sensation; PAD = peripheral artery disease. *: Screening frequency is based on expert opinion, since no evidence is available to support these intervals. When the screening interval is close to a regular diabetes check-up, consider to screen the foot at that check-up.

Someone without LOPS and without PAD is classified as IWGDF risk 0 and is at very low risk for ulceration. This person requires only annual screening. All other categories are considered "at-risk," and require more frequent foot screening, regular inspection and foot examination than patients who are not at-risk.

A person with either LOPS or PAD, but no additional risk factors, is stratified as IWGDF risk 1, and is considered at low risk. They should be screened once every 6-12 months. When a combination of risk factors is present, a person is stratified as IWGDF risk 2 and is considered to be at moderate risk. As their risk is higher, they should be screened every 3-6 months. All persons with either LOPS or PAD *and* a history of foot ulcer or lower-extremity amputation are stratified as IWGDF risk 3 and considered to be at high risk of ulceration. These persons should be screened once every 1-3 months. We also regard people with LOPS or PAD in combination with end-stage renal disease (27-29) as being at high risk, irrespective of their ulcer history, and have therefore added these to IWGDF risk 3.

A person's risk status may change over time, thus requiring continual monitoring. The screening frequencies we have provided help guide such monitoring. If findings lead to a change in risk status, screening frequency should be adjusted accordingly. As someone's diabetes course progresses, upgrading is the most likely change. Downgrading risk status might occur after (surgical) interventions that normalize foot structure or improve lower extremity blood flow. Further, in patients with longstanding LOPS, it is not required to repeat the assessment of LOPS at each screening.

In view of the lack of evidence for the effectiveness of a screening interval in at-risk patients we recommend these intervals based on expert opinion. The aim of more frequent screening is early identification of risk factors that can increase the chances of developing a foot ulcer. This should then be followed by providing appropriate preventative foot care. For example, early diagnosis and treatment of pre-ulcerative signs on the foot may prevent foot ulcers, as well as more severe complications such as

infection and hospitalization. Screening for all these factors should help increase awareness; while it might also raise concern or feelings of anxiety in some patients we think that in general the potential for harm is limited. All screening can be done without the need for intrusive interventions and may also provide an opportunity to provide patient education, counselling and support. We suggest that the benefits associated with targeted preventative treatment following screening likely outweigh potential harms, provided appropriate treatment is given by an adequately trained healthcare professional. Screening takes relatively little time, and while this is feasible, acceptable and inexpensive at the individual level, it may be harder to organize and costlier on a societal level. Taking all evidence together, we strongly recommend such screening.

3. EDUCATING THE PATIENT, FAMILY AND HEALTHCARE PROVIDERS

3A – Instructions on foot self-care

PICO: In people with diabetes at risk for foot ulceration, is foot self-care compared to no self-care, effective for preventing a first-ever or recurrent DFU?

Recommendation 3: Instruct a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to protect their feet by not walking barefoot, in socks without shoes, or in thin-soled slippers, whether indoors or outdoors. (Strong; Low)

Rationale: The feet of an at-risk person with diabetes need to be protected against high mechanical stresses, as well as external physical trauma, as both may cause foot ulcers (20). To protect their feet, these patients should therefore not walk barefoot, in socks without shoes, in thin-soled slippers, either at home or outside. This also includes any other open type footwear that increases risk for direct skin damage by a foreign object. While no studies have been performed on the effect of walking barefoot, in socks, or in thin-soled standard slippers, on risk of foot ulceration, there are many large prospective studies that show that at-risk patients with diabetes have elevated levels of mechanical plantar pressure during walking barefoot, in socks and in thin-soled slippers (30,31). These high pressures are a significant independent risk factor for foot ulceration and should therefore be avoided (4). In addition, walking barefoot, in socks without shoes, or in thin-soled standard slippers has other harmful effects in at-risk patients with diabetes, such as lack of protection against thermal or external mechanical trauma. Thus, despite the lack of direct evidence for this recommendation, we feel strongly that patients should be advised to avoid these walking conditions to reduce risk of damaging the foot.

Patients might prefer not to adhere to this recommendation, especially inside their house (32,33). However, given the harms of walking unprotected outweigh patient preferences, we strongly recommend to instruct at-risk patients with diabetes not to walk barefoot, in socks, or in thin-soled standard slippers, whether at home or when outside.

Recommendation 4: Instruct, and after that encourage and remind, a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to: inspect daily the entire surface of both feet and the inside of the shoes that will be worn; wash the feet daily (with careful drying, particularly between the toes); use emollients to lubricate dry skin; cut toe nails straight across; and, avoid using chemical agents or plasters or any other technique to remove callus or corns. (Strong; Low)

Rationale: Although no direct evidence is available for the effect of these self-care interventions in preventing foot ulcers, they enable a person to detect early signs of DFU and contribute to basic foot hygiene. This is likely to help prevent a foot ulcer, although it may pose some burden to patients. It can be expected that people will generally accept basic foot hygiene, and that the benefits outweigh potential harms associated with either inappropriate or inadequate or no foot self-care at all. These foot self-care behaviours are feasible, accessible and come at a low cost per person who is at risk for DFU. Despite the limited evidence for the effect of these self-care activities on ulcer prevention, this is a strong recommendation.

3B – Providing structured education about foot self-care

PICO: In people with diabetes at risk of foot ulceration, is providing structured education about foot specific self-care compared to not providing it, effective for preventing a first-ever or recurrent DFU?

Recommendation 5: Provide structured education to a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) about appropriate foot self-care for preventing a foot ulcer. (Strong; Low)

Rationale: Structured education is considered an essential and integral part of foot ulcer prevention, as it is widely thought that patients with diabetes at-risk for foot ulceration need to understand their disease in order to engage in foot self-care (34-36). Structured education is defined as any educational modality that is provided to patients in a structured way. This can take many forms, such as one-to-one verbal education, motivational interviewing, educational group sessions, video education, booklets, software, quizzes, and pictorial education via animated drawing or descriptive images. Despite this myriad of forms available and education being ingrained in clinical practice all over the world, research on its effectiveness is limited. There is insufficient robust evidence that limited patient education alone is effective in achieving clinically relevant ulcer risk reduction (37,38). However, education may improve knowledge and foot self-care behaviour (38). Therefore, education should aim to improve the patient's foot care knowledge and self-care behaviour, and encourage the patient to adhere to the foot self-care education provided.

Structured foot care education should consist of information on:

- Foot ulcers and their consequences
- Preventative foot self-care behaviours, such as: not walking barefoot or in socks without shoes or in thin-soled slippers
- Wearing adequately protective footwear
- Undergoing regular foot checks

- Practicing proper foot hygiene
- Seeking professional help in a timely manner after identifying a foot problem (see recommendations 3 and 4).

As there is evidence of the benefits of treatment adherence on ulcer outcomes (39,40), encourage people at risk of DFU to adhere to the foot self-care education provided. It is best if such education is integrated with regular foot screenings (see recommendations 1 and 2), and is part of integrated foot care (see recommendation 16). Structured education should be culturally appropriate, account for gender differences, and align with a patient's health literacy and personal circumstances. It is therefore not possible to provide globally applicable recommendations on the best form of education. We suggest that structured foot self-care education should be provided individually or in small groups of patients. It should be provided over several sessions and with periodical reinforcement, to maximise effect.

Despite low quality of evidence, we strongly recommend providing structured education on foot self-care. While education could potentially lead to harm such as an increased fear of complications (41), it may also provide an opportunity for patients to clarify misunderstandings and seek answers to questions they have (26). Overall, we assess that the benefits outweigh the potential harms. Patients will probably prefer structured education when it is appropriate to their circumstances, feasible, equitable and accessible. While structured education is inexpensive at the individual level, it may be harder to organize and costlier on a societal level. Taken together, we strongly recommend providing structured education.

3C – Instructions about foot self-management

PICO: In people with diabetes at risk for foot ulceration, is foot self-management compared to no self-management, effective for preventing a first-ever or recurrent DFU (O)?

Recommendation 6: Consider instructing a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) to self-monitor foot skin temperatures once per day to identify any early signs of foot inflammation and help prevent a first or recurrent plantar foot ulcer. If the temperature difference is above-threshold between similar regions in the two feet on two consecutive days, instruct the patient to reduce ambulatory activity and consult an adequately trained health care professional for further diagnosis and treatment. (Weak; Moderate)

Rationale: Foot self-management differs from foot self-care as it involves more advanced interventions that are specifically designed for ulcer prevention, such as home-monitoring tools and telemedicine approaches. Self-management can include many interventions, but we found no evidence to support the use of any specific intervention, with the exception of home monitoring of foot skin temperature (42-45). We found evidence that home monitoring of plantar foot skin temperature once per day with an easy to use infrared thermometer, combined with subsequent preventative action when elevated temperatures were noted for two consecutive days, is more effective than standard treatment for preventing foot ulcers in high risk-patients (IWGDF risk 2-3) (42-45). These preventative actions include: reduction of ambulatory activity, consultation with an adequately trained healthcare professional to discuss the findings, and further preventative treatment as per the healthcare professional's assessment. For this recommendation to be effective a person needs to have ready access to and the ability to use

an appropriate thermometer and be in communication with an adequately trained healthcare professional.

Professionals may value home monitoring of foot temperatures as an easy to use and relatively inexpensive method that may have high clinical value and helps empower people in their care of their own feet. However, the available evidence shows that adherence to measuring foot temperatures was an important factor in its effectiveness, and people, in particular those who have not had a foot ulcer, may find the requirement for daily assessment a burden (43,46). False-positive and false-negative outcomes of temperature measurements may unnecessarily concern people and affect their confidence in using this approach (47,48). To our knowledge, home monitoring of foot temperature is currently not routinely implemented in foot care of people with diabetes at moderate to high risk of DFU. This may be due to how people value the need for and ease of use of daily temperature measurements, lack of easy access to calibrated equipment, lack of information on cost-effectiveness and implementation feasibility. Because of these potential limitations, the recommendation is graded as weak.

4. ENSURING ROUTINE WEARING OF APPROPRIATE FOOTWEAR

PICO: In people with diabetes at-risk for foot ulceration, is any one specific orthotic intervention, including therapeutic footwear (e.g. shoes, insoles or orthoses) and walking aids, compared to no intervention or another type of orthotic, effective for preventing a first-ever or recurrent DFU?

Recommendation 7: Instruct a person with diabetes who is at moderate risk for foot ulceration (IWGDF risk 2) or who has healed from a non-plantar foot ulcer (IWGDF risk 3) to wear therapeutic footwear that accommodates the shape of the feet and that fits properly, to reduce plantar pressure and help prevent a foot ulcer. When a foot deformity or a pre-ulcerative sign is present, consider prescribing custom-made footwear, custom-made insoles, or toe orthoses. (Strong; Low)

Recommendation 8: Consider prescribing orthotic interventions, such as toe silicone or (semi-)rigid orthotic devices, to help reduce abundant callus in a person with diabetes who is at risk for foot ulceration (IWGDF risk 1-3). (Weak; Low).

Rationale: People at moderate or high risk for foot ulceration (IWGDF risk 2-3) have often lost their ability to feel pain or pressure, and may not adequately judge the fit of their footwear or the level of pressure on their foot. Being at increased risk for ulceration, it is important that their footwear fits, protects and accommodates the shape of their feet; this includes having adequate length, width and depth (49). When a foot deformity or pre-ulcerative sign is present, it becomes even more important to change foot biomechanics and reduce plantar pressure on at-risk locations. This may require custom-made footwear, custom-made insoles or toe orthoses. For people who have healed from a plantar foot ulcer, follow recommendation 9. Based on 3 RCTs (50-52), therapeutic footwear, including shoes, insoles or orthoses may reduce the risk of a first-ever foot ulcer in someone at moderate risk for foot ulceration (IWGDF risk 2). Additionally, such footwear can reduce the plantar pressure during walking

(53,54). High plantar pressures are a significant independent risk factor for foot ulceration and should therefore be avoided (4,55). Because patients with LOPS cannot adequately judge footwear fit, footwear should be evaluated by appropriately trained professionals. Evaluate the fit with the patient in the standing position, preferably at the end of the day (49).

To reduce abundant callus and the associated increased foot pressure, patients at risk of ulceration (IWGDF risk 1-3) can be provided with toe silicone and (semi-)rigid orthoses or felted foam in addition to therapeutic footwear.

Persons with diabetes may value the role of properly fitting footwear to prevent ulcers, but some still consider their footwear to be the cause of their problems, especially when the footwear does not fit properly. Properly fitting footwear may also not align with personal comfort and style preferences, while in some countries wearing footwear is not customary at all or may lead to inconvenience (e.g. in warmer or wet climates). However, we know little about the adherence of patients at moderate risk for ulceration to wearing properly fitting footwear. Therapeutic footwear or adequately trained professionals may also not be present in all countries, which limits access to orthotic interventions. However, with the additional benefit of protection against thermal and mechanical trauma, and the evidence of reducing ulcer risk, we judge the benefits to outweigh the harm and therefore assign a strong recommendation.

Recommendation 9: In a person with diabetes who has a healed plantar foot ulcer (IWGDF risk 3), prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking, to help prevent a recurrent plantar foot ulcer; furthermore, encourage the patient to consistently wear this footwear. (Strong; Moderate).

Rationale: For people with a healed plantar foot ulcer (IWGDF risk 3), therapeutic footwear needs to reduce plantar pressure at high-risk areas, including the previous ulcer location. Two RCTs with very low risk of bias have demonstrated a reduction in ulcer risk with custom-made orthopaedic footwear (56) or custom-made insoles (57) that were demonstrably optimised for pressure reduction, provided the patient wears the footwear. Demonstrated plantar pressure relieving effect means that at high pressure locations there should be a ≥30% reduction in the peak pressure during walking (compared to the current therapeutic footwear), or a peak pressure <200kPa (if measured with a validated and calibrated pressure measuring system with sensor size of 2cm^2) (56,57). The way to achieve such a pressure relief or level is by applying available state-of-the-art scientific knowledge on footwear designs that effectively offload the foot (49,56-64).

The benefits of continuously wearing optimised footwear or insoles with a proven offloading effect outweigh the potential harm, as available trials have infrequently reported any harm related to such therapeutic footwear (56,57,65-69). On the other hand, non-appropriate footwear (inadequate length or width) increases the risk of ulceration (70), and we again stress the importance of ensuring adequate fit (49). Clinicians should also encourage patients to wear their prescribed footwear whenever possible. The costs of prescribing therapeutic footwear with demonstrated offloading effect may be quite high, as it requires the measurement of barefoot or in-shoe plantar pressure, which to date is relatively expensive. However, these costs should always be considered in association with the benefit of ulcer prevention. Cost-effectiveness has not been studied to date but, in our opinion, footwear designed or

evaluated using plantar pressure measurement is likely to be cost-effective when it can reduce ulcer risk by 50%, a risk reduction demonstrated in most of the above-mentioned trials on this topic (46). This is therefore a strong recommendation.

Note that this recommendation is predicated on the availability of both therapeutic footwear and accurate technology for pressure measurement. We acknowledge that the technology and expertise for such measurements are not yet widely available. For regions and settings where this can be made available, we encourage services to invest in regular plantar pressure measurements. For regions and clinical setting where this cannot yet be accommodated, we suggest to prescribe therapeutic footwear using available state-of-the-art scientific knowledge on footwear designs that effectively offload the foot (49,56-59).

5. TREATING RISK FACTORS FOR ULCERATION

5A – Treatment of risk factors or pre-ulcerative signs on the foot

PICO: In people with diabetes at risk for foot ulceration, is treating pre-ulcerative signs on the foot compared to not treating them, effective for preventing a first-ever or recurrent DFU (O)?

Recommendation 10: Provide appropriate treatment for any pre-ulcerative sign or abundant callus on the foot, for ingrown toe nails, and for fungal infections on the foot, to help prevent a foot ulcer in a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3). (Strong; Low)

Rationale: Pre-ulcerative signs on the foot, such as blisters, fissures or haemorrhage appear to be strong predictors of future ulceration (4,23,25). Other risk factors that require treatment include abundant callus, ingrown or thickened toe nails and fungal infections. These signs require immediate treatment by an appropriately trained healthcare professional. Appropriate treatment means: removing abundant callus; protecting blisters and draining them when necessary; treating fissures; treating ingrown or thickened toe nails; treating cutaneous haemorrhage; and, prescribing antifungal treatment for fungal infections. The effectiveness of treating these signs on the prevention of a foot ulcer has not been directly investigated. Indirect evidence of benefit is that removal of callus reduces plantar pressure, an important risk factor for ulceration (71,72).

The benefit-harm ratio of treatment of pre-ulcerative signs by an appropriately trained foot care professional will likely be positive, and come at relatively low costs. However, these treatments do have the potential to harm when improperly performed, and should therefore only be done by an appropriately trained healthcare professional. It can be expected that persons educated to the dangers of pre-ulcerative signs prefer that they be treated. Despite a lack of evidence, we consider this standard practice and therefore the recommendation is strong.

5B – Surgical interventions

PICO: In people with diabetes who are at risk of foot ulceration, is performing surgical interventions in comparison to non-surgical intervention, effective for preventing a first-ever or recurrent DFU?

Recommendation 11: In a person with diabetes and abundant callus or an ulcer on the apex or distal part of a non-rigid hammertoe that has failed to heal with non-surgical treatment, consider digital flexor tendon tenotomy for preventing a first foot ulcer or recurrent foot ulcer once the active ulcer has healed (Weak; Low).

Rationale: While controlled studies on this topic are lacking, various studies have shown that a digital flexor tendon tenotomy may reduce the risk of a recurrent plantar foot ulcer in selected patients with initially nonhealing ulcers when compared with non-surgical treatment for these ulcers (73-79). Flexor tenotomy may also reduce the risk of ulcer development in patients with abundant callus on the tip of their toes or thickened nails (75,76,78). We consider flexor tenotomy a promising procedure in a patient who has a toe ulcer, or a pre-ulcerative sign on the toe, that fails to respond to non-surgical treatment, and requires normalization of foot structure to prevent ulceration. Preventative surgery should only be considered after full evaluation of non-surgical treatment options by an appropriately trained healthcare professional.

The possible benefits of digital flexor tenotomy likely outweigh the harm, as few complications have been reported (73-79). Patients who have pre-ulcerative lesions for which they have frequent non-surgical treatment that does not improve outcome may value and prefer treatment by flexor tenotomy. The procedure is easily performed in an outpatient setting, with no need for subsequent immobilization, and is not likely to negatively affect foot function. Costs and cost-effectiveness of this procedure have not been evaluated. Possible adverse effects of the surgery should be discussed with the patient. In patients with poor arterial supply to the foot, this includes potential non-healing of the surgical incision or wound. Taken together, the recommendation is weak.

Recommendation 12: In a person with diabetes and a plantar forefoot ulcer that has failed to heal with non-surgical treatment, consider Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection, metatarsophalangeal joint arthroplasty or osteotomy, to help prevent a recurrent plantar forefoot ulcer once the active ulcer has healed. (Weak; Low)

Rationale: Studies primarily aimed at healing recalcitrant forefoot plantar ulcers have found that Achilles tendon lengthening, single or pan-metatarsal head resection and metatarsophalangeal joint arthroplasty may reduce the risk of a recurrent plantar foot ulcer in selected patients with initially nonhealing ulcers when compared with non-surgical treatment (80-99). While effect sizes are often large, very few well-designed controlled studies show the efficacy of these interventions.

This recommendation applies to a patient who: a) has a plantar ulcer that is unresponsive to evidence-based non-surgical treatment; b) is expected to have a high risk of recurrence if the foot structure is not changed; c) has elevated forefoot plantar pressures; and d) in the case of Achilles tendon lengthening, has a limited ankle joint range of motion, not passing neutral.

Possible complications and side effects of these surgical offloading techniques include post-operative infection, new deformities, gait problems and transfer ulcers (83,100-102). Therefore, it is not clear if the benefits outweigh the harm. In any case, these techniques should be primarily used in patients to heal a foot ulcer that is unresponsive to evidence-based non-surgical treatment and that is expected to have a high risk of recurrence if the foot structure is not changed. Patient values and preferences for these approaches are unknown, although we expect patients to value an intervention as high when it can both heal and prevent an ulcer, but as low when it causes complications such as major gait or balance problems. The costs of surgical interventions can be much higher than for non-surgical treatment, but cost-effectiveness is unknown. Clinicians should carefully discuss possible adverse effects of the surgery with the patient. In patients with poor blood supply, this includes potential non-healing of the surgical incision or wound. We therefore offer a weak suggestion to consider these interventions.

Recommendation 13: We suggest not to use a nerve decompression procedure, in preference to accepted standards of good quality care, to help prevent a foot ulcer in a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) and who is experiencing neuropathic pain. (Weak; Low)

Rationale: While observational studies on nerve decompression procedures have demonstrated low ulcer incidence rates over extended follow-up periods in patients with or without a prior foot ulcer experiencing neuropathic pain (103-107), there is no evidence to support an ulcer prevention effect of nerve decompression. With various non-surgical interventions available that can be considered standard of good quality care to prevent a foot ulcer in an at-risk patient, we suggest not to use nerve decompression as surgical procedure.

5C – Foot-related exercises and weight-bearing activity

PICO: In people with diabetes at-risk for foot ulceration, are foot-related exercises compared to no foot-related exercises, effective for preventing a first-ever or recurrent DFU?

Recommendation 14: Consider advising a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) to perform foot and mobility-related exercises with the aim of reducing risk factors of ulceration, i.e., decreasing peak pressure and increasing foot and ankle range of motion, and with the aim of improving neuropathy symptoms. (Weak; Moderate).

Rationale: There is no direct evidence to suggest that foot-related exercises prevent DFU, as studies on this topic are non-existent. Various forms of foot-related exercises are possible when aiming to improve modifiable risk factors for foot ulceration such as plantar pressure distribution, neuropathy symptoms, deficits in foot sensation, foot-ankle joint mobility and strength (108-117). These exercises can include stretching and strengthening of the foot and ankle musculature and functional exercises such as balance and gait exercises, and are provided or supervised by physical therapists or similarly trained professionals. Multiple RCTs and non-controlled studies have shown some benefit of these exercises on a range of modifiable risk factors for foot ulceration, including plantar pressure, foot and ankle range of motion, and neuropathy symptoms (108-117) .

Foot-related exercises are relatively easy to perform autonomously, are inexpensive and do not require intensive supervision. As people at risk will likely not be aware of appropriate exercises, we recommend them to undergo a foot assessment and exercise prescription by an adequately trained healthcare professional prior to commencing exercise. Regular evaluation of progress with training and modification of the program in collaboration with the professional is recommended. Persons with pre-ulcerative signs or with an active foot ulcer should not partake in foot-related exercises in which the foot is mechanically loaded.

Advising patients at low to moderate risk for foot ulceration (IWGDF risk 1 or 2) to perform foot-related exercises is based on moderate quality evidence. Any potential for harm is outweighed by both general health benefits of exercise and specific improvements to the complex musculoskeletal deficits that develop with diabetes. The foot-related exercises are relatively easy to perform autonomously, inexpensive and do not need intensive supervision. Minimal exercise equipment is required, for example elastic bands or exercise balls. As adherence may be a challenge, we advise health practitioners to continue to motivate patients to complete the exercise program as prescribed. We recommend performing a foot assessment prior to the patient commencing exercise, and that exercise be prescribed by an adequately trained healthcare professional. Patients with pre-ulcerative signs or active ulceration should avoid weight-bearing or foot-related exercises. We recommended regularly evaluating the training and outcome progress and updating the program when required.

PICO: In people with diabetes who are at-risk for foot ulceration, can the level of weight-bearing daily activities be safely increased without increasing first-ever or recurrent DFU risk?

Recommendation 15: Consider communicating to a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) that a moderate increase in the level of walking-related weight-bearing daily activity (i.e. an extra 1.000 steps/day) is likely to be safe. Advise this person to wear appropriate footwear when undertaking weight-bearing activities, and to frequently monitor the skin for pre-ulcerative signs or breakdown. (Weak; Low).

Rationale: Exercise has general health benefits for people with diabetes, including specific improvements to the complex musculoskeletal deficits that develop with diabetes (118). However, when this exercise is weight-bearing, it might increase the cumulative plantar tissue stress, which in turn might increase the risk for skin breakdown (119). Based on 2 RCTs (120,121) where patients at risk of foot ulceration participated in a training program that increased their weight-bearing activity, but where this did not result in increased incidence of ulceration, we suggest to consider advising people at low or moderate risk for ulceration (IWGDF 1 or 2) that a small increase in the level of weight-bearing daily activities is likely to be safe. We define a small increase as 1000 steps/day, based on the increases seen in these 2 studies (120,121), and an RCT that showed such an increase to be beneficial for glycaemic control in people with diabetes (122). It is advisable to increase daily steps by a maximum of 10% per week, until a person reaches an overall increase of 1000 steps/day in comparison to baseline. For people at high-risk for ulceration (IWGDF 3) there is insufficient evidence to provide a recommendation on safe increase in activity, as the people in abovementioned RCTs who did develop an ulcer were all at high risk (120,121).

The quality of the evidence to support this recommendation is low, as it is based on only 2 RCTs that were each not powered to detect a difference in ulcer healing (120,121). The lack of evidence is a concern (and an important area for future research). However, we think the lack of differences in rates of ulceration between the groups in these trials and the known benefits of increasing weight-bearing exercises on general health and foot-related outcomes, outweighs the harms. However, patients should remain cautious to avoid adverse outcomes such as falls. To prevent adverse outcomes, advise patients to wear appropriate footwear when undertaking weight-bearing activities (see recommendations 8-11), and to monitor their skin for pre-ulcerative signs or breakdown (see recommendations 4-6). Increasing the level of weight-bearing daily activity as recommended can be considered feasible and acceptable to patients. However, high drop-out rates in some trials and lack of statistical power show that this may not hold for all patients. Exercise programs are a relatively cheap intervention. Primarily because of the low quality of evidence in relation to ulcer prevention, this is a weak recommendation.

6. INTEGRATED FOOT CARE

PICO: In people with diabetes at risk for foot ulceration, is providing integrated foot care compared to not providing integrated foot care, effective for preventing a first-ever or recurrent DFU (O)?

Recommendation 16: Provide integrated foot care for a person with diabetes who is at high risk of foot ulceration (IWGDF risk 3) to help prevent a recurrent foot ulcer. This integrated foot care includes professional foot care, adequate footwear and structured education about self-care. Repeat this foot care or re-evaluate the need for it once every one to three months, as necessary. (Strong; Low)

Rationale: We define integrated foot care as an intervention that at a minimum integrates regular foot care and examination by an adequately trained professional, structured education, and adequate footwear. One RCT, one cohort study and four non-controlled studies all reported a significantly lower percentage of recurrent ulcers in patients who received integrated foot care compared to those who did not (123-125), or in those patients who were adherent to a program compared to those who were not (126-128). None of the studies reported any complications from, or other harm related to, the programme.

Professional foot care, by an adequately trained healthcare professional, consists of: treating risk factors and pre-ulcerative signs as described in recommendation 10; structured education about foot self-care according to recommendations 3-5; and, providing adequate footwear following recommendations 7-9. The patient's feet should be regularly examined (see recommendations 1 and 2). Integrated foot care may further include foot self-management (recommendation 6), access to surgery (recommendations 11-13), and foot-related exercises and weight-bearing activity (recommendations 14 and 15).

While integrated foot care programs have been directly investigated in the above-mentioned controlled and non-controlled studies, none included all potential components of integrated foot care. The effectiveness of a state-of-the-art integrated foot care program that combines all recommendations from this guideline can be expected to be much higher than with the programs researched to date. The effect sizes of the various components of integrated foot care have been investigated in two reviews (4,46). Our recommendation that integrated foot care at minimum consists of professional foot care,

structured patient education, and adequate footwear, with a regular examination of a person's feet, is based on analysing these reviews (4,46). However, the largest effect sizes in ulcer prevention can be found for self-management and surgical interventions, and a complete integrated approach should include these as well. For all aspects of an integrated foot care program, adherence to what is recommended increases the benefits (4,46), and this should be given adequate attention in communication with the patient. Taken together, state-of-the-art integrated foot care may prevent up to 75% of all diabetic foot ulcers (46).

We found no information on costs and cost-effectiveness of integrated foot care. However, a publication from the US suggested that there was an increase in hospital admissions for a diabetic foot ulcer after Medicare cancelled financial coverage in one US state for preventative treatment given by podiatrists (129). Two further studies suggested that there was a reduction in amputations following the introduction of integrated foot care that included both ulcer prevention and ulcer treatment (130,131).

Integrated foot care should be provided by an adequately trained healthcare professional. People with diabetes at risk for foot ulceration who are cared for by professionals without specific expertise on diabetic foot disease should refer them to integrated foot care services. Educational interventions targeting healthcare professionals to improve completion rates of yearly foot examinations and to improve knowledge of healthcare professionals not daily involved in diabetic foot care may be important, but the effectiveness of such education is unclear (132-146). Teams that provide integrated foot care may perform educational outreach activities to healthcare professionals in primary or secondary care. The teams should be aware, however, that the effect of such education is limited with respect to knowledge improvement and performance of yearly foot examination, and may have to be repeated frequently.

The benefits of integrated foot care by an adequately trained healthcare professional outweigh the potential harm of such treatment. We think it is likely that patients prefer integrated footcare, rather than undergoing this care separately by different healthcare professionals, or not at all. We consider the combined effect size of the various interventions that make up integrated footcare high. Despite the low quality of the evidence, given the other advantages described, we rate our recommendation as strong.

CONSIDERATIONS

1. The recommendations in this guideline are aimed at health care professionals treating people with diabetic foot disease. However, these professionals treat patients within a healthcare system or organisation, which itself may have an effect on outcomes. Although direct evidence for this is not available, indirect evidence comes from the effect of increasing podiatrists and multidisciplinary teams in the Netherlands (147), which resulted in a reduction of lower-extremity amputations. Another study showed that the discontinuation of podiatry care from Medicare in the US (129) resulted in an increase in hospitalizations for diabetic foot disease. Both studies point to the potential importance of health care organisation in diabetic foot care, including ulcer prevention. We suggest that a health care system includes the multiple levels of foot care as described in our practical guidelines (20), that patients can be referred from primary care to secondary care without delay, and that evidence-based preventative interventions are reimbursed within the system. Also, all

healthcare professionals should be adequately trained to triage patients to ensure they are treated by the right professional. Investment in these aspects of the healthcare system is important to provide adequate preventative foot care for at-risk patients. This guideline is not written for governments or other agencies investing in healthcare organisations, but we do urge politicians and managers responsible to invest in healthcare systems that facilitate these characteristics.

2. All recommendations in this guideline are targeted at just three strata within the IWGDF risk stratification system (Table 1). Some specifications are given in relation to the location of a previous ulcer (e.g. plantar vs. non-plantar; toes vs. forefoot) or the presence of foot deformities, when recommending orthotic or surgical interventions. However, many differences between patients in the same stratum exist, and may limit providing the right treatment for the right person at the right time. No research has been done on such personalised medicine and its effects in the prevention of diabetic foot ulcers, which means that specific personalised recommendations cannot be made. This may change in the near future, as the medical community is moving more and more towards personalised solutions for medical problems.
3. An important factor for most recommendations made is patient's adherence to the recommendations. As we noted in our previous guideline (13), adherence to an intervention has been shown to be crucial in preventing foot ulcers, and it is consistently reported that patients who do not adhere present with higher rates of ulceration (46). Some pilot studies have investigated methods to improve adherence (148), but a stronger focus on the development, evaluation and implementation of methods that improve adherence to preventative diabetic foot treatment remains urgently needed.
4. Probably the two most common preventative actions in daily clinical foot practice globally are foot screening (recommendations 1 and 2), and (structured) education (recommendation 5). Despite the widespread application of these recommendations in clinical foot practice, the evidence underlying these recommendations is poor. Frequency of foot screening is based on expert opinion only, and structured education has not been studied adequately. Lack of effect shown does not imply that these interventions do not work, but more research is needed to provide a stronger evidence base.
5. Costs and cost-effectiveness have not been investigated for any of the interventions described in this guidance, and more attention to cost aspects is warranted. While some interventions are relatively inexpensive at the individual level (such as foot screening), they can be costly at a societal level, considering the millions of people with diabetes. Other interventions are costly at the individual level (such as custom-made footwear), but reduce ulcer recurrence risk to a level that they are expected to be cost-saving at a societal level. More research in this area is needed.

FUTURE RESEARCH AGENDA

Based on the gaps in the evidence as identified in our systematic reviews (14), and the recommendations and considerations made in this guideline, we consider the following topics as the most important for future research:

- A state-of-the-art integrated foot care approach that combines up-to-date interventions as recommended in this guideline has not been investigated to date on efficacy to prevent foot ulcers, while the effect sizes of various interventions found suggest that up to 75% of foot ulcers can be prevented. This needs to be investigated in well-designed randomized controlled trials.
- Current treatment recommendations are based on stratified healthcare. Future research is needed to explore the potential of a more personalised medicine approach in diabetic foot ulcer prevention, so to deliver the right treatment, to the right person, at the right time.
- Organisation of healthcare and healthcare setting likely plays a significant role in ulcer prevention, but this has not yet been investigated.
- Structured education is by many considered a key aspect of a foot ulcer prevention program, but it remains unknown what the exact effect is and which educational approach works best. Future research should assess the effectiveness of various educational interventions, as well as the frequency of education provided. This includes but is not limited to motivational behavioural interventions, e-health applications and (online) social support systems by peers or health professionals.
- Adherence to treatment is crucial to achieve the best possible outcome in ulcer prevention, but it is unknown how adherence can be improved. Research on interventions that have the potential to improve adherence is needed. These interventions may include, among others, assistive technology, educational interventions or shoe technical solutions.
- The costs and the cost-effectiveness of interventions that aim to prevent foot ulcers needs to be investigated.
- Peripheral neuropathy is the most important risk factor for the development of foot ulcers in people with diabetes, but there is little research on the prevention or treatment of neuropathy. A stronger research focus in this area is needed.
- Robust data are lacking on whom, how, and when to screen for the risk of foot ulceration. High quality data on the benefit of interventions to prevent a first foot ulcer are scarce. As the event rate (foot ulceration) is relatively low in a population without a previous ulcer, large groups of patients need to be targeted and it is unclear if the benefits will outweigh harm and costs. Studies are urgently needed to better define the categories of patients that will benefit from preventative interventions and what specific types of interventions should be included.
- While there is some evidence to support surgical interventions for the prevention of a recurrent ulcer in selected patients, these interventions are not without risk. The exact role of these surgical procedures compared to conservative approaches in the prevention of ulceration is still unclear, and requires appropriately designed controlled studies.

CONCLUDING REMARKS

The global patient and economic burden of diabetic foot disease can be considerably reduced when evidence-based preventative treatment is implemented in the foot care of people with diabetes who are at risk of developing a foot ulcer. Reducing the risk of ulceration also reduces the risk of infection, hospitalization, and lower-extremity amputation in these patient. While not drawing most attention of clinicians and researchers, foot ulcer prevention is the best way to prevent severe morbidity and mortality in people with diabetes. We think that following the recommendations for preventative treatment in this guideline will help health care professionals and teams provide better care for diabetic patients who are at risk of ulceration.

We encourage our colleagues, both those working in primary care and in diabetic foot clinics, to consider developing forms of surveillance (e.g., registries, pathways) to monitor and attempt to improve their outcomes in patients at risk of foot ulceration. We also encourage our research colleagues to consider our key controversies and considerations and conduct properly-designed studies (17) in areas of prevention in which we find gaps in the evidence base, so to better inform the diabetic foot community on effective treatment for preventing a foot ulcer in a persons with diabetes.

GLOSSARY

Abundant callus: Callus assessed by an appropriately trained healthcare professional as requiring debridement to reduce risk for ulceration.

Adherence: The extent to which a person's behaviour corresponds with agreed recommendations for treatment from a healthcare provider, expressed as quantitatively as possible; e.g. the proportion of time, steps or instances that the prescribed intervention (or comparator) is used (149).

Adequately trained healthcare professional: a person who according to national or regional standards has the knowledge, expertise, and skills to perform a specified task in screening, examining, or managing a person with diabetes who is at risk of foot ulceration.

Custom-made insole: An insole that is custom-made to the individual's foot using a 2D or 3D impression of the foot, and that is often built-up in a multi-layer construction. This may also incorporate other features, such as a metatarsal pad or metatarsal bar. The insole is designed to conform to the shape of the foot, providing cushioning and redistribution of plantar pressure. The term "insole" is also known as "insert" or "liner"

Custom-made (medical grade) footwear: Footwear uniquely manufactured for one person, when this person cannot be safely accommodated in pre-fabricated (medical grade) footwear. It is made to accommodate deformity and relieve pressure over at-risk sites on the plantar and dorsal surfaces of the foot. In-depth assessment, multiple measurements, impressions or a mould, and a positive model of a person's foot and ankle are generally required for manufacture. This footwear includes a custom-made insole. Also known as "bespoke footwear" or "orthopaedic footwear".

Extra-depth footwear: Footwear constructed with additional depth and volume in order to accommodate deformity such as claw/hammer toes and/or to allow for space for a thick insole. Usually a minimum of 5 millimetres (~3/16") depth is added compared to off-the-shelf footwear. Even greater depth is sometimes provided in footwear that is referred to as double depth or super extra-depth.

Foot deformity: see IWGDF definitions and criteria document (150).

Foot-related exercises: Any physical exercise specifically targeting the foot or lower-extremity with the aim of changing foot function. These exercises can include stretching and strengthening of the foot and ankle musculature and functional exercises such as balance and gait training. These exercises are provided and/or supervised by a physical therapist or a similarly adequately trained healthcare professionals.

Foot self-care: Foot care interventions the patient can do at home, consisting of but not limited to: foot inspection, washing of feet, careful drying between the toes, nail cutting, using emollients to lubricate skin, not using chemical agents or plasters to remove callus, footwear inspection, avoidance of walking barefoot or on socks only or in thin-soled slippers, avoidance of wearing tight socks, avoiding exposure to excessive cold and heat.

Foot self-management: Advanced assistive interventions the patient can use at home, consisting of but not limited to: home monitoring systems, lifestyle interventions, telemedicine, technological applications, peer support programs.

Footwear: defined broadly as any shoe-gear and including insoles.

Footwear modification: Modification to existing footwear with an intended therapeutic effect, e.g. pressure relief.

Hosiery: Stockings or socks of any kind. See further Stockings or Socks.

In-shoe (semi-)rigid orthosis: Term used for device put inside the shoe to achieve pressure reduction or alteration in the function of the foot. Can be pre-fabricated or custom-made.

Limited joint mobility: see IWGDF definitions and criteria document (150).

Medical grade footwear: Footwear that meets the specific needs of a person. Can be either pre-fabricated (see "Pre-fabricated medical grade footwear") or custom-made (see "Custom-made medical grade footwear"). Also known as pedorthic footwear

Off-the-shelf footwear: Readily available footwear that has not been modified and has no intended therapeutic functions. Preferred term is pre-fabricated footwear.

Pre-fabricated medical grade footwear: Pre-fabricated footwear that meets the specific needs of a person, on the basis of footwear that provides extra depth, multiple width fittings and features designed to accommodate a broader range of foot types. Other features may include modified soles, fastenings and smooth internal linings. This type of footwear is usually available at specialty shoe shops.

Pre-fabricated insole: An "off-the-shelf" flat or contoured insole made without reference to the shape of the patient's foot.

Shoe last: Last used to make footwear. The upper of the footwear is moulded or pulled over the last. The last shape defines the footwear shape including the outsole shape, heel pitch and toe spring. For off-the-shelf or pre-fabricated footwear generically generated lasts in different sizes are used.

Slipper: Low-cut, open type footwear that is easily slipped onto the foot. Includes thin-soled slippers and flip-flops (thongs).

Socks: Garment for the foot and lower part of the leg, typically knitted from wool, cotton, or nylon.

Stockings: Garment that fits closely over the foot and lower leg, typically elastic. Includes compression stockings for medical purposes.

Structured education: Any educational modality that is provided in a structured way. This can take many forms, such as one-to-one verbal education, motivational interviewing, educational group sessions, video education, booklets, software, quizzes, and pictorial education via animated drawing or descriptive images.

Therapeutic footwear: Generic term for footwear designed to have some therapeutic effect that cannot be provided by or in a conventional shoe. Custom-made shoes or sandals, custom-made insoles, extra-depth shoes, and custom-made or prefabricated medical grade footwear are examples of therapeutic footwear.

Toe orthosis: an in-shoe orthosis to achieve some alteration in the function of the toe.

Weight-bearing activity: Activity during which the foot is loaded by supporting the body weight of the person, and expressed as quantitatively as possible. Incudes walking and standing.

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at: *www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies*.

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published online, this current version will be replaced.

IWGDF Guidelines

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IWGDF Guideline on offloading foot ulcers in persons with diabetes

Part of the 2019 IWGDF Guidelines
on the Prevention and Management
of Diabetic Foot Disease

IWGDF
Guidelines

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KEYWORDS
diabetic foot; foot ulcer; guidelines; offloading; footwear; cast; surgery

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This guideline is on the use of offloading interventions to promote healing foot ulcers in persons with diabetes and updates the previous IWGDF guideline.

We followed the GRADE methodology to devise clinical questions and critically important outcomes in the PICO format, to conduct a systematic review of the medical-scientific literature, and to write recommendations and their rationale. The recommendations are based on the quality of evidence found in the systematic review, expert opinion where evidence was not available, and a weighing of the benefits and harms, patient preferences, feasibility and applicability, and costs related to the intervention.

For healing a neuropathic plantar forefoot or midfoot ulcer in a person with diabetes, we recommend that a non-removable knee-high offloading device is the first-choice of offloading treatment. A removable knee-high and removable ankle-high offloading device are to be considered as the second- and third-choice offloading treatment, respectively, if contraindications or patient intolerance to non-removable offloading exist. Appropriately fitting footwear combined with felted foam can be considered as the fourth-choice offloading treatment. If non-surgical offloading fails, we recommend to consider surgical offloading interventions for healing metatarsal head and digital ulcers. We have added new recommendations for the use of offloading treatment for healing ulcers that are complicated with infection or ischemia, and for healing plantar heel ulcers.

Offloading is arguably the most important of multiple interventions needed to heal a neuropathic plantar foot ulcer in a person with diabetes. Following these recommendations will help health care professionals and teams provide better care for diabetic patients who have a foot ulcer and are at risk for infection, hospitalisation and amputation.

LIST OF RECOMMENDATIONS

1. a) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, use a non-removable knee-high offloading device with an appropriate foot-device interface as the first-choice of offloading treatment to promote healing of the ulcer. (GRADE strength of recommendation: Strong; Quality of evidence: High)

   b) When using a non-removable knee-high offloading device to heal a neuropathic plantar forefoot or midfoot ulcer in a person with diabetes, use either a total contact cast or non-removable knee-high walker, with the choice dependent on the resources available, technician skills, patient preferences and extent of foot deformity present. (Strong; Moderate)
2. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a non-removable knee-high offloading device is contraindicated or not tolerated, consider using a removable knee-high offloading device with an appropriate foot-device interface as the second-choice of offloading treatment to promote healing of the ulcer. Additionally, encourage the patient to consistently wear the device. (Weak; Low)
3. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a knee-high offloading device is contraindicated or not tolerated, use a removable ankle-high offloading device as the third-choice of offloading treatment to promote healing of the ulcer. Additionally, encourage the patient to consistently wear the device. (Strong; Low)
4. a) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, do not use, and instruct the patient not to use, conventional or standard therapeutic footwear as offloading treatment to promote healing of the ulcer, unless none of the above-mentioned offloading devices is available. (Strong; Moderate)

   b) In that case, consider using felted foam in combination with appropriately fitting conventional or standard therapeutic footwear as the fourth choice of offloading treatment to promote healing of the ulcer. (Weak; Low)
5. In a person with diabetes and a neuropathic plantar metatarsal head ulcer, consider using Achilles tendon lengthening, metatarsal head resection(s), or joint arthroplasty to promote healing of the ulcer, if non-surgical offloading treatment fails. (Weak; Low)
6. In a person with diabetes and a neuropathic plantar digital ulcer, consider using digital flexor tenotomy to promote healing of the ulcer, if non-surgical offloading treatment fails. (Weak; Low)
7. a) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with either mild infection or mild ischemia, consider using a non-removable knee-high offloading device to promote healing of the ulcer. (Weak; Low)

   b) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both mild infection and mild ischemia, or with either moderate infection or moderate ischaemia, consider using a removable knee-high offloading device to promote healing of the ulcer. (Weak; Low)

   c) In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both moderate infection and moderate ischaemia, or with either severe infection or severe ischemia, primarily address the infection and/or ischemia, and consider using a removable offloading

intervention based on the patient's functioning, ambulatory status and activity level, to promote healing of the ulcer. (Weak; Low)

8. In a person with diabetes and a neuropathic plantar heel ulcer, consider using a knee-high offloading device or other offloading intervention that effectively reduces plantar pressure on the heel and is tolerated by the patient, to promote healing of the ulcer. (Weak; Low)
9. In a person with diabetes and a non-plantar foot ulcer, use a removable ankle-high offloading device, footwear modifications, toe spacers, or orthoses, depending on the type and location of the foot ulcer, to promote healing of the ulcer. (Strong; Low)

INTRODUCTION

Diabetes-related foot ulceration (DFU) results in a large global morbidity, mortality and cost burden (1-5). DFU annually affects around 26 million people worldwide (2, 4). Without appropriate care, these foot ulcers can lead to hospitalisation, amputation and death (1-5). Thus, healing of DFU is of paramount global importance (1-5).

Peripheral neuropathy affects around half of all people with diabetes and leads to loss of protective sensation in the feet (2-4). Elevated levels of mechanical stress in the presence of loss of protective sensation is one of the most common causes of DFU (2, 6-8). Mechanical stress is composed of plantar pressures and shear accumulated during repetitive cycles of weight-bearing activity (2, 6-8). Peripheral neuropathy can also lead to further changes in gait, foot deformity and soft tissue, all of which can further elevate mechanical stress (7-9). Thus, the combination of loss of protective sensation and elevated mechanical stress leads to tissue damage and DFU (2, 6, 10). Once a DFU forms, healing is chronically delayed if the area is not effectively offloaded (2, 6, 10).

Multiple interventions are typically required to effectively heal a DFU, including local wound management, infection management, revascularisation and pressure offloading (11, 12). The first three of those interventions are covered in other parts of the International Working Group of the Diabetic Foot (IWGDF) Guidelines (12-15). In people with neuropathic DFUs, pressure offloading is arguably the most important of these interventions (10-12). There is a long standing clinical tradition of using different offloading devices, footwear, surgery, and other offloading interventions to heal DFUs (6, 10, 16-18). Previous IWGDF Guidelines have shown that sufficient evidence is available to support the use of non-removable knee-high offloading devices to heal plantar forefoot ulcers, over all other offloading interventions (10, 12, 19). It also identified that more high-quality studies are needed to confirm the promising effects of other offloading interventions to heal DFUs, in order to better inform practitioners about effective treatments (10, 19). Over the last few years, several well-designed controlled studies have been performed in this field that add to the evidence base for offloading foot ulcers in patients with diabetes (20-23).

This guideline aims to update the previous IWGDF guideline on footwear and offloading. However, unlike the previous guideline, this guideline no longer includes footwear and offloading for the prevention of foot ulcers; it focusses only on offloading for the management of foot ulcers. Footwear

and offloading for the prevention of foot ulcers is now covered by the IWGDF guideline on prevention (24). Other IWGDF guidelines in this series include those on peripheral artery disease, infection, wound healing and ulcer classification (25-28).

METHODS

In this guideline we have followed the GRADE methodology, which is structured around clinical questions in the PICO-format (Patient-Intervention-Comparison-Outcome), systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale (29, 30).

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF Editorial Board. The members of the working group devised the clinical questions, which were revised after consultation with external experts from various geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and other health care professionals in providing useful information on offloading interventions to heal foot ulcers in people with diabetes. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate et al. (11) as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as 'high', 'moderate' or 'low'. The systematic review supporting this guideline is published separately (31).

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system we provided the rationale for how we arrived at each recommendation, based on the evidence from our systematic review (31), expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method (29, 30). Based on these factors, we graded the strength of each recommendation as 'strong' or 'weak', and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

We refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (32).

RECOMMENDATIONS

A diagrammatic overview of the recommended offloading treatment approach to heal a foot ulcer in a person with diabetes can be found in Figure 1.

In this guideline, many different offloading interventions are mentioned. We refer to the glossary for a definition and description of each of these offloading interventions. Furthermore, many of the offloading devices and interventions recommended require specific training, skills, and experience to apply properly. As these specific skills and training are not described in the studies performed and may differ between countries, we suggest that the person applying the offloading should be a properly trained healthcare professional who according to their national or regional standards has the knowledge, expertise, and skills necessary to manage patients with a DFU.

What's new?

We have made several changes to the recommendations included in this updated 2019 IWGDF offloading guideline when compared to the previous IWGDF offloading guideline. The main changes are the following:

- Removed any recommendations on the prevention of foot ulcers (these are now covered in the updated 2019 IWGDF prevention guideline (24))
- Outlined clearly the first-, second-, third- and fourth-choice of offloading treatment to heal a neuropathic plantar forefoot or midfoot ulcer
- Added one new recommendation on considerations for choosing between either a total contact cast or non-removable knee-high walker
- Added three new recommendations on offloading treatments for people with neuropathic plantar forefoot ulcers that are complicated by infection or ischemia
- Added a new recommendation on offloading treatments for people with neuropathic plantar heel ulcers

OFFLOADING DEVICES

PICO 1: In people with a plantar DFU, are non-removable offloading devices compared to removable offloading devices effective to heal the DFU?

Recommendation 1a: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, use a non-removable knee-high offloading device with an appropriate foot-device interface as the first-choice of offloading treatment to promote healing of the ulcer (GRADE strength of recommendation: Strong; Quality of evidence: High).

Rationale: Non-removable knee-high offloading devices consist of total contact casts (TCCs) and non-removable walkers (19). TCCs are custom-made, knee-high, non-removable casts and non-removable

walkers are prefabricated, knee-high, removable walkers rendered irremovable by applying a layer of cast or tie wrap around the device. These walkers may involve a modular insole system or have an (custom) insole added. In any case, an appropriate foot-device interface is required, meaning that peak pressures are adequately distributed and reduced at the ulcer location. Non-removable offloading devices offer several benefits for healing a DFU over other offloading interventions, including better redistribution of pressure over the foot and lower leg and enforced adherence (6, 10, 19, 33). These factors play an important role in the healing of foot ulcers with non-removable offloading.

Our updated systematic review (31) identified five high-quality meta-analyses of controlled trials on this topic (33-37), with much overlap present between the meta-analyses on the trials included. All found that non-removable offloading devices result in significantly improved healing outcomes for neuropathic plantar forefoot ulcers when compared with removable devices (removable offloading devices or footwear) (33-37). For those meta-analyses reporting relative risks, they found non-removable offloading devices were 17-43% more likely than removable devices to heal a neuropathic plantar forefoot ulcer ($p<0.05$) (34, 36, 37). For those reporting time-to-healing, they found non-removable offloading devices healed ulcers 8-12 days quicker than removable devices ($p<0.05$) (33, 35). We conclude that non-removable knee-high offloading devices have clear healing benefits over removable devices. The quality of evidence is rated as high.

Possible adverse effects of non-removable offloading devices include muscle weakness, falls, new ulcers due to poor fitting, and knee or hip complaints due to the acquired limb-length discrepancy when wearing the device (38-40). One may consider a shoe raise for the contralateral limb to minimize this acquired limb-length discrepancy. In most randomized controlled trials (RCT), the wide variation in type of adverse events, relatively small sample sizes and low incidence of reported events prevented statistical testing between non-removable and removable devices (22, 23, 38, 41-43). However, two meta-analyses reported no differences in skin maceration or treatment discontinuation (combination of adverse events, voluntary withdrawal or losses to follow-up) (34, 36). Additionally, six RCTs described low overall incidences (0-20%) of adverse events, with no differences evident between non-removable and removable devices for these events, including falls, maceration, abrasions, new ulcers, infections and hospitalisations (22, 23, 38, 41-43). Nevertheless, clinicians and other health care providers should still be aware of these adverse events. We conclude non-removable and removable offloading devices have similar low incidences of harm.

Many patients are thought to not prefer non-removable knee-high offloading devices as they limit daily life activities, such as walking, sleeping, bathing, or driving a car (34). Two RCTs reported on patient preferences with one reporting lower patient satisfaction with non-removable compared with removable offloading devices (23) and the other reporting no differences in patient satisfaction or comfort (43). One large health technology assessment reported on qualitative interviews with 16 patients with DFU who were familiar with a variety of off-loading devices (34). They found that patients rated non-removable offloading devices as preferable after they understood the healing benefits of non-removable devices, even though they rated removable offloading devices as more comfortable, allowing greater freedom and mobility (34). Practitioners may not prefer some non-removable offloading, as surveys and epidemiological studies show low use of TCCs in clinical practice, but similar (and

moderate) use of non-removable and removable walkers (16-18, 44). We conclude that non-removable and removable offloading devices may be equally preferred by both patients and clinicians.

Two RCTs reported on costs with one finding one-off device/material costs were higher for non-removable and removable walkers than for TCCs (38), and the other finding that TCCs and non-removable walkers were less expensive over the course of treatment than removable walkers (23). One large health technology assessment study systematically reviewed the literature and found no papers on economic evaluations of non-removable offloading devices (34). The authors then performed their own cost-effectiveness analysis, using existing literature and expert opinion, which showed that the cost per patient for three months of treatment (including all device/materials, dressings, consultations, labour, complication costs etc.) was lowest for non-removable walkers ($876) and TCCs ($1,137), compared with removable walkers ($1,629) and therapeutic footwear ($1,934) (34). They concluded that non-removable walkers and TCCs were superior to the other offloading interventions because they were both less expensive and more effective than removable walkers and therapeutic footwear. They also performed a cost utility analysis which also showed that the cost per patient for 6 months of treatment (including all treatment costs and heath gains from ulcers healed and quality of life) was again lowest for non-removable walkers ($2,431) and TCCs ($2,924), compared with removable walkers ($4,005) and therapeutic footwear ($4,940) (34). We conclude non-removable offloading devices to be more cost-effective than removable offloading devices.

Contraindications for the use of non-removable knee-high offloading devices, based predominantly on expert opinion, include presence of both mild infection and mild ischemia, moderate-to-severe infection, moderate-to-severe ischaemia, or heavily exudating ulcers (34-36, 39, 45). We refer to the IWGDF infection and PAD guidelines and the IWGDF definitions and criteria document for definitions on infection and ischemia (27, 28, 46). We identified no RCTs in this field that have included participants with these conditions, seemingly for safety reasons. However, we did identify controlled and non-controlled studies that indicate no additional adverse events in people with mild infection or mild ischaemia (39, 45, 47-51). One low-quality systematic review investigating mostly non-controlled studies of TCC use in people with ischaemia recommended an ankle brachial index threshold of >0.55 for safe use of a TCC (52). The use of non-removable knee-high offloading devices may also induce an increased risk of falls with several studies reporting abnormal gait changes and imbalance in people with DFU wearing knee-high offloading devices (53-55). However, in the aforementioned RCTs there was no increase in reported falls-related adverse events in those wearing non-removable knee-high offloading devices (22, 23, 38, 41-43). Further, studies investigating ankle foot orthoses, devices that share functional similarities to knee-high offloading devices, have shown ankle foot orthoses may help to improve balance and reduce falls in older people with neuropathy (56, 57). Future studies should specifically investigate the effect of knee-high offloading devices on risk of falls, and we suggest falls risk assessment should be done on a patient-by-patient basis.

In summary, the quality of the evidence from the meta-analyses performed was high, even though the quality of evidence from individual RCTs varied. All meta-analyses favoured the use of non-removable knee-high over removable offloading to heal neuropathic plantar forefoot ulcers without infection or ischemia present. These benefits outweigh the low incidence of harm, and with positive cost-

effectiveness and mixed patient preference for the use of non-removable over removable offloading devices, we grade this recommendation as strong. We refer to recommendations 7a, 7b, and 7c for DFU that are infected or where ischemia is present.

PICO 2: In people with a plantar DFU, are total contact casts (TCC) compared to other non-removable knee-high offloading devices effective to heal the DFU?

Recommendation 1b: When using a non-removable knee-high offloading device to heal a neuropathic plantar forefoot or midfoot ulcer in a person with diabetes, use either a total contact cast or non-removable knee-high walker, with the choice dependent on the resources available, technician skills, patient preferences and extent of foot deformity present (Strong; Moderate).

Rationale: The TCC had been considered for decades the gold standard offloading intervention to heal a neuropathic plantar forefoot ulcer (19, 58). Our previous guideline broadened the recommendation to a non-removable offloading device (19), to include both a TCC and a prefabricated removable knee-high walker rendered non-removable with an appropriate foot-device interface. However, the previous guideline did not provide a recommendation on which one is preferable to use (19).

Our updated systematic review (31) identified one high-quality meta-analysis on this topic (34) that included three high-quality RCTs (23, 59, 60). The meta-analysis found no difference in ulcers healed using TCCs and non-removable walkers ($p=0.82$) (34). Another low-quality RCT also found no significant difference between a TCC and non-removable knee-high walker for ulcers healed ($p=0.99$) or time-to-healing ($p=0.77$) (61). However, none of these four RCTs was based on a sample size calculation for equivalence (59). Thus, the non-significant results of the individual RCTs may reflect low statistical power to detect differences, although the meta-analysis should have had sufficient power. We conclude that TCCs and non-removable knee-high walkers are equally effective to heal DFUs.

As healing outcomes were similar, we analysed effects on the surrogate outcomes of plantar pressures and weight-bearing activity (11). One RCT found a significantly greater plantar pressure reduction from barefoot pressure baselines in a knee-high walker compared with a TCC at the ulcer site (91% v 80%), the forefoot (92% v 84%) and midfoot (77% vs 63%) (all, $p<0.05$), but no difference in the rearfoot ($p=0.11$) (62). However, several non-controlled within-subject studies found no significant difference in plantar pressure reduction from standard footwear baselines in knee-high walkers compared with TCCs at the ulcer site, hallux and forefoot (63-66). We found no controlled studies investigating weight-bearing activity. We consider TCCs and non-removable knee-high walkers to have similar effects on reducing plantar pressures.

Three high-quality RCTs reported adverse events for TCCs and non-removable knee-high walkers and found no significant differences ($p>0.05$) (23, 59, 60). Additionally, one meta-analysis found no significant difference for treatment discontinuation between these two devices ($p=0.52$) (34). While the low numbers of adverse events and treatment discontinuations may have resulted in low power to detect differences, we consider these devices to have similarly low levels of harm. The same RCTs reported on patient preferences. One reported higher patient satisfaction with a non-removable knee-

high walker than with a TCC ($p<0.05$) (60), whilst another reported no differences ($p>0.05$) (23). Two of these RCTs also found that it took a significantly longer time to apply and remove a TCC than a non-removable knee-high walker (by up to 14 minutes, $p<0.01$) (59, 60). We conclude that patient and practitioner preference for either device is mixed.

Four RCTs reported on the costs of using a TCC or non-removable knee-high walker. One low-quality RCT reported that the one-off device/material costs for a TCC were lower than for a non-removable offloading device ($20 v $35, $p<0.01$) (61). Three other, high-quality, RCTs reported that treatment costs were lower for non-removable knee-high walkers than for TCCs (23, 59, 60). One reported that device/material costs were lower ($158 v $211, p=not reported) (59), another that all offloading treatment costs (i.e. device/materials, cast changes, dressings, cast technician salary) were significantly lower ($162 v $727, $p<0.001$) (60), and the third that average costs per day of treatment were significantly lower with a non-removable walker than with a TCC (€83 v €243, $p<0.05$) (23). The cost-effectiveness analysis of a health technology assessment showed that the cost per patient for three months treatment was lower per patient for a non-removable walker than for a TCC ($876 v $1,137) (34). When the costs and healing probabilities were modelled over 1000 patients with a DFU, they reported the TCC would heal 15 more ulcers (741 v 726), but cost $260,420 more than the non-removable knee-high walker ($1.137 million v $0.876 million). Thus, from a population-based perspective they suggest that for each additional DFU healed using a TCC compared with using a non-removable walker would cost a service $17,923, and therefore would not be more cost-effective in most services (34). The same study found in a cost-utility analysis that the cost per patient for six months treatment were lower for a non-removable walker than for a TCC ($2,431 v $2,924) (34). We conclude that non-removable walkers are generally more cost-effective than TCCs.

In summary, based on one high-quality meta-analysis of three high-quality RCT's showing consistent results for healing between the TCC and non-removable knee-high walkers, and with a need for larger trials to test for equivalence, we rate the quality of evidence as moderate. Additionally, considering the equivalence in plantar pressure benefits and adverse events, and slight preference and lower costs for a non-removable knee-high walker, we grade this recommendation as strong. However, we recommend to base the choice for either a TCC or a non-removable knee-high walker on availability of the device/materials (i.e. resources), skills of available cast technicians, appropriateness of the device to fit the level of any foot deformity (i.e. a TCC with a severely deformed foot), and patient preferences.

PICO 3: In people with a plantar DFU, are removable knee-high offloading devices compared to other removable offloading devices effective to heal the DFU?

Recommendation 2: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a non-removable knee-high offloading device is contraindicated or not tolerated, consider using a removable knee-high offloading device with an appropriate foot-device interface as the second-choice of offloading treatment to promote healing of the ulcer. Additionally, encourage the patient to consistently wear the device (Weak; Low).

Rationale: There are circumstances when a non-removable knee-high offloading device is contraindicated (see rationale for recommendation 1) or cannot be tolerated by the patient. Intolerance by the patient can include refusal to wear the device or the patient's circumstances do not support its use, such as unable to use the device as part of the patient's job. A removable knee-high offloading device may be a solution to these conditions (19). A removable knee-high device redistributes peak pressures in a similar fashion as a non-removable knee-high device (6, 10, 19, 33), although one study showed higher peak pressures during walking after a TCC was bivalved and made removable (66). A removable knee-high device also does this more effectively than a removable ankle-high offloading device (such as ankle-high walker, forefoot offloading shoes, half-shoes, cast shoes, or post-operative sandal) (6, 10, 19, 33).

Our systematic review (31) identified one high-quality meta-analysis (34), that included two low-quality RCTs (38, 43), and found no difference in the proportion of plantar forefoot ulcers healed between removable knee-high and ankle-high offloading devices (healing sandal or half-shoe) ($p=0.20$) (34). A more recent high-quality RCT also found no difference in plantar forefoot ulcers healed between a removable knee-high device (bivalved TCC) and either a removable ankle-high cast shoe or forefoot offloading shoe, at either 12 weeks ($p=0.703$) or 20 weeks ($p=0.305$) (20). However, the authors noted the removable knee-high device group had significantly more deep ulcers (University of Texas grade 2) than both ankle-high device groups at baseline ($p<0.05$) (20). None of the RCTs conducted were sufficiently powered for equivalence. We conclude from the current evidence available that removable knee-high and removable ankle-high offloading devices have comparable effects on healing neuropathic plantar DFUs.

As healing outcomes were comparable between devices, we assessed surrogate measures (11). One high-quality RCT (20) found a removable knee-high device (bivalved TCC) had greater plantar pressure reductions from standard footwear baseline levels at the ulcer site than a removable ankle-high cast shoe or forefoot offloading shoe (67% v 47% v 26%, respectively, $p=0.029$) (20). Several within-subject studies also found that removable knee-high devices show greater forefoot plantar pressure reduction than removable ankle-high devices (53, 54, 64-67). Three RCTs investigated weight-bearing activity. One high-quality RCT found no differences in average daily step count between a removable knee-high device (bivalved TCC) and removable ankle-high cast shoe or forefoot offloading shoe device (4,150 v 3,514 v 4,447, respectively, $p=0.71$) (20), but it should be noted the study was not powered for this outcome. Another low-quality RCT found a large but non-significant reduction in daily steps in a removable knee-high device compared to a removable ankle-high half-shoe (768 v 1,462 steps, $p=0.15$) (38). A third, low-quality, RCT found significant reductions in average daily step count in those patients wearing a removable knee-high device compared to wearing a healing sandal (1,404 v 4,022, $p<0.01$) (43). We conclude that removable knee-high devices reduce plantar pressures at ulcer sites and weight-bearing activity more effectively than removable ankle-high devices, and therefore have more potential for healing plantar neuropathic forefoot ulcers when worn.

Adverse events for removable knee-high offloading devices are likely to be the same as for non-removable knee-high devices. However, ankle-high offloading devices may potentially have fewer adverse events compared with knee-high offloading devices as they either have lower or no device walls

that reduce the risk for abrasions, lower-leg ulcers, imbalance, and gait challenges (33), and they may have lower treatment discontinuation (20). One high-quality meta-analysis including two low-quality RCTs (38, 43) found higher treatment discontinuation with removable knee-high devices compared with removable ankle-high devices ($p<0.01$) (34). One high-quality RCT found no differences in adverse events between a removable knee-high device and either a removable cast shoe or forefoot offloading shoe (45% v 30% v 25%, respectively, $p=0.377$) (20). Further, those events reported were mostly minor pressure points, blisters and abrasions; with smaller numbers of serious hospitalisation and fall events (15% v 5% v 5%, respectively, p=not reported) (20). A low-quality RCT also found no difference in adverse events for new ulcers or infections between removable knee-high and removable ankle-high devices (15% v 13%, $p>0.05$) (43). A third, low-quality, RCT reported no adverse events in either group (38). We conclude there is no clear difference in adverse events between removable knee-high and removable ankle-high offloading devices.

We identified one low-quality RCT reporting preference outcomes that found no difference in patient satisfaction, comfort or preference to wear again between wearing a removable knee-high and removable ankle-high offloading device ($p>0.05$) (43). The same study reported that the removable knee-high group was more non-adherent than the removable ankle-high group (11% vs 0% of participants were deemed non-adherent with their device and were removed from the study as drop outs, p=not reported) (43). A high-quality RCT also reported non-significantly higher non-adherence with removable knee-high offloading than with two removable ankle-high devices (17% vs 5% vs 5% of the time, $p=0.236$) (20). We conclude patients have similar preference for removable knee-high and ankle-high devices and non-adherence does not seem to be very different between devices, although one should note that these studies were not powered to detect a difference in non-adherence between devices.

One low-quality RCT reported on costs, finding that one-off device costs was more expensive for a removable knee-high offloading device (walker) than an ankle-high offloading device (half-shoe) ($150-200 v $25-75, p=not reported) (38). Based on only one, already rather old study, we provisionally conclude that the device costs of treatment are higher in removable knee-high devices than in removable ankle-high offloading devices.

Contraindications for the use of removable knee-high offloading devices, based predominantly on expert opinion, include presence of both moderate infection and moderate ischemia, or severe infection or severe ischaemia. We refer to the IWGDF infection and PAD guidelines and the IWGDF glossary for definitions on infection and ischemia (27, 28, 46) .

In summary, based on similar healing outcomes in a small number of mostly low-quality controlled studies, but consistently superior plantar pressure offloading and induced reduction of walking activity and thus superior healing potential in those studies and other non-controlled studies, we rate the quality of evidence favouring removable knee-high devices over removable ankle-high devices as low. Additionally, considering this healing benefit, no apparent differences in adverse events or preferences, and slightly higher non-adherence and treatment costs with removable knee-high offloading, we favour removable knee-high offloading over ankle-high offloading in our recommendation, but grade the

recommendation as weak. Nevertheless, as such a device is removable and there is potential for non-adherence, we stress that the patient should (repeatedly) be educated on the benefit of adherence to wearing the device to improve the effectiveness of the device for healing (55).

Recommendation 3: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a knee-high offloading device is contraindicated or not tolerated, use a removable ankle-high offloading device as the third-choice of offloading treatment to promote healing of the ulcer. Additionally, encourage the patient to consistently wear the device (Strong; Low).

Rationale: Overall, evidence indicates that removable and non-removable knee-high offloading devices give better clinical outcomes or potential for healing than ankle-high devices (see rationales for recommendations 1 and 2). However, there may be contraindications (see rationales for recommendations 1 and 2) or patient intolerance for wearing a knee-high device, such as expected or experienced device-induced gait instability, abrasions or other complications from the cast or device wall, or patient refusal to wear the device. Another reason may be lack of available knee-high offloading devices. In those cases, removable ankle-high offloading can be considered. This includes ankle-high walkers, cast shoes, half shoes, forefoot offloading shoes, post-operative healing shoes and custom-made temporary shoes.

Our systematic review identified (31) no controlled studies specifically comparing removable ankle-high devices to conventional or standard therapeutic footwear or other offloading interventions, for effectiveness of healing, surrogate healing outcomes, adverse events, patient preferences or costs.

Several non-controlled studies show that 70–96% of plantar foot ulcers can be healed in a reasonable time frame (mean 34–79 days) with ankle-high removable offloading devices, provided they are used regularly (68-72). Multiple within-subject studies also consistently found that a variety of removable ankle-high offloading devices were more effective in reducing plantar pressure at the forefoot than a variety of footwear interventions (custom-made, therapeutic, extra-depth, conventional or standard footwear) (53, 54, 64, 65, 73-77). No studies were found for weight-bearing activity or adherence. Thus, we conclude that removable ankle-high devices have higher potential for healing than conventional or therapeutic footwear or other non-knee-high offloading interventions when worn.

Adverse events comparing ankle-high offloading devices to footwear interventions have not been reported in the literature. Based on expert opinion, we consider ankle-high offloading devices to have a low adverse event rate, and comparable to conventional or therapeutic footwear. Adverse events may include minor abrasions, blisters, minor gait challenges or instability, and, with poor casting, new ulcers with cast shoes. However, it should be noted that the traditional form of half-shoes, that only support the midfoot and heel (71), contrary to a forefoot offloading shoe, are contraindicated owing to risk of midfoot fracture.

Two studies reported on patient preferences (74, 75). They showed that patient comfort was similar between ankle-high walkers and standard footwear (75), but was lower in different forefoot offloading shoe models compared with standard footwear (74). A recent study reported that the use of ankle-high

walkers had similar patient comfort levels to athletic shoes when the contralateral leg had a shoe raise to compensate for leg-length discrepancy (53). Based on expert opinion, patients may prefer an ankle-high walker over a forefoot offloading shoe, because the latter has a significant negative rocker outsole that may cause problems during gait.

We found no studies comparing costs of ankle-high offloading devices with conventional or therapeutic footwear. The cost of treatment is likely to be low for some ankle-high offloading devices (e.g. cast shoes, forefoot offloading shoes), particularly when they require no replacement during treatment. However, costs for therapeutic footwear are expected to be higher than for these other ankle-high devices.

In summary, all evidence for this recommendation comes from cross-sectional studies and expert opinion, and therefore the quality of evidence for this recommendation is rated as low. When weighing the potentially higher healing benefits of removable ankle-high devices over conventional or therapeutic footwear, better outcomes on plantar pressure, with expected similar low incidence of harms, patient preferences, and costs we grade this recommendation as strong. In particular, for countries with low resources or lack of trained cast technicians, these removable ankle-high devices may be an appropriate offloading intervention for treating plantar neuropathic forefoot ulcers.

FOOTWEAR

PICO 4: In people with a plantar DFU, are conventional or standard therapeutic footwear compared to other (non-surgical) offloading interventions effective to heal the DFU?

Recommendation 4a: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, do not use, and instruct the patient not to use, conventional or standard therapeutic footwear as offloading treatment to promote healing of the ulcer, unless none of the above-mentioned offloading devices is available (Strong; Moderate).

Rationale: There are no studies that show the efficacy of conventional or standard-therapeutic footwear as the primary intervention to heal neuropathic plantar foot ulcers. In the few studies in which this footwear has been tested as a comparison intervention, the conventional or standard therapeutic footwear proved inferior to other offloading devices (custom-made or prefabricated, non-removable or removable, knee-high or ankle-high devices) to both reduce mechanical stress and effectively heal a neuropathic plantar forefoot ulcer. Two high-quality meta-analyses found non-removable knee-high offloading devices were 62-68% more likely to heal a neuropathic plantar forefoot ulcer than therapeutic footwear ($p<0.01$) (34, 37). Another high-quality meta-analysis (35), including two lower quality RCTs (49, 78), reported removable offloading devices were 76% more likely to heal these ulcers than therapeutic footwear, but the difference was non-significant ($p=0.184$) (35). A low quality RCT not included in the meta-analyses found no difference between TCCs, non-removable knee-high walkers or modified footwear for healing rates ($p=0.99$) and time-to-healing ($p=0.77$) (61).

Four low-quality RCTs reported adverse events using therapeutic footwear and all were compared to TCCs. Two found similar low proportions of abrasions or new ulcers for TCCs (0-4%) and footwear (0-4%, no p=not reported) (61, 79). Whilst another two found lower proportions of infections with TCC (0-3%) compared with footwear (19-26%) ($p<0.05$) (49, 78). One high-quality meta-analysis reported significantly more treatment discontinuations due to a combination of adverse events, voluntary withdrawal or losses to follow-up in those patients treated with TCCs compared to therapeutic footwear ($p=0.003$) (34).

One low-quality RCT reported on patient preference and found that those patients using TCCs and those using therapeutic footwear had no difference in an acceptance of treatment score (p="not significant") (79). One low-quality RCT reported the material costs for modified footwear were lower than for TCCs and non-removable walkers in treating patients with a foot ulcer ($7 v $20 v $35, respectively; $p<0.01$) (61). However, the aforementioned large health technology assessment showed therapeutic footwear was far less cost-effective than other non-removable (TCC and non-removable knee-high offloading device) and removable offloading devices (removable walkers) (34).

Taken together, based on data from multiple meta-analyses consistently favouring the use of offloading devices over conventional or standard therapeutic footwear to heal neuropathic plantar forefoot ulcers, we rate the quality of evidence as moderate. Based additionally on worse outcomes for adverse events and costs using therapeutic footwear, and similar outcomes for preferences, we grade this recommendation as strong.

OTHER OFFLOADING TECHNIQUES

PICO 5: In people with a plantar DFU, are any other offloading techniques that are not device or footwear-related, effective to heal a DFU?

Recommendation 4b: In that case, consider using felted foam in combination with appropriately fitting conventional or standard therapeutic footwear as the fourth choice of offloading treatment to promote healing of the ulcer (Weak; Low).

Rationale: Despite many practitioner surveys reporting high use of other offloading techniques (particularly for felted foam) (17, 18), there has been limited evidence to support any other offloading techniques to effectively heal a neuropathic plantar foot ulcer (10). Other offloading techniques are defined as any intervention undertaken with the intention of relieving mechanical stress from a specific region of the foot that is not an offloading device, footwear or surgical approach.

Our updated systematic review (31) identified just three low-quality controlled trials (70, 80, 81) on other offloading techniques to heal a neuropathic plantar foot ulcer. All three trials investigated felted foam padding (70, 80, 81). No controlled trials were identified for bed rest, crutches, wheelchairs, offloading dressings, callus debridement, foot-related strength and stretching exercises, or gait retraining to effectively heal DFUs.

One low-quality RCT showed significantly shorter time-to-healing with felted foam worn in a post-operative shoe when compared with a half-shoe used without the felted foam (81). Another low-quality RCT showed no difference in ulcer size reduction at 4 weeks between felt fitted to the foot worn in a post-operative shoe compared with felt fitted to a post-operative shoe (80). A low-quality retrospective cohort study found no differences in ulcers healed or time-to-healing between felted foam fitted to the foot in a post-operative shoe, felted foam fitted to a post-operative shoe, a walking splint or TCC (70). Additionally, two within-subject studies found that felted foam in addition to post-operative shoes moderately reduced plantar pressures over one week compared to post-operative shoes alone (82, 83). We conclude that felted foam used with an ankle-high offloading device may be more effective than wearing just the device alone, to reduce plantar pressure and heal a plantar neuropathic DFU. Furthermore, we consider the same effectiveness may be apparent if the felted foam was used with an appropriately fitting conventional or standard therapeutic footwear as opposed to just wearing the footwear alone.

The only two controlled studies reporting adverse events found similar levels of adverse events for the use of felted foam in combination with an ankle-high offloading device compared with an ankle-high device alone, including minor skin tear/maceration (10% v 20%) and new infection (25% v 23%) (80, 81). No controlled studies were identified that investigated patient preferences or costs; however, patients will likely value and prefer the use of felted foam as an easy-to-use modality. The costs of felted foam are relatively low, but it does require frequent replacement, by a clinician, the patient, a relative, or a home-care nurse. Based on the evidence from the studies performed, felted foam may be used in ankle-high offloading devices or when no offloading devices are available then may be used in addition to appropriately fitting conventional or standard therapeutic footwear. We define appropriately fitting footwear as providing sufficient room for the patients' foot shape and the added felted foam. This enables for some offloading treatment of the ulcer if other forms of offloading devices, as mentioned in recommendation 1 to 3, are not available. Whether the felted foam is fitted to the foot or to the shoe or insole does not make a difference in healing, although fitting it to the foot provides some offloading when the patient is non-adherent to wearing the shoes.

In summary, based on few low-quality controlled studies, and the difficulty in determining the added effect of felted foam in these studies, we rate the quality of evidence as low. Any benefit found with the use of felted foam will likely outweigh the harm. Together with a lack of information on costs and patient preference, we rated the strength of this recommendation as weak. Finally, based on the evidence from all offloading intervention studies performed and our expert opinion, felted foam may be used in addition to offloading devices, or if no offloading devices are available then felted foam may be used in combination with appropriately fitting conventional or standard therapeutic footwear as the fourth-choice of offloading treatment for healing the ulcer. However, felted foam should never be used as a single treatment modality.

SURGICAL OFFLOADING TECHNIQUES

PICO 6: In people with a DFU, are surgical offloading techniques compared to non-surgical offloading interventions effective to heal the DFU (O)?

Recommendation 5: In a person with diabetes and a neuropathic plantar metatarsal head ulcer, consider using Achilles tendon lengthening, metatarsal head resection(s), or joint arthroplasty to promote healing of the ulcer, if non-surgical offloading treatment fails (Weak; Low).

Rationale: Surgical offloading techniques have been traditionally used for plantar ulcers that are considered hard-to-heal with non-surgical offloading interventions (58). These techniques change the structure of the foot and therefore provide a more permanent offloading solution for areas of elevated mechanical stress, even when the patient is not adherent to wearing an offloading device. However, surgical offloading potentially comes with increased risk of complications (58). Surgical offloading is defined as a surgical procedure undertaken with the intention of relieving mechanical stress from a specific region of the foot, and typically include Achilles tendon lengthening, metatarsal head resection, osteotomy, arthroplasty, ostectomy, exostectomy, external fixation, flexor tendon transfer or tenotomy, and tissue fillers such as silicone or fat.

Our updated systematic review (31) identified one high-quality meta-analysis on this topic (84). This meta-analysis included two 2 RCTs, one high-quality (85) and one low-quality (86), and investigated Achilles tendon lengthening and gastrocnemius recession compared with TCC controls (84). It found no differences in proportion of ulcers healed or time-to-healing (84). The high-quality RCT did find small effects, but these were not statistically significant, on ulcers healed (100% v 88%, p=0.12) and time-to-healing (40.8 days v 57.5 days, p=0.14) favouring Achilles tendon lengthening with TCC compared with TCC alone in patients with reduced ankle dorsiflexion (85). Four retrospective non-controlled studies showed 80–95% healing in 3 months with Achilles tendon lengthening (87-90).

One high-quality RCT found that metatarsal head resection(s) in combination with therapeutic footwear compared with therapeutic footwear alone healed more ulcers (95% v 79%, p<0.05) with shorter time-to-healing (47 v 130 days, p<0.05) (91). Three low-quality retrospective controlled cohort studies also found metatarsal head resection(s) had shorter time-to-healing (by 21-350 days, p<0.05) than non-surgical offloading interventions (removable walker, healing sandals and therapeutic footwear) (92-94). Additionally, six non-controlled studies showed positive effects of single or pan metatarsal head resection in time-to-healing of plantar neuropathic metatarsal head ulcers, in patients in whom non-surgical treatment had failed (95-100).

Two small lower-quality retrospective controlled cohort studies investigated metatarsal-phalangeal joint arthroplasty in addition to TCC and found shorter time-to-healing (by 24-43 days, p<0.05) compared with non-removable offloading devices (TCC or non-removable walker) (101, 102). Four non-controlled studies showed between 91% and 100% healing of plantar, lateral, or dorsal toe ulcers using interphalangeal or metatarsal-phalangeal joint arthroplasty (103-106).

The potential harm of applying these surgical techniques includes post-operative complications, infection, gait problems, acute Charcot neuro-osteoarthropathy, ruptured Achilles tendons and transfer ulcers (87, 97, 99). The controlled trials reporting adverse events found mixed results (85, 91-93, 101, 102). These included a significant increase in heel ulcers after Achilles tendon lengthening compared with TCC alone (13% v 0%, $p<0.05$), but similar number of abrasions (13% v 18%), infection (3% v 0%), amputation (0% v 3%), falls (7% v 0%) and death (10% v 9%) (85). Most other trials compared surgical techniques to removable offloading devices or footwear and found mixed results on adverse events that were not significantly different between interventions, including infection (5-40% v 13-65%) and amputation (5-7% v 10-13%) ($p>0.05$) (91-93, 101). One recent low-quality controlled study of metatarsal head resection(s) found significant decreases in number of hospitalisations and infections compared with non-surgical offloading controls described as "non-weight bearing, and sometimes specialized footwear" ($p<0.05$) (94).

Only one controlled study reported on patient preferences, finding higher discomfort in a surgical offloading group during healing ($p<0.05$), but higher satisfaction after treatment when compared with therapeutic footwear ($p<0.01$) (91). We found no controlled trials investigating costs. Costs of treatment for surgical interventions are generally considered higher than for non-surgical treatment, although one study showed no difference in costs between metatarsal head resection and non-surgical treatment of a plantar foot ulcer (99).

In summary, there is some evidence to support surgical versus non-surgical offloading to improve time-to-healing of plantar foot ulcers that prove to be hard-to-heal after unsuccessful non-surgical treatment. However, based on the low number of controlled trials for each surgical intervention, the general low-quality of these trials and the mixed benefits, we consider the quality of evidence for this recommendation is low. When considering that the benefits predominantly relate only to time-to-healing and not to healing proportion, it is unclear if the benefits outweigh the potential harm. Patients may value and prefer surgical treatment after long and unsuccessful non-surgical treatment (such as with knee-high offloading devices). Thus, we rate the strength of this recommendation as weak. However, we recommend considering surgical offloading when non-surgical offloading treatment fails in healing the foot ulcer. Surgical offloading is contra-indicated when severe ischemia is present; the ischemia should be primarily addressed in that case.

Recommendation 6: In a person with diabetes and a neuropathic plantar digital ulcer, consider using digital flexor tenotomy to promote healing of the ulcer, if non-surgical offloading treatment fails (Weak; Low).

Rationale: Two recent systematic reviews were identified on the efficacy of digital flexor tenotomy on DFU outcomes (107, 108). Both reviews identified the same five non-controlled studies (109-113) and one of the reviews identified a sixth non-controlled study (114). The larger systematic review reported an overall healing rate of 97% in a mean 29.5 days (107). The majority of the studies that reported on adverse events, reported moderate incidences of infection (2-7%), transfer lesions (5-16%) amputations (2-9%) or ulcer recurrence (0-21%) (107). None reported patient preference or cost outcomes.

While controlled studies on this topic are lacking, we consider this procedure to be a promising intervention in patients with hammertoes and recalcitrant digital ulcers in particular that fail non-surgical treatment. However, the quality of the evidence for this recommendation is low. The possible benefits of digital flexor tenotomy may outweigh the potential harm. Patients who have digital ulcers that will not heal with non-surgical treatment may value and prefer treatment by flexor tenotomy, which may be performed in an outpatient setting, without need for subsequent immobilization. Costs and cost-effectiveness of this procedure have not been evaluated. Thus, we consider the strength of this recommendation to be weak.

OTHER ULCERS

PICO 7: In people with a plantar DFU complicated by infection or ischaemia, which offloading intervention is effective for healing the DFU?

Recommendation 7a: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with either mild infection or mild ischemia, consider using a non-removable knee-high offloading device to promote healing of the ulcer (Weak; Low).

Recommendation 7b: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both mild infection and mild ischemia, or with either moderate infection or moderate ischaemia, consider using a removable knee-high offloading device to promote healing of the ulcer. (Weak; Low).

Recommendation 7c: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both moderate infection and moderate ischaemia, or with either severe infection or severe ischemia, primarily address the infection and/or ischemia, and consider using a removable offloading intervention based on the patient's functioning, ambulatory status and activity level, to promote healing of the ulcer (Weak; Low).

Rationale: Many plantar ulcers seen in clinical practice are not purely neuropathic ulcers, but have some level of infection and/or ischemia present. Due to the neuropathic origin and mechanical stress that often caused and still affects these ulcers, they do require offloading. However, health care professionals should be more cautious about which kind of offloading to use and when to use them if ulcers are complicated by infection or ischaemia.

As identified in Recommendation 1, non-removable knee-high offloading devices can be considered for healing neuropathic plantar forefoot ulcers that have mild infection, mild-to-moderate amounts of exudate or mild ischaemia (34-36, 39, 45, 52). Non-removable offloading should not be used for moderate-to-severe infections or heavily exudating ulcers that require frequent local wound care or inspection, or moderate-to-severe ischaemia where there may be doubt on the potential for wound healing, or when both mild infection and mild ischaemia are present (34-36, 39, 45, 52). Removable knee-high offloading devices can be considered for healing ulcers with both mild infection and mild

ischaemia present, or with heavy exudate, moderate infection or moderate ischaemia present, which all require frequent local wound care or inspection. However, if a neuropathic plantar forefoot ulcer is complicated by both moderate infection and moderate ischemia, or by severe infection or severe ischaemia, then the infection or ischemia should primarily be addressed and an offloading intervention should be applied based on the patient's function, ambulatory status, and activity level.

The overall quality of evidence for these recommendations are low as they are collectively based on only a few observational studies (39, 45, 47, 48), interpretations from small sub-groups of patients with these complications in some larger controlled trials (49-51), and expert opinion, but with the notion that these plantar ulcers still require offloading for healing (33, 34). Furthermore, based on the lack of evidence, data missing on harm and benefits, patient preferences and costs, the strength of these recommendations are weak.

PICO 8: In people with a plantar rearfoot DFU, which offloading intervention is effective to heal the DFU?

Recommendation 8: In a person with diabetes and a neuropathic plantar heel ulcer, consider using a knee-high offloading device or other offloading intervention that effectively reduces plantar pressure on the heel and is tolerated by the patient, to promote healing of the ulcer. (Weak; Low).

Rationale: Neuropathic plantar rearfoot ulcers are less prevalent than forefoot ulcers (115), but are considered more of a challenge to offload and heal (58). There is a paucity of evidence available on offloading interventions to treat plantar rearfoot ulcers (58).

Our updated systematic review (31) identified only one controlled study that specifically reported healing outcomes for plantar rearfoot ulcers (78). This low-quality RCT reported that those ulcers offloaded with a TCC had shorter time-to-healing than those using therapeutic footwear (69 days vs 107 days), but no statistical significance was reported (78). Another high-quality RCT compared a custom-made fiberglass heel cast with standard wound care in patients with heel ulcers, but of which most (72%) were non-plantar (21). The authors did not specifically report on plantar heel ulcers. This RCT is discussed under non-plantar ulcers.

As outcomes on healing were limited, we assessed surrogate measures for offloading as previously recommended (11) and identified three controlled trials investigating plantar pressure reductions. One high-quality RCT found slightly greater rearfoot plantar pressure reductions from baseline barefoot pressure in participants wearing a TCC compared with those wearing a knee-high walker, but this difference was not significant (54% v 40%, p=0.11) (62). Another high-quality RCT found a significant increase in rearfoot plantar pressures in those undergoing an Achilles tendon lengthening procedure in combination with a TCC compared with those treated with a TCC alone (70.6±28.1 vs 55.8±30.7 N/cm2, p=0.018) (116). The other low-quality non-randomized controlled trial reported rearfoot plantar pressures in a removable ankle-high walker intervention increased by 10% from baseline pressures in conventional footwear (117).

A number of cross-sectional within-subject designed studies also investigated the effect of different offloading interventions on rearfoot plantar pressures (65, 66, 118). Three investigated TCCs compared with knee-high walkers and found mixed results. One found TCCs had slightly greater rearfoot plantar pressure reduction (118), another found knee-high walkers reduced more rearfoot pressure (65), and a third found they were the same in pressure relief (66). Several others found removable knee-high devices (walkers and bivalved TCCs) had slightly greater rearfoot plantar pressure reductions than ankle-high devices (walkers, cast shoes, post-operative healing shoes) (65-67, 76), but not always to a statistically significant level (66, 67). Other studies found that removable ankle-high devices give greater rearfoot plantar pressure reduction than footwear (therapeutic and standard) (74-76). Heel-relief shoes are specifically designed to offload the heel, but have not been tested for efficacy on pressure relief to date.

No controlled studies specifically reported on adverse events when treating those with rearfoot ulcers. However, one RCT found an increase in new plantar heel ulcer development in those undergoing Achilles tendon lengthening in combination with a TCC to heal forefoot ulcers compared with a TCC alone, but did not report significance (13% v 0%) (85). Otherwise we suggest the adverse events from different offloading interventions would be similar to those to heal a forefoot DFU. Thus, we consider that non-removable and removable knee-high devices have similar low incidence of harm, but potentially slightly higher than removable ankle-high devices. No studies have reported on preferences or costs for treating plantar rearfoot ulcers.

In summary, there is some evidence that using knee-high offloading devices may be more effective in time-to-healing and reducing plantar pressures on the heel than other offloading interventions. However, based on one low-quality controlled trial comparing sub-groups and several non-controlled studies we rate the quality of evidence as low. When considering the benefits predominately related to small effects on time-to-healing and plantar pressure reductions compared to other offloading interventions, and given the paucity of data on harms, patient preferences and costs, we rate the strength of this recommendation as weak. Therefore, we recommend considering using a knee-high offloading device or any other offloading intervention that can demonstrate effective reduction of plantar pressure on the heel.

PICO 9: In people with a non-plantar DFU, which offloading intervention is effective to heal the DFU?

Recommendation 9: In a person with diabetes and a non-plantar foot ulcer, use a removable ankle-high offloading device, footwear modifications, toe spacers, or orthoses, depending on the type and location of the foot ulcer, to promote healing of the ulcer (Strong; Low).

Rationale: Overall, there is very little evidence available on how to treat non-plantar foot ulcers. This is despite non-plantar DFU being prevalent and also needing relief from mechanical stress (115). Our updated systematic review (31) identified just one controlled trial that could partly address this topic (21). This large high-quality RCT compared a custom-made, fiberglass heel cast in additional to usual care with usual care alone ("usual care was not uniform") in patients that mostly (72%) had non-plantar heel DFUs (21). They found no differences in ulcer healing, adverse events or patient preferences, but

did find the heel cast had higher overall costs (21). Although patients with non-plantar DFU made up the majority of included patients, the RCT did not report outcomes specifically for the non-plantar DFU (21).

Therefore, until new evidence becomes available and depending on the location of the non-plantar ulcer, we recommend that various modalities can be considered, including ankle-high offloading devices, modifications to conventional or therapeutic footwear, toe spacers, and orthoses. Footwear does not have to be therapeutic but can consist of properly fitting conventional footwear that prevents, or is modified to prevent, direct contact with the ulcer. The modality chosen should be based on the principal that it prevents any mechanical stress or contact with the ulcer and is an appropriate fit for the rest of the foot so as not to produce new lesions.

Based on the RCT and our expert opinion, we expect any potential harm such as lesions directly caused by these other modalities on the foot to be minimal. We also anticipate that patients will likely prefer the use of these modalities for treatment of their non-plantar foot ulcers, as they should increase the protection of their ulcer, compared with standard care. We also suggest the additional costs for applying these modalities are relatively low.

In summary, due to the paucity of data, we rate the quality of evidence for this recommendation as low. However, we assessed the strength of this recommendation as strong. This is based on our opinion that these modalities compared with standard wound care alone would produce benefits in terms of DFU healing, mechanical stress reduction and patient preference, that should outweigh any harms or small costs of treatment.

KEY CONTROVERSIES AND CONSIDERATIONS

1. Since the last guidelines, the TCC is no longer the only gold standard treatment option to effectively heal plantar forefoot ulcers. Prefabricated removable knee-high walkers that are rendered non-removable have been shown with more evidence over the last 4 years, to be as effective as the TCC. This has changed the traditional view on offloading, in which the main comparison was TCC versus any other offloading interventions, but is now non-removable knee-high offloading devices versus other offloading interventions. This has positive implications for those settings where casting materials or trained casting technicians are not available. In these settings, depending on patient preferences and fit, reliance on the correct use of prefabricated removable walkers made non-removable for offloading is appropriate.
2. In the large number of studies conducted on the efficacy of the TCC or non-removable knee-high walkers, many different versions, types and methods of devices and casts have been used. These different versions of devices may potentially lead to different outcomes and varied costs. Trials are needed in which these different versions of casting or walkers used are compared with each other, so that a more informed decision can be made on which type of cast or walker is best to use for non-removable knee-high offloading.

3. Likewise, there are many different offloading devices that are defined as an "ankle-high offloading device" such as ankle-high walker, forefoot offloading shoe, cast shoe, healing sandal, post-operative healing shoe, custom-made temporary shoe, etc. These devices can be just above-ankle or below-ankle, prefabricated or custom-made and may lead to different outcomes and varied costs. More consideration should be given to studying the efficacy of each of these ankle-high offloading devices in healing foot ulcers to determine which of these devices are most effective on healing and plantar pressure outcomes, so that more informed decisions can also be made in clinical practice on which type is best to use for removable ankle-high offloading.
4. Many RCTs on offloading do not directly measure the degree to which the mechanical stress on the ulcer has been changed by the offloading intervention. Such measurements improve not only our understanding of the role of offloading in healing but also other outcomes. A stronger focus is required on measuring the factors impacting on the mechanical stress levels that lead to different healing outcomes, such as plantar pressure, shear stress, weight-bearing activity that includes steps and standing duration, and adherence to using offloading devices.
5. Offloading studies have focused almost exclusively on the treatment of non-complicated neuropathic plantar forefoot ulcers. Little data are available on the value of offloading in healing plantar foot ulcers complicated by infection or ischaemia, rearfoot ulcers, or non-plantar ulcers, even though these ulcers are from clinical experience now much more common than years ago. We have now addressed these specific foot ulcers in separate PICOs and recommendations, which are largely based on expert opinion. High quality studies on offloading ulcers other than the non-complicated neuropathic plantar forefoot ulcer are still urgently needed.
6. Adherence to an intervention is crucial in healing foot ulcers. It is consistently reported that those who do not adhere to an intervention present with worse healing outcomes. A stronger focus is required, both in research and in clinical practice, on the measurement and improvement of offloading treatment adherence.
7. Surgical offloading has primarily been applied to heal foot ulcers in selected patients typically where other non-surgical offloading interventions have failed. More high-quality RCTs concerning surgical offloading procedures are required to determine the impact of surgical interventions on the healing of both non-complicated and complicated foot ulcers.
8. Information on harms and other adverse events are critical to determine whether to use an offloading intervention or not, and if so, which one. Most RCTs are underpowered to determine if there are any differences in adverse events between offloading interventions. It is unlikely a RCT will be established to test for adverse events as the primary outcome. However, if future trials collect the same adverse events with the same definitions there is the possibility of pooling adverse event data in more homogenous meta-analyses that may better answer questions on which interventions cause fewer or more adverse events. We recommend future trials ensure they collect adverse events based on standard definitions as recommended by Jeffcoate et al. (11).
9. Costs and cost-effectiveness have also received little attention in offloading studies, despite the fact that reimbursement through insured care is more and more dependent on proven cost-effectiveness. While some cost studies have been performed since our previous guidelines in 2015, more attention is still warranted in view of the continuing pressure of healthcare cost containment.

10. The majority of interventions discussed are from studies from more economically developed countries with relatively temperate climates. While some of these interventions are broadly applicable, there is a need for more specific guidance on approaches to ulcer healing in these lower income regions where climate and/or resources may be a factor in which offloading device can be used, adherence to wearing the device and its efficacy.

CONCLUDING REMARKS

The global patient and economic burden of diabetic foot disease can be considerably reduced when evidence-based treatment is implemented by health-care professionals and multidisciplinary teams working on this medical problem. Arguably, offloading the foot ulcer, is one of the, if not the, most important intervention with the strongest evidence available for healing foot ulcers and reducing the global burden of diabetic foot disease. We think that following the recommendations for offloading treatment of diabetic foot ulcers in this guideline will help health care professionals and teams provide better care for persons with diabetes who have a foot ulcer and are at risk for infection, hospitalization and amputation.

We encourage our colleagues, especially those working in diabetic foot clinics, to consider developing some forms of surveillance (e.g., registries, pathways) to monitor and attempt to improve their outcomes in persons with diabetes and a foot ulcer. We also encourage our research colleagues to consider our key controversies and considerations and conduct well-designed studies (11) in areas of offloading in which we find gaps in the evidence base so to better inform the diabetic foot community in the future on effective offloading treatment for persons with diabetes and a foot ulcer.

GLOSSARY

Adverse events in relation to offloading treatment: general or local complications related directly or indirectly to the intervention regardless of whether they are serious. These include but are not limited to: falls; new pre-ulcerative lesion formation (abrasions, calls and blisters); new DFU formation; acute Charcot foot; infection; hospital admissions; amputation; death.
Adherence to offloading intervention: The extent to which a person's behaviour corresponds with agreed recommendations for treatment from a healthcare provider, expressed as quantitatively as possible; usually defined as the proportion of time using the prescribed offloading intervention of the total time in which the intervention is prescribed to be used (e.g. % of the total weight bearing time that the patient was wearing the prescribed offloading device).
Ambulatory activity: usually defined as the weight-bearing activity (average daily steps or strides of the foot on which the specific region of interest is located, e.g. DFU site).
Ankle-high offloading device: an offloading device that extends no higher up the leg than just above the ankle level. Includes ankle-high walker, forefoot offloading shoe, cast shoe, healing sandal, post-operative healing shoe, and custom-made temporary shoe.
Cast shoe: a removable plaster or fibreglass cast that extends to just below or at the ankle joint, moulded around the shape of the foot with total contact of the entire plantar surface. Examples are Mabal cast shoe, Ransart boot, or Scotch-cast boot.
Complicated DFU: a plantar DFU that is complicated by infection and/or ischemia.
Conventional footwear: off-the-shelf footwear with no specific properties for fitting or intended therapeutic effect.
Custom-made insole: An insole that is custom-made to the individual's foot using a 2D or 3D impression of the foot, and that is often built-up in a multi-layer construction. This may also incorporate other features, such as a metatarsal pad or metatarsal bar. The insole is designed to conform to the shape of the foot, providing cushioning and redistribution of plantar pressure. The term "insole" is also known as "insert" or "liner"
Custom-made (medical grade) footwear: Footwear uniquely manufactured for one person, when this person cannot be safely accommodated in pre-fabricated (medical grade) footwear. It is made to accommodate deformity and relieve pressure over at-risk sites on the plantar and dorsal surfaces of the foot. In-depth assessment, multiple measurements, impressions or a mould, and a positive model of a person's foot and ankle are generally required for manufacture. This footwear includes a custom-made insole. Also known as "bespoke footwear" or "orthopaedic footwear".
Custom-made temporary shoe: a unique, usually handmade shoe that is manufactured in a short time frame and is used temporarily to treat a foot ulcer. The shoe is built on a positive model of the patient's foot to accommodate deformity and relieve pressure over the ulcer site on the plantar surface of the foot.
Diabetes-related foot ulcer (DFU): see IWGDF definitions and criteria document (46).
DFU healing: defined as number or percentage of healed DFUs by a fixed time (e.g. % of DFUs healed after 12 weeks of intervention), or time-to-healing a DFU.
Extra-depth footwear: Footwear constructed with additional depth and volume in order to accommodate deformity such as claw/hammer toes and/or to allow for space for a thick insole. Usually

a minimum of 5 millimetres (~3/16") depth is added compared to off-the-shelf footwear. Even greater depth is sometimes provided in footwear that is referred to as double depth or super extra-depth.
Footwear: defined broadly as any shoe-gear and including insoles.
Forefoot offloading shoe: prefabricated shoe especially designed for relieving forefoot locations on the foot. The footwear has a specific shape with a wedge design and the outsole portion missing in the forefoot. These shoes are usually worn unilaterally.
Half-shoe: prefabricated shoe designed to offload the forefoot. The anterior part of the shoe is cut out, leaving the heel and the midfoot as the only weight-bearing surfaces.
Healed DFU: see IWGDF definitions and criteria document (46).
Heel-relief shoe: shoe designed to offload the heel. The heel part is missing from the footwear, and its sole arrangement is constructed in such a way that the heel is not loaded when walking.
In-shoe orthoses: devices put inside the shoe to achieve some alteration in the function of the foot.
Knee-high offloading device: an offloading device that extends up the leg to a level just below the knee (e.g. knee-high total contact cast (TCC), knee-high removable walker).
Non-plantar: see IWGDF definitions and criteria document (46).
Non-removable offloading device: an offloading device that cannot be removed by the patient (e.g. TCC, removable knee-high walker rendered non-removable (non-removable walker), etc.).
Non-surgical offloading intervention: any intervention undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot that does not involve a surgical procedure (includes offloading devices, footwear, and other offloading techniques).
Non-removable walker: prefabricated removable knee-high walker wrapped with a layer(s) of fiberglass cast material circumferentially rendering it non-removable to the patient (also known as "instant total contact cast").
Offloading: the relief of mechanical stress (pressure) from a specific region of the foot.
Offloading device: any custom-made or prefabricated device designed with the intention of relieving mechanical stress (pressure) from a specific region of the foot (e.g. total contact cast (TCC), (non-)removable walker, knee-high walker, ankle-high walker, ankle foot orthoses, healing sandal, cast shoe, forefoot offloading shoe, etc.). Note that this excludes footwear.
Offloading intervention: any intervention undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot (includes surgical offloading techniques, offloading devices, footwear, and other offloading techniques).
Other offloading techniques: any other technique undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot that is not a surgical offloading treatment, offloading device or footwear (e.g. bed rest, crutches, wheelchairs, offloading dressings, felted foam/padding, callus debridement, gait retraining, foot-related exercises, patient education, etc.).
PICO: the PICO process is a technique used to frame evidence-based clinical questions. PICO stands for: (P): Population; (I): Intervention; (C): Control; (O): Outcome.
Plantar: see IWGDF definitions and criteria document (46).
Plantar pressure: see IWGDF definitions and criteria document (46).
Post-operative healing shoe: prefabricated shoe with roomy and soft upper worn after an operation of the foot.
Removable offloading device: an offloading device that can be removed by the patient (e.g. removable walker, forefoot offloading shoe, cast shoe, healing sandal, etc.).

Rocker outsole: rigid outsole with a sharp transition that aims to rock the shoe forward. during late support to allow walking without extension of the metatarsal-phalangeal joints.
Shoe modification: modification to an existing shoe with an intended therapeutic effect, for example, pressure relief.
Standard therapeutic footwear: off-the-shelf shoe with intended therapeutic effect but without any customization to the patient's foot.
Surgical offloading intervention: a surgical procedure or technique undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot (e.g. Achilles tendon lengthening, metatarsal head resection, osteotomy, arthroplasty, ostectomy, exostectomy, external fixation, flexor tendon transfer or tenotomy, silicone injections, tissue augmentation, etc.).
Therapeutic footwear: Generic term for footwear designed to have some therapeutic effect that cannot be provided by or in a conventional shoe. Custom-made shoes or sandals, custom-made insoles, extra-depth shoes, and custom-made or prefabricated medical grade footwear are examples of therapeutic footwear.
Toe orthosis: an in-shoe orthosis to achieve some alteration in the function of the toe.
Total contact cast (TCC): a custom-made, well-moulded, minimally padded, knee-high non-removable fiberglass or plaster cast that maintains total contact with the entire plantar surface and lower leg. The cast is often worn with an attachable sole that protects the cast and facilitates walking.
Ulcer area reduction: defined as the proportion of ulcer area reduction from baseline over a given period of time (e.g. % ulcer area reduction at 4 or 6 weeks from the start of the observation period) (1).
Uncomplicated DFU: non-infected, non-ischaemic neuropathic plantar DFU.

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at: *www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies*

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published online, this current version will be replaced.

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FIGURES

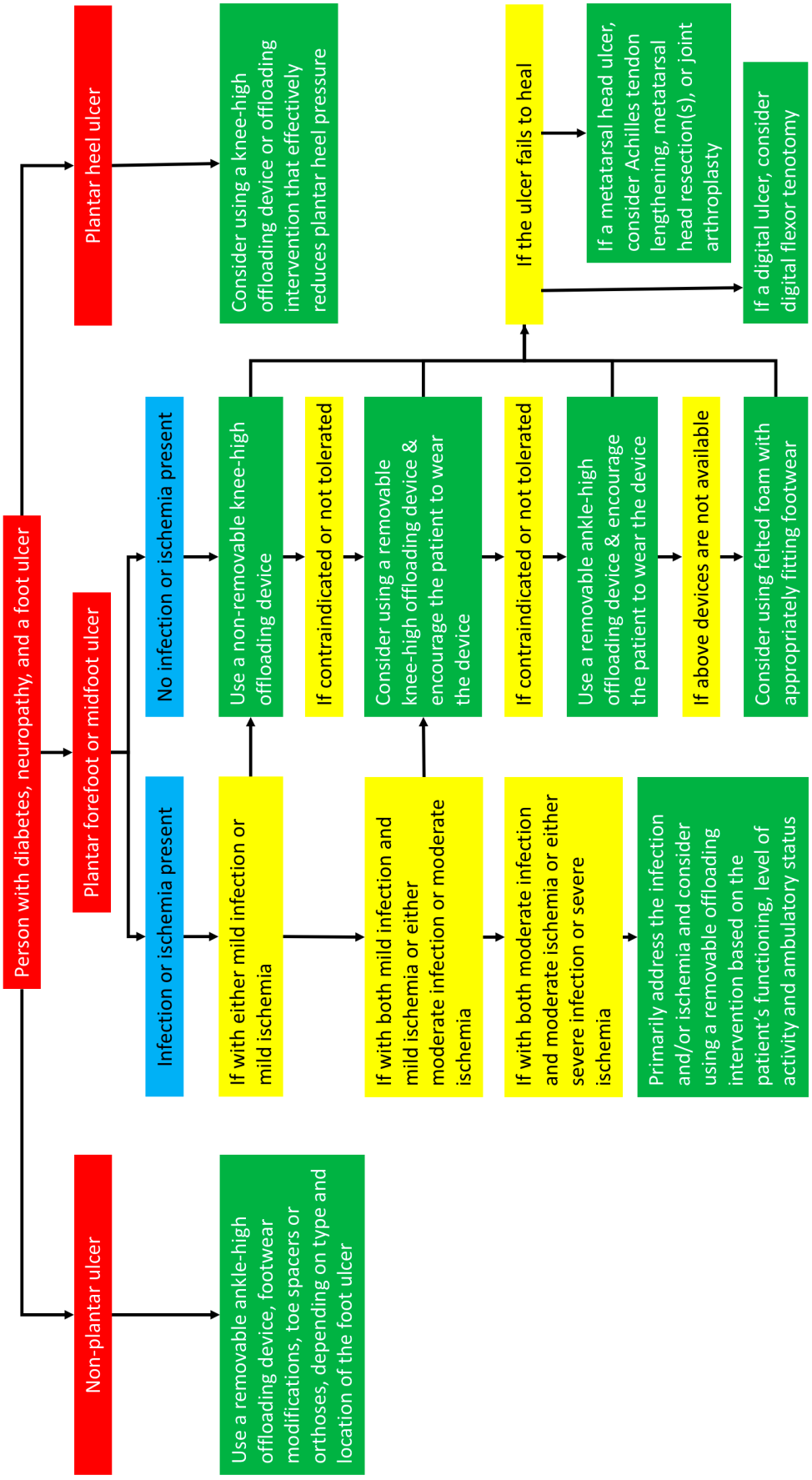
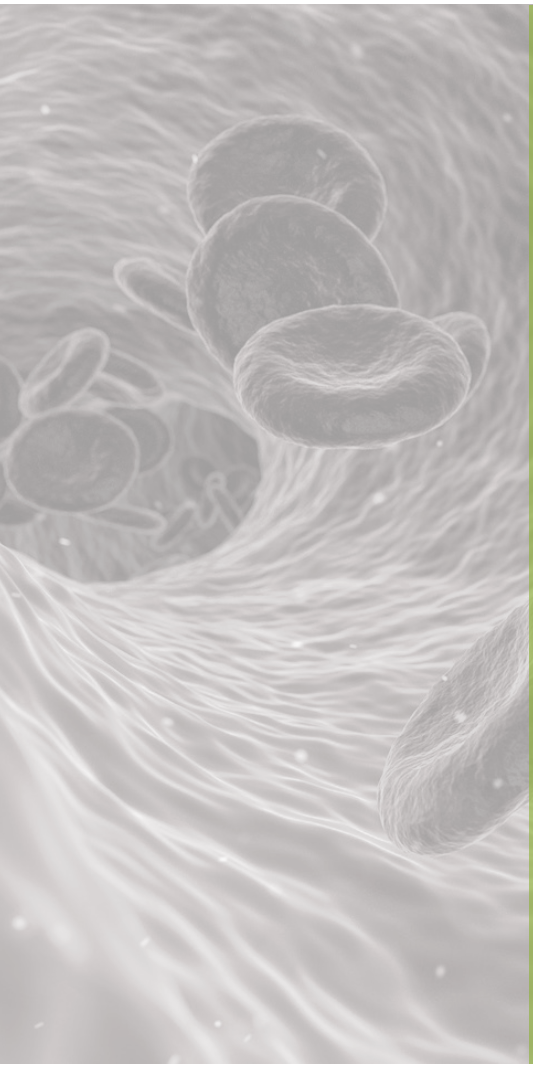


Figure 1. Flow diagram on the recommended offloading treatment for a person with diabetes and a foot ulcer.



IWGDF Guideline on diagnosis, prognosis and management of peripheral artery disease in patients with a foot ulcer and diabetes

Part of the 2019 IWGDF Guidelines
on the Prevention and Management
of Diabetic Foot Disease

IWGDF
Guidelines

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KEYWORDS

diabetic foot; foot ulcer; guidelines; peripheral artery disease; surgery; diagnosis; prognosis; vascular disease

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This guideline is on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers and diabetes and updates the previous IWGDF guideline.

Up to 50% of patients with diabetes and foot ulceration have concurrent peripheral artery disease (PAD), which confers a significantly elevated risk of adverse limb events and cardiovascular disease. We know that the diagnosis, prognosis and treatment of these patients are markedly different to patients with diabetes who do not have PAD and yet there are few good quality studies addressing this important sub-set of patients.

We followed the GRADE methodology to devise clinical questions and critically important outcomes in the PICO format, to conduct a systematic review of the medical-scientific literature, and to write recommendations and their rationale. The recommendations are based on the quality of evidence found in the systematic review, expert opinion where evidence was not available, and a weighing of the benefits and harms, patient preferences, feasibility and applicability, and costs related to the intervention.

We here present the updated 2019 guidelines on diagnosis, prognosis and management of PAD in patients with a foot ulcer and diabetes, and we suggest some key future topics of particular research interest.

RECOMMENDATIONS

1. Examine the feet of all patients with diabetes annually for the presence of peripheral artery disease, even in the absence of foot ulceration. At a minimum, this should include taking a relevant history and palpating foot pulses. (Strength of the recommendation: Strong; Quality of the evidence: Low)
2. Clinically examine (by relevant history and palpation of foot pulses) all patients with diabetes and foot ulceration for the presence of peripheral artery disease. (Strong; Low)
3. As clinical examination does not reliably exclude peripheral artery disease (PAD) in most persons with diabetes and a foot ulcer, evaluate pedal Doppler arterial waveforms in combination with ankle systolic pressure and systolic ankle brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement. No single modality has been shown to be optimal and there is no definite threshold value above which PAD can reliably be excluded. However, PAD is a less likely diagnosis in the presence of ABI 0.9-1.3, toe brachial index ≥0.75 and triphasic pedal Doppler waveforms. (Strong; Low)
4. Perform at least one of the following bedside tests in a patient with a diabetic foot ulcer and peripheral artery disease, any of which increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥40 mmHg; a toe pressure ≥30 mmHg; or, a transcutaneous oxygen pressure (TcPO2) ≥25 mmHg. (strong; moderate)
5. Use the WIfI (Wound/Ischaemia/foot Infection) classification system as a means to stratify amputation risk and revascularisation benefit in a patient with a diabetic foot ulcer and peripheral artery disease. (Strong; Moderate)
6. Always consider urgent vascular imaging, and revascularisation, in a patient with a diabetic foot ulcer and an ankle pressure <50mmHg, ABI <0.5, a toe pressure <30 mmHg or a TcPO2 <25 mmHg. (Strong; Low)
7. Always consider vascular imaging in patients with a diabetic foot ulcer, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite good standard of care. (Strong; Low)
8. Always consider revascularisation in a patient with a diabetic foot ulcer and peripheral artery disease, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite optimal management. (Strong; Low).
9. Do not assume diabetic microangiopathy, when present, is the cause of poor healing in patients with a diabetic foot ulcer, therefore always consider other possibilities for poor healing. (Strong; Low)
10. Use any of the following modalities to obtain anatomical information when considering revascularising a patient's lower extremity: colour Duplex ultrasound; computed tomographic angiography; magnetic resonance angiography; or, intra-arterial digital subtraction angiography. Evaluate the entire lower extremity arterial circulation with detailed visualisation of below-the-knee and pedal arteries, in an anteroposterior and lateral plane. (Strong; Low)
11. When performing revascularisation in a patient with a diabetic foot ulcer, aim to restore direct blood flow to at least one of the foot arteries, preferably the artery that supplies the anatomical

region of the ulcer. After the procedure, evaluate its effectiveness with an objective measurement of perfusion. (Strong; Low)

12. As evidence is inadequate to establish whether an endovascular, open or hybrid revascularisation technique is superior, make decisions based on individual factors, such as morphological distribution of peripheral artery disease, availability of autogenous vein, patient co-morbidities and local expertise. (Strong; Low)
13. Any centre treating patients with a diabetic foot ulcer should have expertise in, and rapid access to facilities necessary to diagnose and treat, PAD, including both endovascular techniques and bypass surgery. (Strong; Low)
14. Ensure that after a revascularisation procedure in a patient with a diabetic foot ulcer, the patient is treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)
15. Urgently assess and treat patients with signs or symptoms of peripheral artery disease and a diabetic foot infection, as they are at particularly high risk for major limb amputation. (Strong; Moderate)
16. Avoid revascularisation in patients in whom, from the patient's perspective, the risk–benefit ratio for the probability of success of the procedure is unfavourable. (Strong; Low)
17. Provide intensive cardiovascular risk management for any patient with diabetes and an ischaemic foot ulcer, including support for cessation of smoking, treatment of hypertension, control of glycaemia and treatment with a statin drug as well as low-dose clopidogrel or aspirin. (Strong; Low)

INTRODUCTION

The global burden of diabetes has increased rapidly over the past decade and many international bodies now consider diabetes a public health emergency. Health professionals and patients are becoming increasingly aware of the seriousness of diabetes-related complications. Yet despite substantial increase in awareness, the introduction of dedicated screening programmes and specialised interdisciplinary care teams in many developed countries, the number of people with diabetes has quadrupled since 1980 and the pooled estimate of worldwide prevalence of diabetes and foot ulceration is approximately 3% [1] in community-based cohorts, with a wide variation in rates of major amputation across the world [2].

It is estimated that in middle and high income countries up to 50% of patients with diabetes and foot ulceration have underlying peripheral artery disease (PAD) [3 4], whereas neuropathic ulcers are possibly more prevalent in low income countries [5 6]. In patients with diabetes, PAD may remain undiagnosed until the patient presents with (severe) tissue loss, as many patients typically lack the classic preceding clinical symptoms of PAD such as claudication or rest pain [7 8]. Diagnostic tests may be less reliable due to the presence of peripheral neuropathy, medial arterial calcification [9] and peripheral oedema. However, it is important to identify PAD in patients with diabetic foot ulceration (DFU) at the earliest possible stage, as the presence of PAD is associated with increased risk of non-healing ulcers, infection and major limb amputation, as well as an elevated risk of cardiovascular morbidity and overall mortality

[10] [11] [12] [13] [14]. The prognosis of a patient with diabetes, PAD and foot ulceration requiring amputation is worse than many common cancers – up to 50% of patients will not survive 5 years [4] [15].

There are several guidelines for the management of patients with PAD and chronic limb threatening ischaemia (CLTI). However, most studies reporting on PAD outcomes fail to include a diabetes sub-group, although it is likely that many of the included patients actually have diabetes. Moreover, many studies reporting on PAD and diabetes include only patients with intact feet, or do not adequately describe the presences of neuropathy, ulcer, infection or other contributing factors to poor outcomes [16].

There is no doubt that patients with diabetes and PAD represent a special sub-group. They tend to have a different clinical presentation, natural history and outcomes. Patients frequently present with severe tissue loss without significant symptoms, which may rapidly progress to limb loss; further characteristics are described in Table 1. As such, there is clearly a need for further research into this unique sub-group of patients with diabetes, foot ulceration and PAD in order that we may improve outcomes around the world.

Table 1. [74]

Characteristics of PAD in people with diabetes (compared to people without diabetes)
More common
Affects younger individuals
Multi-segmental and bilateral
More distal
More medial calcification
Impaired collateral formation
Faster progress with higher risk of amputation

This guideline is an update of the previous IWGDF Guideline on PAD [17], and is part of the IWGDF Guidelines on the prevention and management of diabetic foot disease. We aim to provide evidence-based recommendations on the diagnosis, prognosis, and management of PAD in patients with a foot ulcer and diabetes.

METHODS

In this guideline we have followed the GRADE methodology, which is structured around clinical questions in the PICO-format (Patient-Intervention-Comparison-Outcome), systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale [18] [19].

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF editorial board. The members of the working group devised the clinical questions, which were revised after consultation with external experts from various geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and

other health care professionals in providing useful information on the diagnosis, prognosis and management of peripheral artery disease in persons with diabetes and a foot ulcer. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate et al. [16] as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as 'high', 'moderate' or 'low'. The systematic review(s) supporting this guideline are published separately [20] [21] [22].

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system we provided the rationale for how we arrived at each recommendation, based on the evidence from our systematic review(s) [20] [21] [22], expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method [18] [19]. Based on these factors, we graded the strength of each recommendation as 'strong' or 'weak', and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

We refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document [23].

DIAGNOSIS

PICO: In a person with diabetes and no foot ulceration, which symptoms and signs (clinical examination) should clinicians examine in order to identify or exclude peripheral artery disease?

Recommendation 1: Examine the feet of all patients with diabetes annually for the presence of peripheral artery disease, even in the absence of foot ulceration. At a minimum, this should include taking a relevant history and palpating foot pulses. (Strong; Low)

Rationale: This recommendation is in line with other (inter)national guidelines on the management of diabetes, recommending yearly screening for PAD in subjects with diabetes [24] [25] [26]. In addition to absent foot pulses, specific clinical findings that alert the healthcare professional to the presence of PAD include the presence of femoral bruits and a slow venous filling time [27] [8] . Symptoms and signs of PAD, such as claudication, absent pulses and a low ABI, were identified as predictors of future ulceration in a recent systematic review [28], however classical signs may be absent in patients with PAD and a DFU. Patients with diabetes and these signs of PAD should therefore be reviewed more frequently. Moreover, individuals with PAD have an elevated risk of other cardiovascular diseases, necessitating strategies to address these problems as well [29].

PICO: In a person with diabetes and a foot ulcer, which symptoms and signs (clinical examination) should clinicians examine in order to identify or exclude peripheral artery disease?

Recommendation 2: Clinically examine (by relevant history and palpation of foot pulses) all patients with diabetes and foot ulceration for the presence of peripheral artery disease. (Strong; Low)

Rationale: Few data exist about the accuracy of symptoms or clinical examination for the identification of PAD in patients with diabetes and foot ulceration. Although a properly performed medical history and clinical examination can suggest the presence of PAD in a patient with a foot ulcer, their sensitivity is too low to rule out PAD in all patients. Many patients with diabetes and PAD have few or atypical symptoms[7] and in our experience, patients can have severe tissue loss with limited symptoms. The paucity of symptoms may be related to the presence of co-existing neuropathy and loss of pain sensation. Foot temperature may be unreliable due to arterio-venous shunting resulting in a relatively warm foot [30]. The palpation of foot pulses should form a key part of the initial clinical examination, however the presence of palpable foot pulses cannot be used in isolation to reliably exclude PAD. For example, in a screened primary care population of patients > 50 years more than two thirds of patients with PAD had a detectable pulse [31]. Even in the hands of a skilled examiner, palpable pulses may be present despite the presence of significant ischaemia [32]. Therefore, a more objective evaluation should be performed in all patients with a foot ulcer.

PICO: In a person with diabetes and a foot ulcer which 'bedside' diagnostic procedure, alone or in combination, has the best performance in diagnosing or excluding peripheral artery disease?

Recommendation 3: As clinical examination does not reliably exclude peripheral artery disease (PAD) in most persons with diabetes and a foot ulcer, evaluate pedal Doppler arterial waveforms in combination with ankle systolic pressure and systolic ankle brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement. No single modality has been shown to be optimal and there is no definite threshold value above which PAD can reliably be excluded. However, PAD is a less likely diagnosis in the presence of ABI 0.9-1.3, toe brachial index ≥0.75 and triphasic pedal Doppler waveforms. (Strong; Low)

Rationale: In addition to clinical history and examination, an objective evaluation should be performed in all patients with a foot ulcer. As discussed in our systematic review [20], an ABI (<0.9) is a useful test for the detection of PAD. However, an ABI >0.9 does not rule out PAD. The majority of patients with PAD and a foot ulcer will have (autonomic) peripheral neuropathy, which is associated with medial wall calcification (Mönckeberg sclerosis) of the arteries in the lower leg, resulting in rigid arteries and an elevated ABI, adversely affecting the utility of the test [9]. It should be noted that medial calcification does not necessarily cause arterial stenosis and reduced blood flow [33] [29]. The detection of a triphasic pedal Doppler arterial waveform with a handheld Doppler appears to provide stronger evidence for the absence of PAD. The same applies for measurement of a toe brachial index, which makes the presence of PAD unlikely if it is ≥0.75 [20] and provides additional information compared to the ABI, particularly in patients with severe PAD below the ankle [34]. Unfortunately, toe pressures may also be falsely elevated by the same factors that affect ABI (including digital artery calcification). There is insufficient evidence to

support the use of a single bedside diagnostic test for PAD that may be used for all patients with diabetes and foot ulceration [35]. However recent studies suggest that TBI and tibial waveforms (measured at the level of the medial malleolus, the dorsalis pedis and in the mid-calf for the peroneal artery) are the most useful non-invasive tests to select patients for diagnostic imaging [36 37]. Using more than one test in parallel certainly improves diagnostic accuracy [35 38 39].

There are no definitive data on the absolute threshold or 'normal' values of non-invasive tests for people with diabetes and foot ulceration. Previous studies examining the use of bedside tests to diagnose PAD have used pre-determined threshold values, however there is no information available about other thresholds that may be of interest. We suggest that PAD is a less likely diagnosis in the presence of ABI 0.9-1.3, toe brachial index ≥0.75 and triphasic pedal Doppler waveforms, however this should be complimented by definitive imaging where uncertainty remains.

All bedside techniques should be performed by trained healthcare professionals in a standardised manner. There is insufficient evidence to confidently recommend the use of any of the aforementioned bedside non-invasive diagnostic modalities over another for the detection of PAD. Healthcare professionals should be aware of the limitations of each modality and must decide which, either singly or in combination, to use, given their local expertise and test availability.

PROGNOSIS

PICO: In a person with diabetes foot ulceration and PAD, which clinical signs, symptoms or non-invasive bedside tests may predict ulcer healing and amputation?

Recommendation 4: Perform at least one of the following bedside tests in a patient with a diabetic foot ulcer and peripheral artery disease, any of which increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥40 mmHg; a toe pressure ≥30 mmHg; or, a transcutaneous oxygen pressure (TcPO2) ≥25 mmHg. (strong; moderate)

Recommendation 5: Use the WIfI (Wound/Ischaemia/foot Infection) classification system as a means to stratify amputation risk and revascularisation benefit in a patient with a diabetic foot ulcer and peripheral artery disease. (Strong; Moderate)

Recommendation 6: Always consider urgent vascular imaging, and revascularisation, in a patient with a diabetic foot ulcer and an ankle pressure <50mmHg, ABI <0.5, a toe pressure <30 mmHg or a TcPO2 <25 mmHg. (Strong; Low)

Recommendation 7: Always consider vascular imaging in patients with a diabetic foot ulcer, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite good standard of care. (Strong; Low).

Recommendation 8: Always consider revascularisation in a patient with a diabetic foot ulcer and peripheral artery disease, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite optimal management. (Strong; Low).

Recommendation 9: Do not assume diabetic microangiopathy, when present, is the cause of poor healing in patients with a diabetic foot ulcer, therefore always consider other possibilities for poor healing. (Strong; Low)

Rationale: In our systematic review, the most useful tests for predicting healing in an ulcerated foot were skin perfusion pressure (≥40 mmHg), toe pressure (≥30 mmHg) and $TcPO_2$ (≥25 mmHg) [21]. All increased the pre-test probability of healing by at least 25% in one or more study. Given the variability of PAD in terms of its distribution, severity and symptoms, it is unsurprising that no single measure performed with consistent accuracy for the prediction of healing. Interpretation of the specific characteristics of PAD that predict healing, or failure to heal, of a diabetic foot ulcer should be taken in the context of the quality of the published literature, which is limited.

Most available data in the literature are based on univariable analysis, and these PAD measures should all be interpreted in the context of other determinants of outcome. Given the relatively poor chance of healing and the increased risk of amputation in patients with a toe pressure<30mmHg or a $TcPO_2$ <25mmHg, we suggest imaging and consideration of revascularisation in these patients. The ABI has very little value in predicting ulcer healing [40], but an ABI <0.5 and/or an ankle pressure <50mmHg does confer a higher risk of amputation. Urgent imaging and treatment should also be considered in patients with PAD and higher pressure levels, in the presence of other predictors of poor prognosis, including infection or large ulcer surface area [41]. A recent study has suggested that perfusion angiography may predict early major amputation but this needs further confirmation [42]. Finally, in light of their limited diagnostic and prognostic utility, none of the tests described earlier can completely rule out PAD as a cause of impaired wound healing in a foot ulcer that does not respond to optimal treatment. Vascular imaging should therefore be performed in these patients in order to determine if the patient would benefit from revascularisation. In an observational study, shorter time to revascularisation (<8 weeks) was associated with a higher probability of healing of ischaemic foot ulcers [43]. Additionally, a recent retrospective study demonstrated that patients with diabetes who experienced a delay of greater than 2 weeks from presentation to revascularisation were at a significantly increased risk of limb loss [44]. These studies suggest that an aggressive approach with early revascularisation might improve outcome but these procedures are not without risk as summarised below [22]. The zealous approach of 'the sooner the better' may be tempting, however this should be also mitigated by the finding that up to 50% of patients with DFU and PAD who do not undergo revascularisation may be expected to heal their foot ulcers [10]. There is therefore no 'one size fits all approach' and each case should be evaluated on an individual basis.

We recommend considering revascularisation in all patients with diabetes, PAD and a foot ulcer, irrespective of the results of bedside tests, when the ulcer does not improve within 4-6 weeks despite optimal management. Due to the multiple factors contributing to non-healing, it is impossible to determine the optimal duration of a trial of conservative management before considering imaging and

vascular intervention. A post hoc analysis of a clinical trial suggested that a 4-week period is sufficient in patients with uncomplicated neuropathic foot ulcers to assess the likelihood of healing [45]. For pragmatic reasons, based on expert opinion, we suggest considering vascular imaging and subsequent revascularisation in neuro-ischaemic ulcers that do not improve within 6 weeks and have no other likely cause of poor wound healing.

Healing is related to the interplay of the severity of the perfusion deficit with other characteristics of the foot and the patient, such as amount of tissue loss, presence of infection, mechanical load on the ulcer, comorbidities such as heart failure and end-stage renal disease [46]. As discussed in our IWGDF classification guideline [47], the Wound, Ischemia and Foot infection (WIfI) classification system can guide the clinician in estimating the risk of amputation and potential benefit of revascularisation. This system categorises the patient's ulcer, severity of ischaemia based on non-invasive tests and the severity of infection based on the IWGDF/IDSA classification. The WIfI system was generated from expert consensus and subsequently validated in diabetes and non-diabetes populations[48]. The scoring system is summarised in Table 2, is discussed in our classification guideline, and is freely available to download as a calculator tool [47 49]. Finally, the chance of healing will be related to the subsequent quality of care, which should address any of these aforementioned problems.

Table 2. [48]

Wound Grade	DFU	Gangrene
0	No ulcer	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
	Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard transmetatarsal amputation (TMA) ± skin coverage.	
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis 6 calcaneal involvement
	Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect	

Ischemia Grade	Ankle-Brachial Index	Ankle systolic pressure (mmHg)	Toe Pressure, Transcutaneous oxygen pressure (mmHg)
0	≥ 0.80	>100	≥60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤0.39	<50	<30

Foot Infection Grade	Clinical manifestations
0	No symptoms or signs of infection Infection present, as defined by the presence of at least 2 of the following items: • Local swelling or induration • Erythema >0.5 to ≤2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
2	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 (as described below)
3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg • White blood cell count >12,000 or <4000 cu/mm or 10% immature (band) forms

SIRS = systemic inflammatory response signs

In the past, microangiopathy was thought to be an important cause of poor healing of a diabetic foot ulcer. However, there is currently no evidence to support this notion, and PAD remains the most important cause of impaired perfusion of the foot in a patient with diabetes [50]. However, it should be noted that PAD is not the only cause of reduced perfusion in a lower extremity because oedema and infection can also result in a decrease in tissue oxygenation, and these should all be treated appropriately [51 52].

TREATMENT

PICO: In a person with diabetes and foot ulceration, which diagnostic imaging modalities to obtain anatomical information are most useful when considering revascularisation?

Recommendation 10: Use any of the following modalities to obtain anatomical information when considering revascularising a patient's lower extremity: colour Duplex ultrasound; computed tomographic angiography; magnetic resonance angiography; or, intra-arterial digital subtraction angiography. Evaluate the entire lower extremity arterial circulation with detailed visualisation of below-the-knee and pedal arteries, in an anteroposterior and lateral plane. (Strong; Low)

Rationale: Deciding who needs lower limb arterial revascularisation and determining what procedure is the most appropriate to achieve revascularisation requires appropriate imaging to guide therapy. It is unacceptable to rely on clinical examination alone prior to performing a revascularisation procedure. Anatomical information on the arteries of the lower limb should be obtained to assess the presence, severity and distribution of arterial stenoses or occlusions. Obtaining detailed imaging of below-the-knee and pedal arteries, especially with a dedicated assessment of the pedal circulation, is critically important in patients with diabetes. Techniques to define the lower limb arterial system in patients with diabetes include Duplex ultrasound, magnetic resonance angiography, computed tomography angiography and digital subtraction angiography [50].

Briefly, Colour Duplex ultrasound (CDUS) provides both anatomic details and a physiologic assessment of blood flow at specific arterial sites. By scanning sequentially from the abdominal to the tibial arteries, the entire lower extremity arterial circulation can be directly evaluated. However, diffuse multi-segmental involvement, calcification and oedema may hamper the investigation. CDUS has the advantage of being a non-invasive test but it requires sophisticated equipment and specialized expertise and is not appropriate as a routine screening test. In computed tomography angiography (CTA), an iodinated contrast medium is injected intravenously and the vascular tree from the level of the renal arteries down to the foot can be visualised. Severe calcification may hamper the evaluation of smaller arteries, especially in the lower leg. Further disadvantages are potential allergic reactions and the development of contrast-induced nephropathy, particularly in patients with pre-existing renal disease or cardiac failure. In contrast-enhanced magnetic resonance angiography (CE-MRA) gadolinium is used as contrast and with dedicated techniques images can be obtained from the abdominal aorta down to the foot. A major advantage of CE-MRA is the use of a contrast agent with low nephrotoxicity, disadvantages include the limited special resolution and artefacts because of previous stent placement. However, its use is limited in patients with implants, such as pacemakers and claustrophobia and in patients with severe renal insufficiency (creatinine clearance <30mL/min) use of gadolinium-containing contrast is (relatively) contraindicated because of the risk of developing nephrogenic systemic fibrosis. Newer non-gadolinium agents, such as ultrasmall superparamagnetic particles of iron oxide (which has a number of magnetic resonance applications), may be alternative and safer agents in patients with compromised renal function [53].

Intra-arterial digital subtraction angiography is still regarded as the gold standard for arterial imaging because of its high spatial resolution. It has the advantage of allowing endovascular therapy during the same procedure but has the disadvantage of the use of an iodinated contrast medium and is an invasive procedure, associated with potential complications of arterial puncture.

Healthcare professionals should be aware of these techniques and of their limitations in individual patients. The decision on which imaging modality to use will depend upon patient contraindications as well as local availability and expertise.

PICO: What are the aims and methods of revascularisation and onward management in a person with diabetes, foot ulceration and PAD?

Recommendation 11: When performing revascularisation in a patient with a diabetic foot ulcer, aim to restore direct blood flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the ulcer. After the procedure, evaluate its effectiveness with an objective measurement of perfusion. (Strong; Low)

Rationale: The natural history of patients with diabetes, PAD and an ulcerated foot remains poorly defined, but in two studies reporting the outcomes of patients with diabetes and limb ischaemia who were not revascularised, the limb salvage rate was around 50% at 1 year [10 54]. After a revascularisation procedure, most studies report limb salvage rates of 80–85% and ulcer healing in >60% at 12 months [22]. The quality of evidence is generally low due to the poorly defined population cohorts, variability of indications for intervention and multiple potentially confounding factors. Patients undergoing revascularisation are at increased risk of peri-operative mortality and the highest risk group is those patients with diabetes, PAD and end-stage renal disease, who have a 5% peri-operative mortality, 40% 1-year mortality and 1-year limb salvage rates of around 70% [22].

Historically, the aim of revascularisation in patients with PAD has been to achieve inline pulsatile flow to the foot, usually by targeting the best vessel available. However, more recently, the angiosome-directed approach has been advocated but remains a subject of much debate [55 56]. According to this theory, the foot can be divided into three-dimensional blocks of tissue, each with its own feeding artery. Direct revascularisation would result in a restoration of pulsatile blood flow through the feeding artery to the area where the ulcer is located, while with indirect revascularisation flow is restored through collateral vessels deriving from neighbouring angiosomes. By targeting revascularisation at the vessel directly supplying the anatomical area (angiosome) of tissue loss, the theory is that this will be a more effective method of revascularisation than simply targeting the best vessel, which may not supply the area of tissue loss. A recent retrospective study of endovascular limb salvage attempts in patients with DFU suggested that indirect angiosome revascularisation was associated with poorer outcomes than direct revascularisation [57]. However, due to lack of clear definitions and factors like selection bias, the effectiveness of the angiosome concept in patients with diabetes is unknown [58 59 60 55]. Particularly in patients with diabetes who usually have poor collaterals, restoration of flow to an artery directly supplying the affected area seems the best approach during an endovascular procedure [56]. Successfully opening one or more occluded vessels is not the same as a clinically successful procedure and before the procedure is terminated blood flow to the ulcer area should therefore be assessed. If feasible, opening multiple arteries may be useful provided at least one supplies the ischaemic area directly [55].

The effectiveness of a revascularisation procedure should preferably be evaluated with objective perfusion measurements. We have not provided target perfusion pressures in this recommendation, as

there is no robust evidence to support such an approach. We previously suggested revascularisation should achieve a minimum skin perfusion pressure of 40mmHg, toe pressure >30mmHg or $TcPO_2$ >25mmHg in order to be considered effective [17]. However, we now recommend that revascularisation should aim to improve perfusion to the foot *as much as possible*, which will vary according to the individual patient. As skin oxygen tension increases progressively in a period of several weeks after a successful PTA, TcPO2 measurements should preferably be performed at least 1-3 weeks after the procedure [61].

Recommendation 12: As evidence is inadequate to establish whether an endovascular, open or hybrid revascularisation technique is superior, make decisions based on individual factors, such as morphological distribution of peripheral artery disease, availability of autogenous vein, patient co-morbidities and local expertise. (Strong; Low)

Recommendation 13: Any centre treating patients with a diabetic foot ulcer should have expertise in, and rapid access to facilities necessary to diagnose and treat, PAD, including both endovascular techniques and bypass surgery. (Strong; Low)

Recommendation 14: Ensure that after a revascularisation procedure in a patient with a diabetic foot ulcer, the patient is treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)

Recommendation 15: Urgently assess and treat patients with signs or symptoms of peripheral artery disease and a diabetic foot infection, as they are at particularly high risk for major limb amputation. (Strong; Moderate)

Rationale: There is still no consensus on the most appropriate approach to revascularisation in a patient with diabetes and foot ulceration. In our systematic review, we found that the major outcomes of wound healing and amputation were broadly similar between endovascular and open interventions[22]. Each of these techniques has its advantages and disadvantages. A successful distal venous bypass can result in a marked increase of blood flow to the foot but general anaesthesia is usually necessary and a suitable vein, as a bypass conduit, should be present. An endovascular procedure has several logistical advantages but sometimes very complex interventions are necessary to obtain adequate blood flow in the foot and a failed endovascular intervention may lead to worse outcomes when an open procedure is subsequently performed [62]. Over the past few decades, there have been significant advancements in endovascular techniques, however parallel to this, we have seen improvements in anaesthesia and peri-operative care that have helped improve surgical outcomes. Whilst the BASIL trial is often quoted as a guide to revascularisation of patients with limb ischaemia [63], the cohort included a small proportion of patients with diabetes, of which there was no sub-group analysis, and was not focused on patients with ulceration. Therefore, we cannot extrapolate these findings to our patients with diabetes, foot ulceration and PAD. Finally, it is becoming increasingly common to adopt a combined open and endovascular (hybrid) approach. Therefore, we recommend that in each patient requiring lower-limb revascularisation, an endovascular, an open procedure and a hybrid procedure should be considered. As

there is no 'one-fits-all' approach to treatment for patients with diabetes, foot ulceration and PAD, it is important that a treating centre has the expertise and facilities to provide a range of treatment options with availability of both endovascular and open methods.

As discussed in other parts of the IWGDF Guidance, restoration of perfusion in the foot is only part of the treatment, which should be provided by multi-disciplinary care team [64]. Any revascularisation procedure should therefore be part of a comprehensive care plan that addresses other important issues including: prompt treatment of concurrent infection, regular wound debridement, biomechanical off-loading, control of blood glucose and treatment of co-morbidities [64]. In particular, patients with a foot infection are at high risk for limb loss and should be treated as a medical emergency. The 1-year major amputation rate for such patients has been reported to be as high as 44% [65] and delay in treatment can lead to rapid tissue destruction and life-threatening sepsis [66] as described in our guidelines on infection. In patients with deep infection, such as a foot abscess, infection of deep a foot compartment that needs immediate drainage or extensive tissue loss/ gangrene that must be removed to control the infection, immediate drainage should be considered first, in order to control sepsis [14]. As described in our Infection Guidelines, this should be accompanied by aggressive antibiotic therapy, initially broad-spectrum, and rationalised according to tissue culture [14] - 'time is tissue' in these patients. Once the sepsis is controlled and the patient is stabilised, evaluation of the arterial tree should lead to consideration for prompt revascularisation (ie within a few days). Once blood flow is improved and infection is treated, a definitive operation may be required in order to create a functional foot, which may require soft tissue and bone reconstruction. In patients with severely impaired perfusion and severe tissue loss, but without infection, extensive debridement or amputation of part of the foot should preferably not be performed until perfusion is restored.

PICO: In a patient with a diabetic foot ulcer and PAD are there any circumstances in which revascularisation should not be performed?

Recommendation 16: Avoid revascularisation in patients in whom, from the patient's perspective, the risk–benefit ratio for the probability of success of the procedure is unfavourable. (Strong; Low)

Rationale: Revascularisation should not be performed if there is no realistic chance of wound healing, or when major amputation is inevitable. Many patients pose high anaesthetic risk due to comorbidities and major reconstructive surgery confers significant risk of peri-operative complications. In particular, the following patients may not be suitable for revascularisation: those who are very frail, have short life expectancy, poor functional status, are bed bound, have a large area of tissue destruction that renders the foot functionally unsalvageable, and those who cannot realistically be expected to mobilise following revascularisation. The decision to proceed to primary amputation, or to adopt a palliative approach, should be made in conjunction with the patient and a multi-disciplinary team that includes a vascular surgeon or another specialist with expertise in vascular interventions [67].

In those patients in whom the risk-benefit ratio of revascularisation is unclear, it should be taken into account that some severely ischaemic ulcers heal without revascularisation - two observational studies

demonstrated healing rates of around 50% (with or without minor amputations) in patients unsuitable (either because they were deemed too frail or where revascularisation was not technically possible) for revascularisation [10].

There are several other techniques that have been investigated for patients with diabetes, PAD and ulceration in whom there are no options for revascularisation. These include venous arterialisation and intermittent pneumatic compression therapy. [68] [69]. However, there are insufficient data to provide any recommendation on their utility in patients where no revascularisation option exists.

PICO: In patients with diabetes, foot ulceration and PAD, is it possible to reduce the risk of future cardiovascular events?

Recommendation 17: Provide intensive cardiovascular risk management for any patient with diabetes and an ischaemic foot ulcer, including support for cessation of smoking, treatment of hypertension, control of glycaemia and treatment with a statin drug as well as low-dose clopidogrel or aspirin. (Strong; Low)

Rationale: Patients with diabetes, PAD and ulceration have an overall 5-year mortality of around 50% due to the markedly increased risk of cardiovascular events [70]. In line with other guidelines [26] [25], we recommend prompt and thorough management of other cardiovascular risk factors in patients with diabetes and PAD.

Patients should receive support to stop smoking and should maintain their blood pressure and blood glucose according to hypertension and diabetes guidelines recommendations. In addition, all patients should be prescribed a statin and anti-platelet therapy. This strategy has been shown to reduce the 5-year mortality in patients with neuro-ischaemic ulcers [71]. There is no specific evidence supporting the most appropriate anti-platelet agent in patients with diabetes, PAD and ulceration, however a number of recent guidelines have favoured clopidogrel over aspirin in the management of patients with PAD [26]. A sub-analysis of a recent trial of anti-platelets and anti-coagulation suggested that the combination of aspirin and the direct oral anticoagulant rivaroxaban was more effective at reducing major limb events when compared to aspirin alone in patients with PAD, however this strategy was at the expense of an increase in (non-fatal) bleeding events [72]. Although 45% had diabetes, no information was provided about the presence of a foot ulcer and the outcomes of these patients were not reported separately. It should be noted that we did not address the effect of lipid lowering therapies, blood glucose lowering medication or anticoagulant therapies on wound healing and amputation, as we felt that the evidence in these areas is still too limited.

FUTURE RESEARCH PRIORITIES

Our systematic reviews have demonstrated that that there is a paucity of contemporary high-quality data concerning the specific sub group of patients with diabetes, ulceration and PAD. [73]. Further research is required in order to address the issues surrounding the appropriate management, including diagnosis, prognosis and deciding whether, when and how to revascularise. The IWGDF and EWMA published in 2016 the core details required in the planning and reporting of intervention studies in the prevention and management of diabetic foot ulcers, including those with PAD [16]. These guidelines can serve as a roadmap to increase the quality of studies published in this area.
In addition, there are a number of other key areas of interest that deserve further attention:

- What is the natural history of the diabetic foot ulcer with PAD with optimal conservative treatment?
- What is the optimal combination of diagnostic tests to predict healing in patient with a diabetic foot ulcer and PAD
- What is the role of novel methods of perfusion assessment (including the microcirculation) to inform the decision to revascularise patients with diabetic foot ulceration and PAD?
- Is there any role for pre-emptive revascularisation in patients with diabetes with intact feet who are at high risk for ulceration / amputation?
- Is angiosome-directed revascularisation more effective than a best vessel approach in patients with diabetic foot ulceration?
- Is venous arterialisation effective in healing ulcers or preventing amputation in people who are not appropriate for standard revascularisation?
- Are novel medical therapies including stem cells or peripheral blood mononuclear cells effective in healing patients with DFU and PAD where standard revascularisation is inappropriate?

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at: *www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies*.

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published online, this current version will be replaced.

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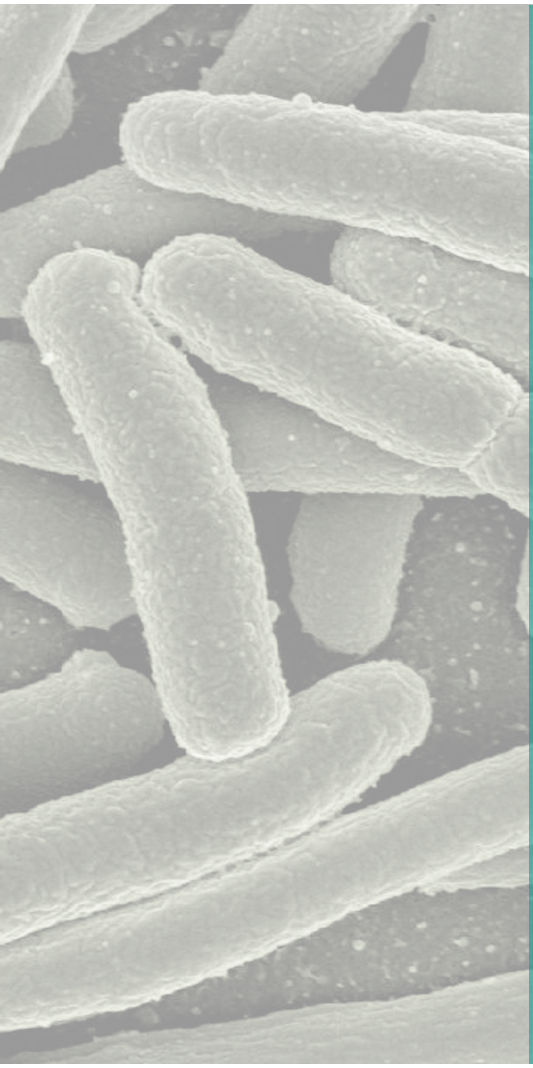

IWGDF Guideline on the diagnosis and treatment of foot infection in persons with diabetes

Part of the 2019 IWGDF Guidelines on the Prevention and Management of Diabetic Foot Disease

IWGDF Guidelines

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This guideline is on the diagnosis and treatment of foot infection in persons with diabetes, and updates the 2015 IWGDF infection guideline. Based on PICOs developed by the infection committee, in conjunction with internal and external reviewers and consultants, and on systematic reviews the committee conducted on the diagnosis of infection (new) and treatment of infection (updated from 2016), we offer 27 recommendations. These cover various aspects of diagnosing soft tissue and bone infection, including the classification scheme for diagnosing infection and its severity. Of note, we have updated this scheme for the first time since we developed it 15 years ago. We also review the microbiology of diabetic foot infections, including how to collect samples and to process them to identify causative pathogens. Finally, we discuss the approach to treating diabetic foot infections, including selecting appropriate empiric and definitive antimicrobial therapy for soft tissue and for bone infections, when and how to approach surgical treatment and which adjunctive treatments we think are or are not useful for the infectious aspects of diabetic foot problems. For this version of the guideline we also updated four tables and one figure from the 2016 guideline. We think that following the principles of diagnosing and treating diabetic foot infections outlined in this guideline can help clinicians to provide better care for these patients.

LIST OF RECOMMENDATIONS

1. a) Diagnose a soft tissue diabetic foot infection clinically, based on the presence of local or systemic signs and symptoms of inflammation. (Strength of recommendation: Strong; Quality of evidence: Low)
   b) Assess the severity of any diabetic foot infection using the Infectious Diseases Society of America/International Working Group on the Diabetic Foot classification scheme. (Strong, Moderate)
2. Consider hospitalizing all persons with diabetes and a severe foot infection, and those with a moderate infection that is complex or associated with key relevant morbidities. (Strong; Low)
3. In a person with diabetes and a possible foot infection for whom the clinical examination is equivocal or uninterpretable, consider ordering an inflammatory serum biomarker, such as C-reactive protein, erythrocyte sedimentation rate and perhaps procalcitonin, as an adjunctive measure for establishing the diagnosis. (Weak; Low)
4. As neither electronically measuring foot temperature nor using quantitative microbial analysis has been demonstrated to be useful as a method for diagnosing diabetic foot infection, we suggest not using them. (Weak; Low)
5. In a person with diabetes and suspected osteomyelitis of the foot, we recommend using a combination of the probe-to-bone test, the erythrocyte sedimentation rate (or C-reactive protein and/or procalcitonin), and plain X-rays as the initial studies to diagnose osteomyelitis. (Strong; Moderate)
6. a) In a person with diabetes and suspected osteomyelitis of the foot, if a plain X-ray and clinical and laboratory findings are most compatible with osteomyelitis, we recommend no further imaging of the foot to establish the diagnosis. (Strong; Low).
   b) If the diagnosis of osteomyelitis remains in doubt, consider ordering an advanced imaging study, such as magnetic resonance imaging scan, ^{18}F-FDG- positron emission tomography/computed tomography (CT) or leukocyte scintigraphy (with or without CT). (Strong; Moderate)
7. In a person with diabetes and suspected osteomyelitis of the foot, in whom making a definitive diagnosis or determining the causative pathogen is necessary for selecting treatment, collect a sample of bone (percutaneously or surgically) to culture clinically relevant bone microorganisms and for histopathology (if possible). (Strong; Low)
8. a) Collect an appropriate specimen for culture for almost all clinically infected wounds to determine the causative pathogens. (Strong; Low)
   b) For a soft tissue diabetic foot infection, obtain a sample for culture by aseptically collecting a tissue specimen (by curettage or biopsy) from the ulcer. (Strong; Moderate)
9. Do not use molecular microbiology techniques (instead of conventional culture)for the first-line identification of pathogens from samples in a patient with a diabetic foot infection. (Strong; Low)
10. Treat a person with a diabetic foot infection with an antibiotic agent that has been shown to be effective in a published randomized controlled trial and is appropriate for the individual patient. Some agents to consider include: penicillins, cephalosporins, carbapenems, metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. (Strong; High)

11. Select an antibiotic agent for treating a diabetic foot infection based on: the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of efficacy of the agent for diabetic foot infections; risk of adverse events, including collateral damage to the commensal flora; likelihood of drug interactions; agent availability; and, financial costs. (Strong; Moderate)
12. Administer antibiotic therapy initially by the parenteral route to any patient with a *severe* diabetic foot infection. Switch to oral therapy if the patient is clinically improving, has no contraindications to oral therapy and if there is an appropriate oral agent available. (Strong; Low)
13. Treat patients with a mild diabetic foot infection, and most with a moderate diabetic foot infection, with oral antibiotic therapy, either at presentation or when clearly improving with initial intravenous therapy. (Weak; Low)
14. We suggest not using any currently available topical antimicrobial agent for treating a mild diabetic foot infection. (Weak; Moderate)
15. a) Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1 to 2 weeks. (Strong; High)
    b) Consider continuing treatment, perhaps for up to 3-4 weeks, if the infection is improving but is extensive, is resolving slower than expected, or if the patient has severe peripheral artery disease. (Weak; Low)
    c) If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient and reconsider the need for further diagnostic studies or alternative treatments. (Strong; Low)
16. For patients who have not recently received antibiotic therapy and who reside in a temperate climate area, target empiric antibiotic therapy at just aerobic gram-positive pathogens (beta-hemolytic streptococci and *Staphylococcus aureus*) in cases of a mild diabetic foot infection. (Strong; Low)
17. For patients residing in a tropical/subtropical climate, or who have been treated with antibiotic therapy within a few weeks, have a severely ischemic affected limb, or a moderate or severe infection, we suggest selecting an empiric antibiotic regimen that covers gram-positive pathogens, commonly isolated gram-negative pathogens, and possibly obligate anaerobes in cases of moderate to severe diabetic foot infections. Then, reconsider the antibiotic regimen based on both the clinical response and culture and sensitivity results. (Weak; Low)
18. Empiric treatment aimed at *Pseudomonas aeruginosa* is not usually necessary in temperate climates, but consider it if *P. aeruginosa* has been isolated from cultures of the affected site within the previous few weeks or in tropical/subtropical climates (at least for moderate or severe infection). (Weak; Low)
19. Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy with the goal of reducing the risk of infection or promoting ulcer healing. (Strong; Low)
20. Non-surgeons should urgently consult with a surgical specialist in cases of severe infection, or of moderate infection complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess or compartment syndrome, or severe lower limb ischemia. (Strong; Low)

21. a) In a patient with diabetes and uncomplicated forefoot osteomyelitis, for whom there is no other indication for surgical treatment, consider treating with antibiotic therapy without surgical resection of bone. (Strong; Moderate)
    b) In a patient with probable diabetic foot osteomyelitis with concomitant soft tissue infection, urgently evaluate for the need for surgery as well as intensive post-operative medical and surgical follow-up. (Strong; Moderate)
22. Select antibiotic agents for treating diabetic foot osteomyelitis from among those that have demonstrated efficacy for osteomyelitis in clinical studies. (Strong; Low)
23. a) Treat diabetic foot osteomyelitis with antibiotic therapy for no longer than 6 weeks. If the infection does not clinically improve within the first 2-4 weeks, reconsider the need for collecting a bone specimen for culture, undertaking surgical resection, or selecting an alternative antibiotic regimen. (Strong; Moderate)
    b) Treat diabetic foot osteomyelitis with antibiotic therapy for just a few days if there is no soft tissue infection and all the infected bone has been surgically removed. (Weak; Low)
24. For diabetic foot osteomyelitis cases that initially require parenteral therapy, consider switching to an oral antibiotic regimen that has high bioavailability after perhaps 5-7 days, if the likely or proven pathogens are susceptible to an available oral agent and the patient has no clinical condition precluding oral therapy. (Weak; Moderate)
25. a) During surgery to resect bone for diabetic foot osteomyelitis, consider obtaining a specimen of bone for culture (and, if possible, histopathology) at the stump of the resected bone to identify if there is residual bone infection. (Weak; Moderate)

    b) If an aseptically collected culture specimen obtained during the surgery grows pathogen(s), or if the histology demonstrates osteomyelitis, administer appropriate antibiotic therapy for up to 6 weeks. (Strong; Moderate)
26. For a diabetic foot infection do not use hyperbaric oxygen therapy or topical oxygen therapy as an adjunctive treatment if the only indication is specifically for treating the infection. (Weak; Low)
27. To specifically address infection in a diabetic foot ulcer:
    a) do not use adjunctive granulocyte colony stimulating factor treatment (Weak; Moderate) and,
    b) do not routinely use topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative-pressure wound therapy (with or without instillation). (Weak; Low)

INTRODUCTION

The prevalence of diabetes continues to increase worldwide, leading to a rising incidence of foot complications, including infections.[1] Diabetic foot infections (DFIs) are associated with substantial morbidities, requiring frequent healthcare provider visits, daily wound care, antimicrobial therapy, surgical procedures, with associated high health care costs.[2,3] Of particular importance, DFIs remain the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation.[4-6] Outcomes in patients presenting with an infected diabetic foot ulcer are poor: in one large prospective study at the end of one year the ulcer had healed in only 46% (and it later recurred in 10% of these), while 15% had died and 17% required a lower extremity amputation.[5] Thus, it is not surprising that a bibliographic analysis of global research on diabetic foot ulcers in the past 10 years found that infection (DFI) scored among the most frequent topics and the most highly cited publications.[7]

Managing DFIs requires careful attention to properly diagnosing the condition, obtaining appropriate specimens for culture, thoughtfully selecting antimicrobial therapy, quickly determining when surgical interventions are required and providing any needed additional wound and overall patient care. A systematic, evidence-based approach to managing DFIs likely improves outcomes, specifically resolution of infection and avoidance of complications, such as lower extremity amputation. This is best delivered by interdisciplinary teams, which should include among the membership, whenever possible, an infectious diseases or clinical/medical microbiology specialist.[8] This team should, of course, also attempt to ensure optimal local wound care (e.g., cleansing and debridement), pressure off-loading, vascular assessment and treatment if needed, and metabolic (particularly glycemic) control.

Several guidelines are available to assist clinicians in managing DFIs. A panel of infectious diseases experts convened by the International Working Group on the Diabetic Foot (IWGDF) has published widely used guideline documents quadrennially since 2004.[9] This current guideline updates both the format and content of the most recent previous guideline, published in 2016. [9] Specifically, it incorporates information from the concurrently published systematic reviews of the literature developed by the infection committee: an update of the 2016 systematic review on interventions in the management of infection in the diabetic foot [10] and a newly conducted review of issues related to diagnosis of DFIs. Of note, we have slightly modified the classification system for defining the presence and severity of an infection of the foot in a person with diabetes (see Table 1) that the IWGDF and the Infectious Diseases Society of America (IDSA) first developed in 2004.[11,12] In this guideline we have broadly divided our recommendations into those related to diagnosis, microbiologic assessment, and treatment (antibiotic, surgical, adjunctive).

BACKGROUND

Infection is best defined as an invasion and multiplication of microorganisms in host tissues that induces a host inflammatory response, usually followed by tissue destruction. Almost all DFIs occur in open wounds; as these are colonized with microorganisms, infection cannot be defined using only the results of wound cultures. Instead, DFI is defined clinically as the presence of manifestations of an inflammatory process in any tissue below the malleoli in a person with diabetes mellitus. In persons with diabetic foot complications, signs and symptoms of inflammation may, however, be masked by the presence of peripheral neuropathy or peripheral artery disease or immune dysfunction. DFIs usually begin with a break in the protective cutaneous envelope, typically in a site of trauma or ulceration, most often in a person with peripheral neuropathy and frequently with peripheral artery disease.[13] While rarely the primary cause of foot ulcers, the presence of limb ischemia increases the risk of an ulcer becoming infected,[4,14-16] and adversely affects the outcome of infection.[4,17,18] Foot ulcers in persons with diabetes often become chronic, related to increased biomechanical stress, hyperglycemia and its metabolic consequences, persistent inflammation, apoptosis and ischemia.[19,20] Factors that predispose to foot infection include having: an ulcer that is deep, long-standing or recurrent, or of traumatic etiology; ill-defined diabetes-related immunological perturbations, particularly with neutrophil dysfunction; or, chronic renal failure.[14,16,21-24] Although examined in only a few studies, a history of chronic hyperglycemia may predispose to DFIs and its presence at presentation may suggest a rapidly progressive or destructive (necrotizing) infection.[25,26]

While most DFIs are relatively superficial at presentation, microorganisms can spread contiguously to subcutaneous tissues, including fascia, tendons, muscles, joints and bones. The anatomy of the foot, which is divided into several separate but intercommunicating compartments, fosters proximal spread of infection.[27] The inflammatory response induced by infection may cause compartmental pressure to exceed capillary pressure, leading to ischemic tissue necrosis and thereby progressive infection.[28,29] The tendons within the compartments facilitate proximal spread of infection, which usually moves from higher to lower pressure areas. Bacterial virulence factors may also play a role in these complex infections.[30,31]

Systemic symptoms (e.g., feverishness, chills), marked leukocytosis or major metabolic disturbances are uncommon in patients with a DFI, but their presence denotes a more severe, potentially limb-threatening (or even life-threatening) infection.[4,32,33] If not diagnosed and properly treated, DFIs tend to progress, sometimes rapidly.[34] Thus, an experienced consultant (or team) should optimally evaluate a patient with a severe DFI within 24 hours.[35] Accumulations of purulent secretions, especially if under pressure or associated with necrosis, require prompt (usually within 24 hours) decompression and drainage. Although bone resection (preferably limited, avoiding amputation) is often useful for treating osteomyelitis, it is usually soft tissue infection that requires urgent antimicrobial therapy and surgical intervention.

The aim of this document is to provide guidelines for the diagnosis and treatment of foot infections in people with diabetes. These are intended to be of practical use for treating clinicians, based on all available scientific evidence.

METHODS

In this guideline we have followed the GRADE methodology, which is structured around clinical questions in the PICO-format (Patient-Intervention-Comparison-Outcome), systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale.[36,37]

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF editorial board. The members of the working group devised the clinical questions, which were revised after consultation with external experts from various geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and other health care professionals in providing useful information on the management of foot infections in persons with diabetes. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate *et al*.[38] as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as 'high', 'moderate' or 'low'. The systematic reviews supporting this guideline are published separately.[39,40]

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system we provided the rationale for how we arrived at each recommendation, based on the evidence from our systematic reviews [39,40], expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method [36,37]. Based on these factors, we graded the strength of each recommendation as 'strong' or 'weak', and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

We refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document.[41]

DIAGNOSIS

PICO 1a: In a person with diabetes and a foot infection, do increasing levels of severity of the IWGDF/IDSA criteria correlate with increasing rates of adverse outcomes (e.g., need for hospitalization, failure to resolve infection, lower extremity amputation)?

Recommendation 1:
a) Diagnose a soft tissue diabetic foot infection clinically, based on the presence of local or systemic signs and symptoms of inflammation. (Strong; Low)
b) Assess the severity of any diabetic foot infection using the Infectious Diseases Society of America/International Working Group on the Diabetic Foot classification scheme. (Strong, Moderate)

Rationale: The clinician seeing a patient with a diabetic foot ulcer should always assess for the presence of an infection and, if present, classify the infection's severity. Experts have proposed many classification schemes for diabetic foot ulcers (see IWGDF guideline on classification in this issue), many of which only include the presence of absence of "infection" (which is rarely specifically defined), but in the past decade most authorities have recommended using the IWGDF/IDSA classification that was first published in 2004. Two prospective cohort studies have validated all or part of the IWGDF/IDSA DFI classification, and one prospective and four retrospective cohort studies have validated the IWGDF/IDSA as part of a larger diabetic foot classification system. These and other studies from around the world have provided some evidence that increasing severity of infection is associated with higher levels of inflammatory markers,[42] a greater likelihood of the patient being hospitalized for treatment, longer duration of hospital stay, greater likelihood and higher level of lower extremity amputation, and higher rate of readmission.[4,33,43,44] Sepsis is uncommonly reported (perhaps partly being unrecognized) in patients with a DFI, even in the presence of extensive local signs and symptoms of infection. Thus, we considered whether we should replace using the findings of the systemic inflammatory response syndrome (SIRS) by another classification for severe infection, e.g., national early warning score (NEWS),[45,46] or quick sequential organ failure assessment (qSOFA).[47] These were, however, developed for identification or prediction of outcomes in patients with sepsis and there are no data to support changing from using SIRS to other classifications for DFIs.

Two commonly used classifications for diabetic foot ulcers, WIfI (wound, ischemia, foot infection) and SINBAD (site, ischemia, neuropathy, bacterial Infection, and depth), which use the IWGDF/IDSA classification for the infection component, have been validated with patient data.[48,49] The IWGDF/IDSA classification has several advantages, including having the most studies to validate its use in different populations. It is relatively easy for the clinician to use, requiring only a clinical examination and standard blood and imaging tests, helps direct diagnostic and therapeutic decisions about infection, has no obvious harms and has been widely accepted by the academic community and practicing clinicians. Furthermore, other available classification schemes were not specifically developed or validated for DFIs.[50]

For the current guideline we have made a *clarification* in the infection classification scheme (Table 1). We define infection based on the presence of evidence of: 1) inflammation of any part of the foot, not just an ulcer or wound; or, 2) findings of the systemic inflammatory response. We have also made one change in the classification scheme. Because of the important diagnostic, therapeutic and prognostic implications of osteomyelitis, we now separate it out by indicating the presence of bone infection with" (O)" after the grade number (3 or 4) (see Table 1). Although uncommon, bone infection may be documented in the absence of local inflammatory findings. In this case, the foot should be classified as infected (either grade 3/moderate if there are no SIRS findings or 4/severe if there are), with an (O). As the presence of osteomyelitis means the foot is infected it cannot be grade 1/uninfected, and because the infection is subcutaneous it cannot be grade 2/mild. As the grade 3 (moderate) classification is the largest and most heterogeneous group, we considered dividing it into subgroups of just lateral spread (≥2 cm from the wound margin), or just vertical spread (deeper than the subcutaneous tissue). We discarded this idea as it would add to the complexity of the diagnostic scheme, especially with our decision to add the (O) for osteomyelitis.

Table 1. The classification system for defining the presence and severity of an infection of the foot in a person with diabetes

Clinical classification of infection, with definitions	IWGDF classification
Uninfected	
No systemic or local symptoms or signs of infection	1 (uninfected)
Infected	
At least two of these items are present: ▪ Local swelling or induration ▪ Erythema >0.5 cm* around the wound ▪ Local tenderness or pain ▪ Local increased warmth ▪ Purulent discharge And no other cause(s) of an inflammatory response of the skin (e.g. trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis or venous stasis)	
Infection with no systemic manifestations (see below) involving ▪ only the skin or subcutaneous tissue (not any deeper tissues), and ▪ any erythema present does not extend >2 cm** around the wound	2 (mild infection)
Infection with no systemic manifestations, and involving: ▪ erythema extending ≥2 cm* from the wound margin, and/or ▪ tissue deeper than skin and subcutaneous tissues (e.g. tendon, muscle, joint, bone,)	3 (moderate infection)
Any foot infection with associated systemic manifestations (of the systemic inflammatory response syndrome [SIRS]), as manifested by ≥2 of the following: ▪ Temperature >38 °C or <36 °C ▪ Heart rate >90 beats/minute ▪ Respiratory rate >20 breaths/minute or $PaCO_2$ <4.3 kPa (32 mmHg) ▪ White blood cell count >12,000/mm^3, or <4,000/mm^3, or >10% immature (band) forms	4 (severe infection)
Infection involving bone (osteomyelitis)	Add "(O)" after 3 or 4***

Note: * Infection refers to any part of the foot, not just of a wound or an ulcer; ** In any direction, from the rim of the wound. The presence of clinically significant foot ischemia makes both diagnosis and treatment of infection considerably more difficult; *** If osteomyelitis is demonstrated in the absence of ≥2 signs/symptoms of local or systemic inflammation, classify the foot as either grade 3(O) (if <2 SIRS criteria) or grade 4(O) if ≥2 SIRS criteria) (see text).

PICO 1b: Which persons presenting with diabetes and foot infection should be hospitalized for management of infection?

Recommendation 2: Consider hospitalizing all persons with diabetes and a severe foot infection, and those with a moderate infection that is complex or associated with key relevant morbidities. (Strong; Low)

Rationale: Hospitalization is an expensive and finite resource, and may subject the patient to some inconvenience and potential nosocomial risks. But while many patients with a DFI do not need to be hospitalized, some certainly should be. Possible reasons to hospitalize a person with diabetes who presents with a more complex foot infection include: more intensive assessment for progression of local and systemic conditions; expediting obtaining diagnostic procedures (such as advanced imaging or vascular assessment); administering parenteral antibiotic therapy and fluid resuscitation; correcting metabolic and cardiovascular disturbances; and, more rapidly accessing needed specialty (especially surgical) consultation. Limited evidence suggests that monitoring and correcting severe hyperglycemia may be beneficial.[26] Patients with a complex infection, e.g., those needing urgent surgery (e.g., because of extensive gangrene, deep abscess or compartment syndrome), having selected comorbidities (e.g., severe peripheral artery disease, renal failure, immunocompromised state) or having social, physical or psychological vulnerabilities, may also benefit from (or even require) hospitalization (see Table 2). The presence of bone infection does not necessarily require hospitalization unless because of substantial associated soft tissue infection, for diagnostic testing, or for surgical treatment. Fortunately, almost all patents with a mild infection, and many with a moderate infection, can be treated in an ambulatory setting. Most published studies of DFIs have enrolled hospitalized patients, but over the past two decades several have reported good results with outpatient treatment.[51-53] The IDSA/IWGDF classification scheme was not designed to help determine when an infection has *resolved* (i.e., the absence of signs and symptoms that were used to diagnose infection), but it makes sense that it could be used this way and has been in some studies of antibiotic therapy for DFIs.

Table 2. Characteristics suggesting a more serious diabetic foot infection and potential indications for hospitalization

A – Findings suggesting a more serious diabetic foot infection	
Wound specific	
Wound	Penetrates to subcutaneous tissues (e.g. fascia, tendon, muscle, joint or bone)
Cellulitis	Extensive (>2 cm), distant from ulceration or rapidly progressive (including lymphangitis)
Local signs/symptoms	Severe inflammation or induration, crepitus, bullae, discoloration, necrosis or gangrene, ecchymoses or petechiae and new anesthesia or localized pain
General	
Presentation	Acute onset/worsening or rapidly progressive
Systemic signs	Fever, chills, hypotension, confusion and volume depletion
Laboratory tests	Leukocytosis, highly elevated C-reactive protein or erythrocyte sedimentation rate, severe or worsening hyperglycemia, acidosis, new/worsening azotemia and electrolyte abnormalities
Complicating features	Presence of a foreign body (accidentally or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphedema, immunosuppressive illness or treatment, acute kidney injury
Failing treatment	Progression while on apparently appropriate antibiotic and supportive therapy
B – Some Factors suggesting hospitalization may be necessary	
Severe infection (see findings suggesting a more serious diabetic foot infection above)	
Metabolic or hemodynamic instability	
Intravenous therapy needed (and not available/appropriate as an outpatient)	
Diagnostic tests needed that are not available as an outpatient	
Foot ischemia is present	
Surgical procedures (more than minor) required	
Failure of outpatient management	
Patient unable or unwilling to comply with outpatient-based treatment	
Need for more complex dressing changes than patient/caregivers can provide	
Need for careful, continuous observation	

PICO 2a: In a person with diabetes and a suspected foot infection, how well do the IWGDF/IDSA clinical criteria for diagnosing soft tissue infection correlate with other diagnostic tests?

Recommendation 3: In a person with diabetes and a possible foot infection for whom the clinical examination is equivocal or uninterpretable, consider ordering an inflammatory serum biomarker, such as C-reactive protein, erythrocyte sedimentation rate and perhaps procalcitonin, as an adjunctive measure for establishing the diagnosis. (Weak; Low)

Rationale: There are several diagnostic methods against which clinical examinations could be compared to evaluate their ability to assess the presence or severity of foot infection, or to differentiate soft tissue

from bone infection. Most available studies assessed the value of blood tests, especially white blood cell counts (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin (PCT), by comparing them to results of IDSA/IWGDF criteria for infection.[9,42,54]. Unfortunately, the severity of infection in patients included in the available studies was not always clearly defined, which may account for interstudy differences in findings. In addition, many studies do not specify if enrolled patients were recently treated with antibiotic therapy, which could affect results.

Of particular note is the WBC level, as it is used as part of the IDSA/IWGDF criteria for classifying infection as severe/grade 4. The available studies[55-58] found little correlation with infection severity, with about half of the patients diagnosed with a DFI having a normal WBC.[59,60] In most studies ESR values have been higher in patients with an infected diabetic foot ulcer (IDFU) compared with a noninfected DFU (NIDU).[55,56] ESR values can be affected by various co-morbidities (e.g., anemia, azotemia) and may not be elevated in acute infections, due to the relatively slow response of this inflammatory biomarker, but a highly elevated ESR (≥70 mm/h) is more common in patients with bone than with just soft tissue infections.

Most studies of serum PCT levels have also found that levels were significantly higher in IDFU than NIDFU, but there was little correlation between the values and the infection severity. Furthermore, PCT has, until recently in some areas, been costlier than CRP, and it may be unavailable in many clinical laboratories. Compared to ESR, CRP levels tend to rise more quickly with infection and fall more quickly with resolution of infection. Serum values of CRP[55,56,61] have consistently been found to be significantly higher in IDFU than in NIDFU, and higher in patients with NIDFU than in those with no foot ulcer, with levels increasing significantly with the severity of infection.[56,62]

Overall, CRP and PCT have shown higher diagnostic accuracy than WBC or ESR. Some studies have investigated using various combinations of these inflammatory markers, but none seemed especially useful and the highly variable cut off values make the results difficult to interpret. Serum tests for these common biomarkers are widely available, easily obtained, and most are relatively inexpensive. A few studies investigated other inflammatory markers for their role in diagnosing or following DFIs, but they were small and of low quality.[42]

PICO 2b: In a person with diabetes and a suspected foot infection, do the IDSA/IWGDF criteria for diagnosing soft tissue infection correlate with results of skin temperature measurement or quantitative microbiology?

Recommendation 4: As neither electronically measuring foot temperature nor using quantitative microbial analysis has been demonstrated to be useful as a method for diagnosing diabetic foot infection, we suggest not using them. (Weak; Low)

Rationale: While various imaging tests are widely used for diagnosing bone infection (see PICO D3 below), there are few data on their usefulness for soft tissue infections. Other diagnostic tests studied for assessing DFI include photographic foot imaging and infrared thermography. Several studies with these instruments have examined their value in predicting foot ulcerations. A few studies have demonstrated that an increase in temperature in one area on the foot, and perhaps various

photographic assessments, have a relatively weak correlation with clinical evidence of infection on examination.[63-66] Overall, employing either infrared or digital thermography does not appear to provide substantial help in diagnosing infection or predicting clinical outcome in patients with a DFU seen in the hospital setting. While infrared imaging likely has no harms, it is limited by low availability. It is possible that it may be of value when coupled to photographic assessment through telemedicine in the early diagnosis of DFI.

Some advocate using the presence of high numbers of bacteria on culture (usually defined as $\geq 10^5$ colony-forming units per gram of tissue) as a basis for differentiating infected from uninfected DFUs.[67,68] However, there is no convincing data (from conventional culture or molecular methods) supporting this concept.[69] In the studies that assessed the validity of clinical signs for the diagnosis of DFI using microbial analysis as a referent test, the criteria used to define infection varied among the authors and even between studies conducted by the same team. In some microbial analysis studies, patients receiving antibiotics at the time of the wound sampling (which may cause diminished organism counts) were included, while others failed to provide information on this important confounding issue. Of note, these methods of measuring what is sometimes called "wound bioburden" are time-consuming and relatively expensive. Furthermore, neither quantitative classical culture nor molecular microbiological techniques are currently available for most clinicians in their routine practice.

PICO 3: In a person with diabetes and suspected bone infection of the foot, which diagnostic tests best correlate with the presence of osteomyelitis, as diagnosed based on culture and/or histopathology of a bone specimen?

Recommendation 5: In a person with diabetes and suspected osteomyelitis of the foot, we recommend using a combination of the probe-to-bone test, the erythrocyte sedimentation rate (or C-reactive protein and/or procalcitonin), and plain X-rays as the initial studies to diagnose osteomyelitis. (Strong; Moderate)

Rationale: Diagnosing osteomyelitis in the diabetic foot may be difficult, partly because of a lack of a universally accepted definition or criterion standard, and partly related to low levels of inter-test agreement among commonly used diagnostic tests.[70] Osteomyelitis may be present underlying any DFU, especially those that have been present for many weeks or that are wide, deep, located over a bony prominence, showing visible bone or accompanied by an erythematous, swollen ("sausage") toe.[71,72] Among clinical examinations, the probe-to-bone (PTB) test is the most useful, but the performing clinician's technique and experience, the ulcer's location and its etiology may affect the test's reliability.[73,74] A systematic review of the PTB test found that for detecting DFO the sensitivity was 0.87 and specificity 0.83.[75] Overall, in diagnosing DFO the PTB test suggests the diagnosis if it is positive in a high risk patient and helps rule it out if it is negative in a low risk patient. The procedure is easy to learn and perform, requiring only a sterile blunt metal probe (gently inserted into the wound, with a positive test defined by feeling a hard, gritty structure),[76] is inexpensive and essentially harmless, but interobserver agreement is only moderate.

Among blood tests, the ESR is the most useful, with a highly elevated rate (>70 mm/hr) suggesting bone infection.[57,77] Any patient with possible bone infection should initially have plain x-rays of the foot.

Interpreted by an experienced reader, characteristic findings of bone infection (see Table 2) are highly suggestive of osteomyelitis, but x-rays are often negative in the first few weeks of infection and abnormal findings can be caused by Charcot osteoarthropathy and other disorders. Plain x-rays are widely available, relatively inexpensive and associated with minimal harm. A retrospective study of 107 patients with histologically proven DFO found that after adjusting for confounders, the WBC was not useful for diagnosing DFO, but ESR (in particular), as well as CRP and plain radiographs, were actually more useful than MRI.[78]

Recommendation 6:
a) In a person with diabetes and suspected osteomyelitis of the foot, if a plain X-ray and clinical and laboratory findings are most compatible with osteomyelitis, we recommend no further imaging of the foot to establish the diagnosis. (Strong; Low).
b) If the diagnosis of osteomyelitis remains in doubt, consider ordering an advanced imaging study, such as magnetic resonance imaging scan, 18F-FDG- positron emission tomography/computed tomography (CT) or leukocyte scintigraphy (with or without CT). (Strong; Moderate)

Rationale: Depending on the patient setting, advanced imaging for diagnosing osteomyelitis is not needed in many patients. When needed, magnetic resonance imaging (MRI), with a sensitivity of about 0.9 and specificity of about 0.8, has been the most widely used test for decades.[79] One retrospective study of 32 cases of pathologically proven DFO found that, compared to plain X-rays, MRI had added value in guiding surgical treatment in 65%, and a five times higher agreement with surgical findings.[80] MRI is widely available (in high income countries), with lower costs than some of the newer advanced imaging technologies, and gives an overview of the presence and anatomy of both soft tissue and bone infections in the foot. The presence of reactive bone marrow edema from non-infectious pathologies, such as trauma, previous foot surgery or Charcot neuroarthropathy, lowers the specificity and positive predictive value.[81,82] In selected patients with possible neuro-osteoarthropathy, newer techniques such as MR angiography, dynamic contrast-enhanced MRI or neurography may better distinguish Charcot from osteomyelitis.[83-86] Newer advanced imaging tests, especially ^{18}F-fluorodeoxyglucose (FDG)-PET/CT and ^{99m}Tc- exametazime (HMPAO)-labeled leukocyte scintigraphy can be used in patients with a contraindication to MRI, and appear to have a higher specificity than MRI (especially when noninfectious bony changes are more likely), but are limited in availability, require special expertise and are more expensive.[87,88] Compared to other nuclear medicine techniques (e.g., leukocyte imaging), PET (especially with CT) offers high spatial resolution and precise anatomic localization, possibly higher sensitivity for chronic infection, easier performance, faster results, and low radiation exposure. However, currently supportive data for PET are less robust and it is less able to differentiate infection from inflammation (including from acute Charcot foot).[89,90] The availability and cost of these advanced imaging techniques may vary in different locations, but they might be useful in situations when the diagnosis remains in doubt and there are limited options to obtain a bone biopsy. Advanced imaging (especially MRI) is also useful for surgical planning in selected cases, such as to identify purulent collections or the extent of bone involvement pre-operatively.

As with soft tissue infections (see above), it may be difficult to know when DFO has been successfully treated. There are often few clinical signs and symptoms, although resolution of overlying soft tissue infection is reassuring. A decrease in previously elevated serum inflammatory markers suggests improving infection. Plain x-rays showing no further bone destruction, and better yet signs of bone healing, also

suggest improvement. And, some of the newer advanced imaging studies, e.g., WBC-labelled SPECT/CT, FDG PET/CT, may be more sensitive in demonstrating resolution of infection. The current state of the art, however, is that DFO is at best in "remission" if diagnostic tests suggest improvement, but should probably not be considered "cured" until there has been no evidence of recurrence for at least a year after the end of treatment.[91,92] An additional outcome in patients treated for DFI is recurrence of the infection at the same location. In one study of over 1000 episodes of moderate or severe DFI (including osteomyelitis), recurrent infection was noted in 25% of patients within three years. Risk of recurrence was higher in those with type 1 diabetes, immunosuppression, a sequestrum, who did not undergo amputation or revascularization, but was unrelated to the route or duration of antibiotic therapy.[91]

Recommendation 7: In a person with diabetes and suspected osteomyelitis of the foot, in whom making a definitive diagnosis or determining the causative pathogen is necessary for selecting treatment, collect a sample of bone (percutaneously or surgically) to culture clinically relevant bone microorganisms and for histopathology (if possible). (Strong; Low)

Rationale: Obtaining a specimen of bone to diagnose osteomyelitis of the diabetic foot is the generally accepted criterion standard for diagnosing the infection and the only definitive way to determine the causative pathogen. Available evidence suggests that collecting a bone specimen in an aseptic manner (i.e., percutaneously or per-operative, not through the wound), is safe and provides the most accurate assessment of true pathogens.[93-96] A prospective direct comparison of 46 paired per-wound and transcutaneous bone biopsies in patients with suspected DFO found that results were identical in only 42%.[97] To avoid a false-negative culture, some experts suggest delaying bone biopsy in a patient receiving antibiotics until they have been off therapy for at least a few days, and ideally for at least two weeks [93,94]. While this seems theoretically sensible, reports from studies of various types of bone infection,[98-101] including DFO,[102] suggest that having receiving antibiotic therapy before a bone culture does not appear to reduce the percentage of positive cultures or time to culture positivity. Biopsy is generally not painful (as the majority of affected patients have sensory neuropathy) and complications are very rare.[103] While it would be theoretically useful to obtain a bone specimen in almost all cases, this is often impractical as the procedure requires some time, experience and expense. Thus, it is most important to perform bone biopsy when it is difficult to guess the causative pathogen or its antibiotic susceptibility, e.g., in patients at risk for antibiotic-resistant isolates, who have been previously treated with antibiotics or who have had a soft tissue sample that grew multiple pathogens. Biopsy may not be needed if an aseptically collected deep tissue specimen from a soft tissue infection grows only a single virulent pathogen, especially *S. aureus*.[93,94] The diagnosis of osteomyelitis is most assured if one or more bone specimens has both a positive culture and characteristic histopathological findings.[104] Culture has the advantage of determining the causative pathogen, but histology may be more sensitive if the patient is on antibiotic therapy and more specific if specimen contamination is a concern. Of note, the inter-rater agreement on the diagnosis of osteomyelitis by histopathology is low (<40% in one study)[105] and concordance between histopathology and culture of foot bone specimens is also poor (41% in one study).[106] Culture of soft tissue specimens (even those collected close to the bone) often miss causative pathogens or yield likely contaminants, and thus less accurate than bone cultures. The reported concordance rates between contemporaneous cultures of soft tissue and bone are mostly ≤50%.[93,107,108]

Table 3. Features characteristic of diabetic foot osteomyelitis on plain X-rays [109-114]

New or evolving radiographic features* on serial radiographs**, including: ▪ Loss of bone cortex, with bony erosion or demineralization ▪ Focal loss of trabecular pattern or marrow radiolucency (demineralization) ▪ Periosteal reaction or elevation ▪ Bone sclerosis, with or without erosion
Abnormal soft tissue density in the subcutaneous fat, or gas density, extending from skin towards underlying bone, suggesting a deep ulcer or sinus tract.
Presence of sequestrum: devitalized bone with radiodense appearance separated from normal bone
Presence of involucrum*: layer of new bone growth outside previously existing bone resulting and originating from stripping off the periosteum.
Presence of cloacae*: opening in the involucrum or cortex through which sequestrum or granulation tissue may discharge.

Note: *Some features (e.g. sequestrum, involucrum and cloacae) are seen less frequently in diabetic foot osteomyelitis than in younger patients with osteomyelitis of larger bones. **Usually spaced several weeks apart.

MICROBIOLOGY

PICO 4: In a person with diabetes and a foot infection, do specimens of wound tissue (obtained by curettage or biopsy) provide more clinically useful information on growth of pathogens or avoidance of contaminants than wound swabs?

Recommendation 8:
a) Collect an appropriate specimen for culture for almost all clinically infected ulcers to determine the causative pathogens. (Strong; Low)
b) For a soft tissue diabetic foot infection, obtain a sample for culture by aseptically collecting a tissue specimen (by curettage or biopsy) from the ulcer. (Strong; Moderate)

Rationale: In the great majority of cases obtaining a specimen (after cleansing and debridement, avoiding contamination) for culture from a DFI provides useful information on the causative pathogen(s) and their antibiotic susceptibility, allowing appropriate selection of antibiotic therapy. In cases of an acute, non-severe DFI in a patient who has not recently received antibiotic therapy and has no other risk factors for unusual or antibiotic-resistant pathogens (e.g., based on specific exposures or previous culture results), selecting empiric therapy without culture may be reasonable. In most clinical situations it is easiest to collect a soft tissue specimen by superficial swab, but recent studies, including two systematic reviews[115,116] (with low quality evidence), one small prospective study[117] and one well-designed prospective study,[118] have generally shown that the sensitivity and specificity of tissue specimens for culture results are higher than for swabs. Collecting a tissue specimen may require slightly more training and poses a slight risk of discomfort or bleeding, but we believe the benefits clearly outweigh these minimal risks. The evidence informing what method of specimen collection to use is limited by the absence of a definitive criterion standard for defining ulcer infection. Repeating cultures may be useful for a patient who is not responding to apparently appropriate therapy, but this may result

in isolating antibiotic-resistant strains that may be contaminants rather than pathogens. A key caveat is that the accuracy of results depends on the quality of information provided between clinical and microbiology staff throughout the sample pathway, from collecting to transporting to processing to reporting. Collaboration is important: clinicians should provide key clinical details associated with the sample and clinical microbiology services should provide adequately comprehensive reporting of the isolated organisms and their susceptibility profiles. For persons presenting in a low income or limited resources setting without ready access to culture or follow-up care, performing a Gram-stain smear of material from a DFI could be a relatively easy and inexpensive way to visualize the class of the likely causative pathogens, thus helping direct empiric therapy.[119]

PICO 5: In a person with diabetes and a foot infection, do the results of molecular (genotypic) microbiological tests better distinguish likely clinically relevant pathogens requiring antibiotic therapy than standard (phenotypic) cultures?

Recommendation 9: Do not use molecular microbiology techniques (instead of conventional culture) for the first-line identification of pathogens from samples in a patient with a diabetic foot infection. (Strong; Low)

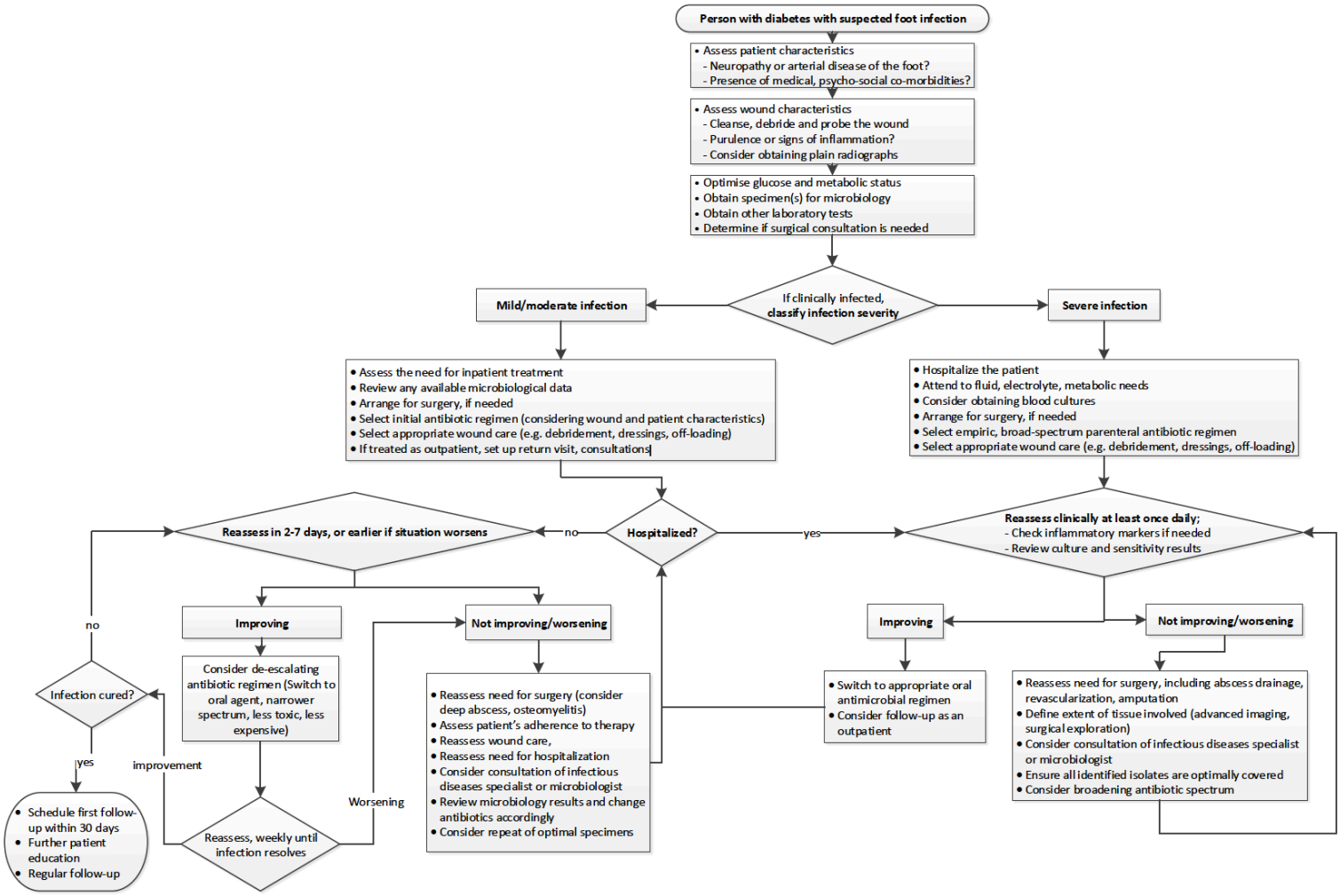
Rationale: Molecular microbiology techniques have demonstrated that the flora in most DFIs is more diverse and abundant than that revealed by conventional culture methods.[120-122] Although *Corynebacterium* spp. and obligate anaerobes appear to be more prevalent using sequencing techniques, their pathogenic role as part of a polymicrobial infection is unclear.[123] Overall, there is generally good agreement between molecular sequencing and conventional culture methods regarding the most clinically relevant pathogens identified.[124] The few studies employing molecular sequencing for either soft tissue or bone infection have enrolled relatively few subjects, were at high risk of bias and have not provided information on the value of the findings for guidance on clinical management. Specifically, we do not know which of the many bacterial genera identified by molecular methods contribute to the clinical state of infection or require directed antibiotic therapy. Furthermore, molecular approaches identify both living and dead organisms and generally do not assess for the antibiotic sensitivities of identified isolates. It remains unclear whether or not determining the number of microorganisms (microbial load or operational taxonomic units) present in a wound, or seeking gene markers for virulence factors or toxin production as a diagnostic or prognostic aid will provide any additional clinical benefits beyond current practice. Finally, compared to standard culture techniques, molecular methods may be more expensive and require more processing time, but less so using newer methods and considering the full testing pathway. Thus, for now clinicians should continue to request conventional culture of specimens to determine the identity of causative microorganisms and their antibiotic sensitivity.

Regardless of the method of determining the causative pathogens from a specimen, collaboration and consultation between the clinical and laboratory staff will help each to be most helpful to the other. Clinicians should provide the microbiology laboratory key clinical information (e.g., type and site of infected lesion, recent antimicrobial therapy), either on order forms or by direct communication.

Similarly, laboratory personnel should offer clear information (when requested) on how to obtain optimal specimens and provide preliminary and final identifications as soon as practical.

TREATMENT

Figure 1. Suggested overview of a stepwise approach to managing a patient with diabetes and a suspected foot infection



PICO 6: In a person with diabetes and a foot infection, is any particular antibiotic regimen (specific agent[s], route, duration) better than any other for treating soft tissue or bone infection?

SOFT TISSUE INFECTION

Recommendation 10: Treat a person with a diabetic foot infection with an antibiotic agent that has been shown to be effective in a published randomized controlled trial and is appropriate for the individual patient. Some agents to consider include: penicillins, cephalosporins, carbapenems, metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. (Strong; High)

Recommendation 11: Select an antibiotic agent for treating a diabetic foot infection based on: the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of efficacy of the agent for diabetic foot infections; risk of adverse events, including collateral damage to the commensal flora; likelihood of drug interactions; agent availability; and, financial costs. (Strong; Moderate)

Recommendation 12: Administer antibiotic therapy initially by the parenteral route to any patient with a *severe* diabetic foot infection. Switch to oral therapy if the patient is clinically improving, has no contraindications to oral therapy and if there is an appropriate oral agent available. (Strong; Low)

Recommendation 13: Treat patients with a mild diabetic foot infection, and most with a moderate diabetic foot infection, with oral antibiotic therapy, either at presentation or when clearly improving with initial intravenous therapy. (Weak; Low)

Recommendation 14: We suggest not using any currently available topical antimicrobial agent for treating a mild diabetic foot infection. (Weak; Moderate)

Rationale: Antibiotic therapy, administered by an appropriate route, is required in virtually all patients with a soft tissue DFI. For mild and most moderate infections treatment with well-absorbed oral antibiotic agents is generally effective. In patients with a more severe infection (some 3 and most 4), initial parenteral antibiotic therapy is preferable to achieve immediate high serum levels, but can usually be switched to oral therapy within a week. Based on many studies (most limited by methodological flaws) that compared various oral or parenteral antibiotic agents in patients with DFI, treatment with any appropriately selected agent of most classes of antibiotics is effective in the great majority of cases.[125] Empiric therapy should be based on the clinician's best guess at the likely causative pathogen(s) and their local antibiotic susceptibilities, along with a variety of other factors (e.g., history of drug allergies, recent hospitalization, patient co-morbidities [e.g., renal dialysis], likelihood of adverse events or potential drug interactions, availability and cost of various agents). In light of the complexity and often polymicrobial nature of DFI, definitive treatment should especially be based on principles of antibiotic stewardship (preferably selecting, when appropriate, a regimen with the narrowest spectrum, shortest duration, fewest adverse effects, safest and least expensive route). Wound culture results from a DFI are often polymicrobial; while virulent pathogens (e.g., *Staphylococcus aureus* or beta-hemolytic streptococci) that are isolated should be treated, some less virulent isolates (e.g., corynebacteria or coagulase-negative staphylococci) are often contaminants or colonizers that may not need targeted antibiotic treatment.

Some countries or institutions restrict the use of certain antibiotics (e.g., fluoroquinolones, rifampicin) for various reasons. In general, "first line" antibiotic choices are most often well-established agents while newer agents are often held in reserve for antibiotic-resistant pathogens. Clinicians should consider consulting an infectious diseases/microbiology expert about antibiotic therapy for difficult cases, such as those caused by unusual or highly resistant pathogens.

Treatment with topical antimicrobial therapy has many theoretical advantages, particularly using a small dose only at the site of infection, thus potentially limiting issues of cost, adverse events and antibiotic resistance. Unfortunately, no published studies support treating either mild infections (with topical therapy alone) or moderate infections (with topical therapy adjunctive to systemic antibiotics).[126] Specifically, recent large unpublished studies of topical therapy for a mild DFI with pexiganan (an antimicrobial peptide)[127,128] or with the gentamicin-collagen sponge[129] failed to demonstrate superiority to standard of care treatment alone. Similarly, a published trial of the gentamicin-collagen sponge for treating mild DFI[130] or as adjunctive therapy (to systemic antibiotics) for moderate or severe DFI showed no benefit.[131]

No one antibiotic class or agent has been shown to be superior to others, but tigecycline was found to be clinically inferior to ertapenem (with or without added vancomycin) for treating soft tissue (and, in a small subset, bone) infections in a well-designed clinical trial of over 1000 patients.[132] This study also showed that rates of adverse events were significantly higher in the tigecycline treated patients. A prospective observational study of 105 patients treated with tigecycline for DFI reported clinical success in only ~57% of patients with a moderate or severe infection, significantly lower cure rates in those with peripheral artery disease, and adverse treatment effects in 44%.[133] Other studies have shown high failure rates with long-term treatment with tigecycline and it is associated with a high rate of nausea.[134] Recent studies suggest that many (perhaps most) DFIs are caused by bacteria in a biofilm mode, although biofilm infection is difficult to diagnose clinically.[135,136] Pathogens in biofilm, compared to planktonic, infections are more difficult to treat but some antibiotics (e.g., rifampicin, daptomycin, fosfomycin) appear to be more effective for biofilm infection than others.[137,138] With appropriately selected antibiotic therapy (combined with any necessary surgery and proper metabolic control and wound care), most DFIs can treated be successfully with limited harms.

Recommendation 15:
a) Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1 to 2 weeks. (Strong; High)
b) Consider continuing treatment, perhaps for up to 3-4 weeks, if the infection is improving but is extensive, is resolving slower than expected, or if the patient has severe peripheral artery disease. (Weak; Low)
c) If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient and reconsider the need for further diagnostic studies or alternative treatments. (Strong; Low)

Rationale: Principles of antimicrobial stewardship include limiting the duration of antibiotic therapy for treating wounds to the minimum number of days needed for good results.[139,140] More prolonged antibiotic therapy is associated with increased risks of adverse events, greater disruption of host microbiomes, higher costs and more patient inconvenience. In published studies of DFIs, duration of

antibiotic therapy ranged from 5 to 28 days, but they do not provide any data upon which to recommend an optimal duration nor criteria for when stopping antibiotic therapy is appropriate.[18] In most of these studies patients underwent any needed superficial or deep debridement of necrotic or purulent tissue and patients with severe peripheral artery disease were excluded.[51,132,141,142] Based on expert opinion, minor soft tissue infections that resolve quickly can be treated with less than one week of antibiotic therapy, while extending antibiotic therapy to 2—4 weeks may be appropriate for some patients with extensive infection or when limb ischemia limits antibiotic delivery and ulcer healing. When apparently appropriate treatment for a DFI appears to be failing, rather than extending the course of antibiotic therapy the clinician should re-consider what therapy might be more appropriate. Key questions to ask (see Figure 1) include: were all likely pathogens covered by the selected antibiotic agent; are there new pathogens (perhaps related to intercurrent antibiotic treatment); was the antibiotic agent being administered/taken as prescribed (whether in hospital or ambulatory setting); could intestinal absorption be impaired; was the possibility of insufficient perfusion due to peripheral artery disease not addressed; could there be an undiagnosed abscess, foreign body, osteomyelitis or other complication that may require surgery? While the evidence for most of these suggestions is either low or limited, decades of clinical experience support our making these strong recommendations.

Recommendation 16: For patients who have not recently received antibiotic therapy and who reside in a temperate climate area, target empiric antibiotic therapy at just aerobic gram-positive pathogens (beta-hemolytic streptococci and *Staphylococcus aureus*) in cases of a mild diabetic foot infection. (Strong; Low)

Recommendation 17: For patients residing in a tropical/subtropical climate, or who have been treated with antibiotic therapy within a few weeks, have a severely ischemic affected limb, or a moderate or severe infection, we suggest selecting an empiric antibiotic regimen that covers gram-positive pathogens, commonly isolated gram-negative pathogens, and possibly obligate anaerobes in cases of moderate to severe diabetic foot infections. Then, reconsider the antibiotic regimen based on both the clinical response and culture and sensitivity results. (Weak; Low)

Recommendation 18: Empiric treatment aimed at *Pseudomonas aeruginosa* is not usually necessary in temperate climates, but consider it if *P. aeruginosa* has been isolated from cultures of the affected site within the previous few weeks or in tropical/subtropical climates (at least for moderate or severe infection). (Weak; Low)

Rationale: Initial antibiotic therapy for most patients with a DFI will be empiric; the goal is to cover the likely pathogens without prescribing an unnecessarily broad-spectrum regimen. Definitive therapy should then be tailored to the clinical response to empiric therapy and the results of properly collected specimens. For decades, studies (almost exclusively from temperate climates in North America and Europe) consistently demonstrated that the most common pathogens in DFIs are aerobic gram-positive cocci, especially *S. aureus*, and to a lesser extent streptococci and coagulase-negative staphylococci. More recent studies of DFIs from patients in tropical/subtropical climates (mainly Asia and northern Africa) have shown that aerobic gram-negative bacilli are often isolated, either alone or in combination with gram-positive cocci. These considerations, along with whether or not the patient has recently

received antibiotic therapy, has had gram-negative bacilli isolated from a recent previous culture, has had frequent exposure to water (a source for *P. aeruginosa*) or comes from an environment in which pathogens are often resistant to commonly used antibiotics, are key in selecting an empiric antibiotic regimen. Empiric treatment aimed at *P. aeruginosa*, which usually requires either an additional or broader-spectrum agent, is generally unnecessary in temperate climates. It should, however, be considered in tropical/subtropical climates or if *P. aeruginosa* has been isolated from previous cultures of the affected patient. Of course, clinicians should reassess the regimen based on the clinical response and culture and sensitivity results and consider changing to more appropriate, safer, more convenient, or less expensive agent(s).

Obligate anaerobes can play a role in DFI, especially in ischemic limbs and in case of abscesses, [121,143] Empiric treatment of these pathogens, e.g. with an imidazole (metronidazole), or beta-lactam with beta lactamase inhibitor, should be considered for DFI associated with ischemia or a foul-smelling discharge. Some newer cephalosporins (combined with enzyme inhibitors) and fluoroquinolones have activity against most obligate anaerobes, which might preclude the need for combining them with anti-anaerobic agents. There are, however, insufficient published data recommend use of these agents to target anaerobes in diabetic foot infections.

Table 4. Selecting an empiric antibiotic regimen for diabetic foot infections*

Infection severity	Additional factors	Usual pathogen(s) [a]	Potential empirical regimens [b]
Mild	No complicating features	GPC	S-S pen; 1st gen ceph
	ß-lactam allergy or intolerance	GPC	Clindamycin; FQ; T/S; macrolide; doxy
	Recent antibiotic exposure	GPC+GNR	ß-L-ase-1; T/S; FQ
	High risk for MRSA	MRSA	Linezolid; T/S; doxy; macrolide
Moderate or Severe [c]	No complicating features	GPC±GNR	ß-L-ase 1; second/third gen ceph
	Recent antibiotics	GPC±GNR	ß-L-ase 2; 3rd gen ceph; group 1 carbapenem (depends on prior therapy; seek advice)
	Macerated ulcer or warm climate	GNR, including Pseudomonas	ß-L-ase 2; S-S pen + ceftazidime; S-S pen + cipro; group 2 carbapenem
	Ischemic limb/necrosis/gas forming	GPC±GNR± Anaerobes	ß-L-ase 1 or 2; group 1 or 2 carbapenem; 2nd/3rd gen ceph + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider adding, or substituting with, glycopeptides; linezolid; daptomycin; fusidic acid T/S (±rif)**; doxycycline
	Risk factors for resistant GNR	ESBL	Carbapenems; FQ; aminoglycoside and colistin

Note: * Recommendations are based upon theoretical considerations and results of available clinical trials. Abbreviations:GPC: Gram-positive cocci (staphylococci and streptococci); GNR: Gram-negative rod; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum ß-lactamase-producing organism; S-S pen: semisynthetic penicillinase-resistant penicillin; ß-L-ase: ß-lactam, ß-lactamase inhibitor; ß-L-ase 1: amoxicillin/clavulanate, ampicillin/sulbactam; ß-L-ase 2: ticarcillin/clavulanate, piperacillin/tazobactam; doxy: doxycycline; group 1 carbapenem: ertapenem; group 2 carbapenem: imipenem, meropenem, doripenem; ceph: cephalosporin; gen: generation; Pip/tazo: piperacillin/tazobactam; FQ: fluoroquinolone with good activity against aerobic Gram-positive cocci (e.g., levofloxacin or moxifloxacin); cipro: antipseudomonal fluoroquinolone, e.g., ciprofloxacin: T/S, trimethoprim/sulfamethoxazole; rif: rifamp(ic)in. ** Rifamp(ic)in: because it is associated with higher risk of adverse events and its use is restricted in some countries, it may be most appropriately used for treating osteomyelitis or metal implant related infections. [a] Refers to isolates from an infected foot ulcer, not just colonization at another site. [b] Given at usual recommended doses for serious infections. Where more than one agent is listed, only one of them should be prescribed, unless otherwise indicated. Consider modifying doses or agents selected for patients with comorbidities such as azotemia, liver dysfunction, obesity. [c] Oral antibiotic agents should generally not be used for severe infections, except as follow-on (switch) after initial parenteral therapy.

Recommendation 19: Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy with the goal of reducing the risk of infection or promoting ulcer healing. (Strong; Low)

Rationale: There are no convincing data to support the concept that prescribing antibiotic therapy for clinically uninfected ulcers either accelerates healing or reduces the risk of developing clinically apparent infection.[144] One study of 77 patients with an uninfected DFU followed with repeated cultures found that no culture parameter demonstrated predictive value for any DFU outcomes.[145]

It may sometimes be difficult to know if a diabetic foot ulcer is infected, especially in the presence of co-morbidities such as peripheral neuropathy or peripheral artery disease. For this reason, some clinicians accept "secondary" signs or symptoms, such as friable granulation tissue, ulcer undermining, foul odor, or increase in amount of exudate as evidence of infection. All open ulcers will harbor microorganisms, including ones that are potentially pathogenic, and some evidence suggests these may impair healing. And, clinically uninfected ulcers may become infected during the long time it takes for them to heal. For these (and other) reasons many clinicians prescribe antibiotic therapy for clinically uninfected ulcers. But, there are no convincing data to support that this is beneficial. Furthermore, as about half of all DFUs are clinically uninfected at presentation, this could result in a substantial exposure of patients to potentially unnecessary and often harmful antibiotic therapy. We strongly believe that for patients with a clinically uninfected ulcer the potential harms (to the patient, the health care system and society as a whole) of antibiotic therapy (adverse effects of antibiotic therapy, inconvenience to the patient, cost for the drug, likelihood of driving antibiotic resistance) clearly outweigh any theoretical benefits.

SURGICAL TREATMENT AND OSTEOMYELITIS

PICO 7a: In a person with diabetes and osteomyelitis of the foot, are there circumstances in which non-surgical (antibiotic only) treatment is as safe and effective (in achieving remission) as surgical treatment?

Recommendation 20: Non-surgeons should urgently consult with a surgical specialist in cases of severe infection, or of moderate infection complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess or compartment syndrome, or severe lower limb ischemia. (Strong; Low)

Recommendation 21:
a) In a patient with diabetes and uncomplicated forefoot osteomyelitis, for whom there is no other indication for surgical treatment, consider treating with antibiotic therapy without surgical resection of bone. (Strong; Moderate)
b) In a patient with probable diabetic foot osteomyelitis with concomitant soft tissue infection, urgently evaluate for the need for surgery as well as intensive post-operative medical and surgical follow-up. (Strong; Moderate)

Recommendation 22: Select antibiotic agents for treating diabetic foot osteomyelitis from among those that have demonstrated efficacy for osteomyelitis in clinical studies. (Strong; Low)

Recommendation 23:
a) Treat diabetic foot osteomyelitis with antibiotic therapy for no longer than 6 weeks. If the infection does not clinically improve within the first 2-4 weeks, reconsider the need for collecting a bone specimen for culture, undertaking surgical resection, or selecting an alternative antibiotic regimen. (Strong; Moderate)
b) Treat diabetic foot osteomyelitis with antibiotic therapy for just a few days if there is no soft tissue infection and all the infected bone has been surgically removed. (Weak; Low)

Recommendation 24: For diabetic foot osteomyelitis cases that initially require parenteral therapy, consider switching to an oral antibiotic regimen that has high bioavailability after perhaps 5-7 days, if the likely or proven pathogens are susceptible to an available oral agent and the patient has no clinical condition precluding oral therapy. (Weak; Moderate)

Rationale: While antibiotic therapy is necessary for DFIs, it is often not sufficient. Most patients with a DFI require some surgical treatment, ranging from minor bedside debridement or incision and drainage to major operative procedures, including resection of deep infected tissue, drainage of abscesses or infected compartments, resection of necrotic or infected bone, or revascularization. While some of these procedures can be scheduled for convenience, a few require immediate surgery. The presence or severity of deep infection is often difficult to assess and may only be identified during surgery. While there is little published evidence addressing this issue, we strongly believe the non-surgeon should consider when and how urgently to consult with a surgeon for most DFIs.

Surgical resection of infected bone has long been the standard treatment of osteomyelitis, but over the past two decades evidence from several retrospective case series[146-149], one retrospective cohort study,[150] and one prospective controlled study[151] has demonstrated that in properly selected patients antibiotic therapy alone is effective. While treatment of DFO with antibiotics without surgical resection of bone may be considered for any patient with DFO, based on published data the strongest cases for considering non-surgical treatment include patients with limited DFO of the forefoot, who are medically stable, for whom there is no other mechanical need for surgical treatment of the foot, and for whom there is an appropriate antibiotic regimen.[152] There are advantages and disadvantages to both predominantly surgical or medical therapy of DFO, so the clinician should involve the patient (and family) in this decision.[152]

In the absence of soft tissue infectious complications, such as deep abscesses, extensive necrosis or gangrene, tissue gas, or compartment syndrome, most cases of DFO do not require *urgent* surgery. Performing any required surgery as an elective procedure allows the treating team to decide which diagnostic studies are needed and to select appropriate empirical antibiotic therapy, as well as to prepare and educate the patient. This suggestion is largely based on expert opinion, as published studies have generally not stratified patients with DFO based on the presence or severity of any concomitant soft tissue infection. The few studies that have provided data on this issue have generally found that patients with DFO who had concomitant soft tissue infection (and perhaps those with peripheral artery disease) required more urgent and extensive surgery and had longer lengths of stay and worse outcomes.[153] One small study suggests that patients not requiring urgent surgery can be treated using a two-step approach for combined soft tissue and bone infection: prescribe antibiotic therapy (empiric if necessary, then adapted to culture results) for the soft tissue infection, followed by ≥2 week off antibiotic therapy, then a bone biopsy (with further treatment only if it demonstrates osteomyelitis).[154] This approach requires further study.

When prescribing antibiotic therapy for DFO the clinician must consider several issues. Penetration of antibiotic agents into bone is variable, but most classes can attain adequate levels in infected bone. We suggest administering antibiotic agents at the higher end of their recommended dosage range and usually for a total duration of treatment (see below) substantially longer than for soft tissue infection.[155] Most published studies have initially administered antibiotics parenterally, at least for a few day, but it is unclear if this is necessary. We think clinicians can prescribe initial therapy by the oral route in carefully selected patients with mild and limited soft tissue and bone infection. Many antibiotic agents have shown efficacy in treating DFO, including clindamycin, various beta-lactam beta-lactamase inhibitors (e.g., ampicillin/sulbactam) and fluoroquinolones. One antibiotic agent that may (based on limited data) be particularly effective for biofilm-related staphylococcal (generally *S. aureus*) infections such as DFO or hardware infections is rifampin (or rifampicin).[147,154] Data supporting this use is limited and rifampin must always be used cautiously (especially in patients taking multiple medications or at risk for tuberculosis) and combined with another agent to which the causative pathogen is susceptible (e.g., a fluoroquinolone). An ongoing large, multicenter US trial (VA INTREPID) is examining the role of rifampin in treating DFO.[156] Several case series, and a recent large RCT, have shown that oral antibiotic therapy (usually after at least a few days of intravenous therapy) is as effective as, safer, and less expensive than intravenous therapy for complex bone and joint infection (including DFO).[157]

The recommended duration of treatment for osteomyelitis has traditionally been 4-6 weeks, but this is based mostly on animal models and clinical experience. Some studies of DFO (and other types of osteomyelitis) have shown that therapy for longer than 6 weeks offers no additional benefit,[158] and based mostly on theoretical considerations, treatment for just 1-2 weeks should be sufficient for patients in whom all infected bone has been resected.[159] One retrospective cohort study of 1018 DFI episodes (including some with DFO) found that neither the duration of antibiotic therapy, nor the use of parenteral therapy, affected the risk of recurrence of DFI.[91] Unfortunately, there are no definitive signs or tests to inform the clinician when DFO is in remission, so long term (usually at least a year) follow-up is recommended before declaring the infection cured. If underlying conditions that predisposed to the index episode of DFO are not adequately addressed, another infection at the same site may be a new recurrence, rather than relapse. Consideration of long-term suppressive antibiotic therapy is warranted only for individuals with retained orthopedic hardware or extensive necrotic bone that is not amenable to complete debridement.

PICO 7b: In a person with diabetes and osteomyelitis of the foot who is undergoing foot surgery, is obtaining biopsy of the presumed uninfected residual bone margin useful for determining the need for additional anti-infective treatment?

Recommendation 25:
a) During surgery to resect bone for diabetic foot osteomyelitis, consider obtaining a specimen of bone for culture (and, if possible, histopathology) at the stump of the resected bone to identify if there is residual bone infection. (Weak; Moderate)
b) If an aseptically collected culture specimen obtained during the surgery grows pathogen(s), or if the histology demonstrates osteomyelitis, administer appropriate antibiotic therapy for up to 6 weeks. (Strong; Moderate)

Rationale: Several studies have shown that one-third to two-thirds of patients from whom the surgeon obtains a specimen of clinically uninfected bone (variously called "marginal", "distal" or "proximal" bone) after resection have culture or pathological evidence of residual infection.[160-164] This finding presumably means infected bone remains, requiring further antibiotic and/or surgical treatment. It is crucial that the bone specimen be collected as aseptically as possible, including using a new set of sterile instruments. A bone specimen obtained during an operation may be more likely than a percutaneous biopsy to be contaminated from adjoining infected soft tissue. The possibility that many of the positive bone cultures are false positive is supported by the substantially lower rate of positive histology on the same specimen in two studies.[160,163] Of course, cultures may also be falsely negative, especially in patients treated with antibiotics or when samples are not transported and processed appropriately. An additional problem is the lack of an agreed definition of osteomyelitis in the diabetic foot. As three studies have found that patients who had evidence of residual osteomyelitis after foot bone resection were significantly more likely to have poorer outcomes than those with negative bone biopsy results [160-162], we think it would be prudent to offer most patients with a positive bone culture further anti-infective treatment.

PICO 8: In a person with diabetes and a foot infection, does the addition of any specific adjunctive treatment to systemic antibiotic therapy improve resolution of clinical findings of infection or accelerate ulcer healing?

We define adjunctive treatments as those that are neither antibiotic nor surgical treatments, but which are often used in conjunction with these standard treatments. Many types of treatment have been proposed, but the available published evidence of their efficacy is limited and generally of very low quality.

Recommendation 26: For a diabetic foot infection do not use hyperbaric oxygen therapy or topical oxygen therapy as an adjunctive treatment if the only indication is specifically for treating the infection. (Weak; Low)

Rationale: Many diabetic foot ulcers fail to heal, and colonizing microorganisms may play a role in this process. Hyperbaric oxygen therapy (HBOT), in addition to its purported ulcer healing benefits, is also believed to have a variety of antimicrobial effects in soft tissue and bone.[165-170] Thus, it is reasonable to consider whether or not adjunctive HBOT might help cure various types of DFIs. Several organizations (some with a bias favoring using HBOT) have suggested that HBOT should be considered for treating infections (especially anaerobic), including osteomyelitis (especially if chronic or refractory).[171] A systematic review (of case reports and cohort studies) of adjunctive HBOT treatment of various forms of chronic osteomyelitis suggested it may be beneficial, but few of the studies were on DFO and the quality of available evidence was low.[172] Notwithstanding that the role of HBOT in healing diabetic foot ulcers is still controversial, only one of the many studies on patients with a diabetic foot ulcer was specifically focused on the issue of foot infections. The results of that small size, poor quality study,[173] using non-standardized methods and lacking clear definitions (including of infection), do not adequately support recommending HBOT to treat diabetic foot infections. HBOT is certainly associated with financial expense, potential adverse events and inconvenience (requiring daily treatments in a medical setting). Thus, in the absence of any substantial data to support its effect in treating either soft tissue or bone infection, nor in accelerating ulcer healing via an antimicrobial effect, we think the costs and inconvenience outweigh any theoretical benefits.

In addition to systemic HBOT, high levels of oxygen can be delivered to a wound by local or topical methods.[174] Although various methods of topical oxygen therapy have been investigated for decades, there are only a few published case reports in patients and insufficient evidence to support using this form of adjunctive treatment.[174-176]

Recommendation 27: To specifically address infection in a diabetic foot ulcer:
a) do not use adjunctive granulocyte colony stimulating factor treatment (Weak; Moderate) and,
b) do not routinely use topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative-pressure wound therapy (with or without instillation). (Weak; Low)

Rationale: Because granulocyte colony-stimulating factor (G-CSF) increases the release of neutrophil endothelial progenitor cells from the bone marrow and improves neutrophil functions, which are often impaired in people with diabetes, studies have investigated their potential role in treating infection in

diabetic foot ulcers. A Cochrane Database Systematic review updated in 2013 concluded that treatment with G-CSF does not appear to increase the likelihood of resolution of infection or healing of the foot ulcer.[177] We found no relevant published studies on this topic since this review. While G-CSF may reduce the need for surgical interventions, especially amputations, or the duration of hospitalization, it is not clear which patients might benefit and G-CSF preparations are not generally available and are expensive.

The increasing problem of infection with antibiotic resistant organisms demands development of alternative treatments to standard antibiotic therapy. Various types of antiseptics have been used to treat diabetic foot ulcers, but the available evidence does not support any beneficial effect for most of these.[126] Silver has been shown to have an antibacterial effect and topical silver-containing treatments (creams, dressings, etc.) are widely used for infected diabetic foot ulcers. While silver compounds may offer some benefits in ulcer healing,[178] there is little evidence (including from several systematic reviews) to support their effectiveness in treating or preventing ulcer infection.[179] Several small studies have, however, demonstrated anti-infective benefits for some antiseptic agents (e.g., cadexomer iodine, hypochlorous solutions) in infected DFUs. There is evidence that dressings with silver, cadexomer iodine and hypochlorous solutions reduce microbial load in the ulcers.[180,181] The available evidence is insufficient to establish whether or not silver-containing dressings or topical agents promote ulcer healing or prevent ulcer infection. To avoid promoting the development of resistance, we suggest avoiding using topical antibiotic agents that can also be administered systemically.

Honey has long been used in the treatment of various types of ulcers, including diabetic foot ulcers, for its apparent ulcer healing effects. This may at least be partly mediated by its anti-bacterial, anti-oxidant and anti-inflammatory properties, in addition to its effects on osmolarity, acidifying pH and increasing growth factors.[182] Topical honey appears to be safe and is relatively inexpensive. Some studies have demonstrated antibacterial effects of honey on various microorganisms obtained from diabetic foot ulcers, either *in vitro* or in a wound, but there are no published studies clearly demonstrating efficacy against clinical findings of infection.[183,184] In some populations, especially in low-income countries, use of various home remedies for treating DFIs has been reported. While some may have beneficial effects (e.g., chloramines,[185] *Kalanchoe pinnata*,[186] others are clearly harmful,[187] either by their direct effects or by patients delaying seeking more appropriate treatment.

Bacteriophages have been used clinically for over 100 years, but the available data on efficacy (mostly from Eastern Europe, much of it *in vitro*) are limited. The few publications on using bacteriophages are low quality case series lacking a control group[188,189] that suggest it may be safe and effective for some types of infected ulcers, but commercial products are limited and unavailable in many countries. Although the incidence of infection with extensive, or even complete, antimicrobial resistance is rising in some contries, antibiotic therapy is still preferable given the sparse available evidence for bacteriophages. Antimicrobial therapy with bacteriophages might, however, be an option in the future.

Negative pressure wound therapy (NPWT) involves the application of a special wound dressing attached to a vacuum suction machine that aspirates wound and tissue fluid from the treated area into a canister.[190] Some evidence demonstrates that NPWT results in more pro-angiogenic and anti-inflammatory molecular conditions in wounds.[191] NPWT with instillation (NPWTi) is a system incorporating both instillation (using one of various types of sterile fluids) and aspiration that is intended

to cleanse, and possibly disinfect, wounds.[192] While many published studies have demonstrated the safety and wound healing efficacy of NPWT/NPWTi, the quality of most is relatively low, few have addressed diabetic foot complications[193] and none have specifically addressed if there was benefit in resolving evidence of wound infection. NPWT is widely available, but in most countries rather expensive.

Several other types of adjunctive therapy look promising but based on limited data and lack of wide availability it is difficult to offer a recommendation on any at this time. One example is photodynamic therapy (PDT), which uses a combination of a photosensitizing drug and visible light, and has been shown *in vitro* to kill various bacteria, fungi and viruses. Almost all photosensitizers show photodynamic activity against gram-positive bacteria, but activity against gram-negative bacteria is limited to certain cationic photosensitizers. A few small published studies of low quality have reported that PDT lowered bacterial load, cured infections and may have helped reduce lower extremity amputations.[194-197] While PDT appears to be safe and well-tolerated, commercial products are not yet available in most countries and it is unclear if using PDT without systemic antibiotic therapy will be possible for most patients.

KEY CONTROVERSIES IN DIABETIC FOOT INFECTION

There is still uncertainty regarding many areas concerning the management of the infectious aspects of the diabetic foot. We have selected some that with think may be in most need of further studies.

1. *How should clinicians monitor treatment of a DFI and determine when infection has resolved?*
   This is an important unmet need as it serves as one means to limit unnecessarily prolonged antibiotic therapy.
2. *What is the optimal duration of antimicrobial treatment for diabetic foot osteomyelitis?*
   Since infection of bone is more difficult to eradicate than just soft tissue, the recommended duration of antibiotic therapy is more prolonged, but we do not know the most appropriate duration.
3. *How should clinicians adapt approaches to DFI management in low-income countries?*
   The rise in incidence of DFIs in some of these countries is steep and with their constrained resources, finding optimal approaches, without recommending second-class care, is key to improve outcomes.
4. *When, and which, imaging studies should clinicians order for a patient with a DFI?*
   Advanced imaging studies can be expensive and time-consuming, and may delay appropriate treatment. Thus, evaluating their cost-effectiveness to help optimize use could improve DFI (and especially DFO) management.
5. *In diabetic foot osteomyelitis cases, is obtaining a specimen of residual or marginal bone after surgical resection useful for deciding which patients need further antibiotic or surgical treatment?*
   Several studies suggest that a substantial minority of patients who have had surgical resection of infected bone have remaining infection in residual bone. Determining the best way to identify these cases and whether or not further treatment improves outcomes could help inform management.

6. *When is it appropriate to select primarily medical versus primarily surgical treatment for diabetic foot osteomyelitis?*
   While the results of a variety of types of trials inform this choice, an additional large, well-designed prospective study is needed to more definitively answer this question.
7. *Is there a definition of, and practical clinical use for, the concept of wound "bacterial bioburden"?*
   This term is widely used in the wound healing community (and by industry) but has no agreed upon definition. Deciding if it has value, and standardizing the definition, could help industry develop useful products and clinicians to know which to employ for selected clinical situations.
8. *What is the value and proper interpretation of molecular (genotypic) microbiological testing for DFI?*
   The era of molecular microbiology is inexorably expanding, but it is crucial that we have studies to provide data to help clinicians understand the value of information derived from these techniques.
9. *Are there any approaches (methods or agents) to topical or local antimicrobial therapy that are effective as either sole therapy for mild infections or adjunctive treatment for moderate or severe infections?*
   Although there are many types of local or topical treatment available there is no convincing data to support if and when they should be used. These approaches, especially if they support using agents that are not administered systemically, could reduce the accelerating problem of antibiotic resistance.
10. *How can clinicians identify the presence of biofilm infection and what is the best way to treat it?*
    Studies suggest most chronic wound infections involve microorganisms in difficult to eradicate biofilm phenotype, but we currently have no clear information on how to diagnose or treat these infections.

POSTSCRIPT

Foot infections in persons with diabetes certainly can be associated with poor outcomes, especially amputation. In a large prospective study in the UK of patients with an infected DFU, after one year of follow-up the ulcer had healed in only 46%, and it recurred in 10% of those patients.[5] Among these patients with an infected DFI, 17% underwent a lower extremity amputation, 6% had a lower extremity revascularization and 15% died. Those with a DFU present for >2 months or with a higher IDSA/IWGDF score had worse outcomes. In a recent review of over 150,000 patients hospitalized for a DFI in the US, over one-third underwent a lower extremity amputation and almost 8% had a lower-extremity revascularization procedure.[6] But, studies of patients enrolled in antibiotic trials and our own experience with patients treated by interdisciplinary teams at expert centers suggest that better outcomes are possible. We think that following the principles of diagnosing and treating DFIs outlined in this guideline can help clinicians to provide better care for these at-risk patients. We also encourage our colleagues, especially those working in diabetic foot clinics or hospital wards, to consider developing some forms of surveillance (e.g., registries, pathways, interdisciplinary group meetings) to monitor and attempt to improve their outcomes in patients with DFIs.

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at: *iwgdfguidelines.org/about-iwgdf-guidelines/biographies*

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published online, this current version will be replaced.

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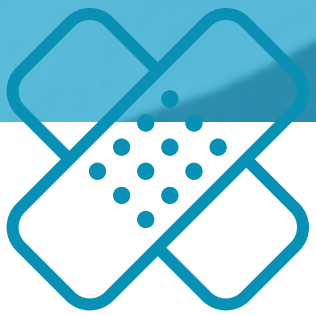
IWGDF Guideline on interventions to enhance healing of foot ulcers in persons with diabetes



Part of the 2019 IWGDF Guidelines on the Prevention and Management of Diabetic Foot Disease

IWGDF Guidelines

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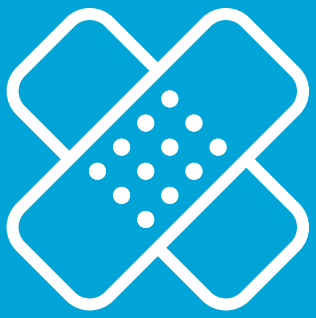

KEYWORDS

diabetic foot; foot ulcer; guidelines; wound healing; dressing

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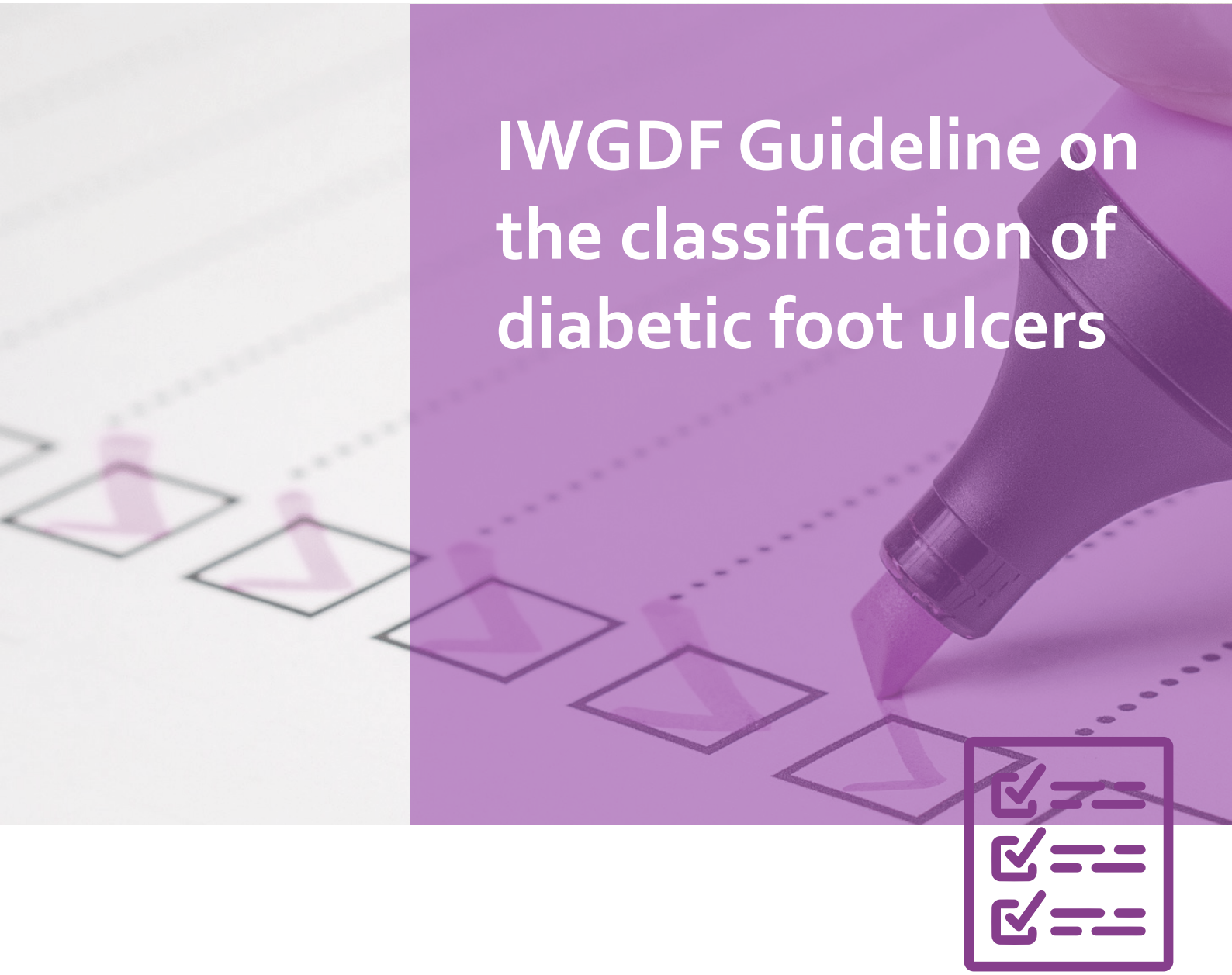
LIST OF RECOMMENDATIONS

1. Remove slough, necrotic tissue and surrounding callus of a diabetic foot ulcer with sharp debridement in preference to other methods, taking relative contraindications such as pain or severe ischemia into account. (GRADE Strength of recommendation: Strong; Quality of evidence: Low)
2. Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)
3. Do not use dressings/applications containing surface antimicrobial agents with the sole aim of accelerating the healing of an ulcer. (Strong; Low)
4. Consider the use of the sucrose-octasulfate impregnated dressing in non-infected, neuro-ischaemic diabetic foot ulcers that are difficult to heal despite best standard of care. (Weak; Moderate)
5. Consider the use of systemic hyperbaric oxygen therapy as an adjunctive treatment in non-healing ischaemic diabetic foot ulcers despite best standard of care. (Weak; Moderate)
6. We suggest not using topical oxygen therapy as a primary or adjunctive intervention in diabetic foot ulcers including those that are difficult to heal. (Weak; Low)
7. Consider the use of negative pressure wound therapy to reduce wound size, in addition to best standard of care, in patients with diabetes and a post-operative (surgical) wound on the foot. (Weak; Low)
8. As negative pressure wound therapy has not been shown to be superior to heal a non-surgical diabetic foot ulcer, we suggest not using this in preference to best standard of care. (Weak; Low)
9. Consider the use of placental derived products as an adjunctive treatment, in addition to best standard of care, when the latter alone has failed to reduce the size of the wound. (Weak; Low)
10. We suggest not using the following agents reported to improve wound healing by altering the wound biology: growth factors, autologous platelet gels, bioengineered skin products, ozone, topical carbon dioxide and nitric oxide, in preference to best standard of care. (Weak; Low)
11. Consider the use of autologous combined leucocyte, platelet and fibrin as an adjunctive treatment, in addition to best standard of care, in non-infected diabetic foot ulcers that are difficult to heal. (Weak, Moderate)
12. Do not use agents reported to have an effect on wound healing through alteration of the physical environment including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to best standard of care. (Strong; Low)
13. Do not use interventions aimed at correcting the nutritional status (including supplementation of protein, vitamins and trace elements, pharmacotherapy with agents promoting angiogenesis) of patients with a diabetic foot ulcer, with the aim of improving healing, in preference to best standard of care. (Strong; Low)

IWGDF Guideline on the classification of diabetic foot ulcers



Part of the 2019 IWGDF Guidelines
on the Prevention and Management
of Diabetic Foot Disease

IWGDF
Guidelines

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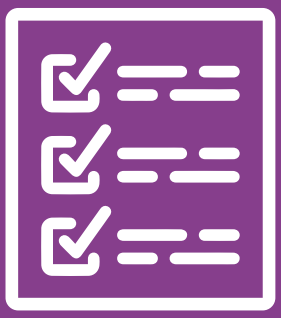

KEYWORDS

diabetic foot; foot ulcer; guidelines; classification

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has been publishing evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This publication represents a new guideline addressing the use of classifications of diabetic foot ulcers in routine clinical practice and reviews those which have been published. We only consider systems of classification used for active diabetic foot ulcers and do not include those that might be used to define risk of future ulceration.

This guideline is based on a review of the available literature and on expert opinion leading to the identification of eight key factors judged to contribute most to clinical outcomes. Classifications are graded on the number of key factors included as well as on internal and external validation, and the use for which a classification is intended.

Key factors judged to contribute to the scoring of classifications are of three types: *patient related* (end-stage renal failure), *limb-related* (peripheral artery disease and loss of protective sensation) and *ulcer-related* (area, depth, site, single or multiple and infection). Particular systems considered for each of the following five clinical situations: (i) communication among health professionals, (ii) predicting the outcome of an individual ulcer, (iii) as an aid to clinical decision-making for an individual case, (iv) assessment of a wound, with/without infection and peripheral artery disease (assessment of perfusion and potential benefit from revascularisation) and (v) audit of outcome in local, regional or national populations.

We recommend: (i) for communication among health professionals the use of the SINBAD system; (ii) no existing classification for predicting outcome of an individual ulcer; (iii) the Infectious Diseases Society of America/International Working Group on the Diabetic Foot (IDSA/IWGDF) classification for assessment of infection; (iv) the WIfI (Wound, Ischemia, foot Infection) system for the assessment of perfusion and the likely benefit of revascularisation; and (v) the SINBAD classification for the audit of outcome of populations.

RECOMMENDATIONS

1. In a person with diabetes and a foot ulcer, use the SINBAD system for communication among health professionals about the characteristics of the ulcer. (Strength of recommendation: Strong; Quality of evidence: Moderate)
2. Do not use any of the currently available classification/scoring systems to offer an individual prognosis for a person with diabetes and a foot ulcer. (Strong; Low)
3. In a person with diabetes and an infected foot ulcer, use the IDSA/IWGDF infection classification to characterise and guide infection management. (Weak; Moderate)
4. In a person with diabetes and a foot ulcer who is being managed in a setting where appropriate expertise in vascular intervention is available, use WIfI scoring to aid decision making in the assessment of perfusion and likelihood of benefit from revascularisation. (Weak; Moderate)
5. Use the SINBAD system for any regional/national/international audits to allow comparisons between institutions on the outcomes of patients with diabetes and an ulcer of the foot. (Strong; High)

INTRODUCTION

It is estimated that diabetes affects 422 million people worldwide, 8.5% of the adult population, and the increase in prevalence is occurring at a faster rate in low- and middle- income countries (1). Around one in four people with diabetes will develop a diabetic foot ulcer (DFU) in their lifetime (2). The risk of developing a DFU, and the factors associated with development of complications such as hospitalisation, lower extremity amputation (LEA) and mortality may be patient related, limb related or ulcer related. The impact of individual factors on the outcome of DFUs will vary across communities and across countries. For example, infection will more strongly influence outcome in countries where antibiotics are not readily available, whereas ischaemia will have a greater impact in countries where peripheral artery disease is more prevalent. Of note, 80% of people with diabetes live in low- and middle- income countries (1), where many diagnostic tools are not easily available and are not expected to become so in the near future.

In our review (3), we found a large number of proposed classification and scoring systems for DFUs, which suggests that none is ideal for routine use in populations worldwide. This perhaps also reflects the differing purpose of classification and scoring systems: for communication among health professionals (independent of the level of clinical care), for clinical prognostication and guidance of treatment, and for clinical audit of outcomes across units and populations. With this in mind a classification system may be defined as a descriptive tool, dividing patients into groups but not necessarily relating this to risk of adverse outcome, whereas a scoring system will attribute a scale by which the contribution of factors within the system will be amalgamated to produce an overall (usually numerical) score with increased score being associated with higher risk of adverse outcomes.

The intended use of a classification or scoring system will influence its content. A system designed to assess risk or prognosis for a person with diabetes and an active ulcer on their foot will necessarily require more detailed information to provide a personalised outcome. By contrast a system aiming to

compare outcomes between populations, in which there is a need to minimise the requirement for additional data input by busy clinicians while including factors that influence outcome across differing populations, should have a less burdensome data collection and processing requirement if it is to be taken up by clinicians treating DFUs. Classifications used for communication between health professionals should ideally be simple to memorise and use. The aim of this guideline is to provide recommendations on the use of classifications of diabetic foot ulcers for various purposes.

METHODS

This guideline has been compiled based on our review (3), and following consideration of recent review articles on DFU classification systems (4-8). To identify factors associated with DFU outcome (healing, hospitalisation, amputation, mortality), and to select the most pertinent, we searched for reports of large clinical cohorts (9-15). A consensus was then reached, based upon expert opinion, of eight factors that were consistently and meaningfully related to DFU outcomes that would ideally constitute the basis of a classification system:

1. Patient factors: End stage renal disease
2. Limb factors: Peripheral artery disease; loss of protective sensation
3. Ulcer factors: Area; depth; location (forefoot/hindfoot); number (single/multiple); infection.

For determining the quality of evidence, we conducted a review (3) and assessed the presence and number of reliability (namely inter-observer agreement) studies, and internal and external validation studies for one or more clinical outcomes. Consistency and precision of the reported results was determined.

For providing the strength of recommendations, we analysed the quality of evidence, the complexity and components of the classification, the number of variables included that correspond to those eight factors selected by the group as being the most relevant, and if the classification corresponds to the purpose defined by its creators.

By consensus, we defined the following five clinical scenarios considered to be the most frequently encountered requiring classification of ulcers of the foot in patients with diabetes:

1. Communication among health professionals about the characteristics of a diabetic foot ulcer
2. To assess an individual's prognosis with respect to the outcome of their diabetic foot ulcer
3. To guide management in the specific clinical scenario of a patient with an infected diabetic foot ulcer
4. To aid decision-making as to whether a patient with a diabetic foot ulcer would benefit from revascularisation of the index limb
5. To support regional/national/international audit to allow comparisons between institutions

RECOMMENDATIONS AND RATIONALE

PICO: In individuals with an active diabetic foot ulcer, which classification system should be used in communication among health professionals to optimise referral?

Recommendation 1: In a person with diabetes and a foot ulcer, use the SINBAD system for communication among health professionals about the characteristics of the ulcer. (Strength of recommendation: strong; Quality of evidence: moderate)

Rationale: For a classification system to be used by all health professionals managing people with a diabetic foot ulcer, it should be quick and simple to apply, and require no specialist equipment. For it to be useful to the receiving specialist, it should contain appropriate information to allow triage of patients to ensure timely review. Such a classification system should also be confirmed to have a high inter-observer reliability.

Although all people with diabetes and an active DFU should be referred to a multidisciplinary diabetic foot team without delay, factors necessitating urgent review include the size of the ulcer (area and depth), presence of infection and ischaemia. Any classification system for use as a triage tool will therefore need to include these criteria without the need for measurements requiring specialist equipment (e.g. toe pressures, $TcPO_2$).

Classification systems which have been broadly externally validated for ulcer healing and lower extremity amputation (LEA) occurrence include Meggitt-Wagner, SINBAD, University of Texas and WIfI (3). Whilst simple to use, the Meggitt-Wagner classification does not allow for identification of PAD or infection, and whilst it has been validated for both healing and LEA (16-23), there are also concerns regarding its consistency (24). Thus, its use as a triage tool is limited. WIfI requires the use of specialist measurement of foot perfusion indices and although it therefore contains most of the key variables to allow for triage of people with a DFU, it is not ideal for use in primary/community care. The University of Texas system classifies DFUs using a bi-dimensional 4 x 4 matrix, according to depth (Grade 0, 1, 2, 3) and presence of infection (Stage B), ischaemia (Stage C) or both (Stage D) (25). The original publication (25) described a combination of clinical signs and symptoms, plus one or more non-invasive criteria (transcutaneous oxygen measurements, ankle-brachial index, or toe systolic pressure) to assess perfusion, and so is less useful for communication among health professionals, as such equipment may not be available. In addition, loss of protective sensation and size (area) are not included in this classification.

The SINBAD system grades area, depth, sepsis, arteriopathy, and denervation plus site as either 0 or 1 point (see below), creating an easy to use scoring system that can achieve a maximum of 6 points (26), as follows:

Table 1. SINBAD System

Category	Definition	Score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischemia	Pedal blood flow intact: at least one palpable pulse	0
	Clinical evidence of reduced pedal flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial infection	None	0
	Present	1
Area	Ulcer < 1 cm^2	0
	Ulcer ≥ 1 cm^2	1
Depth	Ulcer confined to skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon or deeper	1
Total possible score		6

The SINBAD system is simple and quick to use, requiring no specialist equipment beyond clinical examination alone, and contains the necessary information to allow for triage by a specialist team. It would therefore be feasible to employ this classification system in localities where such equipment, including non-invasive measures of perfusion, are not readily available, which is the case for the majority of geographic settings where DFUs occur. If used for the purpose of communication between health professionals, it is important to use the individual clinical descriptors not merely the total score. This classification has been validated for both ulcer healing and amputation prediction (12, 13, 16-20, 22, 26), presenting good results, and has good reliability (24, 27). Thus, the quality of the evidence was considered to be moderate.

PICO: In individuals with an active diabetic foot ulcer, which classification/scoring system should be considered when assessing an individual patient to estimate their prognosis?

Recommendation 2: Do not use any of the currently available classification/scoring systems to offer an individual prognosis for a person with diabetes and a foot ulcer. (Strong; Low)

Rationale: We identified eight factors from large clinical DFU cohort studies associated with non-healing, amputation and death: end-stage renal failure; peripheral artery disease; loss of protective sensation; area; depth; location (forefoot/hindfoot); single/multiple ulcers; and infection (3). No existing classification system includes all eight of these factors.

To be used as a prognostic tool, a classification system needs to be complex enough to provide individualised outcome prediction, yet quick to use within a busy clinical service, ideally not requiring

measurements in addition to those performed for routine clinical care. The classification also needs to be validated for the population in which its use is proposed, as the dominant factors for poor outcomes in DFU vary worldwide. This validation should include how well the classification system predicts both ulcer healing and risk of amputation. The system should also have good inter-observer and intra-observer reliability to provide consistent prognostic outcomes and allow for monitoring of progress with intervention. None of the systems met these criteria, and so further research may be required to either appropriately validate an existing classification or to develop a classification/scoring system according to these criteria.

Meggitt-Wagner, PEDIS, SINBAD, SEWSS, University of Texas and WIfI have been externally validated for prediction of both ulcer healing and LEA within cohorts (3), but not at an individual level. Further, validation of WIfI has been largely performed in cohorts of patients with severe limb ischaemia across several continents, with one cohort specific to DFU and five additional papers including >75% patients with DFU (28-32).

PEDIS was originally developed as a descriptive classification for use in research, and not designed for prognostic purposes. It does not include patient factors (end-stage renal disease), or either the location or the number of foot ulcers. PEDIS has been validated in two studies for both wound healing and a composite endpoint of non-healing, amputation and death (16, 17). It has also been demonstrated to have good reliability (27). Despite this, it is not a scoring system.

The Meggitt-Wagner classification is simple, but there are concerns regarding its consistency. It does not include reference to loss of protective sensation, infection and ischaemia and thus its utility may vary between countries. It is also too simplistic to provide prognostic information at an individual level, including only two of the eight factors identified by the expert panel.

University of Texas is a descriptive classification, rather than a scoring system, containing only three of the eight prognostic factors identified by the expert panel. Good reliability has been reported (24, 27).

SINBAD and SEWSS are scoring systems designed to provide prognostic information. Both have been externally validated for prediction of wound healing and LEA occurrence on more than one continent (12, 19, 20, 26, 33), and both have good reliability (27, 34). Both also contain six of the eight prognostic factors identified by the expert panel. The SEWSS classification is complex and time consuming to complete. Although studies have shown good reliability, in a comparison of 11 classifications scores for LEA, SEWSS had one of the lowest areas under the curve on ROC analysis for discrimination between healing and non-healing outcomes (20).

The quality of evidence for the prediction of DFU outcomes is weak and not directly applicable to the accuracy of a classification system in predicting individual patient outcomes, leading to our strong recommendation against the use of any system for prediction of individual patient outcomes.

PICO: In persons with an active diabetic foot ulcer, can any classifications/scoring system aid decision-making in specialty areas to improve healing and/or reducing amputation risk?

Recommendation 3: In a person with diabetes and an infected foot ulcer, use the IDSA/IWGDF infection classification to characterise and guide infection management. (Weak; Moderate)

Recommendation 4: In a person with diabetes and a foot ulcer who is being managed in a setting where appropriate expertise in vascular intervention is available, use WIfI scoring to aid decision making in the assessment of perfusion and likelihood of benefit from revascularisation. (Weak; Moderate)

Rationale: Only two classification systems have been developed that provide stratification that aligns to clinical decision-making: IWGDF/IDSA and WIfI (3). Of note: whilst the IWGDF/IDSA is incorporated into the WIfI, in situations where only infection is being assessed and equipment is not available to use WIfI, the IWGDF/IDSA infection classification can stand alone.

IWGDF/ISDA classification consists of four grades of severity for diabetic foot infection (See Table 2). It was originally developed as part of the PEDIS classification for research purposes and is used as a guideline for management, in particular to identify which patients required hospital admission for intravenous antibiotics. Although the components of each grade are complex, and a previous study has shown only moderate reliability, the criteria are widely used. Unsurprisingly, given the context of the IWGDF/IDSA classification, it is a strong predictor of the need for hospitalisation (35). However it has also been validated for risk of both major and minor amputation (20, 24).

Both classifications have been validated on multiple occasions for various clinical outcomes with consistent results and presented adequate reliability values. So, the quality of the evidence was considered to be strong. Due to their complexity and limited assessment in different populations and contexts, however, a weak strength of recommendation was given.

Table 2. IWGDF/IDSA System

Clinical manifestations	Infection severity	PEDIS grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of ≥2 manifestations of inflammation (purulence, or erythema, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤2cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥1 of the following characteristics: cellulitis extending >2cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

WIfI (See Table 3) uses a combination of scores for wound (based on depth of ulcer or extent of gangrene), ischaemia (based on ankle pressure, toe pressure or $TcPO_2$) and foot infection (based on IWGDF/IDSA criteria) to provide a one-year risk for amputation and one-year benefit for revascularisation, both stratified as very low, low, moderate or high. This has benefit over perfusion pressures alone by including associated wound and infection criteria to provide a more holistic wound overview in revascularisation decision-making. Whilst WIfI has not been subject to reproducibility assessment in a DFU cohort, it has impressive reproducibility in a PAD setting (32). It has been validated in only one cohort exclusively of patients with an active DFU, but has been shown in multiple validation studies to predict outcomes relevant to this clinical group such as healing, time to healing, need for revascularisation, LEA, LEA-free-survival and mortality (28-31). Both need for revascularisation and timing of revascularisation can be guided by the combination of risk estimate for amputation and benefit estimate for revascularisation.

Table 3. WIfI System

Wound Grade	DFU	Gangrene
0	No ulcer	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
	Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard transmetatarsal amputation (TMA) ± skin coverage.	
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis 6 calcaneal involvement
	Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect	

Ischemia Grade	Ankle-Brachial Index	Ankle systolic pressure (mmHg)	Toe Pressure, Transcutaneous oxygen pressure (mmHg)
0	≥ 0.80	>100	≥60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤0.39	<50	<30

Foot Infection Grade	Clinical manifestations
0	No symptoms or signs of infection Infection present, as defined by the presence of at least 2 of the following items: • Local swelling or induration • Erythema >0.5 to ≤2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
2	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 (as described below)
3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg • White blood cell count >12,000 or <4000 cu/mm or 10% immature (band) forms

SIRS = systemic inflammatory response signs

PICO: In persons with an active diabetic foot ulcer, which classification/scoring system should be considered for regional/national/international audit to allow comparisons between institutions?

Recommendation 5: Use the SINBAD system for any regional/national/international audits to allow comparisons between institutions on the outcomes of patients with diabetes and an ulcer of the foot. (Strong; High)

Rationale: In this document, the term 'audit' refers to characterisation of all DFUs managed in a particular area or centre, in order to compare outcomes with a reference population or national

standard, and does not allude to the financial implications of care. Ideally one classification system should be used internationally to allow comparisons of outcomes. In order to do this, such a classification system would need to accurately assess DFU severity across the spectrum of aetiologies. Thus, healthcare systems where peripheral artery disease is a major contributor to non-healing and LEA can be compared with health care systems where infection is a major cause of LEA due to limited antibiotic availability. Further, the system should be simple to use, and require no specialist equipment, to allow the necessary clinical data to be collected routinely from all patients in all health care settings spanning the spectrum from low to high resource availability. Currently, SINBAD is the only classification system that meets all of these criteria. It has been validated for healing and LEA in diverse DFU populations (12, 19, 20, 26, 33), and has been shown to be acceptable to clinicians from use in the UK National Diabetes Foot Care audit of over 20,000 DFUs (12). For these reasons, the quality of evidence was high and strength of recommendation was considered strong.

CONSIDERATIONS

- We were unable to recommend any of the currently available classification/ scoring systems to provide an individual prognosis, which would guide management and could help the patient/family. Future research should be directed to develop and validate a simple reproducible classification system for the prognosis of the individual person with a diabetic foot ulcer, their index limb or their ulcer.
- None of the currently validated systems contained all 8 of the important prognostic clinical features identified as part of the review process. Future research should be undertaken to establish whether increasing the complexity of classifications by the addition of features such as ESRD, single/multiple ulcers, more detailed site of ulcers (such as plantar/dorsum) or more detailed measures of limb ischaemia significantly improves the validity of the system to predict the outcome, without compromising reliability or clinical utility.
- We consider that there may never be a single DFU classification system, since the specification of any classification will depend heavily on its purpose and clinical setting.

CONCLUDING REMARKS

Classification of DFUs is of paramount importance in daily practice. It helps in communication between health professionals, assessment of prognosis and choice of best treatment strategy and audit of clinical outcomes across units and populations.

The decision on which classification to use should rely on the included variables, available evidence around its validity and reliability, associated clinical outcomes and purpose. We encourage clinicians to use the classifications described in this guidance document. To do so, specific diagnostic tools are required and standardised definitions should be used.

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at: *iwgdfguidelines.org/about-iwgdf-guidelines/biographies*.

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published, this current version will be replaced.

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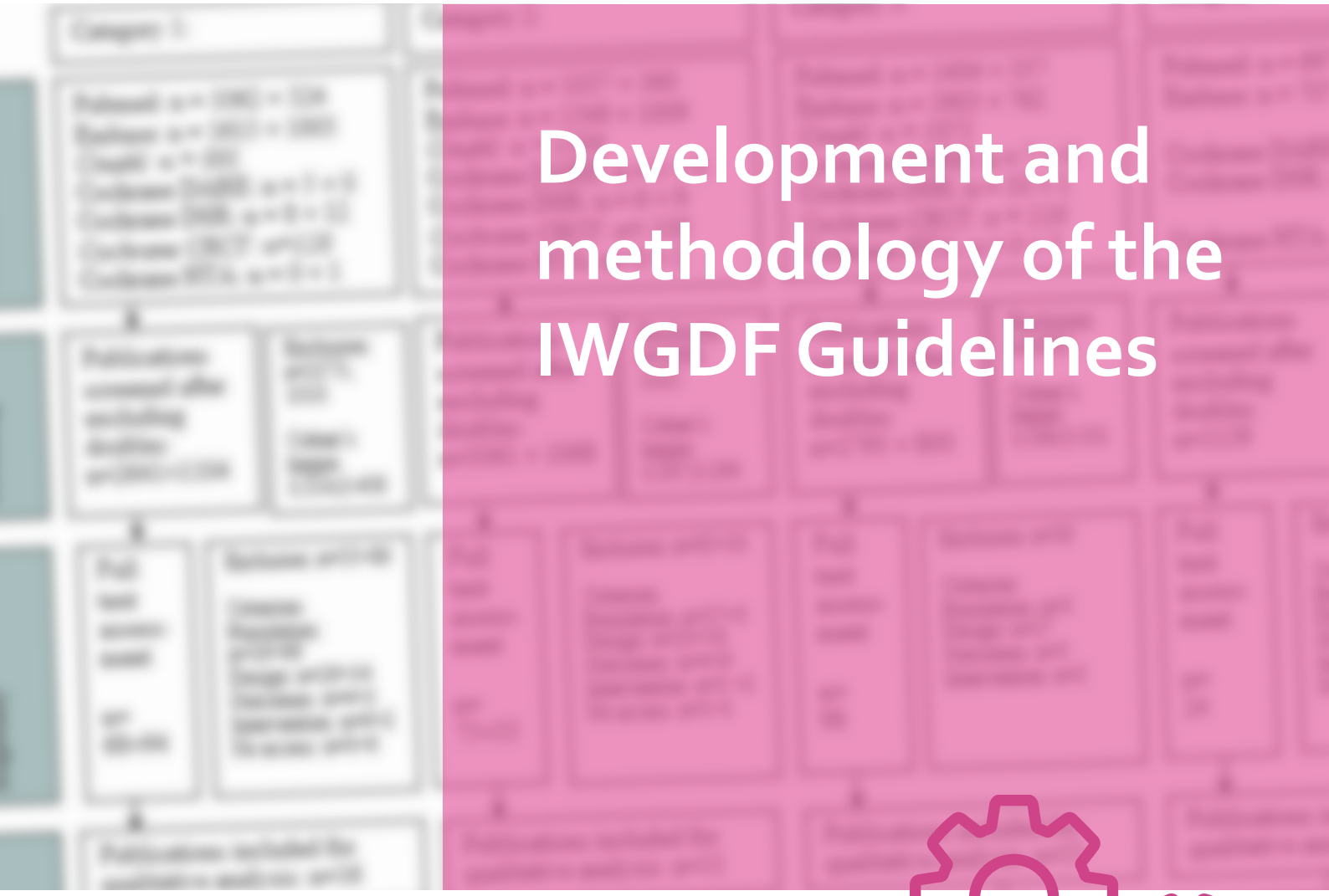
Development and methodology of the IWGDF Guidelines



Part of the 2019 IWGDF Guidelines
on the Prevention and Management
of Diabetic Foot Disease

IWGDF
Guidelines

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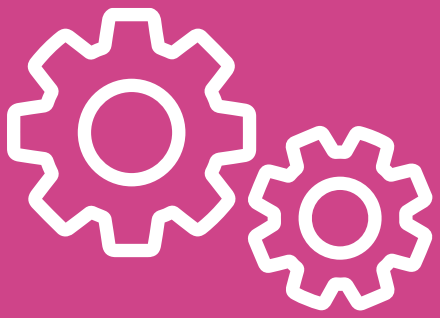

KEYWORDS

guideline development; GRADE; IWGDF; systematic review; evidence-based; diabetic foot; foot ulcer

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ABSTRACT

Diabetic foot disease is a source of major patient suffering and societal costs. Investing in evidence-based international guidelines on diabetic foot disease is likely among the most cost-effective forms of healthcare expenditure, provided the guidelines are goal-focused, evidence-based and properly implemented.

The International Working Group on the Diabetic Foot (IWGDF) has published and updated international guidelines since 1999. The 2019 updates are based on formulating relevant clinical questions and outcomes, rigorous systematic reviews of the literature, and as specific, clear, and unambiguous as possible recommendations and their rationale, all using the Grading of Recommendations Assessment Development and Evaluation (GRADE) system.

We herein describe the development of the 2019 IWGDF Guidelines on the prevention and management of diabetic foot disease, which consist of six chapters, each prepared by a separate working group of international experts. These documents provide guidelines related to diabetic foot disease on: prevention; offloading; peripheral artery disease; infection; wound healing interventions; and, classification of diabetic foot ulcers. Based on these six chapters, the IWGDF Editorial Board also produced a set of practical guidelines. Each guideline underwent extensive review by the members of the IWGDF Editorial Board as well as independent international experts in each field.

We believe that if healthcare professionals follow the recommendations of the 2019 IWGDF guidelines, and when necessary adopt them to local circumstances, it will result in improved prevention and management of diabetic foot disease and a subsequent worldwide reduction in the patient and societal burden it causes.

INTRODUCTION

The global prevalence of diabetes mellitus was 425 million in 2017 and is estimated to rise to 629 million by 2045; 75% of these people live in low- or middle-income countries (1). Diabetic foot disease is a source of major patient suffering and societal costs. The frequency and severity of foot problems in persons with diabetes varies by region, largely due to differences in socio-economic conditions and standards of foot care (2). Foot ulcers are the most recognizable problem, with a yearly incidence of around 2%-4% in higher income (2), likely even higher in lower income countries, and an estimated lifetime prevalence of 19%-34% (3).

The most important factors underlying the development of foot ulcers are peripheral neuropathy, foot deformities related to motor neuropathy, minor foot trauma, and peripheral artery disease (3). These conspire to put the patient at risk for skin ulceration, making the foot susceptible to infection-- an urgent medical problem. Only two-thirds of diabetic foot ulcers will eventually heal (4), and up to 28% may result in some form of lower extremity amputation (5). Every year, more than 1 million people with diabetes lose at least a part of their leg due to diabetic foot disease. This translates into the estimate that every 20 seconds a lower limb is lost to diabetes somewhere in the world (6).

Diabetic foot disease not only represents a personal tragedy for the affected patient, it also affects that person's family and places a substantial financial burden on healthcare systems and society in general. In low-income countries, the cost of treating a complex diabetic foot ulcer can be equivalent to 5.7 years of annual income, potentially resulting in financial ruin for the patient and their family (7). Investing in evidence-based, internationally appropriate guidelines on diabetic foot disease is likely among the most cost-effective forms of healthcare expenditure, provided it is goal-focused and properly implemented (8, 9).

International Working Group on the Diabetic Foot

The International Working Group on the Diabetic Foot (IWGDF; *www.iwgdfguidelines.org*), founded in 1996, consists of experts from almost all disciplines involved in the care of patients with diabetic foot disease. The IWGDF aims to prevent, or at least reduce, the adverse effects of diabetic foot disease, in part by developing and continuously updating international guidelines for use by all health care providers involved in diabetic foot care. Developing and updating guidelines is in the hands of the IWGDF-Guidelines working groups. In 1999, the IWGDF published its first version of "International Consensus on the Diabetic Foot" and "Practical Guidelines on the Management and the Prevention of the Diabetic Foot". This publication has been translated into 26 languages, and more than 100,000 copies have been distributed globally. As health care systems and prevalence of pathologies differ across regions in the world, the guidelines have to be adopted to local circumstances, if necessary. These documents have since been updated five times.

From consensus to evidence-based guidelines

The initial guidelines, and each subsequent update, were developed by a consensus process and written by a panel of experts in the field. Since 2007 the guidelines have been informed by systematic reviews of the literature. These guidelines were reviewed and revised by the IWGDF Editorial Board, then sent for

critical evaluation to IWGDF representatives throughout the world, culminating in an agreed upon text. Finally, the IWGDF recruited representatives from over 100 countries around the world to help implement the recommended practices. In 2015, we took our methodological process a step further by formulating recommendations for clinical practice using the GRADE system (see below), based on both the available evidence and expert opinion.

The 2019 update

For the 2019 IWGDF guidelines, the Editorial Board invited chair persons with whom they selected international experts to constitute six multidisciplinary working groups, each tasked with producing a guideline on one of the following topics:

- Prevention of foot ulcers in at-risk people with diabetes
- Offloading interventions to heal foot ulcers in persons with diabetes
- Diagnosis, prognosis and management of peripheral artery disease in patients with diabetic foot ulcers
- Diagnosis and management of foot infections in persons with diabetes
- Interventions to enhance healing of chronic ulcers of the foot in persons with diabetes
- Classification of diabetic foot ulcers

The first five guideline chapters are updates of the 2015 guideline on the topic, while the guideline on classification of diabetic foot ulcers is new for 2019. All can be found at *www.iwgdfguidelines.org*. As in earlier versions, the IWGDF Editorial Board produced a document titled "Practical Guidelines on the prevention and management of diabetic foot disease", based on these six guideline chapters, intended as a brief outline of the essential parts of prevention and management of diabetic foot disease. We advise clinicians and other healthcare professionals to read the full guideline chapter on each topic for the specific and detailed recommendations and the rationale underpinning them, as well as the associated systematic reviews for detailed discussion of the evidence. In addition, and new in 2019, this publication provides a more detailed description of the GRADE methodology followed and the writing of recommendations and the rationale supporting them.

Also new in 2019, each working group first formulated clinical questions and relevant outcomes to guide the systematic review of the available literature and the writing of recommendations. These clinical questions were reviewed by both an international panel of independent external experts and the six members of the IWGDF Editorial Board. Once the drafted guidelines with recommendations were produced, these were sent for review to external experts (please see below for more detail). Finally, new in 2019 is that we also developed a "Definitions and Criteria" document for the most commonly used terms in diabetic foot disease. The IWGDF Editorial Board members (the authors of this publication), a total 49 working group members, and a total 50 external experts from 40 countries and 5 continents were involved in the development of the 2019 IWGDF Guidelines.

The six guidelines, the systematic reviews supporting them, the practical guidelines, this development and methodology document and the definitions and criteria document are all published as freely

accessible articles online, *www.iwgdfguidelines.org*. We recommend that health care provides use these guidelines as the basis for developing their own local (regional or national) guidelines.

METHODOLOGY USED FOR THE 2019 IWGDF SYSTEMATIC REVIEWS AND GUIDELINES

This section describes the various steps and methods set up by the IWGDF Editorial Board for use by the designated multidisciplinary working groups to develop guidelines for the prevention and management of diabetic foot disease. The aims were to produce high-quality systematic reviews to help inform each guideline, promote consistency among the guidelines developed, and ensure high quality documents.
In the IWGDF Guidelines we have followed the GRADE methodology, which is structured around clinical questions in the PICO-format (Patient-Intervention-Comparison-Outcome), systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale (10, 11). We will describe five key tasks in the development of guidelines: 1) formulation of the clinical questions, 2) selection of relevant outcome measures, 3) performing a systematic review of the available literature, 4) writing the recommendations for clinical practice, and 5) external review and feedback

1. Formulation of clinical questions

Each working group started the guideline writing process with formulating the key clinical questions they intended to address. This was to provide focus and structure to the setup of the evidence-based guidelines along the line of what a clinician or a patient would ask regarding the care provided in clinical practice to persons with diabetic foot disease. The questions generally involved diagnosis or treatment and the members of the working group reached consensus on the clinical questions they planned to address.

These clinical questions take the format of the "PICO", an acronym that at least includes the population (P) at risk (who are you studying?), the intervention (I) planned (what will you be doing?) and the outcome (O) of interest (what are the consequences of the intervention?). The C is for comparator or control, and concerns the main alternative to the intervention considered, but this is not always required or available.

The clinical questions developed by each working group were reviewed by the IWGDF Editorial Board, and by a panel of independent international external experts in the field to ensure global relevance. These experts (in total 6-13 per working group) were selected by the working groups, under guidance of the Editorial Board. After revision based on these reviews the clinical questions were finalized in June 2018.

2. Selection of relevant outcome measures

Each working group devised outcome measures to help focus on selecting the relevant topic(s) for the systematic review. The evidence was to be reported for these specific outcomes. While the working

groups had no validated core outcome set for diabetic foot disease to consult, they used the set of outcomes defined by the IWGDF-EWMA (12) as a guide to define their outcomes.
Each outcome was classified regarding its role in decision making as: "critically important"; "important, but not critical"; or "not important". Working groups were informed that critical outcomes, which have a larger effect on decision-making and recommendations, were the most important to address.

3. Performing a systematic review

Each working group undertook at least one systematic review of the medical literature that was designed to form the basis for the evidence-based guidelines. Each systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13) (*www.prisma-statement.org*). Each working group used the AMSTAR tool to check that they were addressing the most important aspects in their systematic review (www.amstar.ca/Amstar_Checklist.php). Systematic reviews were prospectively registered in the PROSPERO database for systematic reviews (www.crd.york.ac.uk/prospero/).
The literature databases used for each systematic review were PubMed (via Medline), and either EMBASE (via Ovid SP), the Cochrane database, or both. Each working group devised a search string for each database. Individual working groups could consult a medical librarian to help in devising their search string. Study designs included in the systematic review were meta-analyses, systematic reviews, and randomized controlled trials. Depending on the number of papers found with these higher-level study designs, working groups could also include lower level designs, e.g., non-randomized controlled trials, case–control studies, cohort studies, (controlled) before-and-after studies, interrupted time series, prospective and retrospective non-controlled studies, cross-sectional studies and case series. Case reports were excluded from the systematic reviews.

Trial registries

The working groups searched trial registries that can contain valuable information about studies that have been performed but as yet not published. Trial registries searched were The World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) (*apps.who.int/trialsearch/default.aspx*) and the ClinicalTrials.gov registry (*www.clinicaltrials.gov*). A simplified search string derived from the original search string for the systematic review was used to search for relevant studies in these trial databases.

Validation set

To ensure that the search string used for the systematic review was robust, workgroups created a validation set of approximately 20 known key publications for each systematic review before performing the literature search. If each of the papers in the validation set was not identified in the literature search performed, the working group modified the search string.

Date of search

The time window used to conduct the literature search for all systematic reviews was between 1st and 15th of July 2018. If highly relevant studies for the systematic review and guideline appeared between the date of search and the writing of the systematic review they could be included, but only with using the

set date of 1st of September 2018 for a second search of the literature, encompassing the period between the date of the first search and 1st of September 2018.

Assessing retrieved publications from the search
Two members of each working group independently reviewed publications by title and abstract to assess their eligibility for inclusion in the analysis based on four criteria: population; study design; outcomes; and intervention. At their discretion the working groups could calculate Cohen's kappa values to test for agreement between the two reviewers. The two reviewers discussed any disagreement on which publications to include and reached consensus. The same two reviewers independently assessed selected full-paper copies of included publications on the same four criteria for final eligibility. Reference lists of included papers were not tracked.

To assess for possible publication bias or selective reporting of results, the working groups assessed studies identified by trial registries in the WHO and ClinicalTrial.gov databases. From relevant trials identified from these databases, related publications were searched for in the original literature search database, using the trial registration number of these relevant trials. If no publications were identified, the principal investigator of the trial was contacted and asked about the status of the trial and any possible results from the trial.

Classifying study design and level of evidence
For each included publication, we used the Scottish Intercollegiate Grouping Network (SIGN) algorithm for classifying study design for questions of effectiveness (*www.sign.ac.uk/assets/study_design.pdf*). The same two reviewers that reviewed publications for eligibility independently assessed included publications with a controlled study design for methodological quality (i.e., risk of bias), using scoring sheets developed by the Dutch Cochrane Centre (*netherlands.cochrane.org/beoordelingsformulieren-en-andere-downloads*).

The two reviewers discussed any disagreement regarding risk of bias and reached consensus. The SIGN level of evidence was determined based on the risk of bias for each publication using the SIGN Grading System for Levels of Evidence (*www.sign.ac.uk/assets/sign_grading_system_1999_2012.pdf*) (14). Level 1 refers to randomized controlled trials and Level 2 refers to case–control, cohort, controlled before-and-after designs or interrupted time series. Risk of bias was scored for each study as: ++ (very low risk of bias); + (low risk of bias); or, – (high risk of bias).

Additionally, individual working groups had the discretion to assess all publications with a controlled study design for quality using the 21-item scoring system for reports of clinical studies developed by the IWGDF in collaboration with EWMA (12). The outcomes on the 21-item scoring list were added to the comment box in the evidence table for controlled studies.

To prevent any conflict of interest, reviewers who were one of the authors of any study assessed for inclusion did not participate in the assessment, data extraction or discussion of publications of that study.

Rating of the quality of evidence

The quality of the evidence (QoE) obtained through the systematic review was rated per PICO and for each outcome, even if there were multiple outcomes for a specific intervention. The quality of evidence was rated as high, moderate, or low. We discarded the category "very low" used by some.
The starting point in the QoE rating when level I studies (RCTs) were involved was "high", the starting point for observational controlled studies (level 2, i.e. cohort, case-control) for rating was "low".
Working group members could then lower the QoE based on the presence of:

- Risk of bias (scored from the risk of bias assessment per paper)
- Inconsistency of results (i.e., true differences in the underlying treatment effect may be likely when there are widely differing estimates of the treatment effect [i.e. heterogeneity or variability in results] across studies)
- Publication bias (as could be obtained from the Clinical Trials search), where appropriate

For each of these three items that was scored as 'present', the QoE rating was lowered by one. For example: quality of the evidence could be reduced from "high" to "moderate" when risk of bias of included studies was high.

The QoE could be raised based on the presence of a large effect size or evidence of a dose–response relationship (for observational studies only). For each of these two items that was scored as 'present', the QoE rating was raised by one. For example, quality of the evidence was raised from "low" to "moderate" when the effect size was large

Many of the older papers identified in the systematic reviews lacked data to calculate or assess for indirectness or imprecision, two other factors that can be used to determine the QoE. Ideally, these items help to fully assess the QoE, but unfortunately we could not take them into account.

Data extraction

Data was extracted from each included publication that had a controlled study design and was summarized in an evidence table. This table included patient and study characteristics, characteristics of the intervention and control conditions, and primary and secondary outcomes. One of the reviewers of the original team of two extracted the data, while the other reviewer checked the table for content and presentation. All members of the working group discussed the data in the evidence tables.

Each working group created a PRISMA flow diagram showing the process of selection of papers for the qualitative analysis, and a risk of bias table presenting in detail the risk of bias per included publication.

Conclusions and evidence statements

Finally, the working group drew conclusions for each clinical question formulated. These were based on the strength of the available evidence and formulated as evidence statements. All members of the working group participated in the discussion of these conclusions, reaching consensus on the content and formulation of the conclusions.

Systematic review on diagnostic procedures
We obtained specific methods to the systematic review on diagnostic studies from Brownrigg et al (15) and we asked all groups systematically reviewing studies and writing guidelines on diagnostic procedures to follow the methods used in this study (15). Working groups assessed methodological quality of included studies against parameters included in the QUADAS tool, a consensus quality assessment tool designed specifically for diagnostic accuracy studies (16). Reviewers extracted data and entered them in a QUADAS data extraction form and calculated positive and negative likelihood ratio's for each test in each study (17, 18).

Systematic review on prognosis
The methods used for the systematic review on prognostics in peripheral artery disease were the same as used in the 2016 systematic review on this topic (19). To assess methodological quality of included studies we used the QUIPS tool, designed specifically for prognostic studies (20, 21). To assess risk of bias we used the QUIPS Risk of Bias Assessment Instrument for Prognostic Factor Studies was used.

4. Writing the guideline recommendations
To formulate recommendations for clinical practice, we combined the overall quality of evidence as rated in the systematic review with different factors that were considered to determine the strength of the recommendations. This makes the link between the scientific evidence and recommendations for daily clinical practice (11).

Grading the strength of a recommendation
According to GRADE, we scored the strength of the recommendation as either "Strong" or "Weak". The different factors considered to come to this score were: the QoE rating, the balance between desirable and undesirable effects (benefit and harms); patient values and preferences; feasibility, generalizability and acceptability of the diagnostic procedure or intervention; and, resource utilization (costs). Added to these were other factors, such as expert opinion and clinical relevance. For more explanation of these factors see elsewhere (10, 11).

The working group carefully weighed all these factors to determine the strength of the recommendation, then wrote a rationale for each recommendation to explain the arguments as discussed within the working group on these different factors. The weighing was only to a limited extent a quantitative process that could only be done when literature evidence on harms (e.g. complications), patient preferences or costs were available. Where this was not available, working groups used a more qualitative and subjective approach based on expert opinion. Working group members reached consensus regarding the strength of the recommendations.

5. External review and feedback

The members of the IWGDF Editorial Board met in person on a number of occasions to thoroughly review each of the guideline chapters, which were then revised by the working groups based on this editorial review. The working groups then sent the guideline to the panel of independent international external experts for their critical review. The working group subsequently revised the document further based on these comments, after which the IWGDF Editorial Board did a final review of the recommendations and the rationale provided.

CONCLUDING REMARKS

With the world-wide diabetes epidemic, it is now more imperative than ever that appropriate action be taken to ensure access to quality care for all people with diabetes, regardless of their age, geographic location, economic or social status. The IWGDF Guidelines on the prevention and management of diabetic foot disease are the result of a rather unique process that over 20 years has become more and more founded in a strong evidence base, with procedures to guarantee consistency, transparency and independency. The evidence-base for how to help prevent and optimally manage diabetic foot disease is progressively growing, but it remains a challenge how to use these data to optimize outcomes in different health care systems, in countries with different resources and in different cultures. The IWGDF hopes to see an increase in global awareness of diabetic foot disease and aims to stimulate this process of transforming global guidelines to local guidelines, leading to improved foot care throughout the world. Notwithstanding the limited published evidence of improved outcomes associated with using these IWGDF Guidelines (22), we believe that following the recommendations of the 2019 IWGDF Guidelines will result in improved management of foot problems in diabetes and a subsequent worldwide reduction in the patient, economic and societal burden caused by diabetic foot disease

ACKNOWLEDGEMENTS

We are grateful to the working group members who have collaborated tirelessly, lending their time, expertise and passion to the realization of IWGDF guideline project. We would also like to thank the independent external experts for their time to review our clinical questions and guidelines. In total, 100+ experts from all over the world contributed voluntarily, representing the many different disciplines involved in care for people with diabetic foot disease, resulting in a unique set of multidisciplinary evidence-based guidelines with a global perspective.
In addition, we sincerely thank the sponsors who, by providing generous and unrestricted educational grants for travel and meetings, made development of these guidelines possible.

CONFLICT OF INTEREST STATEMENTS

Production of the 2019 IWGDF Guidelines was supported by unrestricted grants from: Molnlycke Healthcare, Acelity, ConvaTec, Urgo Medical, Edixomed, Klaveness, Reapplix, Podartis, Aurealis, SoftOx, Woundcare Circle, and Essity. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines, and have not seen any guideline or guideline-related document before publication.

All individual conflict of interest statement of authors of this guideline can be found at: *www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies*.

VERSION

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