

Prevention and Management of Foot Problems in Diabetes Guidance Documents and Recommendations

Summary for
Daily Practice

Guidance Documents

Definitions
and Criteria



GUIDANCE ON THE DIABETIC FOOT

The **2015** challenge of the
International Working Group
on the Diabetic Foot



An interactive program on the **International Consensus on the Diabetic Foot 2015**
Including **Summary for Daily Practice**
a **Series of Guidance Documents** and **Definitions and Criteria**



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Prevention and Management of Foot Problems in Diabetes Guidance Documents and Recommendations

Development of
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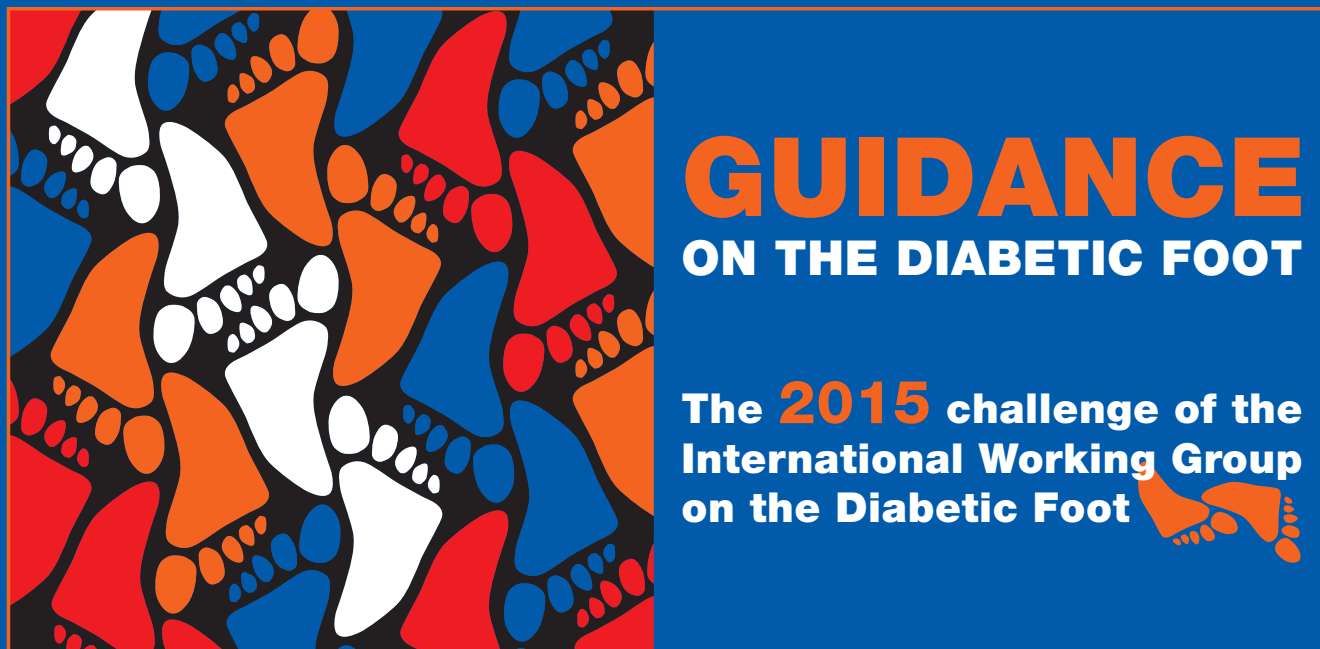
Guidance
Prevention

Guidance
Footwear and
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Guidance
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Summary

Foot problems complicating diabetes are a source of major patient suffering and societal costs. Investing in evidence-based, internationally appropriate diabetic foot care guidance is likely among the most cost-effective forms of healthcare expenditure, provided it is goal-focused and properly implemented.

The International Working Group on the Diabetic Foot (IWGDF) has been publishing and updating international Practical Guidelines since 1999. The 2015 updates are based on systematic reviews of the literature, and recommendations are formulated using the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. As such, we changed the name from “Practical Guidelines” to “Guidance”.

In this article we describe the development of the 2015 IWGDF Guidance documents on prevention and management of foot problems in diabetes. This Guidance consists of five documents, prepared by five working groups of international experts. These documents provide guidance related to foot complications in persons with diabetes on: prevention; footwear and offloading; peripheral artery disease; infections; and, wound healing interventions. Based on these five documents, the IWGDF Editorial Board produced a summary guidance for daily practice.

The resultant of this process, after review by the Editorial Board and by international IWGDF members of all documents, is an evidence-based global consensus on prevention and management of foot problems in diabetes. Plans are already under way to implement this Guidance.

We believe that following the recommendations of the 2015 IWGDF Guidance will almost certainly result in improved management of foot problems in persons with diabetes and a subsequent worldwide reduction in the tragedies caused by these foot problems.

Keywords:

Diabetic foot, foot ulcer, guidelines, guidance, IWGDF, implementation

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It is estimated that by 2035 the global prevalence of diabetes mellitus will rise to almost 600 million, and around 80% of these people will live in developing countries (1). Foot problems complicating diabetes are a source of major patient suffering and societal costs (2). The frequency and severity of foot problems varies from region to region, largely due to differences in socio-economic conditions, type of footwear, and standards of foot care. Foot ulcers are the most prevalent problem, with a yearly incidence of around 2-4% in developed countries (2) and likely even higher in developing countries.

The most important factors underlying the development of foot ulcers are peripheral sensory neuropathy, foot deformities related to motor neuropathy, minor foot trauma, and peripheral artery disease. Once the skin is ulcerated, it is susceptible to becoming infected, an urgent medical problem. Only two-thirds of foot ulcers will eventually heal (3,4), 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 as a consequence of the complications of diabetes. This translates into the estimate that every 20 seconds a lower limb is lost to diabetes somewhere in the world (2).

Foot problems in persons with diabetes not only represent a major personal tragedy, they also affect that person's family and place 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 these patients and their family (6). Investing in evidence-based, internationally appropriate diabetic foot care guidance is likely among the most cost-effective forms of healthcare expenditure, provided it is goal-focused and properly implemented (7,8).

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International Working Group on the Diabetic Foot

The International Working Group on the Diabetic Foot (IWGDF; www.iwgdf.org) was founded in 1996, and consists of experts from almost all disciplines involved in the care of patients with diabetes and foot problems. The IWGDF aims to prevent, or at least reduce, the adverse effects of foot problems in diabetes, in part by developing and continuously updating international guidance documents for use by all health care providers involved in diabetic foot care. 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. These documents have since been updated four times, including the versions published in this supplement (9-12).

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The initial Practical Guidelines, and each subsequent update, were developed by a consensus process: all texts were written by a panel of experts in the field and (since 2007) informed by systematic reviews of the literature. These texts 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 local “champions,” representing over 100 countries around the world, to implement the recommended practices.

However, these Practical Guidelines were not based on high-quality evidence only. Developing such guidelines on foot problems in diabetes that are applicable all over the world and relevant for all disciplines involved is still a “bridge too far”. In many areas solid evidence is lacking, resources and expertise differ widely in various parts of the world, cost-effectiveness of approaches may vary between health care systems, and what is self-evident to experts of one discipline may be debatable for others.

For the 2015 update we have taken our methodological process a step further. Not only did we perform a systematic review on each topic, we have also formulated recommendations of key points for daily practice using the GRADE system (see below), based on both the available evidence and expert opinion. These recommendations should be adapted to local circumstances in each country. For these reasons we changed the name from Practical Guidelines to Guidance. We recommend that this Guidance be used as the basis for developing local guidelines in each country.

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For the 2015 IWGDF Guidance documents, the IWGDF invited five working groups of international experts to produce guidance on the following topics:

- Prevention of foot ulcers in at-risk patients with diabetes (13)
- Footwear and offloading to prevent and heal foot ulcers in diabetes (14)
- Diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes (15)
- Diagnosis and management of foot infections in persons with diabetes (16)
- Interventions to enhance healing of chronic ulcers of the foot in diabetes (17)

The IWGDF Editorial Board produced a “Summary Guidance for Daily Practice,” based on these five documents, that is intended to serve as a short outline of the essential parts of prevention and management of foot problems in diabetes (18). We advise interested clinicians to read the full Guidance on each topic for more detailed recommendations, as well as the systematic review for detailed discussion of the evidence. These are, together with the “Summary Guidance”, published as freely accessible articles in this issue of Diabetes / Metabolism Research and Reviews (13-17,19-25).

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Each of the five working groups followed the same methods in the design of their Guidance document. First, they performed a systematic review of a selected aspect of the available literature on their topic. The reviewers only included controlled studies that drew from the target population of people with diabetes. As might be expected, some papers published by members of the committee were included in the review, but they used strict rules to guard against any conflict of interest. The design and risk of bias of all intervention studies included in the systematic reviews were assessed using the Scottish Intercollegiate Grouping Network (SIGN) algorithm (<http://www.sign.ac.uk/pdf/studydesign.pdf>) and score sheets from the Dutch Cochrane Centre (www.cochrane.nl). Assessment of methodological quality for the Guidance document on diagnosis of peripheral artery disease was performed using the quality assessment for diagnostic accuracy studies (QUADAS) instrument (26), and for the Guidance document on prognosis of peripheral artery disease using the Quality in Prognostic Studies (QUIPS) instrument (27). Evidence from included studies was summarized in evidence tables.

Following the systematic review, the experts in the working groups formulated recommendations based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (28). The GRADE system allows the experts to provide a rating for each recommendation based on both the strength with which it is recommended and the quality of the evidence underlying it. In this manner the link is made between scientific evidence and recommendations for daily clinical practice. We assessed the strength of each recommendation as either 'strong' or 'weak', based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs (resource utilization). We rated the quality of evidence as 'high', 'moderate', or 'low' based on the risk of bias of included studies, the effect size, and expert opinion. Many of the older papers identified in the systematic reviews lacked data for the reviewers to calculate or assess for inconsistency, indirectness or imprecision. Ideally, these items help to fully assess the quality of evidence, but unfortunately they could not usually be taken into account. The rationale behind each recommendation is described in the Guidance documents.

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The members of the IWGDF Editorial Board met in person on a number of occasions to thoroughly review the systematic reviews and the Guidance documents, which were then revised by the working groups based on this editorial review. When found satisfactory, the Editorial Board sent the Guidance documents to the IWGDF representatives for comments; the editorial board processed all comments received and made changes where needed in collaboration with the chair of each working group. Finally, the five Guidance documents were the basis for the ‘Summary Guidance for daily practice’, written by the members of the IWGDF Editorial Board. The result of this process is a series of evidence-based global consensus documents.

On a pre-planned “Consensus-Implementation Day” prior to the 7th International Symposium on the Diabetic Foot, held May 19th 2015 in The Hague, all international representatives were invited to discuss implementation of the IWGDF Guidance documents. Implementation of these Guidance documents is a crucial step, as only when they are used in daily clinical practice throughout the world will they contribute to improvement in outcomes.

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Plans are already under way to ensure continued implementation and evaluation of the IWGDF Guidance on the prevention and management of foot problems in persons with diabetes into the future. 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 evidence base for the prevention and management of foot ulcers in diabetes 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 foot problems in persons with diabetes and aims to stimulate this process of transforming global guidance to local guidelines, leading to improved foot care throughout the world. Notwithstanding the limited published evidence of improved outcomes associated with using these Guidance documents, we believe that following the recommendations of the 2015 IWGDF Guidance will almost certainly result in improved management of foot problems in diabetes and a subsequent worldwide reduction in the tragedies caused by these foot problems.

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We are deeply grateful to the many authors and members of the working groups who have collaborated tirelessly, lending their time, expertise and passion to the realization of this huge project. In addition, we sincerely thank the sponsors who, by providing generous and unrestricted educational grants, made development of this Guidance possible.

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All authors declare no conflict of interest.

The IWGDF Guidance is developed by working groups of independent experts. These documents are written without any influence from commercial, political, academic or other interest groups.

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In this 'Summary Guidance for Daily Practice' we describe the basic principles of prevention and management and of foot problems in persons with diabetes. This summary is based on the International Working Group on the Diabetic Foot (IWGDF) Guidance 2015, consisting of evidence-based international consensus guidance documents on:

- Prevention of foot ulcers in at-risk patients with diabetes (1)
- Footwear and offloading to prevent and heal foot ulcers in diabetes (2)
- Diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes (3)
- Diagnosis and management of foot infections in persons with diabetes (4)
- Interventions to enhance healing of chronic ulcers of the foot in diabetes (5)

In addition, the authors, as members of the Editorial Board of the IWGDF, provide some advice in this summary that is based on expert opinion, in areas for which the guidance documents were not able to provide evidence-based recommendations.

Depending on local circumstances, the principles outlined in this summary will have to be adapted or modified, taking into account regional differences in the socio-economic situation, accessibility to and sophistication of healthcare and various cultural factors. This summary is aimed at healthcare providers throughout the world who are involved in the care of people with diabetes. For more details and information on treatment by specialists in foot care, we refer the reader to the five evidence-based global consensus Guidance documents (1-5).

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Foot problems in diabetes

Foot problems in diabetes are among the most serious complications of diabetes mellitus. Foot problems are a source of major suffering and costs for the patient, and they also place a considerable financial burden on healthcare and society in general. A strategy that includes prevention, patient and staff education, multi-disciplinary treatment of foot ulcers, and close monitoring of people's feet as described in this document can reduce foot problems and their sequelae.

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Although the prevalence and spectrum of foot problems varies in different regions of the world, the pathways to ulceration are probably very similar in most patients. Diabetic foot lesions frequently result from a patient simultaneously having two or more risk factors, with diabetic peripheral neuropathy playing a central role. This neuropathy leads to an insensitive and sometimes deformed foot, often causing an abnormal walking pattern. In people with neuropathy, minor trauma (e.g., from ill-fitting shoes, walking barefoot or an acute injury) can precipitate ulceration of the foot. Loss of sensation, foot deformities, and limited joint mobility can result in abnormal biomechanical loading of the foot. This produces high pressure in some areas, to which the body responds with thickened skin (callus). This leads to a further increase of the abnormal loading, often with subcutaneous haemorrhage and eventually ulceration. Whatever the primary cause, if the patient continues walking on the insensitive foot it impairs wound healing (see Figure 1).

Figure 1: Illustration of ulcer due to repetitive stress



Peripheral artery disease (PAD), generally caused by accelerated 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 minority of foot ulcers are purely ischemic; these are usually painful and caused by minor trauma. The majority of foot ulcers are neuro-ischemic, i.e., caused by combined neuropathy and ischemia. In these patients symptoms may be absent because of the neuropathy, despite severe pedal ischemia. Diabetic microangiopathy (so-called “small vessel disease”) is not likely to be the primary cause of an ulcer or poor wound healing.

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There are five key elements that underpin prevention of foot problems:

1. Identification of the at-risk foot
2. Regular inspection and examination of the at-risk foot
3. Education of patient, family and healthcare providers
4. Routine wearing of appropriate footwear
5. Treatment of pre-ulcerative signs

1. Identification of the at-risk foot

To identify a person with diabetes who is at risk for foot ulceration, examine the feet annually to seek evidence of signs or symptoms of peripheral neuropathy or peripheral artery disease. If a patient with diabetes has peripheral neuropathy, screen for: a history of foot ulceration or lower-extremity amputation; foot deformity; pre-ulcerative signs on the foot; poor foot hygiene; and, ill-fitting or inadequate footwear.

Following examination of the foot, each patient can be assigned to a risk category that should guide subsequent preventative management. The IWGDF risk classification categories 2015 can be found in Table 1. Areas most at-risk are shown in Figure 2.

Table 1: The IWGDF Risk Classification System 2015 and preventative screening frequency

Category	Characteristics	Frequency
0	No peripheral neuropathy	Once a year
1	Peripheral neuropathy	Once every 6 months
2	Peripheral neuropathy with peripheral artery disease and/or a foot deformity	Once every 3-6 months
3	Peripheral neuropathy and a history of foot ulcer or lower-extremity amputation	Once every 1-3 months



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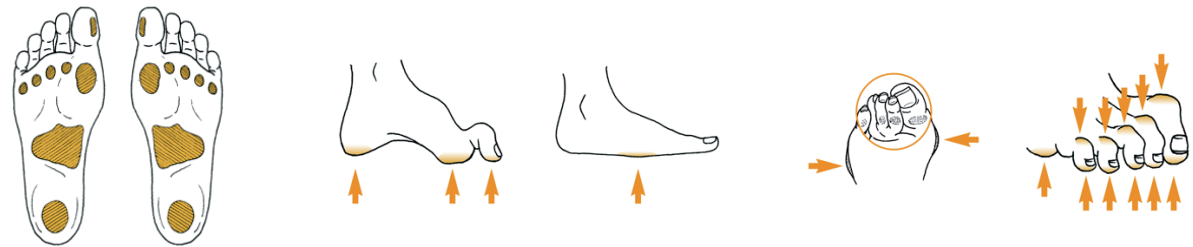
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Figure 2: Areas at risk for foot ulceration



2. Regular inspection and examination

All people with diabetes should have their feet examined at least once a year to identify those at risk for foot ulceration. Patients found to have a risk factor should be examined more often, based on their IWGDF risk category (Table 1).

The absence of symptoms in a person with diabetes does not exclude foot disorders; they may have asymptomatic neuropathy, peripheral artery disease, pre-ulcerative signs or even an ulcer. The clinician should examine the feet with the patient both lying down and standing up, and should also inspect their shoes and socks. Inspection and examination should minimally consist of:

History and foot examination:

- History: Previous ulcer/amputation, end stage renal disease, previous foot education, social isolation, poor access to healthcare, bare-foot walking
- Vascular status: History of claudication, rest pain, palpation of pedal pulses
- Skin: Callus, colour, temperature, oedema
- Bone/joint: Deformities (e.g., claw toes, hammer toes) or bony prominences, limited joint mobility
- Footwear/socks (worn when at home and when outside): Assessment of both their inside and outside



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Assessment of neuropathy, using the following techniques:

- Symptoms, such as tingling or pain in the lower limb, especially at night
- Pressure perception: Semmes-Weinstein monofilaments (see addendum)
- Vibration perception: 128 Hz tuning fork (see addendum)
- Discrimination: Pin prick (dorsum of foot, without penetrating the skin)
- Tactile sensation: Cotton wool (dorsum of foot), or by lightly touching the tips of the toes of the patient with the tip of the index finger of the examiner for 1–2 seconds
- Reflexes: Achilles tendon reflexes

3. Education of patients, family and healthcare providers about foot care

Education, presented in a structured, organized and repeated manner, plays an important role in the prevention of foot problems. The aim is to improve patients' foot care knowledge, awareness, and self-protective behaviour, and to enhance motivation and skills in order to facilitate adherence to this behaviour. People with diabetes should learn how to recognize potential foot problems and be aware of the steps they need to take when problems arise. The educator must demonstrate the skills, such as how to cut nails appropriately. A member of the health care team should provide education (see examples of instructions below) in several sessions over time, and preferably using a mixture of methods. It is essential to evaluate 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, and has sufficient self-care skills. Furthermore, healthcare professionals providing these instructions should receive periodic education to improve their skills in care for patients at high-risk for foot ulceration.

Items that should be covered when instructing the patient at-risk for foot ulceration:

- Determine if the person with diabetes is able to perform a daily foot inspection.
If not, discuss who can assist the person in this task. A substantially visually impaired person cannot adequately do the inspection
- Perform daily foot inspection, including areas between the toes
- Notify the appropriate healthcare provider at once if foot temperature is markedly increased, or if a blister, cut, scratch or ulcer has developed
- Avoid walking barefoot, in socks without footwear, or in thin-soled standard slippers, whether at home or outside
- Do not wear shoes that are too tight, have rough edges or uneven seams



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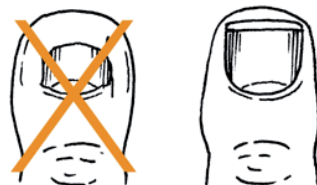
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- Inspect and feel inside all shoes before you put them on
- Wear socks/stocking without seams (or with the seams inside out), do not wear tight or knee-high socks, and change socks daily
- Wash feet daily (with water temperature always below 37°C), 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 provider 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 provider

Figure 3: How to cut toe nails



4. Routine wearing of appropriate footwear

Inappropriate footwear and walking barefoot with insensitive feet are major causes of foot ulceration. Patients with loss of protective sensation should have access to appropriate footwear without financial restraints and should be encouraged to wear this footwear at all times, both indoors and outdoors. All footwear should be adapted to conform to altered biomechanics and deformities affecting the patient's foot. Patients without peripheral neuropathy (IWGDF risk classification 0) can select off-the-shelf footwear, but should ensure that they fit properly. Patients with neuropathy (IWGDF risk classification 1) must take extra care when selecting or being fitted with footwear; this is most important when they also have foot deformities (IWGDF risk classification 2) or have had a previous ulcer/amputation history (IWGDF risk classification 3).



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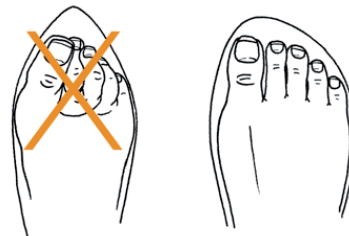
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The shoe should not be either too tight or too loose (see Figure 4). The inside of the shoe should be 1-2 cm longer than the foot. The internal width should equal the width of the foot at the metatarsal phalangeal joints (or the widest part of the foot), and the height should allow enough room for all the toes. Evaluate the fit with the patient in the standing position, preferably at the end of the day. If the fit is poor due to foot deformities, 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), including insoles and orthoses. If possible, demonstrate that there is reduced plantar pressure of this special footwear to prevent a recurrent plantar foot ulcer.

Figure 4: Internal width of the shoe



5. Treatment of pre-ulcerative signs

In a patient with diabetes treat any pre-ulcerative sign on the foot. This includes: removing abundant callus; protecting blisters, or draining them if necessary; treating ingrown or thickened nails; and, prescribing antifungal treatment for fungal infections. This treatment should be repeated until the pre-ulcerative sign resolves and does not recur over time, and should preferably be performed by a trained foot care specialist. If possible, treat foot deformities non-surgically (e.g., with an orthosis).





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

Type

By history and clinical examination, classify the ulcer as neuropathic, neuro-ischemic or 'purely' ischemic. Evaluate all patients for the presence of PAD by taking a symptom-directed history and palpating foot pulses. If possible, 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 and 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 arteries. In selected cases other tests, such as measurements of toe pressure or transcutaneous pressure of oxygen (TcPO₂), are useful. No specific symptoms or signs of PAD reliably predict healing of the ulcer.

Cause

Ill-fitting shoes and walking barefoot with insensitive feet are the most frequent causes of ulceration, even in patients with purely ischemic ulcers. Therefore, meticulously examine shoes and footwear behaviour in all patients.

Site and depth

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

The depth of an ulcer can be difficult to determine, especially in the presence of overlying callus or necrotic tissue. To enable an adequate assessment of the ulcer debride neuropathic ulcers with callus and necrosis as soon as possible. This debridement should not be performed in non-infected ulcers with signs of severe ischemia. In neuropathic ulcers, debridement can usually be performed without any local anaesthetic.



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Signs of infection

Infection of the foot in a person with diabetes presents a serious threat to the affected limb, and must be evaluated and treated promptly. Because all open wounds are colonised with potential pathogens, we 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 ischemia, and systemic findings (e.g., fever, increased white blood count) are often absent. Infections should be classified as mild (superficial with minimal cellulitis), moderate (deeper or more extensive) or severe (accompanied by systemic signs of sepsis).

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 there is a longstanding or deep wound, a wound overlying bone, or if it is possible to touch bone with a sterile metal probe. In addition to the clinical evaluation, plain radiographs suffice for screening for osteomyelitis in most patients. Consider magnetic resonance imaging when more advanced imaging is needed.

For clinically infected wounds obtain a tissue specimen for culture (and Gram-stained smear, if available); avoid culturing superficial swab specimens. Mild (superficial and limited) infection is usually caused by aerobic gram-positive cocci, especially *Staphylococcus aureus*. Chronic and more severe infections are often polymicrobial, with aerobic gram-negative rods and anaerobes accompanying the gram-positive cocci.

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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.

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Relief of pressure and protection of the ulcer

This is a cornerstone in treating an ulcer associated with increased biomechanical stress:

- The preferred treatment for a neuropathic plantar ulcer is a non-removable knee-high offloading device, either total contact cast (TCC) or removable walker rendered irremovable
- When a non-removable TCC or walker is contra-indicated, use a removable device
- When these devices are contra-indicated, use footwear that best offloads the ulcer
- In non-plantar ulcers, consider offloading with shoe-modifications, temporary footwear, toe-spacers or orthoses
- If other forms of biomechanical relief are not available, consider felted foam, in combination with appropriate footwear
- Instruct the patient to limit standing and walking, and to use crutches if necessary

Restoration of skin perfusion

- In patients with either an ankle pressure <50mm Hg or ABI <0.5 consider urgent vascular imaging and, when appropriate, revascularisation. If the toe pressure is <30mmHg or TcpO₂ is <25 mmHg a revascularisation should also be considered
- When an ulcer is not showing signs of healing within 6 weeks, despite optimal management, consider revascularisation, irrespective of the results of the 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
- Select a revascularisation technique based on both individual factors (such as morphological distribution of PAD, availability of autogenous vein, patient co-morbidities) and local expertise
- 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 dyslipidemia, use of aspirin or clopidogrel)



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Treatment of infection

Superficial ulcer with skin infection (mild infection):

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

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

- Urgently evaluate for need for surgical intervention to remove necrotic tissue, including infected bone, and 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 anaerobes
- Adjust (constrain, if possible) the antibiotic regimen based on clinical response and culture and sensitivity results

Metabolic control and treatment of co-morbidity

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

Local wound care

- Inspect the ulcer frequently
- Debride the ulcer (with scalpel), and repeat as needed
- Select dressings to control excess exudation and maintain moist environment
- Consider using negative pressure therapy to help heal post-operative wounds
- Consider systemic hyperbaric oxygen treatment in poorly healing wounds; this treatment may hasten wound healing

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

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

Note: Do not use footbaths in which the feet are soaked, as they induce skin maceration.





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Education for patient and relatives

- Instruct patients (and relatives or carers) on appropriate 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

Prevention of recurrence

- Once the ulcer is healed, include the patient in an integrated foot-care programme with life-long observation, professional foot treatment, adequate footwear, and education
- The foot should never return in the same shoe that caused the ulcer

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Successful efforts to prevent and treat foot complications 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 care is provided, but ideally a foot care programme should provide the following:

- Education for people with diabetes and their carers, for healthcare staff in hospitals and for primary healthcare providers
- A system to detect all people who are at risk, with annual foot examination of all persons with diabetes
- Measures to reduce risk of foot ulceration, such as podiatric maintenance care and appropriate footwear
- Prompt and effective treatment of any foot complication
- Auditing of all aspects of the service to identify 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 be at least three levels of foot-care management:

- Level 1:** General practitioner, podiatrist, and diabetic nurse
- Level 2:** Diabetologist, surgeon (general, orthopaedic, or foot), vascular surgeon, endovascular interventionist, podiatrist and diabetic nurse, in collaboration with a shoe-maker, 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





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Many studies around the world have shown that setting up a multidisciplinary foot care team is associated with a drop in the number 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 be a team that acts with mutual respect and understanding, that works in both primary and secondary care settings, and that has at least a member available for consultation or patient assessment at all times.

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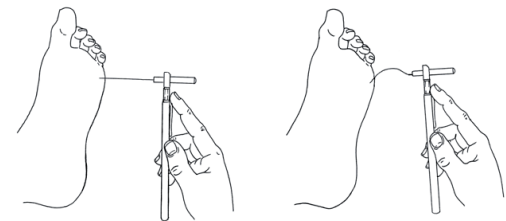
Sensory foot examination

Neuropathy can be detected using the 10 g (5.07 Semmes-Weinstein) monofilament, tuning fork (128 Hz), and/or cotton wisp.

Figure 5: Sites to be tested with the monofilament



Figure 6: Application of the monofilament



Semmes-Weinstein monofilament (Figures 5 and 6)

- Sensory examination should be carried out in a quiet and relaxed setting. First apply the monofilament on the patient's hands (or elbow or forehead) so that he or she knows what to expect.
- The patient must not be able to see whether or where the examiner applies the filament. The three sites to be tested on both feet are indicated in Figure 5.
- Apply the monofilament perpendicular to the skin surface (Figure 6a).
- Apply 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.
- Apply the filament along the perimeter of, not on, an ulcer site, 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 ('left foot'/'right foot').
- Repeat this application twice at the same site, but alternate this with at least one 'mock' application in which no filament is applied (total three questions per site).



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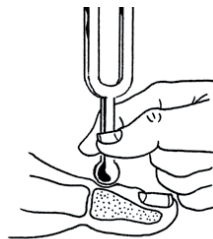
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- Protective sensation is present at each site if the patient correctly answers two out of three applications. Protective sensation is absent with two out of three incorrect answers - the patient is then considered to be at risk of ulceration.
- Encourage the patients during testing by giving positive feedback.
- The healthcare provider should be aware of the possible loss of buckling force of the monofilament if used for too long a period of time.

Figure 7: How to use a tuning fork



Tuning fork (Figure 7)

- The sensory exam should be carried out in a quiet and relaxed setting. First, apply the tuning fork on the patient's wrists (or elbow or clavicle) so that he or she knows what to expect.
- The patient must not be able to see whether or where the examiner applies the tuning fork. The tuning fork is applied on a bony part on the dorsal side of the distal phalanx of the first toe.
- The tuning fork should be applied 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 ('at risk for ulceration') with two out of three incorrect answers.
- If the patient is unable to sense the vibrations on the big toe, the test is repeated more proximally (malleolus, tibial tuberositas).
- Encourage the patient during testing by giving positive feedback.



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Easy to use foot screening assessment sheet for clinical examination

Foot ulcer	
Presence of a full thickness ulcer	Yes / No
Risk factors for foot ulceration	
<i>Neuropathy</i>	
- Monofilament undetectable	Yes / No
- Tuning fork undetectable	Yes / No
- Cotton wool undetectable	Yes / No
<i>Foot pulses</i>	
- Tibial posterior artery absent	Yes / No
- Dorsal pedal artery absent	Yes / No
<i>Other</i>	
Foot deformity or bony prominences	Yes / No
Loss of joint mobility	Yes / No
Signs of abnormal pressure such as callus	Yes / No
Discoloration on dependency	Yes / No
Poor foot hygiene	Yes / No
Inappropriate footwear	Yes / No
Previous ulcer	Yes / No
Amputation	Yes / No

The foot is at-risk if any of the items given are present





IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes

Prepared by the IWGDF Working Group on Prevention of Foot Ulcers

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Systematic review

IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes © 2015



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IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes

Prepared by the IWGDF Working Group on Prevention of Foot Ulcers

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1. To identify a person with diabetes at risk for foot ulceration, examine the feet annually to seek evidence for signs or symptoms of peripheral neuropathy and peripheral artery disease. (GRADE recommendation: strong; Quality of evidence: low)
2. In a person with diabetes who has peripheral neuropathy, screen for: a history of foot ulceration or lower-extremity amputation; peripheral artery disease; foot deformity; pre-ulcerative signs on the foot; poor foot hygiene; and ill-fitting or inadequate footwear. (Strong; Low)
3. Treat any pre-ulcerative sign on the foot of a patient with diabetes. This includes: removing callus; protecting blisters and draining when necessary; treating ingrown or thickened toe nails; treating haemorrhage when necessary; and prescribing antifungal treatment for fungal infections. (Strong; Low)
4. To protect their feet, instruct an at-risk patient with diabetes not to walk barefoot, in socks, or in thin-soled standard slippers, whether at home or when outside. (Strong; Low)
5. Instruct an at-risk patient with diabetes to: daily inspect their feet and the inside of their shoes; daily wash their feet (with careful drying particularly between the toes); avoid using chemical agents or plasters to remove callus or corns; use emollients to lubricate dry skin; and cut toe nails straight across. (Weak; Low)
6. Instruct an at-risk patient with diabetes to wear properly fitting footwear to prevent a first foot ulcer, either plantar or non-plantar, or a recurrent non-plantar foot ulcer. When a foot deformity or a pre-ulcerative sign is present, consider prescribing therapeutic shoes, custom-made insoles, or toe orthosis. (Strong; Low)
7. To prevent a recurrent plantar foot ulcer in an at-risk patient with diabetes, prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking (i.e. 30% relief compared to plantar pressure in standard of care therapeutic footwear), and encourage the patient to wear this footwear. (Strong; Moderate)



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8. To prevent a first foot ulcer in an at-risk patient with diabetes, provide education aimed at improving foot care knowledge and behaviour, as well as encouraging the patient to adhere to this foot care advice. (Weak; Low)
9. To prevent a recurrent foot ulcer in an at-risk patient with diabetes, provide integrated foot care, which includes professional foot treatment, adequate footwear and education. This should be repeated or re-evaluated once every one to three months as necessary. (Strong; Low)
10. Instruct a high-risk patient with diabetes to monitor foot skin temperature at home to prevent a first or recurrent plantar foot ulcer. This aims at identifying the early signs of inflammation, followed by action taken by the patient and care provider to resolve the cause of inflammation. (Weak; Moderate)
11. Consider digital flexor tenotomy to prevent a toe ulcer when conservative treatment fails in a high-risk patient with diabetes, hammertoes and either a pre-ulcerative sign or an ulcer on the toe. (Weak; Low)
12. Consider Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection, or osteotomy to prevent a recurrent foot ulcer when conservative treatment fails in a high-risk patient with diabetes and a plantar foot ulcer. (Weak; Low)
13. Do not use a nerve decompression procedure in an effort to prevent a foot ulcer in an at-risk patient with diabetes, in preference to accepted standards of good quality care. (Weak; Low)

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Foot ulcers are a major complication of diabetes mellitus, with high morbidity, mortality, and costs (1-3). Yearly incidence is estimated to be around 2%, but this increases substantially when patients successfully heal from a foot ulcer, with reported recurrence rates between 30% and 40% in the first year (4,5). Prevention of these ulcers is of paramount importance to reduce the patient and economic burden.

Risk factors & IWGDF definitions

Not all patients with diabetes are at-risk for ulceration. Key risk factors include presence of peripheral neuropathy, foot deformity, peripheral vascular disease, or a history of foot ulceration or amputation of (a part of) the foot or leg (1,6,7). In general, patients without any of these risk factors do not appear to be at-risk for ulceration. For the current guidance, we define the at-risk patient in line with the definition from the International Working Group on the Diabetic Foot (IWGDF) as 'a patient with diabetes who does not have an active foot ulcer, but who has peripheral neuropathy, with or without the presence of foot deformity or peripheral artery disease, or a history of foot ulcer(s) or amputation of (a part of) the foot or leg' (Box 1).

Box 1: IWGDF definitions

Peripheral neuropathy	The presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes
Loss of protective sensation	Inability to sense light pressure, e.g. as applied with a 10 gram Semmes-Weinstein monofilament
Foot deformity	Structural abnormalities of the foot such as hammer toes, mallet toes, claw-toes, hallux valgus, prominent metatarsal heads, residuals of neuro-osteoarthropathy, amputations or other foot surgery.
Peripheral artery disease	Obstructive atherosclerotic vascular disease with clinical symptoms, signs or abnormalities on non-invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities
Therapeutic footwear	Some form of customization to the patients foot regarding insole, shoe, and/or orthosis

Note: for all IWGDF definitions go to www.iwgdf.org.



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Interventions

In most countries with developed healthcare systems, only patients at-risk for ulceration are entitled to reimbursement for preventative foot care. Therefore, only interventions aimed specifically at the prevention of ulcers in at-risk patients are included in this guidance. Within this group, those patients with a previous foot ulcer and/or amputation are considered at higher risk for ulceration when compared to those without (1,6). As such, first foot ulcer and recurrent foot ulcer are considered as 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. These include interventions such as self-management, patient education, therapeutic footwear, or foot surgery, or the combination of two or more of these interventions into integrated foot care.

In this guidance document, recommendations are given for each intervention separately, and include a rationale of how we came to each recommendation.¹ This rationale is based on a systematic review of the literature that underlies this guidance (8), together with a consideration of benefits and harm, patients' values and preferences, and costs related to the intervention.

¹ *Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (68). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence on: the risk of bias of included studies, effect sizes, and expert opinion, and rate the quality of evidence as 'high', 'moderate', or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harm, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.*

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Should a person with diabetes be screened for foot ulcer risk?

Recommendation 1:

To identify a person with diabetes at risk for foot ulceration, examine the feet annually to seek evidence for signs or symptoms of peripheral neuropathy and peripheral artery disease. (GRADE recommendation: strong; Quality of evidence: low)

Rationale 1:

To prevent foot ulceration among patients with diabetes, identification of those at risk for a foot ulcer is essential. Foot examination is an easy method to achieve this goal, and should specifically include screening for the loss of protective sensation caused by peripheral neuropathy, and for signs or symptoms of peripheral artery disease (PAD), as discussed in the IWGDF guidance on PAD (9). Even though evidence for a screening interval is lacking, we recommend a yearly screening for a patient who is not at risk for ulceration.

What should an at-risk person with diabetes be screened for?

Recommendation 2:

In a person with diabetes who has peripheral neuropathy, screen for: a history of foot ulceration or lower-extremity amputation; peripheral artery disease; foot deformity; pre-ulcerative signs on the foot; poor foot hygiene; and ill-fitting or inadequate footwear. (Strong; Low)

Rationale 2:

To identify a patient at risk for foot ulceration, screening is essential. In a patient with signs or symptoms of peripheral neuropathy, foot examination should consist of taking a detailed history of foot ulceration or lower-extremity amputation, and screening for the presence of peripheral artery disease and foot deformities (1,7). Other factors that are associated with foot ulceration that should be screened for include: pre-ulcerative signs on the foot such as callus, blisters and haemorrhage; ill-fitting or inadequate footwear; and, poor foot hygiene, such as improperly cut toenails, unwashed feet, presence of fungal infection, and unclean socks (10-12). Even though evidence does not exist, we advocate screening for these factors.



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At-risk patients require more frequent foot screening than patients who are not at risk. The aim of more frequent screening is early identification of factors that can increase the chances of developing a foot ulcer, 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. Even though evidence for the effectiveness of a screening interval in at-risk patients does not exist, we recommend the following screening frequency:

Table 1: The IWGDF Risk Classification System 2015 and preventative screening frequency

Category	Characteristics	Frequency
0	No peripheral neuropathy	Once a year
1	Peripheral neuropathy	Once every 6 months
2	Peripheral neuropathy with peripheral artery disease and/or a foot deformity	Once every 3-6 months
3	Peripheral neuropathy and a history of foot ulcer or lower-extremity amputation	Once every 1-3 months

Is the treatment of a pre-ulcerative sign on the foot effective in preventing a foot ulcer in an at-risk patient with diabetes?

Recommendation 3:

Treat any pre-ulcerative sign on the foot of a patient with diabetes. This includes: removing callus; protecting blisters and draining when necessary; treating ingrown or thickened toe nails; treating haemorrhage when necessary; and prescribing antifungal treatment for fungal infections. (Strong; Low)

Rationale 3:

Pre-ulcerative signs on the foot, such as callus, blisters or haemorrhage, appear to be a strong predictor of future ulceration (10,12). These signs require immediate treatment by a foot care professional.





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The effectiveness of treating these pre-ulcerative 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 (13,14). The benefits of treatment of pre-ulcerative signs by a trained foot care professional outweigh the potential harm of such treatment, and come at relatively low costs.

What should an at-risk patient with diabetes avoid when walking at home or outside?

Recommendation 4:

To protect their feet, instruct an at-risk patient with diabetes not to walk barefoot, in socks, or in thin-soled standard slippers, whether at home or when outside. (Strong; Low)

Rationale 4:

No studies have been performed on the effect of walking barefoot, in socks, or in thin-soled standard slippers, on risk of foot ulceration. However, there are many large prospective studies that show that at-risk patients with diabetes have elevated levels of mechanical plantar pressure during barefoot walking, which are a significant independent risk factor for foot ulceration and should therefore be reduced (15). In addition, walking barefoot, in socks, 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 trauma

What self-management interventions should a patient perform on a regular basis?

Recommendation 5:

Instruct an at-risk patient with diabetes to: daily inspect their feet and the inside of their shoes; daily wash their feet (with careful drying particularly between the toes); avoid using chemical agents or plasters to remove callus or corns; use emollients to lubricate dry skin; and cut toe nails straight across. (Weak; Low)

Rationale 5:

Although no evidence is available for any of these self-management interventions in relation to the prevention of a foot ulcer, they enable early detection of pre-ulcerative signs on the foot and contribute to basic foot hygiene. This is likely to help prevent a foot ulcer.



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Is footwear effective in preventing a first or recurrent non-plantar foot ulcer in an at-risk patient with diabetes?

Recommendation 6:

Instruct an at-risk patient with diabetes to wear properly fitting footwear to prevent a first foot ulcer, either plantar or non-plantar, or a recurrent non-plantar foot ulcer. When a foot deformity or a pre-ulcerative sign is present, consider prescribing therapeutic shoes, custom-made insoles, or toe orthosis. (Strong; Low)

Rationale 6:

One randomized controlled trial (RCT) with high risk of bias showed a positive effect of therapeutic footwear on the prevention of foot ulcers in at-risk patients, most of whom had no ulcer history (16). Another RCT with high risk of bias showed a clear trend but no significant effect of shear-reducing insoles (17). A third RCT with low risk of bias showed that digital silicon orthoses can significantly reduce first toe ulcer incidence in at-risk patients with pre-ulcerative lesions (18). No controlled studies exist on the specific role of footwear to prevent a non-plantar foot ulcer. However, ill-fitting footwear has been identified as an important cause of non-plantar foot ulceration (11), suggesting that properly fitting footwear may reduce ulcer incidence. In properly fitting footwear, the shoe should not be either too tight or too loose. The inside of the shoe should be 1-2 cm longer than the foot. 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 at the end of the day. Those patients with a foot deformity or a pre-ulcerative sign may need further adaptations to their footwear, which may include therapeutic footwear, custom-made insoles or a toe orthosis.

We know little about the adherence of patients to wearing properly fitting footwear before an ulcer has developed. Patients may value the role of properly fitting footwear to prevent ulcers, but some still consider their footwear to be the cause of their problems. Furthermore, anecdotally, many patients prefer not to wear bulky custom-made shoes when they have not yet experienced a foot ulcer.



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Is therapeutic footwear effective in preventing a recurrent plantar foot ulcer in an at-risk patient with diabetes?

Recommendation 7:

To prevent a recurrent plantar foot ulcer in an at-risk patient with diabetes, prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking (i.e. 30% relief compared to plantar pressure in standard of care therapeutic footwear), and encourage the patient to wear this footwear. (Strong; Moderate)

Rationale 7:

Two RCTs with very low risk of bias have demonstrated that therapeutic footwear, that has proven to effectively offload to the foot, can significantly reduce the risk of a recurrent plantar foot ulcer, provided the patient wears the footwear (5,19). Effect sizes were large (46.1 – 63.6% relative risk reduction compared to standard of care therapeutic footwear), but effect may vary across patients. These data confirm earlier findings in three RCTs of mixed methodological quality on the efficacy of therapeutic footwear: relative risk reductions compared to control condition: 52.5 – 70.2% (16-18). One other RCT, with low risk of bias, assessed the effect of therapeutic insoles and did not show a significant effect on ulcer recurrence compared to standard footwear, the relative risk reduction was only 12% (20). However, this study did not use insoles with proven efficacy in offloading plantar pressure.

The benefits of continuously wearing footwear with a proven offloading effect outweigh the potential harm; available trials have infrequently reported any harm related to footwear. Clinicians should encourage patients to wear 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 for which equipment to date is relatively expensive. However, these costs should always be regarded 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).



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This recommendation is predicated on the availability of both therapeutic footwear and technology for pressure measurement. Not in all regions and clinical settings, however, plantar foot pressure can be measured. For these cases, we recommend to prescribe therapeutic footwear using available state-of-the-art scientific knowledge on footwear designs that effectively offload the foot.

Is patient education effective in preventing a first foot ulcer in an at-risk patient with diabetes?

Recommendation 8:

To prevent a first foot ulcer in an at-risk patient with diabetes, provide education aimed at improving foot care knowledge and behaviour, as well as encouraging the patient to adhere to this foot care advice. (Weak; Low)

Rationale 8:

While the efficacy of patient education to prevent a first foot ulcer has not been studied in a controlled trial design, two large non-controlled studies showed convincingly that those patients who are adherent to the advice given in the education programme are at much lower risk of developing a first foot ulcer than those who are not adherent (21,22). Even though controlled studies on efficacy to prevent a first foot ulcer have not been performed to date, we believe that patients who are at risk for ulceration should receive some form of education. Such education should consist of information on foot complications and their consequences, on preventative behaviour, such as wearing adequate footwear and self-management of foot health, and on seeking professional help in a timely manner when patients identify a foot problem.

Is integrated foot care effective in preventing recurrent foot ulcers in an at-risk patient with diabetes?

Recommendation 9:

To prevent a recurrent foot ulcer in an at-risk patient with diabetes, provide integrated foot care, which includes professional foot treatment, adequate footwear and education. This should be repeated or re-evaluated once every one to three months as necessary. (Strong; Low)

Rationale 9:

We define an integrated foot care programme as an intervention that minimally includes professional foot care, patient education, and adequate footwear, with a regular review of the revision. One RCT, one non-randomized





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controlled trial and three non-controlled studies all reported significantly lower percentages of recurrent ulcers in patients who received integrated foot care compared to those who did not (23,24), or in those patients who were adherent to a program compared to those who were not (25-27). None of the studies reported any complications or other harm related to the program.

Professional foot care, by a professional trained in diabetic foot problems, can consist of callus removal, drainage of large blisters, protection of small blisters, treatment of ingrown or thickened nails, treatment of haemorrhage, or antifungal treatment for fungal infections, as necessary. Patient education should be repeated regularly, as two RCTs (28,29) demonstrated no effect on ulcer prevention of a single session of patient education. Education should be aimed at improving foot care knowledge and behaviour, as well as offering the patient support in adhering to this advice. For suggestions on adequate footwear see Recommendations 6 and 7. There is no information available on costs and cost-effectiveness of integrated foot care. A recent 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 (30).

Is self-management of foot health effective in preventing a first foot ulcer in an at-risk patient with diabetes?

Recommendation 10:

Instruct a high-risk patient with diabetes to monitor foot skin temperatures at home to prevent a first or recurrent plantar foot ulcer. This aims at identifying the early signs of inflammation, followed by action taken by the patient and care provider to resolve the cause of inflammation. (Weak; Moderate)

Rationale 10:

Self-management of foot health is considered by many to be an important component of foot care in at-risk patients with diabetes. Self-management can include many interventions, but we found no evidence to support any specific intervention, with the exception of home monitoring of foot skin temperature. Three RCTs, either with low or very low risk of bias, showed that monitoring of plantar foot skin temperature on a daily basis with an easy to use infrared thermometer, combined with subsequent preventative actions when elevated temperatures were noted, is effective over standard treatment to prevent foot ulcers in high risk-patients (IWGDF risk classification 2 or 3; (31-33)). As all three RCTs were from the same research group, generalizability of these findings is uncertain.

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Professionals may value home monitoring as an easy to use and relatively inexpensive method, with potentially high clinical value, empowering patients in the care of their own feet. However, adherence was an important factor in the conducted RCTs, and patients, in particular those who have not had a foot ulcer, may find the requirement for daily assessment a burden. False-positive and false-negative outcomes of temperature measurements may unnecessarily concern or stress patients and affect their confidence in this approach (34). To our knowledge, home monitoring of foot temperature is currently not implemented in foot care of high-risk patients with diabetes, which may be related to patient values or preferences, lack of easy access to calibrated equipment, lack of information on cost-effectiveness and implementation feasibility.

Are surgical interventions effective in preventing a foot ulcer in an at-risk patient?

Recommendation 11:

Consider digital flexor tenotomy to prevent a toe ulcer when conservative treatment fails in a high-risk patient with diabetes, hammertoes and either a pre-ulcerative sign or an ulcer on the toe. (Weak; Low)

Rationale 11:

Seven retrospective case series of percutaneous digital flexor tendon tenotomy performed to heal apex toe ulcers noted recurrence rates ranging between 0 and 20% in a total 231 treated patients, over a mean follow-up between 11 and 36 months (35-41). Four of these studies also reported on the effects of flexor tendon tenotomy of a toe where no ulcer was present at the time of the procedure. In a cumulative total of 58 patients with impending ulcers (i.e. abundant callus on tip of the toe or thickened nails) no ulcer occurrence was found in a mean 11-31 months follow-up (37,38,40,41). While controlled studies on this topic are lacking, we consider this a promising procedure in a patient who has a toe ulcer, or a pre-ulcerative sign on the toe, that fails to respond to conservative treatment, and requires normalization of foot structure to prevent ulceration.

The possible benefits of digital flexor tenotomy likely outweigh the harm, as few complications have been reported. Patients who have pre-ulcerative lesions for which they have frequent conservative 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, although minimal, should be discussed with the patient.



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Recommendation 12:

Consider Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection, or osteotomy to prevent a recurrent foot ulcer when conservative treatment fails in a patient with diabetes and a foot ulcer. (Weak; Low)

Rationale 12:

Primarily aimed at healing recalcitrant forefoot plantar ulcers, one RCT (with low risk of bias) and several non-controlled studies have shown a positive effect of Achilles tendon lengthening in preventing ulcer recurrence in the short and long term, with generally large effect sizes (42-48). One small RCT (with low risk of bias) (49), two retrospective cohort studies (with varying risk of bias) (50,51), and several non-controlled studies (52-56) found efficacy of single or pan metatarsal head resections to prevent ulcer recurrence, with generally large effect sizes found. One retrospective cohort study with high risk of bias and two small non-controlled studies showed low ulcer recurrence rates after metatarsal-phalangeal or inter-phalangeal joint arthroplasty (57-59). One retrospective cohort study on osteotomy showed a non-significant 60% reduction in ulcer recurrence compared to conservative treatment, while one non-controlled study showed no ulcer recurrence after osteotomy (60,61). While effect sizes are often large, very few studies show the efficacy of these interventions in well-designed controlled studies.

Possible complications and side effects of these surgical offloading techniques include post-operative infection, new deformities, gait problems and transfer ulcers (42,62). 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 recalcitrant to conservative treatment and that is expected to have 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 prevent ulcers, but as low when it causes complications such as significant gait or balance problems. The costs of surgical interventions can be much higher than for conservative treatment, but cost-effectiveness is unknown. Clinicians should carefully discuss possible adverse effects of the surgery with the patient.

Recommendation 13:

Do not use a nerve decompression procedure in an effort to prevent a foot ulcer in an at-risk patient with diabetes, in preference to accepted standards of good quality care. (Weak; Low)



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Rationale 13:

We found two retrospective cohort studies with high risk of bias, and three non-controlled studies that investigated nerve decompression in the prevention of foot ulcers in at-risk patients with diabetes (63-67). Although with positive results (one retrospective cohort study reported a significantly lower ulcer incidence in the operated leg compared to the contralateral non-operated leg of the same patient), the risk of bias of these studies was high, information on post-operative complications was scarce, and (most importantly) nerve decompression was not compared with accepted standards of good quality preventative care. Most studies were also from the same research group, further limiting the generalizability of these results. 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, nerve decompression should not be used, until more evidence for its efficacy compared to conservative treatment is obtained from appropriately designed controlled studies.

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1. Peripheral neuropathy is the most important risk factor for the development of foot ulcers in patients with diabetes, but research on the prevention or treatment of neuropathy is relatively scarce. A stronger research focus in this area is needed.
2. 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.
3. 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.
4. The vast majority of studies underlying this guidance are single intervention studies, yet preventative foot care for at-risk patients with diabetes nearly always consists of an integrated care approach. While studies on integrated foot care show some evidence of effectiveness in preventing a recurrent ulcer, unfortunately the exact content of this integrated strategy is frequently poorly described, hampering generalisability to other settings.
5. Adherence to an intervention has been shown to be crucial in preventing foot ulcers (5,22,25,26,33). It is consistently reported that patients who do not adhere present with higher rates of ulceration. A stronger focus is urgently needed on development, evaluation and implementation of methods that improve adherence to preventative diabetic foot treatment.
6. 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.





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Conflict of interest

LL: is on the speaker's bureau for Osiris, Integra, PamLabs, Smit&Nephew; consultant for KCI, PamLabs, Innovacyne; Stock ownership in Prizm Medical; received research grants from Osiris, MacroCure, ThermoTrek, Integra, GlaxoSmithKline, KCI, Cardinal, Dipexium; SB, JvN, AR, MMS, YJ, PP: none declared.

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1. To heal a neuropathic plantar forefoot ulcer without ischemia or uncontrolled infection in a patient with diabetes, offload with a non-removable knee-high device with an appropriate foot-device interface. (GRADE recommendation: strong, Quality of evidence: high)
2. When a non-removable knee-high device is contraindicated or not tolerated by the patient, consider offloading with a removable knee-high walker with an appropriate foot-device interface to heal a neuropathic plantar forefoot ulcer in a patient with diabetes, but only when the patient can be expected to be adherent to wearing the device. (Weak; Moderate)
3. When a knee-high device is contraindicated or cannot be tolerated by the patient, consider offloading with a forefoot offloading shoe, cast shoe, or custom-made temporary shoe to heal a neuropathic plantar forefoot ulcer in a patient with diabetes, but only and when the patient can be expected to be adherent to wearing the shoes. (Weak; Low)

Therapeutic footwear

4. To protect their feet, instruct an at-risk patient with diabetes not to walk barefoot, in socks, or in thin-soled standard slippers, whether at home or when outside (Strong; Low).
5. Instruct an at-risk patient with diabetes to wear properly fitting footwear to prevent a first foot ulcer, either plantar or non-plantar, or a recurrent non-plantar ulcer. When a foot deformity or a pre-ulcerative sign is present, consider prescribing therapeutic shoes, custom-made insoles, or toe orthosis. (Strong; Low)
6. To prevent a recurrent plantar foot ulcer in an at-risk patient with diabetes, prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking (i.e. 30% relief compared to plantar pressure in standard of care therapeutic footwear), and encourage the patient to wear this footwear. (Strong; Moderate)





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7. Do not prescribe, and instruct a patient with diabetes not to use, conventional or standard therapeutic shoes to heal a plantar foot ulcer. (Strong; Low)
8. Consider using shoe modifications, temporary footwear, toe spacers or orthoses to offload and heal a non-plantar foot ulcer without ischemia or uncontrolled infection in a patient with diabetes. The specific modality will depend on the type and location of the foot ulcer. (Weak; Low)

Surgical offloading interventions

9. Consider Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection, or osteotomy to prevent a recurrent foot ulcer when conservative treatment fails in a high-risk patient with diabetes and a plantar foot ulcer. (Weak; Low)
10. Consider digital flexor tenotomy to prevent a toe ulcer when conservative treatment fails in a high-risk patient with diabetes, hammertoes and either a pre-ulcerative sign or an ulcer on the toe. (Weak; Low)
11. To heal a neuropathic plantar foot ulcer without ischemia or uncontrolled infection in a patient with diabetes, consider Achilles tendon lengthening, single or pan metatarsal head resection, or joint arthroplasty when conservative treatment fails. (Weak; Low)
12. To heal a toe ulcer without ischemia or uncontrolled infection in a patient with diabetes and hammertoes, consider digital flexor tenotomy when conservative treatment fails. (Weak; Low)

Other offloading interventions

13. If other forms of biomechanical relief are not available, consider using felted foam in combination with appropriate footwear to offload and heal a neuropathic foot ulcer without ischemia or uncontrolled infection in a patient with diabetes. (Weak; Low)





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Consideration about side effects / complications

It is important that consideration is given to possible adverse effects of some of the above-mentioned interventions, which include the use of non-removable and removable knee-high offloading devices, and all surgical offloading procedures. These possible adverse effects, discussed below, should be discussed with the patient for informed shared-decision making.



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Foot ulcers are a major complication of diabetes mellitus and are associated with high morbidity, mortality, and costs.¹⁻³ Yearly incidence is estimated to be around 2% in patients with diabetes,⁴ but this increases substantially when patients successfully heal from a foot ulcer, with reported recurrence rates between 30% and 40% in the first year.^{5,6} Prevention and adequate treatment of these ulcers is therefore of paramount importance.

Risk factors

Peripheral neuropathy affects approximately half of people with diabetes mellitus and leads to loss of protective sensation in the feet, which is one of the most important risk factors for ulceration.^{3,7} In the presence of loss of protective sensation, elevated levels of mechanical pressure can contribute to the development of foot ulcers in diabetic patients.⁷⁻⁹ High foot pressure is itself significantly associated with foot deformity and structural changes in soft tissue.¹⁰ From this, it can be inferred that the combination of foot deformity, loss of protective sensation, inadequate off-loading, and a minor trauma leads to tissue damage and ulceration. And once an ulcer has formed, healing may be chronically delayed, if the area is not effectively offloaded.

Interventions

There is a long clinical tradition in the use of casting, footwear, surgery and other offloading techniques for the prevention and healing of foot ulcers in patients with diabetes. Previous reviews have shown that sufficient evidence is available to support the use of non-removable offloading techniques to heal plantar forefoot ulcers,¹¹⁻¹³ but that more high-quality studies are needed to confirm promising effects of other offloading interventions to prevent and heal foot ulcers, in order to better inform clinicians and practitioners about effective treatment.¹¹ Over the last few years, several well-designed controlled studies have been performed to meet this goal.

In this guidance document, recommendations are given for each of the above-listed intervention groups, and include the rationale for how we arrived at a recommendation.¹ This rationale was based on available evidence from a systematic review of the literature, expert opinion where evidence is not available, and the consideration of benefits and harm, patients' values and preferences, and costs related to the intervention.





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¹ Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (65). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence on: the risk of bias of included studies, effect sizes, and expert opinion, and rate the quality of evidence as 'high', 'moderate', or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.

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Are casting or prefabricated offloading effective techniques to heal plantar foot ulcers in patients with diabetes?

Recommendation 1:

To heal a neuropathic plantar forefoot ulcer without ischemia or uncontrolled infection in a patient with diabetes, offload with a non-removable knee-high device with an appropriate foot-device interface.
(GRADE recommendation: strong, Quality of evidence: high)

Rationale 1:

Two high-quality systematic reviews and meta-analyses of randomized and non-randomized controlled trials indicate that the use of non-removable offloading devices (both TCC and walkers rendered irremovable) results in a significantly higher proportion of healed diabetic neuropathic plantar forefoot ulcers when compared to removable off-loading devices (including both walkers and footwear).^{12,13} A Cochrane systematic review and meta-analysis included five RCTs¹⁴⁻¹⁸ with a cumulative total of 230 patients and found a relative risk ratio of 1.17 (95%CI 1.01-1.36; $p=0.04$) for non-removable offloading to achieve healing compared to removable offloading.¹² Another systematic review and meta-analysis included 10 randomized and non-randomized clinical studies with a cumulative total of 524 patients^{14-16,18-24} and showed a significantly higher relative risk ratio of 1.43 (95%CI 1.11-1.84, $p=0.001$) for non-removable offloading to achieve healing compared to removable offloading.¹³ Based on two, relatively small RCTs,^{17,25} there is evidence to suggest that a removable walker rendered irremovable is as effective as a TCC in healing neuropathic plantar forefoot ulcers (RR=1.06; 95%CI 0.88-1.27; $p=0.31$).¹³ Therefore, there is no particular preference for a TCC or prefabricated non-removable knee-high device to heal plantar foot ulcers, as long as an appropriate foot device interface is maintained. We conclude that the quality of evidence is high.

Possible adverse effects of non-removable knee-high devices include ankle joint immobilization, reduced activity level, potential risk of falls, knee or hip complaints due to asymmetry in walking from the unilaterally increased sole height, and pressure ulcers due to poor casting or fitting.^{15,26,27} Nevertheless, we consider the benefits of effective and expedited healing to outweigh such potential harm. Many patients may prefer not to use a non-removable knee-high device as it limits them in their daily life, for example with sleeping, bathing, or driving a





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car. Practitioners may also see several barriers to the application of non-removable offloading, as surveys and epidemiological studies show only limited use of the TCC in clinical practice.^{28,29} Cost-effectiveness has not been assessed to date. One study showed, however, that, while only 6% of patients with a foot ulcer were treated with a TCC, the average cost of treatment of these patients was half that incurred by patients who were not treated with a TCC.³⁰

Non-removable knee-high devices can be considered for healing ulcers that are mildly infected, i.e., under control with antibiotic treatment, and none to only small amounts of exudate.³¹ Non-removable offloading is less suitable for heavily exudating ulcers or active infections that are not yet under control and that require frequent local care or inspection. Non-removable knee-high devices may also be considered in patients with mild peripheral arterial disease, i.e. present to a level that there is potential for wound healing.³¹ If there is any doubt on potential for wound healing, do not use non-removable offloading. Do not use non-removable offloading when both mild infection and mild PAD is present.³¹ With severely infected and/or severe ischemic foot ulcers, the infection and ischemia should first be resolved before offloading can be applied.

Recommendation 2:

When a non-removable knee-high device is contraindicated or not tolerated by the patient, consider offloading with a removable knee-high walker with an appropriate foot-device interface to heal a neuropathic plantar forefoot ulcer in a patient with diabetes, but only when the patient can be expected to be adherent to wearing the device. (Weak; Moderate)

Rationale 2:

A systematic review and meta-analysis, including 10 randomized and non-randomized clinical studies and a cumulative total of 524 patients^{14-16,18-24} showed significantly better healing for non-removable offloading compared to removable offloading (RR 1.43 (95%CI 1.11-1.84, $p=0.001$)).¹³ However, stratified by type of removable device, five RCTs^{14-16,18,22} found a trend but no statistically significant difference between non-removable knee-high off-loading devices and removable knee-high walkers (RR=1.23, 95%CI 0.96-1.58, $p=0.085$).¹³ Based on the availability of five RCTs, and wide confidence interval around the point estimator of relative risk (suggesting inconsistency), we conclude that the quality of evidence is moderate.



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Possible adverse effects of knee-high removable devices include ankle joint immobilization, reduced activity level, potential risk of falls, or knee or hip complaints due to asymmetry in walking from the unilaterally increased sole height. Nevertheless, we consider the benefits of effective treatment to outweigh the potential harm. Patients may value and prefer the use of a removable knee-high offloading device, as it is more practical than non-removable offloading for activities such as bathing, sleeping and driving a car. However, the possibility of non-adherence should always be considered, as one study showed that patients with active ulcers who are prescribed with a removable walker wore their device only 28% of the steps that they took.³² Practitioners may also prefer a removable walker over a TCC, since the former does not require a skilled technician to apply the device. Furthermore, wound care and inspection can take place at any time with a removable device, not only when devices are replaced such as with non-removable offloading. Costs are considered to be relatively high for many of the available removable knee-high walkers, but should always be considered with respect to efficacy in healing; cost-effectiveness has not been reported to date.

Additionally, removable walkers can be considered for healing:

- Heavily exudating plantar foot ulcers or ulcers with active mild infection that is not yet under control, which requires frequent local care or inspection.
- Plantar foot ulcers when there is mild PAD and some doubt regarding the potential for wound healing.
- Plantar foot ulcers when both a mild infection that is under control and mild PAD with potential for healing are present.

With severely infected or ischemic foot ulcers, the infection or ischemia should first be resolved before offloading can be applied.

Recommendation 3:

A knee-high device is contraindicated or cannot be tolerated by the patient, consider offloading with a forefoot offloading shoe, cast shoe, or custom-made temporary shoe to heal a neuropathic plantar forefoot ulcer in a patient with diabetes, but only and when the patient can be expected to be adherent to wearing the shoes. (Weak; Low)

Rationale 3:

Several non-controlled studies show that 70% to 96% of plantar foot ulcers can be healed in a reasonable time frame (mean 34 -79 days) with ankle-high removable offloading shoes such as cast shoes, half shoes, and fore-





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foot offloading shoes.³³⁻³⁷ These outcomes are comparable to those found with TCC. However, in the only controlled study on this topic, half shoes have shown to be inferior to the TCC.¹⁵ The use of custom-made temporary shoes for healing relatively large and deep ulcers, some with mild infection, in neuropathic patients of which many had moderate PAD, was examined in one RCT at low risk of bias. The study found relatively low healing proportions, and equivalence in healing proportion and reduction in ulcer area between the temporary shoes and a TCC.²⁰ Based on the limited number of controlled studies, the quality of evidence is low.

The benefits of treatment with ankle-high offloading shoes compared to other ankle-high modalities such as conventional shoes will likely outweigh potential harm, but compared to knee-high devices the lower efficacy and/or longer healing times associated with such interventions poses a higher risk for infection and hospitalization. The traditional form of half-shoes, that only support the midfoot and heel,³⁶ are contra-indicated due to risk of midfoot fracture. Patients may prefer to use an ankle-high modality over a knee-high device to promote walking, and among ankle-high modalities likely prefer a comfortable cast shoe or custom-made temporary shoe over a half-shoe or forefoot offloading shoe, because the latter have a significant negative rocker outsole that may cause balance problems during gait. The cost of treatment is relatively low for forefoot offloading shoes and cast shoes, both requiring no replacement during treatment. Costs for custom-made temporary shoes are relatively higher; cost-effectiveness has not been reported.



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Is therapeutic footwear effective to prevent first or recurrent foot ulcers in patients with diabetes?

Recommendation 4:

To protect their feet, instruct an at-risk patient with diabetes not to walk barefoot, in socks, or in thin-soled standard slippers, whether at home or when outside (Strong; Low).

Rationale 4:

No studies have been performed on the effect of walking barefoot, in socks, or in thin-soled standard slippers, on risk of foot ulceration. However, there are many large prospective studies that show that at-risk patients with diabetes have elevated levels of mechanical plantar pressure during barefoot walking, which are a significant independent risk factor for foot ulceration,^{7,9} and should therefore be reduced. In addition, walking barefoot, in socks, or in thin-soled standard slippers provides only limited protection against thermal or external trauma.

Recommendation 5:

Instruct an at-risk patient with diabetes to wear properly fitting footwear to prevent a first foot ulcer, either plantar or non-plantar, or a recurrent non-plantar ulcer. When a foot deformity or a pre-ulcerative sign is present, consider prescribing therapeutic shoes, custom made insoles, or toe orthosis. (Strong; Low)

Rationale 5:

One RCT with high risk of bias showed a positive effect of therapeutic footwear over no footwear prescription in at-risk patients, most of which had no ulcer history, to prevent ulcer incidence.³⁸ Another RCT with high risk of bias showed a clear trend, but no significant effect of shear-reducing insoles.³⁹ A third RCT at very low risk of bias showed that digital silicone orthoses can significantly reduce first ulcer incidence in at-risk patients with pre-ulcerative lesions.⁴⁰ Relative risk reduction for use of the intervention varied between 69.8% and 92.9% in these studies, although the 95% confidence intervals show that effect may vary for individual patients. There are no studies on the effect of therapeutic footwear on the prevention of non-plantar lesions. However, ill-fitting footwear has been identified as an important cause of non-plantar ulcers,⁴¹ suggesting that properly fitting footwear can protect against ulceration. In properly fitting footwear, the shoe should not be either too tight or too loose. The inside of the shoe should be 1-2 cm longer than the foot. The internal width should equal the



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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 at the end of the day. Those patients with a foot deformity or a pre-ulcerative sign may need further adaptations to their footwear, which may include therapeutic footwear, custom-made insoles or a toe orthosis. Based on the small number of RCTs, on a wide range of interventions, the quality of evidence is low.

Little harm has been reported from (properly fitting) therapeutic footwear. Therefore the benefits likely outweigh the potential harm. We know little about adherence of patients to wearing therapeutic footwear before an ulcer has developed. Patients will likely value the role of therapeutic footwear to prevent ulcers, but they may still believe that their footwear is the cause if a foot ulcer occurs. Furthermore, anecdotally, many patients prefer not to wear 'bulky' custom-made shoes when they have not yet experienced a foot ulcer. The cost-effectiveness is unknown.

Recommendation 6:

To prevent a recurrent plantar foot ulcer in an at-risk patient with diabetes, prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking (i.e. 30% relief compared to plantar pressure in standard of care therapeutic footwear), and encourage the patient to wear this footwear (Strong; Moderate)

Rationale 6:

Two RCTs with very low risk of bias show that therapeutic footwear that has proven to effectively offload the foot can significantly reduce the risk for a recurrent plantar foot ulcer. One of the trials was specific to metatarsal head ulcers, and in the other trial the effect required adherence to wearing the footwear.^{6,42} Effect sizes were large (46.1 – 63.6% relative risk reduction compared to standard of care therapeutic footwear) but 95% confidence intervals show that effect may vary across patients. These data confirm earlier findings in three RCTs with mixed methodological quality on the efficacy of therapeutic footwear (relative risk reductions compared to control condition: 52.5 – 70.2%).^{38,39,43} One other RCT at low risk of bias assessed the effect of therapeutic insoles and showed no significant effect on ulcer recurrence compared to standard footwear (relative risk reduction 12%).⁴⁴ However, the latter study did not use insoles with proven efficacy in offloading plantar pressure. Based on the availability of several trials at very low or low risk of bias, some inconsistency in findings between trials, and large confidence intervals around effect size, we conclude that the quality of evidence is moderate. The benefits of continuously wearing footwear with a proven offloading effect outweigh the potential harm, since



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few footwear-related complications are reported in these trials. Patients may value the use of therapeutic footwear to protect their feet against ulcer recurrence, but often patients do not wear the footwear, especially when at home.⁴⁵ Some patients may not know that their prescribed footwear should also be worn inside the house. Such patients should be correctly informed about the purpose and value of their therapeutic footwear and be motivated to continuously wear the footwear.⁴⁶ Other patients may prefer not to wear their therapeutic footwear at home because they find their shoes heavy, bulky, dirty, difficult to don and doff, or for religious reasons. In such cases, prescription of an additional pair of offloading footwear specifically for indoor use may be a useful solution, although evidence is currently lacking.⁴⁵ 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 for which equipment to date can be relatively expensive. However, these costs should always be regarded in association with the benefit for ulcer prevention; cost-effectiveness has not been studied to date but, in our opinion, footwear designed or evaluated using plantar pressure measurement will likely be cost-effective when it reduces risk of ulcer recurrence by 50%, as was found in most trials on this topic.

This recommendation is predicated on the availability of both therapeutic footwear and technology for pressure measurement. Not in all regions and clinical settings, however, plantar foot pressure can be measured. For these cases, we recommend to prescribe therapeutic footwear using available state-of-the-art scientific knowledge on footwear designs that effectively offload the foot.

Is therapeutic footwear effective to prevent first or recurrent foot ulcers in patients with diabetes?

Recommendation 7:

Do not prescribe, and instruct the patient with diabetes not to use, conventional or standard therapeutic shoes to heal a plantar foot ulcer (Strong; Low)

Rationale 7:

There are no studies that show the efficacy of conventional or standard therapeutic shoes to heal neuropathic plantar foot ulcers. In the few studies in which this footwear has been tested as comparison condition, the footwear proved inferior to other offloading devices.¹⁹





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Harm will outweigh the benefits for the use of conventional or standard therapeutic footwear for ulcer healing. Patients may prefer such shoes to knee-high offloading devices because they facilitate walking. Costs for conventional or standard therapeutic footwear are relatively low, but this footwear is not expected to be cost-effective in comparison to other commonly used offloading devices.

Recommendation 8:

Consider using shoe modifications, temporary footwear, toe spacers or orthoses to offload and heal a non-plantar foot ulcer without ischemia or uncontrolled infection in a patient with diabetes. The specific modality depends on the type and location of the foot ulcer. (Weak; Low)

Rationale 8:

There is no evidence available on how to treat non-plantar foot ulcers, even though such lesions often also need relief from mechanical stress. Depending on the location of the ulcer, various modalities can be considered, including shoe modifications, temporary footwear, toe spacers and orthoses. Temporary footwear does not have to be custom-made, but can consist of properly-fitting standard therapeutic footwear that prevents direct contact with the ulcer.

Based on expert opinion, we expect the benefits of the use of these modalities to outweigh any potential harm such as lesions caused by the footwear or orthoses. Patients will likely value the use of these modalities and prefer them for treatment of their non-plantar foot ulcers. Costs for applying these modalities are relatively low.



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Recommendation 9:

Consider Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection or osteotomy to prevent a recurrent foot ulcer when conservative treatment fails in a high-risk patient with diabetes and a plantar foot ulcer (Weak; Low)

Rationale 9:

One RCT with low risk of bias and several non-controlled studies show the positive effect of Achilles tendon lengthening (ATL), performed primarily to heal recalcitrant forefoot plantar ulcers, in preventing ulcer recurrence.⁴⁷⁻⁵³ Relative risk reductions over conservative treatment were 75% and 52% at seven months and two years, respectively.⁴⁷ One small RCT with low risk of bias⁵⁴, two retrospective cohort studies with varying risk of bias,^{55,56} and several non-controlled studies,⁵⁷⁻⁶⁰ found efficacy of single or pan metatarsal head resections to prevent ulcer recurrence. The controlled studies showed relative risk reductions between 61.1% and 83.8% over conservative treatment. Two small retrospective cohort studies with high risk of bias and three non-controlled studies showed low ulcer recurrence rates after metatarsal-phalangeal or inter-phalangeal joint arthroplasty.⁶¹⁻⁶⁵ One of the cohort studies showed a relative risk reduction of 83.6% compared to conservative treatment. One retrospective cohort study on osteotomy showed a 60% but non-significant reduction in ulcer recurrence compared to conservative treatment, while one non-controlled study showed no ulcer recurrence after osteotomy.^{66,67}

While effect sizes are often large, only few controlled studies per intervention show the efficacy of these surgical approaches. Furthermore, these surgical procedures apply to selected patients only: for all mentioned surgical procedures they apply to those patients that fail conservative treatment for an active foot ulcer and who are considered at very high risk if foot structure is not permanently changed. Furthermore, ATL applies only to patients with limited ankle dorsiflexion. Considering the small number of controlled studies and the often high risk of bias in the studies on surgical offloading, we conclude that the quality of evidence is low.

Possible complications and side effects of these surgical offloading techniques include infection, gait problems, acute Charcot neuro-osteoarthropathy, and transfer ulcers.^{50,59,68} Risk of a heel ulcer after ATL was 13% in two years in one study that also showed a 34% increase in heel peak pressure.⁴⁷ In another study, risk for heel ulcers



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was 15% at a median 12 months follow-up that also showed that the highest risk for heel ulcers (47%) was in patients with heel anaesthesia and significant dorsiflexion that was possible after ATL; these conditions therefore imply a contraindication.⁵⁰ Other studies report no, or only a small risk of heel ulceration from ATL.⁵¹⁻⁵³ Risk of transfer ulcers after single metatarsal head resection was 41% in an average 13.1 months in one study,⁵⁹ while two other studies did not report any transfer ulcers from this procedure at either six or 12 months follow-up.^{55,56} In non-selected patients with diabetic neuropathy undergoing foot- and ankle surgery, post-operative surgical site infection developed in 9.5%.⁶⁹ Based on these outcomes, it is not clear if the benefits outweigh the potential harm. Patient value and preferences for these approaches are unknown, although we expect patients to value an intervention as high when it can prevent ulcers, but as low when it causes complications. The costs of surgical interventions are generally higher than for conservative treatment, although one study showed no difference in costs between metatarsal head resection and conservative treatment.⁶⁸ Cost-effectiveness is unknown.

Recommendation 10:

Consider digital flexor tenotomy to prevent a toe ulcer when conservative treatment fails in a high-risk patient with diabetes, hammertoes and either a pre-ulcerative sign or an ulcer on the toe. (Weak; Low)

Rationale 10:

Seven retrospective case series of percutaneous digital flexor tendon tenotomy performed in patients primarily to heal apex toe ulcers, reported a recurrence rate after healing between 0 and 20% over a mean follow-up between 11 and 36 months in a cumulative total 231 treated patients.⁷⁰⁻⁷⁶ Four of the seven studies also reported on the effects of digital tenotomy of a toe where no ulcer was present at the time of the procedure. In a cumulative total of 58 patients with impending ulcers (i.e. callus on the tip of the toe) there was no reported ulcer occurrence in a mean 11 to 31 month follow-up.^{72-74,76} While controlled studies on this topic are lacking, we consider this a promising procedure, to prevent both first and recurrent ulcers, in patients with pre-ulcerative lesions that fail conservative treatment. This is based on the low incidence rates found, our expert opinion, and results from healing studies. The quality of evidence is nevertheless low.

The possible benefits of digital flexor tenotomy likely outweigh the harm; very few complications have been reported. Patients who have pre-ulcerative lesions for which they have frequent conservative treatment that does not improve outcome may value and prefer treatment by flexor tenotomy. Furthermore, flexor tenotomy 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.



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Are any other offloading techniques effective to prevent foot ulcers in patients with diabetes?

Recommendation 13:

If other forms of biomechanical relief are not available, consider using felted foam in combination with appropriate footwear to offload and heal a neuropathic foot ulcer without ischemia or uncontrolled infection in a patient with diabetes. (Weak; Low)

Rationale 13:

Two RCTs with high risk of bias and one retrospective cohort study examined the effect of felted foam in ulcer healing. One RCT showed significantly shorter time to healing with felted foam worn in a post-operative shoe when compared to a pressure relief half-shoe used without the felted foam.⁷⁸ Another RCT showed no difference in healing proportion or time to healing between felt fitted to the foot compared with felt fitted to temporary therapeutic footwear.⁷⁹ Felted foam worn in a surgical shoe, a healing shoe, or a walking splint was reported to be as effective as a TCC in both healing proportion and time to healing.³⁵ Based on the lack of well-designed controlled studies, and the difficulty in determining the added effect of felted foam in the studies performed, the quality of evidence is low.

Any benefit found with the use of felted foam will likely outweigh the harm, since studies of felted foam have reported no complications. Patients will likely value and prefer the use of felted foam as an easy to use, non-limiting modality. The costs of felted-foam are relatively low, but it does require frequent replacement, either by the patient, a relative, or a home-care nurse. Based on the evidence from the studies performed, felted foam should only be used in addition to appropriate footwear, walkers or cast, and not as a single treatment modality.

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1. Many clinical studies on offloading do not directly measure the degree to which offloading has been achieved by the intervention. However, such measurements not only improve our understanding of the role of off-loading in prevention and healing, but also improve outcome.
2. To effectively heal plantar forefoot ulcers, the TCC is no longer necessarily the gold standard treatment option.^{12,13} Prefabricated removable walkers that are rendered irremovable have been shown to be as effective as the TCC.¹³ This changes the traditional view on offloading, in which the main comparison was TCC versus any other device, but has now changed in non-removable versus removable offloading. This has positive implications for those settings where casting technicians are not available or where personnel are not specifically trained. In these settings, reliance on the correct use of prefabricated methods for offloading seems appropriate.
3. Offloading studies have focused almost exclusively on the treatment of non-complicated neuropathic plantar forefoot ulcers. Little to no data is available on the value of offloading in healing complicated plantar foot ulcers, midfoot and heel ulcers, or non-plantar ulcers, even though these ulcers are now more common in specialized settings.^{1,31} Complicated ulcers require adjunctive treatment to reduce the infection and the ischemia, before offloading is initiated or during offloading when complications are only mild. High-quality studies on offloading ulcers other than the non-complicated neuropathic plantar forefoot ulcer are urgently needed.
4. Adherence to an intervention is crucial in preventing and healing foot ulcers. It is consistently reported that those who do not adhere to an intervention present with worse clinical outcomes. A stronger focus is required, both in research and in clinical practice, on the measurement and improvement of treatment adherence.
5. Surgical offloading has primarily been applied to heal foot ulcers in selected patients, and only secondarily to prevent ulcer recurrence. It is therefore interesting that surgical offloading, when compared to conservative treatment, has been shown to be more effective in preventing recurrence than in healing foot ulcers. This controversy between application and efficacy needs more attention and may shift the focus of surgical intervention to being more an approach that is valuable for prevention than for healing.
6. Those at-risk patients who have not yet developed a foot ulcer have received little attention in footwear and





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offloading studies. Few interventions have been adequately investigated or are widely accepted in clinical practice. In several cases, benefits in preventing a first foot ulcer may not outweigh possible harm or costs, as large groups of patients will be targeted while event rate is relatively low. These patient categories, however, should be carefully evaluated, before definitive conclusions can be drawn.

7. Costs and cost-effectiveness have also received very little attention in studies on footwear and offloading, despite the fact that reimbursement through insured care is more and more dependent on proven cost-effectiveness. More attention is warranted in view of the continuing pressure of health care cost-containment.
8. 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 prevention and healing in these lower income regions where climate and/or resources may be a factor in adherence to, or efficacy of, treatment.

Conflict of interest

PRC owns stock in DIApedia and is an inventor on US patents 6,610,897 6,720,470 and 7,206,718 that describe a load relieving dressing and a method of insole manufacture for offloading diabetic feet.

SB, RvD, DGA, JL, CC: none declared

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B

Bespoke shoe: British English synonym for Custom-made shoe (see below)

C

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.

Conventional shoe: “off-the-shelf” mass-produced shoe without any intended therapeutic effect.

Custom-made insole: accommodative insole made to the contours of the individual foot of the patient often in a multi-layer construction. May also incorporate other modifications such a Metatarsal pad or Metatarsal bar.

Custom-made shoe: a unique, usually hand-made, shoe built on a positive model of the patient’s foot to accommodate deformity and relieve pressure over at-risk sites on the plantar and dorsal surfaces of the foot. See also Bespoke shoe and Orthopaedic shoe.

Custom-made temporary shoe: a unique, usually hand-made, 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.

Customized insole: loosely used term in American English to denote a pre-fabricated insole to which some minor modifications specific to the patient’s foot may have been made. This term is not synonymous with Custom-made insole.

D

Depth inlay shoe: American English synonym for Extra-depth shoe.



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Depth shoe: American English synonym for Extra-depth shoe.

E

Extra-depth shoe: shoe 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 a conventional shoe. Even greater depth is sometimes provided in shoes that are referred to as double depth or super extra-depth. See also Depth Inlay shoe and Depth Shoe.

F

Felted foam: a fibrous, unwoven material backed by foam with absorbing and cushioning characteristics

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.

H

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.

Healing shoe/sandal: specially designed sandals with insoles that reduce pressure.

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.

I

In-shoe orthosis: term used for devices put inside the shoe to achieve some alteration in the function of the foot.

In-shoe orthotics: term sometimes loosely used for devices put inside a shoe to achieve some alteration in function. Correct plural of orthosis is actually orthoses.



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L

Liner: American English synonym for insole.

M

Mabal cast shoe: removable fibreglass combi-cast shoe existing of minimal padding, a rigid sole with total contact of the entire plantar surface and a soft cast upper part extending to just below the ankle leaving the ankle mobile. A plastic roller sandal is worn underneath the shoe to facilitate walking.

Metatarsal pad: Small pad placed behind the metatarsal head to relieve focal pressure and transfer load more proximally.

Metatarsal bar: bar extending across part of or the entire forefoot placed behind the metatarsal heads to relieve focal pressures and transfer load more proximally.

N

Non-removable (cast) walker: Same as removable (cast) boot/walker but then with a layer(s) of fibreglass cast material circumferentially wrapped around it rendering it irremovable (also known as “instant total contact cast”)

O

Orthopaedic shoe: synonym for Custom-made shoe (see above)

P

Post-operative shoe: prefabricated shoe with roomy and soft upper worn after an operation to the foot.

Pre-fabricated insole: an “off-the-shelf” flat or contoured insole made without reference to the shape of the patient’s foot.

R

Ransart boot: removable fibreglass combi-cast shoe extending to just below the ankle, existing of minimal pad-



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ding and moulded to the shape of the foot with total contact of the entire plantar surface. A window is cut over the ulcer area.

Removable (cast) boot/walker: prefabricated removable knee-high boot with a rocker or roller outsole configuration, padded interior, and an insertable and adjustable insole which may be total contact.

Rocker shoe: Shoe with rigid outsole designed and a sharp transition on the outsole. The shoe rocks forward in the late support phase to allow walking without extension of the metatarsal-phalangeal joints.

Roller shoe: Shoe with rigid outsole similar to the rocker shoe, but with a contoured outsole to provide a smoother transition during walking

S

Scotch-cast boot: a removable well-padded cast cut away at the ankle. Windows are cut over the ulcers if needed. For large heel ulcers, a removable heel cap of fibreglass is added. The boot is worn with a cast sandal to increase patient mobility.

Shoe insert: loosely used American English synonym for insole or in-shoe orthosis.

Shoe modification: modification to an existing shoe with an intended therapeutic effect, e.g. pressure relief.

Standard therapeutic shoe: pre-fabricated form of Therapeutic shoe, without any customization to the patient's foot.

T

Temporary shoe: Pre-fabricated shoe that is used temporarily to treat a foot ulcer.

Therapeutic Shoe: Generic term for footwear designed to allow some form of treatment to be applied to the foot that cannot be applied by or in a conventional shoe. Extra depth shoes, custom-made shoes, etc. are all examples of therapeutic shoes. (Greek therapeutikos, from therapeuein to attend, treat).





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

Total contact cast: a well-moulded, minimally padded, knee-high non-removable fibreglass or plaster cast that maintains total contact with the entire plantar surface and lower leg. The cast is often worn with an attachable sole to facilitate walking.

W

Windowed cast: same a total contact cast but then with a window cut out at the site of an ulcer to facilitate wound assessment and treatment in-between cast replacements





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Diagnosis

1. Examine a patient with diabetes annually for the presence of peripheral artery disease (PAD); this should include, at a minimum, taking a history and palpating foot pulses. (GRADE recommendation: strong; Quality of evidence: low)
2. Evaluate a patient with diabetes and a foot ulcer for the presence of PAD. Determine, as part of this examination, ankle or pedal Doppler arterial waveforms; measure both ankle systolic pressure and systolic ankle brachial index (ABI). (Strong; Low)
3. We recommend the use of bedside non-invasive tests to exclude PAD. No single modality has been shown to be optimal. Measuring ABI (with <0.9 considered abnormal) is useful for the detection of PAD. Tests that largely exclude PAD are the presence of ABI 0.9 - 1.3 , toe brachial index (TBI) ≥ 0.75 and the presence of triphasic pedal Doppler arterial waveforms. (Strong; Low)

Prognosis

4. In patients with a foot ulcer in diabetes and PAD, no specific symptoms or signs of PAD reliably predict healing of the ulcer. However, one of the following simple bedside tests should be used to inform the patient and healthcare professional about the healing potential of the ulcer. Any of the following findings increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg; or, a TcPO₂ ≥ 25 mmHg. (Strong; Moderate)
5. Consider urgent vascular imaging and revascularisation in patients with a foot ulcer in diabetes where the toe pressure is <30 mmHg or the TcPO₂ <25 mmHg. (Strong; Low)
6. Consider vascular imaging and revascularisation in all patients with a foot ulcer in diabetes and PAD, irrespective of the results of bedside tests, when the ulcer does not improve within 6 weeks despite optimal management. (Strong; Low)



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7. Diabetic microangiopathy should not be considered to be the cause of poor wound healing in patients with a foot ulcer. (Strong; Low)
8. In patients with a non-healing ulcer with either an ankle pressure <50mmHg or ABI <0.5 consider urgent vascular imaging and revascularisation. (Strong; Moderate)

Treatment

9. Colour Doppler ultrasound, CT-angiography, MR-angiography or intra-arterial digital subtraction angiography can each be used to obtain anatomical information when revascularisation is being considered. The entire lower extremity arterial circulation should be evaluated, with detailed visualization of below-the-knee and pedal arteries. (Strong; Low)
10. 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, with the aim of achieving a minimum skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg; or, a TcPO₂ ≥ 25 mmHg (Strong; Low)
11. A centre treating patients with a foot ulcer in diabetes should have the expertise in and rapid access to facilities necessary to diagnose and treat PAD; both endovascular techniques and bypass surgery should be available. (Strong; Low)
12. After a revascularisation procedure for a foot ulcer in diabetes, the patient should be treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)
13. Do not use a nerve decompression procedure in an effort to prevent a foot ulcer in an at-risk patient. (Weak; Low)
14. Patients with signs of PAD and a foot infection are at particularly high risk for major limb amputation and require emergency treatment. (Strong; Moderate)
15. Avoid revascularisation in patients in whom, from the patient perspective, the risk-benefit ratio for the probability of success is unfavourable. (Strong; Low)





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- 16.** All patients with diabetes and an ischemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension and prescription of a statin as well as low-dose aspirin or clopidogrel. (Strong; Low)

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Peripheral artery disease

Peripheral artery disease (PAD) is more common in patients with diabetes and around half of patients with a diabetic foot ulcer have co-existing PAD (1-3). PAD has been variously defined in the literature, but for the purposes of this guidance document it is defined as any atherosclerotic arterial occlusive disease below the level of the inguinal ligament resulting in a reduction in blood flow to the lower extremity. Aorto-iliac disease is not considered in the current guidance because the treatment of supra-inguinal disease in people with diabetes does not differ markedly from that in non-diabetic individuals. Peripheral arterial disease in diabetes is a condition predominantly of the infra-inguinal vasculature and is distinct from that in patients without diabetes in its characteristics, treatment and outcomes. Identifying PAD among patients with foot ulceration is important because its presence is associated with worse outcomes, such as a slower (or lack of) healing of foot ulcers, lower extremity amputations, subsequent cardiovascular events and premature mortality (4, 5). Diagnosing PAD is challenging in patients with diabetes, as they frequently lack typical symptoms, such as claudication or rest pain, even in the presence of severe tissue loss (1, 6, 7). Arterial calcification (8-10), foot infection, oedema and peripheral neuropathy, each of which is often present with diabetic foot ulceration, may adversely affect the performance of diagnostic tests for PAD.

Risk-factors & Interventions

When clinicians diagnose PAD they should consider its potential adverse effects on ulcer healing and risk of amputation. For each patient, the clinician should estimate the potential for infection resolution, wound healing and avoidance of amputation by balancing the severity of the perfusion deficit and the perfusion required for good outcomes (11). The amount of blood flow required is affected by factors such as the presence of infection, extent of tissue loss and abnormal mechanical loading of the foot during walking. A revascularisation procedure can have several aims, such as promotion of wound healing, helping to resolve infection and avoiding or limiting the level of amputation. But, it is currently unclear how to identify those patients with PAD and a diabetic foot ulcer (DFU) who are most likely to benefit from revascularisation. Furthermore, there is debate about the selection of the correct revascularisation technique such as when to choose an endovascular approach or a surgical bypass.



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Formulation of recommendations

This guidance document has been prepared by a working group of experts of the International Working Group on the Diabetic Foot (IWGDF) and was subsequently reviewed, revised and approved by the Editorial Board and members of the IWGDF. It is based on three systematic reviews on diagnosis, prognosis and treatment (endovascular or bypass) of PAD in a patient with diabetes and a foot ulcer, which are separately published in this journal (12-14). For each of these topics, we offer recommendations and a rationale of how we arrived at these, as well making a grading according to the GRADE system.¹ For several topics we did not perform a systematic review (e.g., the value of history taking in diagnosing PAD or its medical treatment) and our recommendations for these are based on expert opinion, supported by the available literature.

¹ *Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (37). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence based on: the risk of bias of included studies, effect sizes, and expert opinion, and to rate the quality of evidence as 'high', 'moderate', or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harm, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.*

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Diagnosis

Which 'bedside' diagnostic procedure, alone or in combination, has the best performance in diagnosing or excluding PAD in an asymptomatic person with diabetes?

Recommendation 1:

Examine a patient with diabetes annually for the presence of PAD; this should include, at a minimum, taking a history and palpating foot pulses. (GRADE recommendation: strong; Quality of evidence: low)

Recommendation 2:

Evaluate a patient with diabetes and a foot ulcer for the presence of PAD. Determine, as part of this examination, ankle or pedal Doppler arterial waveforms; measure both ankle systolic pressure and systolic ABI. (Strong; Low)

Rationale 1&2:

These recommendations are in line with other (inter)national guidelines on the management of diabetes, recommending yearly screening for PAD in subjects with diabetes (15). In addition to absent foot pulses, specific clinical findings that alert the healthcare professional to the presence of PAD include the presence of a cool lower limb, femoral bruits and a slow venous filling time (16). 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 (17). Patients with diabetes and these signs of PAD should be reviewed on a regular basis by a member of a specialist foot care team. Moreover, individuals found to have PAD have an elevated risk of other cardiovascular diseases, necessitating strategies to address these problems as well (18).

As discussed above, up to 50% of the patients with diabetes and a foot ulcer have PAD, and these patients have been consistently shown to be at increased risk for failure to heal the ulcer and lower limb loss (4, 19). Few data exist about the accuracy of symptoms or clinical examination for the identification of PAD in patients with a foot ulcer. However, it would seem appropriate that these patients should be initially assessed in a similar manner to the patient with a non-ulcerated (intact) foot. Identification of the patient with PAD is essential to optimise management of the foot ulcer and in undertaking other measures to mitigate cardiovascular risk (20). Patients should be informed that they have PAD and that it confers an increased risk to their foot.



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Which symptoms and signs (clinical examination) should clinicians examine for in a patient with diabetes mellitus in order to identify or exclude PAD?

Recommendation 3:

We recommend the use of bedside non-invasive tests to exclude PAD. No single modality has been shown to be optimal. Measuring ABI (with <0.9 considered abnormal) is useful for the detection of PAD. Tests that largely exclude PAD are the presence of ABI 0.9 - 1.3 , TBI ≥ 0.75 and the presence of triphasic pedal Doppler arterial waveforms. (Strong; Low)

Rationale 3:

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. Even in the hands of a skilled examiner, palpable pulses may be present despite the presence of significant ischemia (21). Therefore, a more objective evaluation should be performed in all patients. As discussed in our systematic review (12), an ABI (<0.9) is a useful test for the detection of PAD in asymptomatic diabetic subjects who do not have peripheral neuropathy. Peripheral neuropathy is associated with medial wall calcification (Mönckeberg sclerosis) of the arteries in the lower leg, which may result in rigid arteries and an elevated ABI, adversely affecting the test. However, medial calcification does not necessarily cause arterial stenosis and reduced blood flow (8, 9, 18). The exclusion of patients with incompressible arteries (defined by an ABI ≥ 1.3), a factor known to be associated with poorer outcome in patients with limb ischemia, in a number of published studies makes it increasingly difficult to evaluate its diagnostic utility (12, 22). In contrast, detection of a triphasic pedal Doppler arterial waveform with a hand-held Doppler appears to provide stronger evidence for the absence of PAD. The same applies for measurement of a toe brachial index (TBI), which makes the presence of PAD unlikely if it is ≥ 0.75 (12). Toe pressures may be falsely elevated by the same factors that affect ABI (including digital calcification). All of the bedside techniques should be performed in a standardised manner by trained healthcare professionals. There is insufficient evidence to support selecting any one of the bedside non-invasive diagnostic modalities for the detection of PAD across a spectrum of patients with diabetes. 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.



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In patients with diabetes and a foot ulcer, which symptoms, signs or bedside tests of PAD or reduced perfusion, and at what level of abnormality, will predict ulcer healing?

Recommendation 4:

In patients with a foot ulcer in diabetes and PAD, no specific symptoms or signs of PAD reliably predict healing of the ulcer. However, one of the following simple bedside tests should be used to inform the patient and healthcare professional about the healing potential of the ulcer. Any of the following findings increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg; or, a TcPO₂ ≥ 25 mmHg. (Strong; Moderate)

Recommendation 5:

Consider urgent vascular imaging and revascularisation in a patient with a foot ulcer in diabetes where the toe pressure < 30 mmHg or a TcPO₂ < 25 mmHg. (Strong; Low)

Recommendation 6:

Consider vascular imaging and revascularisation in all patients with a foot ulcer in diabetes and PAD, irrespective of the results of bedside tests, when the ulcer does not improve within 6 weeks despite optimal management. (Strong; Low).

Recommendation 7:

Diabetic microangiopathy should not be considered to be the cause of poor wound healing in patients with a foot ulcer. (Strong; Low)

Rationale 4-7:

In our systematic review, the most useful tests for predicting healing in an ulcerated patient were skin perfusion pressure (≥ 40 mmHg), toe pressure (≥ 30 mmHg) and TcPO₂ (≥ 25 mmHg) (13). 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



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failure to heal, of a diabetic foot wound, should be taken in the context of the quality of the published literature, which is limited. In addition, predicting healing of a diabetic foot ulcer is a complex endeavour that is associated with several variables other than PAD, such as: amount of tissue loss; presence of infection; mechanical load on the ulcer; and, co-morbidities, such as heart failure and end-stage renal disease (23). Healing is therefore related to the interplay of the severity of the perfusion deficit with these other characteristics of the foot and the patient. Finally, the chance of healing will be related to the subsequent quality of care, which should address any of these aforementioned problems.

The available data in the literature is based on univariable analysis and these PAD measures should all be interpreted in the context of other determinants of outcome that make up a pre-test probability. Given the relatively poor chance of healing in patients with a toe pressure <30mmHg or a TcPO₂ <25 mmHg, we suggest considering imaging and revascularisation in these patients. 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 (24). Finally, in light of their limited diagnostic and prognostic utility, none of the above described tests 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. A post-hoc analysis of a trial suggested that a 4-week period is sufficient to assess the likelihood of healing in patients with uncomplicated neuropathic foot ulcers (25). In an observational study, shorter time to revascularisation (<8 weeks) was associated with a higher probability of healing of ischemic foot ulcers (26). For pragmatic reasons, we suggest to consider vascular imaging and subsequent revascularisation in neuroischemic ulcers that do not improve within 6 weeks and have no other likely cause of poor wound healing. In the past, diabetic 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 is the most important cause of impaired perfusion of the foot in a patient with diabetes (27). 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 poorer tissue oxygenation and these should all be treated accordingly (28, 29).



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Which symptoms, signs or bedside tests of PAD, and at what level of abnormality, help predict the risk of future major amputation in patients with diabetes and a foot ulcer?

Recommendation 8:

In patients with a non-healing ulcer with either an ankle pressure <50mmHg or ABI <0.5 consider urgent vascular imaging and revascularisation. (Strong; Moderate)

Rationale 8:

In contrast to healing, accurate risk prediction for major amputation could help to identify patients who would benefit from early vascular imaging and revascularization in an attempt to salvage the limb. Informative tests for predicting major amputation include: ankle pressure (<50mmHg); fluorescein toe slope (indocyanine green fluorescence angiography) (30); and, most usefully the combined result of an ankle pressure <50mmHg or an ABI <0.5. Again, each of these tests increased the pre-test probability by greater than 25%; in the case of the combined tests interpreted serially (ankle pressure and ABI) this value rose to around 40% (13). In our systematic review we could not identify studies fulfilling our inclusion criteria that assessed the predictive value of TcPO₂ for major amputation. The prediction of major amputation is difficult and dependent on many factors. No measure could be considered a marker of good predictive performance (positive likelihood ratio >10) (13), and the decision to perform a major amputation before any attempt at revascularization should not be made on the basis of a perfusion measure alone.





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When considering a revascularisation, which imaging modalities should be used to obtain anatomical information?

Recommendation 9:

Colour Doppler ultrasound, CT-angiography, MR-angiography or intra-arterial digital subtraction angiography can each be used to obtain anatomical information when revascularisation is being considered. The entire lower extremity arterial circulation should be evaluated, with detailed visualization of below-the-knee and pedal arteries. (Strong; Low)

Rationale 9:

Deciding who needs lower limb arterial revascularisation and what procedure to use is complex and requires appropriate imaging to guide therapy. It is unacceptable to rely on clinical examination alone; prior to a revascularization 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-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, MR angiography, CT angiography and digital subtraction angiography. Each of these techniques has its advantages, disadvantages and contra-indications, as described in a previous “Progress Report” of our working group (27). Healthcare professionals should be aware of all these techniques and of their limitations in individual patients. The decision on which imaging modality to use will depend upon any patient contra-indications as well as local availability and expertise.

What are the aims, outcomes and complications of endovascular therapy and open vascular surgery in people with a foot ulcer in diabetes and PAD?

Recommendation 10:

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, with the aim of achieving a minimum skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg; or, a TcPO₂ ≥ 25 mmHg. (Strong; Low)



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Rationale 10:

Historically, revascularisation of the lower limb was aimed at using the best vessel supplying in-line flow to the foot (18). Recent case series have tried to establish whether revascularisation of the angiosome directly supplying the area of ulceration will improve outcome, i.e. hasten healing or prevent amputation. According to this theory, the foot can be divided into three-dimensional blocks of tissue, called angiosomes, each with its own feeding artery. Restoration of pulsatile blood flow through a feeding artery directly to the area where the ulcer is located has been postulated to have better results than when flow is restored through a collateral vessel deriving from neighbouring angiosomes (31). Unfortunately many of the case series describing the results of this approach are at high risk of bias with confounding by indication and no attempts being made to adequately adjust for ulcer duration or severity (14, 32). Furthermore questions remain about the applicability and feasibility of angiosome directed revascularisation in everyday clinical practice and the effect of diabetes on angiosomes. But, whatever the theoretical concept behind the intervention, it seems preferable to improve blood flow to the anatomical area where the ulcer is located, when that is feasible.

Recommendation 11:

A centre treating patients with a foot ulcer in diabetes should have the expertise in and rapid access to facilities necessary to diagnose and treat PAD; both endovascular techniques and bypass surgery should be available.

Recommendation 12:

There is inadequate evidence to establish which revascularisation technique is superior and decisions should be made in a multidisciplinary team on a number of individual factors, such as morphological distribution of PAD, availability of autogenous vein, patient co-morbidities and local expertise. (Strong; Low)

Recommendation 13:

After a revascularisation procedure for a foot ulcer in diabetes, the patient should be treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)

Rationale 11-13:

The natural history of patients with PAD and an ulcerated foot remains poorly defined, but in two studies that reported the outcomes of patients with diabetes and limb ischemia who were not revascularised, the limb salvage rate was around 50% at one year (5,33). After a revascularisation procedure, most studies report limb salvage rates of 80–85% and ulcer healing in >60% at 12 months (14). The quality of the evidence on which





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revascularisation technique (angioplasty or bypass surgery) to perform in patients with severe PAD and a diabetic foot ulcer is low, due to varying indications for intervention, poorly defined cohorts and multiple potential confounders. In our systematic review the major outcomes of healing, amputation and complications appear broadly similar between the two techniques (14). Some experts have recommended that patients requiring lower limb revascularisation should always receive an angioplasty procedure prior to considering surgical revascularisation. However, there is no published evidence to support this approach and the results of both open and endovascular procedures will greatly depend upon the local availability and expertise in a given centre as well as the morphological distribution of PAD (27). Open and endovascular revascularisations are also increasingly combined and in each patient an individual choice should be made which approach fits best with the specific problems of the patient and the expertise of the vascular specialists. Patients should therefore be managed in centres able to offer both approaches, with determinants of selection of technique including the length of lesion, availability of autogenous venous conduit and patient co-morbidity.

The perioperative mortality rates of revascularisation procedures in patients with diabetes and an ischemic foot ulcer are <5% in most studies, but major systemic in-hospital complications have been observed in about 10% of the patients in both open and endovascular series, probably reflecting the poor general health of these patients (14). The outcomes in patients with diabetes and end-stage renal disease are worse, with a 5% perioperative mortality and 1-year mortality of approximately 40% (14). However, even in these patients, favourable results can be obtained, but the majority of studies report 1-year limb salvage rates of approximately 70% (14). Any revascularisation procedure should be part of a comprehensive care plan that should also include treatment of infection, frequent debridement, biomechanical offloading, blood glucose control and treatment of co-morbidities.

Recommendation 14:

Patients with signs of PAD and a foot infection are at particularly high risk for major limb amputation and require emergency treatment. (Strong; Moderate)

Rationale 14:

As stated in our earlier “Progress Report”, “time is tissue” particularly in patients with infected ischemic diabetic foot ulcers (27). Patients with signs of PAD and a foot infection are at particularly high risk for extensive tissue loss and major limb amputation and they should be treated as a medical urgency. In one large observational



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study the major and minor amputation rates after one year in these patients were 10% and 44%, respectively (4). Infection can spread extremely rapidly in the ischemic diabetic foot and may lead to life-threatening sepsis if treatment is delayed (34). In all patients with a deep foot infection consider immediate drainage with removal of all necrotic tissue and start intravenous antibiotic therapy after material is obtained for culture. At the same time, evaluate the vascular status and consider a revascularisation procedure once the infection is under control and the patient is stabilised. Once blood flow is restored to the foot and infection is treated, a final foot operation with soft tissue and skeletal reconstruction may be necessary to provide coverage and create a functional foot. However, in case of severe infection in the ischemic foot, especially in patients with systemic signs of sepsis (e.g. hemodynamic instability), immediate amputation may be the only option (27). In patients with a non-limb threatening infection and signs of PAD, the blood supply to the foot should be optimized before surgical debridement to ensure that potentially viable tissue is not unnecessarily removed (35,36).

Are there any patients with foot ulcers in diabetes and PAD in whom revascularisation interventions should not be performed?

Recommendation 15:

Avoid revascularisation in patients in whom, from the patient perspective, the risk-benefit ratio for the probability of success is unfavourable. (Strong; Low)

Rationale 15:

Revascularisation of the lower limb in patients with diabetes and PAD can be a particularly high-risk procedure. Patients with a diabetic foot ulcer and PAD have high rates of co-morbidities, such as cardiovascular and renal disease (1, 23). If there is no possibility of wound healing or when major amputation is inevitable, revascularisation should not be considered; an exception is when transtibial amputation is considered and there is no popliteal or femoral pulse, then investigation and vascular intervention should be considered. Because there is no reliable scoring system to identify these patients, clinical decision-making involving both patient and inter-disciplinary experts may be required. For instance, revascularisation may be inappropriate for patients who are severely frail, have a short life expectancy, who have poor functional status or are bed-bound or those with a large volume of tissue necrosis that renders the foot functionally unsalvageable.

In addition to patients where the risk of a revascularisation is clearly too high, there are also patients in whom the risk-benefit ratio of a revascularisation is unclear. In clinical decision making it should be taken into account that



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even severely ischemic ulcers can heal without a revascularisation; as noted, two observational studies reported healing rates of about 50% (with or without minor amputations) (5,37).

Is risk reduction for future cardiovascular events feasible in patients with diabetes and an ischemic foot ulcer?

Recommendation 16:

All patients with diabetes and an ischemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension and prescription of a statin as well as low-dose aspirin or clopidogrel. (Strong; Low)

Rationale 16:

This question was not addressed in our systematic review (14), but this recommendation is in line with other guidelines in subjects with PAD (17, 36). Cardiovascular morbidity and mortality are markedly increased in patients with diabetes, a foot ulcer and PAD; these patients have an overall mortality at 5 years of approximately 50% (14). In one follow-up study in patients with a neuro-ischemic foot ulcer, introduction of aggressive cardiovascular risk management (i.e. antiplatelet agent, statin and antihypertensive medication when indicated) reduced 5-year mortality from 58% to 36% (20).

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Classification/Diagnosis

1. Diabetic foot infection must be diagnosed clinically, based on the presence of local or systemic signs or symptoms of inflammation (Strong; Low).
2. 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)

Osteomyelitis

3. For an infected open wound, perform a probe-to-bone test; in a patient at low risk for osteomyelitis a negative test largely rules out the diagnosis, while in a high risk patient a positive test is largely diagnostic (Strong; High)
4. Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (Weak; Moderate)
5. A definite diagnosis of bone infection usually requires positive results on microbiological (and, optimally, histological) and examinations of an aseptically obtained bone sample, but this is usually required only when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial (Strong; Moderate)
6. A probable diagnosis of bone infection is reasonable if there are positive results on a combination of diagnostic tests, such as probe-to-bone, serum inflammatory markers, plain X-ray, MRI or radionuclide scanning (Strong; Weak)
7. Avoid using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis as they do not accurately reflect bone culture results (Strong; Moderate)
8. Obtain plain X-rays of the foot in all cases of non-superficial diabetic foot infection. (Strong; Low)



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9. Use MRI when an advanced imaging test is needed for diagnosing diabetic foot osteomyelitis (Strong; Moderate)

10. When MRI is not available or contraindicated, consider a white blood cell-labelled radionuclide scan, or possibly SPECT/CT or 18 F- FDG PET/CT scans (Weak; Moderate)

Assessing severity

11. At initial evaluation of any infected foot, obtain vital signs and appropriate blood tests, debride the wound, probe and assess the depth and extent of the infection to establish its severity (Strong; Moderate)

12. At initial evaluation assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (Strong; Low)

Microbiological considerations

13. Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the causative microorganisms and their antibiotic sensitivity (Strong; High)

14. Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (Strong; Low)

15. Send collected specimens to the microbiology laboratory promptly, in sterile transport containers, accompanied by clinical information on the type of specimen and location of the wound (Strong; Low)

Surgical treatment

16. Consult a surgical specialist in selected cases of moderate, and all cases of severe, DFI (Weak; Low)

17. Perform urgent surgical interventions in cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (Strong; Low)

18. Consider surgical intervention in cases of osteomyelitis accompanied by: spreading soft tissue infection; destroyed soft tissue envelope; progressive bone destruction on X-ray, or bone protruding through the ulcer (Strong; Low)



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Antimicrobial therapy

19. While virtually all clinically infected diabetic foot wounds require antimicrobial therapy do not treat clinically uninfected wounds with antimicrobial therapy (Strong; Low)
20. Select specific antibiotic agents for treatment based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for DFI and costs (Strong; Moderate)
21. A course of antibiotic therapy of 1-2 weeks is usually adequate for most mild and moderate infections (Strong; High)
22. Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (Strong; Low)
23. Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection or improving its outcome (Strong; High)
24. For diabetic foot osteomyelitis we recommend 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment if all infected bone is resected. (Strong; Moderate)
25. We suggest not using any adjunctive treatments for diabetic foot infection. (Weak; Low)
26. When treating a diabetic foot infection, assess for use of traditional remedies, previous antibiotic use, and consider local bacterial pathogens and their susceptibility profile. (Strong; Low)

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In the recent decades as the prevalence of diabetes has increased, so too have foot complications, including infections. The development of a foot infection is associated with substantial morbidity, including discomfort, reduced physical and mental quality of life (2), need for healthcare provider visits, wound care, antimicrobial therapy, and often surgical procedures. Furthermore, foot infection remains the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation (3-6). Managing infection requires careful attention to properly diagnosing the condition, obtaining appropriate specimens for culture, thoughtfully selecting empirical and then definitive antimicrobial therapy, quickly determining when surgical interventions are needed and providing all other necessary types of wound care. For these reasons interdisciplinary teams should, whenever possible, include an infectious diseases or clinical microbiology specialist (7). A systematic and, to the extent possible, evidence-based approach to diabetic foot infections (DFIs) should result in better outcomes.

Formulation of recommendations

This report from the expert panel on infectious diseases of the International Working Group on the Diabetic Foot (IWGDF) is an update of the one published in 2012 (8). It incorporates some information from the concurrently published 'Systematic Review of Interventions in the Management of Infection in the Diabetic Foot' (9) as well as non-systematic reviews of the literature covering each of the sections in this guidance. Our intention is to present a brief overview to assist clinicians worldwide in diagnosing and treating foot infections in persons with diabetes. This document follows the newly adopted format of all IWGDF guidance documents, including providing recommendations that are rated based on the GRADE system¹.



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¹ Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (1). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence on: the risk of bias of included studies, effect sizes, and expert opinion, and rate the quality of evidence as 'high', 'moderate', or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.

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Diabetic foot infections

In persons with diabetes, foot infection is an increasingly common problem that is related to the duration of the disease, and therefore the likelihood of diabetic complications. 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. DFI is defined clinically as manifestations of this process in soft tissue or bone anywhere below the malleoli in a person with diabetes. These infections usually begin with a break in the protective cutaneous envelope, typically in a site of trauma or ulceration (10). Peripheral neuropathy (mostly sensory, but also motor and autonomic) is the main factor leading to skin breaks; these open wounds then become colonised (usually with skin flora) and, in many cases, ultimately infected. Foot ischemia, related to peripheral arterial disease, is also common in patients with a DFI. While rarely the primary cause of foot wounds, the presence of limb ischemia increases the risk of a wound becoming infected (11,12) and adversely affects the outcome of infection (6,13). Foot wounds in diabetic patients often become chronic, related to hyperglycemia-induced advanced glycation end-products, persistent inflammation and apoptosis (14,15). Factors that predispose to foot infection include having: a wound that is deep, long-standing or recurrent, or of traumatic aetiology; ill-defined diabetes-related immunological perturbations related to neutrophil function; and, chronic renal failure (11,16-19).

Spread of infection

While most DFIs are relatively superficial at presentation, microorganisms can spread contiguously to subcutaneous tissues, including fascia, tendons, muscle, joints and bone. The anatomy of the foot, which is divided into several rigid but intercommunicating compartments, fosters proximal spread of infection (20). The inflammatory response induced by infection may cause compartmental pressure to exceed capillary pressure, leading to ischaemic tissue necrosis (21,22). 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. Strains of *Staphylococcus aureus* isolated from clinically non-infected ulcers have been shown to have a lower virulence potential than from those that are infected (23). Similarly, a clonal complex 398 methicillin-susceptible *S. aureus* with a tropism for bone has emerged as the main staphylococcal pathogen in one outbreak of diabetic foot osteomyelitis (DFO) (24).





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Systemic symptoms

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 (or even life) threatening infection (6). If not diagnosed and properly treated, DFIs tend to progress, sometimes rapidly (25). Thus, an experienced consultant (or team) should see a patient with a severe DFI within 24 hours (26).

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Diagnosis and Classification

Recommendation 1:

Diabetic foot infection must be diagnosed clinically, based on the presence of local and systemic signs and symptoms of inflammation (Strong; moderate).

Recommendation 2:

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 1& 2:

The clinician seeing a patient with a diabetic foot wound should first assess for the presence of a DFI and, if present, classify the infection's severity. Over the past three decades experts have proposed many classification schemes for diabetic foot wounds. Most of these take into account the size and depth of the ulcer, and the presence or absence of gangrene, neuropathy, or arterial insufficiency. Several diabetic foot ulcer classifications only include the presence or absence of "infection" (which is undefined). Only two, nearly identical, schemes proposed by the Infectious Diseases Society of America and the IWGDF (the "infection" part of the PEDIS classification) describe how to define both the presence and severity of infection (see Table 1) (27-30). Several other guidelines, including ones produced by the Spanish, French and UK (NICE), have adopted the IDSA/IWGDF infection classification (26,31-33).

The full PEDIS system (which includes classification of other wound descriptors, such as arterial disease, neuropathy and wound size) of the IWGDF was originally developed for research purposes, but it can serve as a clinical classification as well (29,34). Classification of DFIs using the full PEDIS system (35,36) or the infection part of the IWGDF/IDSA DFI scheme (6) has been shown in several prospective studies to predict the need for hospitalisation or lower extremity amputation. Two recently published retrospective cohort studies from one centre addressed the issue of whether or not the presence of systemic inflammatory response syndrome (SIRS) findings, which separate moderate from severe infections, actually predicts outcomes. They assessed the differences in outcome between hospitalised patients without and with SIRS (i.e., PEDIS grade 3 versus grade 4) with a DFI (37,38). In one study patients with grade 4 infections experienced a 7.1 fold higher risk of major amputation and had a 4 day longer mean hospital stay compared to patients with grade 3 infections (37). In the other publication, patients with grade 4 compared with grade 3 DFI had a significantly longer length of hospital





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stay (8 versus 5 days) and a non-significantly lower limb salvage rate (80% versus 94%) (38). Another recently published retrospective cohort study reviewed outcomes in 57 DFI patients according to the level of adherence of their clinicians to the IDSA practice guidelines (39). They found that rates of adherence to various recommendations ranged from very high to very low, but in none of the patient treatment courses did clinicians adhere to all. In this small and suboptimally designed study, adherence to the recommendations was not related to clinical outcome, but patients with severe infections were more likely to have adverse outcomes. Surprisingly, appropriate empiric and targeted antibiotic therapy was associated with treatment failure.

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Table 1. The classification systems for defining the presence and severity of an infection of the foot in a person with diabetes developed by the Infectious Diseases Society of America (IDSA) and the infection part of the PEDIS classification of the International Working Group on the Diabetic Foot (IWGDF) (29,30).

Clinical classification of infection, with definitions	IWGDF / IDSA classification
Uninfected: No systemic or local symptoms or signs of infection	1 (Uninfected)
Infected: - At least 2 of the following items are present: • Local swelling or induration • Erythema > 0.5 cm* around the wound • Local tenderness or pain • Local warmth • Purulent discharge - Other causes of an inflammatory response of the skin should be excluded (e.g., trauma, gout, acute Charcot neuro-osteopathy, fracture, thrombosis, venous stasis) - Infection involving only the skin or subcutaneous tissue (without involvement of deeper tissues and without systemic manifestations as described below). - Any erythema present extends < 2 cm* around the wound - No systemic signs or symptoms of infection (see below)	2 (Mild infection)
- Infection involving structures deeper than skin and subcutaneous tissues (e.g., bone, joint, tendon, muscle) or erythema extending >2 cm* from the wound margin. - No systemic signs or symptoms of infection (see below)	3 (Moderate infection)
- Any foot infection with the systemic inflammatory response syndrome (SIRS), as manifested by ≥2 of the following: • Temperature >38° or <36° Celsius • Heart rate >90 beats/minute • Respiratory rate >20 breaths/minute or PaCO₂ < 4.3 kPa (32 mmHg) • White blood cell count >12,000 or <4,000/mm³, or >10% immature (band) forms	4 (Severe infection)

Note: *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.

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Soft tissue infection

Because all skin wounds harbour microorganisms, their mere presence (even if they are virulent species) cannot be taken as evidence of infection. Some maintain that the presence of high numbers of bacteria (usually defined as $\geq 10^5$ colony forming units per gram per tissue) should be a basis for diagnosing infection (40), but no convincing data support this concept for wounds, including in the diabetic foot (41). Furthermore, quantitative microbiology is rarely available outside of research laboratories. Thus, DFI must be diagnosed clinically (Table 1), with wound cultures serving to determine the causative organisms and their antibiotic sensitivities. Clinicians should evaluate a diabetic patient presenting with a foot wound at three levels: the patient as a whole (e.g., cognitive, metabolic, fluid status), the affected foot or limb (e.g., presence of neuropathy, vascular insufficiency), and the infected wound (30). Clinical diagnosis rests on the presence of at least two local findings of inflammation, that is, redness (erythema or rubor), warmth (calor), pain or tenderness (dolor), induration (swelling or tumor) or purulent secretions (29,42). Other (sometimes called secondary) features suggestive of infection include the presence of necrosis, friable or discoloured granulation tissue, non-purulent secretions, foetid odour or the failure of a properly treated wound to heal (43). These findings may be helpful when local and systemic inflammatory signs are diminished because of peripheral neuropathy or ischemia (44-46). Because infection can worsen quickly, clinicians must pursue the diagnosis methodically (44) and aggressively (47). All wounds must be carefully inspected, palpated and probed, both at initial presentation and on follow-up. Various imaging and laboratory studies may be useful in some cases to define the extent of soft tissue infection and any bone involvement.

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Osteomyelitis

Recommendation 3:

For an infected open wound, perform a probe-to-bone test; in a patient at low risk for osteomyelitis a negative test largely rules out the diagnosis, while in a high risk patient a positive test is largely diagnostic (Strong; High)

Recommendation 4:

Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (Weak; Moderate)

Recommendation 5:

A definite diagnosis of bone infection usually requires positive results on both histological and microbiological examinations of an aseptically obtained bone sample, but this is usually required only when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial (Strong; Moderate)

Recommendation 6:

A probable diagnosing of bone infection is reasonable if there are positive results on a combination of diagnostic tests, such as probe-to-bone, serum inflammatory markers, plain X-ray, MRI or radionuclide scanning (Strong; Weak)

Recommendation 7:

Avoid using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis as they do not accurately reflect bone culture results (Strong; Moderate)

Recommendation 8:

Obtain plain X-rays of the foot in all cases of non-superficial diabetic foot infection. (Strong; Low)

Recommendation 9:

Use MRI is when an advanced imaging test is needed for diagnosing diabetic foot osteomyelitis (Strong; Moderate)



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Recommendation 10:

When MRI is not available or contraindicated, consider a white blood cell-labelled radionuclide scan, or possibly SPECT/CT or 18 F- FDG PET scans (Weak; Moderate)

Rationale 3 - 10

Diabetic foot osteomyelitis (DFO) can present the clinician with formidable diagnostic and therapeutic challenges (48). It is found in ~50%-60% of patients hospitalized for a DFI and ~10%-20% of apparently less severe infections presenting in the ambulatory setting. Bone infection typically involves the forefoot (and less often the hindfoot) and develops by contiguous spread from overlying soft tissue, penetration through the cortical bone and into the medullary cavity. Bone destruction related to Charcot neuroosteoarthropathy (CN) may be difficult to distinguish from DFO, but it is: less common; generally occurs in patients with profound peripheral neuropathy (but usually adequate arterial perfusion); usually affects the midfoot; and, most often occurs in the absence of a skin break (49-51). Many cases of DFO are monomicrobial, but most are polymicrobial, with *S. aureus* the most commonly isolated pathogen (found in ~50% of cases), while coagulase-negative staphylococci (~25%), aerobic streptococci (~30%) and Enterobacteriaceae (~40%) are other frequent isolates (49).

Accurately diagnosing bone infection can be difficult, but is essential to ensure appropriate treatment. A definite diagnosis of osteomyelitis requires both the presence of histological findings consistent with bone infection (acute or chronic inflammatory cells, necrosis) and the isolation of bacteria from an aseptically obtained bone sample (52). Because bone sampling and processing are not routinely available in many settings, clinicians must often use surrogate diagnostic markers, including clinical, laboratory and imaging findings.

The clinical presentation of osteomyelitis in the diabetic foot can vary with the site involved, the extent of infected and dead bone, the presence of any associated abscess or soft tissue involvement, the causative organism(s) and the adequacy of limb perfusion. The main problems in diagnosing osteomyelitis are that there is a delay in the ability to detect bony changes in early infection on plain radiographs, while later when bony changes occur it may be difficult to distinguish on imaging studies those caused by infection from those related to CN. As discussed below, analyses from recent expert publications (52,53) and systematic reviews (52,54-56) provide guidance on the best available diagnostic studies for DFO.

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Clinical evaluation

Clinicians should suspect osteomyelitis when an ulcer lies over a bony prominence, particularly when it fails to heal despite adequate off-loading, or when a toe is erythematous and indurated (the so-called “sausage toe”). The likelihood ratio (LR) of a clinician’s suspicion of osteomyelitis is surprisingly good, with a positive LR 5.5 and negative LR 0.54 (54,55). Based on one study, the presence of exposed bone has a positive LR for osteomyelitis of 9.2; large ulcers (area >2 cm²) are much more likely to have underlying bone infection (positive LR 7.2) than smaller ones (negative LR 0.70) (54,55,57,58). Osteomyelitis can, however, occur in the absence of overlying local signs of inflammation (57).

Probe-to-bone test

In the past two decades there have been at least seven published studies of the probe-to-bone test (51). When performed correctly and interpreted appropriately, this is a useful clinical diagnostic tool for diagnosing DFO. If a blunt sterile metal probe gently inserted through a wound strikes bone (detected by its hard, gritty feel), this substantially increases the likelihood (positive LR 7.2, negative LR 0.48) that the patient has osteomyelitis if the prevalence of bone infection is high (i.e., >~60%) in the population under scrutiny (59,60). Conversely, a negative probe-to-bone test in a patient at low risk (i.e., ≤~20%) essentially rules out osteomyelitis (61-63).

The inter-observer variability of the test is relatively high for inexperienced clinicians compared to experienced ones, but low between experienced clinicians (64). One study found a stronger correlation among clinicians’ results for ulcers located in the hallux and in the central metatarsals compared to the lesser toes (65). Combining the results of the probe-to-bone test with those of plain radiography improves overall diagnostic accuracy of osteomyelitis (59,64).

Blood tests

The erythrocyte sedimentation rate has proven to be useful in diagnosing DFO; a highly elevated (usually defined as >70 mm/h) level increases the likelihood of osteomyelitis underlying a diabetic foot wound (positive LR 11), while lower levels reduce the likelihood (negative LR of 0.34) (54,66-69). Based on fewer data, a highly elevated C-reactive protein, procalcitonin or blood leukocyte count may be suggestive of osteomyelitis. These latter tests tend to revert to normal levels within a week of treatment (70), while the ESR drops more slowly and can therefore be useful for monitoring response to therapy. There is insufficient evidence to support the routine use of any other biomarkers to document bone infection in the diabetic foot. A preliminary report suggested that





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interleukin (IL)-6, but not IL-8 may be useful in the diagnosis and follow up of diabetic foot infection (71-73). Combining laboratory testing with clinical findings may improve the diagnostic accuracy for osteomyelitis (74).

Imaging studies

Plain radiography

Plain X-rays are often sufficient for imaging the foot in patients with suspicion of DFO. Characteristic features of osteomyelitis on plain X-rays of the foot are summarized in Table 2. Advantages of this imaging test are that it: is widely available (even in most centres with limited resources); has a relatively low cost; can be adequately read by most experienced clinicians; and, is relatively easy to compare sequential radiographs over time. In addition to bony changes, plain radiographs can demonstrate the presence of gas in the soft tissues or radiopaque foreign bodies. The results of two systematic reviews suggest that radiographic findings are only marginally predictive of osteomyelitis if positive and even less predictive of the absence of osteomyelitis if negative (54,55). While the reported sensitivity of radiography varies considerably in reported studies (57,75-82), the estimated positive likelihood ratio (LR) is 2.3 and negative LR is 0.63 (56). The timing of the imaging greatly influences its usefulness, as longer-standing cases are far more likely to show bony abnormalities on plain radiographs than those present for less than two to three weeks. We know of no study that has evaluated sequential plain radiographs of the foot over time, but changes seen over an interval of at least 2 weeks are more likely to predict the presence of osteomyelitis than a single study. Of course, effective antibiotic therapy may prevent these bony changes from occurring. Advanced imaging techniques are expensive, often limited in availability and difficult to interpret by a non-expert. Thus, they are usually needed only, when there is persistent doubt about the diagnosis of DFO or in the context of preparing a surgical intervention.



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Table 2: Typical features of diabetic foot osteomyelitis on plain X-rays* (57,75,76,103)

Periosteal reaction or elevation
Loss of bone cortex with bony erosion
Focal loss of cortical trabecular pattern or marrow radiolucency
Bone sclerosis, with or without erosion
Presence of sequestrum: devitalized bone with radiodense appearance that has become separated from normal bone
Presence of involucrum: a layer of new bone growth outside previously existing bone resulting from stripping off of the periosteum and new bone growing from the periosteum
Presence of cloacae: opening in the involucrum or cortex through which sequestrae or granulation tissue may discharge
Presence of evidence of a sinus tract from the bone to the soft tissue

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

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a valuable tool for diagnosing osteomyelitis, as well as defining the presence and anatomy of deep soft tissue infections (30,55,83). The key features suggestive of osteomyelitis on MRI are low focal signal intensity on T1-weighted images, high focal signal on T2-weighted images and high bone marrow signal in short tau inversion recovery (STIR) sequences. Meta-analyses have found that the sensitivity of MRI for DFO is about 90% and the specificity about 85%, diagnostic odds ratio (OR) of 24 (55,83) and LR_s estimated at positive of 3.8 and negative of 0.14. More recently performed studies reported lower diagnostic OR compared with older ones, perhaps because they employed better study designs. The subgroups of patients with other diagnoses (e.g., CN) were too small to analyse any differences among the studies. A recent study found that MRI was effective in distinguishing DFO from bone marrow oedema in neuropathic ulcers but was less accurate for the diagnosis of DFO in ischemic ulcers, presumably because of their insufficient interstitial fluid (84).



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Nuclear medicine scans

Among the several types of nuclear imaging procedures, a bone scan, usually performed with ^{99m}Tc -methylene diphosphonate in time-sequence phases, has been used for the longest time and is considered suggestive of osteomyelitis when it discloses increased blood-pool activity and radionuclide intensity localized to the bone (55). Three-phase bone scans are reasonably sensitive (~80%-90%), but not specific (~30-45%) (85); their positive predictive value is only 65% and the pooled diagnostic OR only 2.1 with positive LR of 1.4 and negative LR of 0.40 (56). One meta-analysis found the performance characteristics of a triple-phase bone scan markedly inferior to MRI (83). Thus, a positive bone scan is certainly not specific for osteomyelitis (or CN), especially in the forefoot, but a negative one largely rules it out (85).

Radiolabelled white blood cells (usually using either ^{99m}Tc or ^{111}In) are generally not taken up by healthy bone, making a positive leukocyte scan more specific than a bone scan for diagnosing osteomyelitis (and excluding CN) (85). The positive predictive values for leukocytes scans for osteomyelitis are about 70%-90% and the negative predictive values about 80% (85), the sensitivity is about 75%-80% and specificity about 70%-85%, and the positive LR 2.3 and negative LR 0.38 (56,86). Labelling with ^{99m}Tc rather than with ^{111}In appears to provide superior physical characteristics, leading to better spatial resolution (86). Most nuclear medicine authorities suggest that among radionuclide procedures, labelled leukocyte imaging is the best choice for evaluating DFO (55,57), but MRI generally outperforms leukocyte scanning (81,83,87,88). Some advocate combining a labelled leukocytes scan with a bone scan (dual tracer technique), but this does not substantially improve diagnostic accuracy (89).

More recently, studies have shown that using combined ^{99m}Tc white blood cell-labelled single-photon emission computed tomography and computed tomography (^{99m}Tc WBC labelled-SPECT/CT) imaging provides good spatial resolution with the three-dimensional CT-scan images and WBC uptake intensity yielding more information about the location and extent of infection. Although previous studies have demonstrated the value of SPECT/CT for diagnosing inflammatory bone lesions, most focused on larger osseous structures than the foot (86,90). In a small series of patients with suspected DFO ^{99m}Tc WBC SPECT/CT demonstrated a sensitivity of 87.5%, specificity of 71.4%, positive predictive value of 83.3% and negative predictive value of 77.8% (91). A potential advantage of SPECT/CT is that grading the WBC uptake intensity provides a suggestion of the physiologic response of local tissue; thus, changes in intensity might be used as a prognostic tool to predict outcome of treatment (92,93). Thus, a recent study found that negative uptake on a WBC SPECT/CT was a good marker for remission of DFO and was useful in guiding the optimal duration antibiotic therapy (94).



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Coupling ^{67}Ga SPECT/CT with bedside bone puncture was found to be a simple, safe and efficient procedure for the diagnosis of foot osteomyelitis in one study of diabetic patients (94). Other advantages are that ^{67}Ga SPECT/CT imaging and biopsy can both be done in an ambulatory setting and in this study the results were used to avoid unnecessary use of antibiotics in more than half of the cases of suspected DFO (93).

Other available nuclear medicine techniques include in vivo methods of labelling leukocytes, radio-labelled polyclonal immunoglobulin (IgG) and radio-labelled antibiotics. Results of studies using these techniques have varied and most of the methods are unavailable in many countries. $^{99\text{mTc}}/^{111}\text{In}$ labelled human IgG uptake is related to vascular permeability, not inflamed tissue, and therefore not as specific as radio-labelled leukocytes (85,95,96). Ubiquicidin 29-41 (UBI 29-41) is an antimicrobial peptide fragment reported to be highly infection-specific that has been prospectively evaluated as a radiotracer ($^{99\text{mTc}}$ UBI 29-41) for the diagnosis of DFO in a series of 55 patients (97). Among 38 patients with proven DFO and 17 patients free of bone infection the sensitivity, specificity and accuracy of the $^{99\text{mTc}}$ -UBI 29-41 scan, in combination with a three-phase bone scan, were all 100 % (97). This technique seems worthy of further studies.

Other imaging techniques

Fluorine-18-fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET), which can be combined with computed tomography (PET/CT) to improve the differentiation between osteomyelitis and soft tissue infection, has been evaluated in the diagnosis of DFO (98-100). This technique has excellent spatial resolution and in comparison with labelled leukocyte bone scans can be performed more quickly and does not require blood processing. A meta-analysis of this method reported a sensitivity of 74%, specificity of 91%, positive LR 5.6, negative LR 0.4, and diagnostic OR of 17 (101). While the data on this new procedure are limited, there seems to be a place for CT combined with SPECT or PET scans when MRI is unavailable or contraindicated (e.g., in a patient with a metal implant or claustrophobia). Recently, an interdisciplinary consensus committee was tasked with developing a suggested flow chart for imaging tests for patients with a DFI (102). They recommended that the evaluation should begin with plain radiographs, but when advanced imaging is needed MRI is still the modality of choice, although techniques such as molecular hybrid imaging, PET/CT and SPECT/CT using various radiotracers are playing an increasing role.

While both PET and SPECT combined with CT have shown promise in the diagnosis of DFO, providing both functional and anatomic information, further studies are needed to define the optimal indications and cost-benefit of these techniques (Table 3). A recent narrative review of diagnosing DFO (56) combined a literature review with the 2008 IWGDF proposed guidelines (52) to propose a 2-step score based diagnostic pathway for



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Table 3: Relative merits and approximated likelihood ratios of some currently available advanced imaging techniques for diabetic foot osteomyelitis, listed in descending order of usefulness clinicians. The suggested approach begins with a clinical assessment of 6 items (from physical examination, along with erythrocyte sedimentation rate and plain X-rays) (56). The presence of ≥ 4 items suggests a high probability of DFO; if < 4 are found they recommend advanced imaging techniques to further separate patients at high versus low probability of having DFO. While a logical approach, this scoring system has not yet been validated.

Table 3: Diabetic foot osteomyelitis

Imaging technique	+ LR	– LR	Advantages	Limitations
MRI	3.8	0.14	Good spatial resolution, high accuracy, can assess both soft tissues and bone	Reduced performance with severe ischemia
18F-FDG PET	5.6	0.4	Good spatial resolution	Limited availability; high cost
^{99m}Tc / ^{111}In labelled-leukocytes scans	4.73 / 2.31	0.12 / 0.38	High sensitivity; moderate specificity	Requires blood handling; time consuming
^{99m}Tc or ^{67m}Ga SPECT/CT	3.0	0.18	Good spatial resolution	Limited availability
^{99m}Tc -UBI 29-41 scan	Max*	Min*	Very high predictive values	Limited clinical data
^{99m}T bone scan	1.11	0.71	Widely available	Low specificity

Note: From references (55,56,83,85,86,97); + LR = positive likelihood ratio; – LR = negative likelihood ratio; *: specificity=100%, specificity=100%





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Bone biopsy

Available evidence supports evaluating a bone specimen as the best available diagnostic technique for both diagnosing bone infection and providing reliable data on the responsible organisms and their antibiotic susceptibility profiles (9). Several studies have found that soft tissue or sinus tract cultures are not sufficiently accurate in predicting bone pathogens (104-106). A retrospective review suggested that cultures from wound swabs correlate with bone biopsy culture results in only 23% (107). Although a recent study suggested that cultures of deep wound swabs correlated well enough with osseous cultures to make them useful for assessing and targeting likely pathogens in patients with suspected DFO (108), among the 34 patients who had both types of cultures results were completely the same in only 16 (47%).

Bone samples can be obtained either during a surgical intervention or by percutaneous biopsy. Obtain a specimen by going through intact, uninfected skin; going through a wound risks of contamination of the specimen by soft tissue organisms. Using an 11-gauge (or smaller for phalanges) bone-cutting needle, such as Jamshidi (Perfectum Corporation, distributed by Propper and Sons, or CareFusion), Ostycut (Bard Products, distributed by Angiomed), or T-lok (Angiotech) it is possible to obtain a sample of bone large enough to send one part for microbiological culture and another part for histopathological examination (Figure 1). Histological examination of bone specimens may be helpful in interpreting the results of culture, especially in case of a negative culture or one growing only commensal skin flora (e.g., coagulase-negative staphylococci, *Propionibacterium* spp, corynebacteria). Any properly trained physician can perform a percutaneous bone biopsy; it can usually be done at the bedside (for simple cases with a relatively large area of bone infection) or in the radiology suite (when imaging is need to localize the involved bone). Anaesthesia is often not required because most affected patients have sensory neuropathy. Complications, such as minimal bleeding ($\leq 3\%$), introducing bacteria into bone or inducing a fracture or acute Charcot arthropathy, are extremely rare (94,104,109-111).

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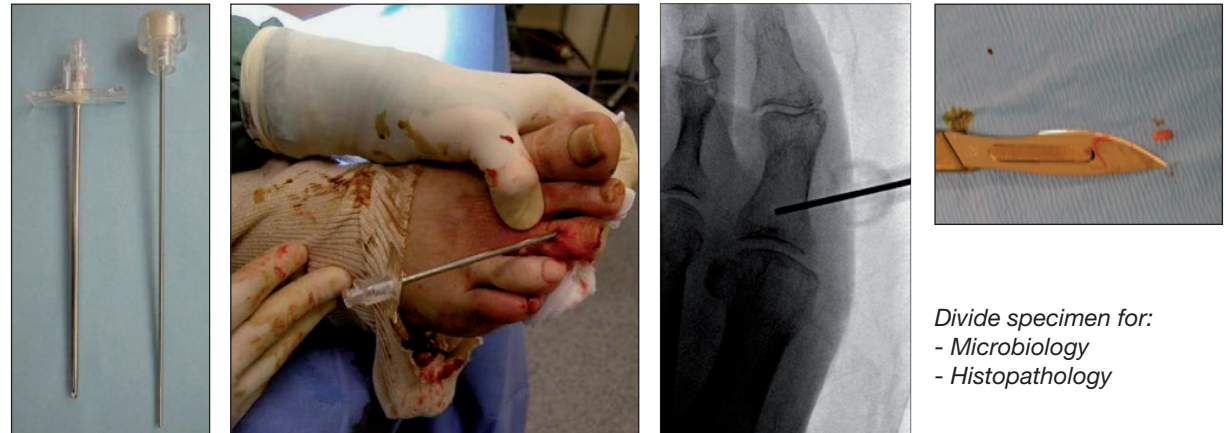
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Figure 1: Technique of percutaneous bone biopsy of the foot



Note: May be done at bedside, in a radiology suite or in the operating theatre. If needed, can use fluoroscopic or computed tomographic guidance. If bone core obtained, send to microbiology for aseptic division with one piece for culture and the other sent to histopathology.

(Photographs courtesy of Dr E. Beltrand, Orthopedic Surgery Department, Dron Hospital, Tourcoing France)

Ideally, the bone specimen should be processed for both culture and histopathology. Infected bone usually has inflammatory cells (granulocytes early and mononuclear cells later), while the histomorphology of uninfected bone is normal in diabetic patients, including those with neuropathy or peripheral arterial disease (112,113). Work by one group has suggested that histopathology examination may help to define three types of DFO: (1) acute, defined by necrosis and infiltration of polymorphonuclear granulocytes in cortical and medullary sites, usually associated with congestion or thrombosis of small vessels; (2) chronic, characterized by destroyed bone and infiltration of lymphocytes, histiocytes or plasma cells; and, (3) acute exacerbation of chronic osteomyelitis, with a background of chronic osteomyelitis with infiltration of polymorphonuclear granulocytes (114). However, we need further evaluation of these findings from other groups. The concordance among several pathologists in diagnosing DFO in bone samples was found to be low in one study, but this may have been related to a lack of





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an agreed definition of histopathological criteria (115). A more recent study using an agreed DFO classification scheme that included the additional histopathological type “fibrosis”, reported a high correlation in the reading by two independent pathologists (116). A review comparing the microbiological versus histopathological aspects of 44 bone specimens of patients with DFI concluded that the two methods performed similarly in identifying the presence of pedal osteomyelitis (117).

Unfortunately, both histology and culture results of bone specimens may be misleading. False-positive results caused by skin contamination can be reduced by using a dorsal route in case of a plantar ulcer and by keeping a minimal distance of 20 mm from the ulcer periphery when introducing the biopsy needle. Culture of a bone specimen may be falsely negative because of sampling errors, prior antibiotic therapy or a failure to isolate fastidious organisms. Similarly, bone histopathology may be falsely negative due to sampling error or falsely positive in patients with some non-infectious inflammatory disorders. To reduce the likelihood of false-negatives it is likely best to perform bone biopsy using fluoroscopic or CT guidance and to impose an antibiotic-free period (ideally 2 weeks, but even a couple of days may be helpful) in clinically stable patients (118). Because DFO in the absence of substantial soft tissue infection is typically a slowly progressive disease, such an antibiotic-free interval is usually safe.

In one retrospective multicentre study, using bone culture guided antibiotic treatment was associated with a significantly better clinical outcome than using soft tissue culture results (119); this finding requires confirmation by a prospective study. A reassuring finding from a retrospective study of 41 patients with suspected DFO is that among those with a negative bone culture only ~25% developed bone infection during a 2 year follow-up (120). While success rates of 75% or higher have been reported with empiric treatment of DFO it is difficult to compare the results of available published studies because of differences in the populations enrolled, in the criteria used for both diagnosis and remission of infection and in the durations of follow-up (48). Bone culture is not always needed when DFO is suspected, but clinicians should consider this procedure when the diagnosis of osteomyelitis remains uncertain despite clinical and imaging evaluations, in cases where data from soft tissue cultures are non-informative, when the infection has failed to respond to initial empiric antibiotic therapy or when considering an antibiotic regimen with a higher potential for selecting resistant organisms (e.g., rifampin, fluoroquinolones, fusidic acid or clindamycin) (52).

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Recommendation 11:

At initial evaluation of any infected foot, obtain vital signs and appropriate blood tests, debride the wound, probe and assess the depth and extent of the infection to establish its severity (Strong; Low)

Recommendation 12:

At initial evaluation assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (Strong; Low)

Rationale 11 & 12:

Accurately assessing a diabetic foot wound usually requires first debriding any callus and necrotic tissue to fully visualize the wound. Keys to classifying a foot infection are defining at initial evaluation the depth and extent of the tissues involved, determining the adequacy of arterial perfusion and possible need for revascularization, and assessing for systemic toxicity (6,30,121). While mild infections are relatively easily treated, moderate infections may be limb-threatening and severe infections may be life-threatening (Table 4A). Infection severity largely guides the choice of the empiric antibiotic regimen and its route of administration and helps to determine the need for hospitalisation (Table 4B), the potential necessity and timing of foot surgery and the likelihood of amputation (6,121-123).

Severity of infection is first determined by the clinical classification scheme described above. Other clinical features of sepsis include acute oliguria or ileus. Laboratory findings suggesting a serious infection include a plasma C-reactive protein or procalcitonin level >2 standard deviations above the upper limit of normal, uncontrolled hyperglycaemia, hyperlactaemia (>1 mmol/L), serum creatinine increase >0.5 mg/dL (44 µmol/L), coagulation abnormalities, or arterial hypoxemia (124)



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Table 4. 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, bone)

Cellulitis

Extensive (>2 cm), distant from ulceration or rapidly progressive

Local signs

Severe inflammation or induration, crepitus, bullae, discoloration, necrosis or gangrene, ecchymoses or petechiae, new anaesthesia

General

Presentation

Acute onset/worsening or rapidly progressive

Systemic signs

Fever, chills, hypotension, confusion, volume depletion

Laboratory tests

Leukocytosis, very high C-reactive protein or erythrocyte sedimentation rate, severe/worsening hyperglycaemia, acidosis, new/worsening azotaemia, electrolyte abnormalities

Complicating features

Presence of a foreign body (accidental or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphedema, immunosuppressive illness or treatment

Current treatment

Progression while on apparently appropriate antibiotic and supportive therapy

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B - Factors suggesting hospitalization may be necessary

- Severe infection (See Table 4A)
- Metabolic or hemodynamic instability
- Intravenous therapy needed (and not available/appropriate as outpatient)
- Diagnostic tests needed that are not available as outpatient
- Critical foot ischemia 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

Note: A deep space infection may have deceptively few superficial signs, but clinicians should consider this possibility in a patient with evidence of systemic toxicity, inflammation distant from the skin wound, persistent infection or elevated inflammatory markers despite apparently appropriate therapy, deterioration of previously controlled glycaemia or pain in a previously insensate foot (21,47,125). The presence of foot ischemia is of particular concern, as it can both diminish clinical findings and worsen prognosis. If in doubt, consider seeking consultation from an experienced surgeon and evaluating with ultrasound, MRI or potentially other imaging techniques.

Some “real-world” data on the presentation and outcome is available from a prospective, multicentre observational study from France of patients hospitalized for DFI (126). Among 291 included patients most infections were graded as moderate, but 42% met criteria for sepsis; of note was that in 8 patients the investigators found the infection was clearly of a higher severity than graded by the treating clinicians. Half the patients were suspected of having accompanying osteomyelitis and more than half had peripheral arterial disease. Despite absent foot pulses in about half the patients, the ankle-brachial index was measured in only a third of all patients. Even though the included centres had a particular interest and expertise in diabetic foot problems, the outcome was considered unfavourable in 48% of the patients. Specifically, lower extremity amputation was performed during hospitalization in 35%, and in another 19% of the 150 non-amputated patients in the year after discharge; risk factors for amputation included severity of the infection and the presence of osteomyelitis. As in other studies (127), the presence of multidrug resistant pathogens (especially methicillin-resistant *Staphylococcus aureus* [MRSA]) was not associated with more severe infection or worse outcome. These findings emphasize the severity of DFI in hospitalized patients and how often this is under-appreciated and inadequately assessed.

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Recommendation 13:

Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the identify of causative microorganisms and their antibiotic sensitivity (Strong; High)

Recommendation 14:

Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (Strong; Low)

Rationale 13 & 14 - When to send specimens for testing:

Since infection is diagnosed clinically, the purpose of microbiological sampling is to identify the likely pathogens and their antibiotic susceptibilities to enable the clinician to select the most appropriate antimicrobial therapy. Acute infection in a previously untreated patient is usually caused by aerobic gram-positive cocci (often as a monomicrobial infection), but deep or chronic wounds often harbour polymicrobial flora, including aerobic gram-negative and obligate anaerobic bacteria (128,129). Skin disorders, environmental exposures, and especially recent antibiotic therapy can predispose to unusual or antibiotic-resistant pathogens. Wound cultures are helpful for most DFIs, but are difficult to obtain in cases of cellulitis without ulceration (where skin aspiration has limited sensitivity) and unnecessary for clinically uninfected wounds. One exception is culturing uninfected wounds when seeking evidence of colonisation with highly resistant organisms to determine if isolation of an institutionalised patient is needed. Clinicians should try to stay updated on antibiotic-resistance patterns of common pathogens in their area of practice. Blood cultures are only indicated for severe infections, where there are signs of systemic manifestations of sepsis (30). When osteomyelitis is suspected a key consideration (discussed in the osteomyelitis section) is when to obtain a specimen of bone for culture (and histopathology).

It is usually best to obtain specimens for culture as soon after the patient presents as possible, but for patients already receiving antibiotic therapy it is sometimes useful to discontinue that treatment (if the patient is stable) and wait a few days before sampling to avoid false-negative cultures. Repeat cultures are usually unnecessary unless the patient is not clinically responding to treatment, or if the initial specimen was likely to be contaminated.



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Recommendation 15:

Send collected specimens to the microbiology laboratory promptly, in sterile transport containers, accompanied by clinical information on the type of specimen and location of the wound (Strong; Low)

Rationale 15 - Obtaining specimens from wounds:

The results of a wound culture are useful only if the specimen is appropriately collected and processed. Although swabs of open wounds are easy to collect, several studies have clearly shown that culture results with these specimens are both less sensitive and specific than tissue specimens. Aseptically obtained deep tissue specimens usually contain only true pathogens, while cultures of superficial lesions often yield a mixture of pathogens, colonising organisms and contaminants, and miss facultative and anaerobic organisms (128,130). Curettage (tissue scraping) with a dermal curette or scalpel from the base of a debrided ulcer, punch biopsy or needle aspirate of purulent secretions, generally provide more accurate results than wound swabbing (128,131,132). If swabs are the only available method, they should be taken only after debriding and cleaning the wound. Specimens of soft tissue or bone should be sent to the laboratory promptly, in suitable sterile transport containers, and all organisms isolated should be identified.

Laboratory testing of wound specimens

Clinicians must provide the microbiology laboratory with key clinical details associated with the sample (e.g., site and type of infection, type of specimen obtained, whether or not the patient is taking antibiotics), as these will influence the specimen processing and reporting. Unfortunately, there are no internationally agreed guidelines for laboratory processing or reporting for either tissue specimens or superficial swabs from an infected foot ulcer. Such a tissue sample or swab would generally be evaluated by one of two distinct routes: phenotypic or genotypic testing.

Phenotypic analysis

Phenotypic testing uses observational physical or biochemical characteristics to determine the identity of a microorganism. This can be accomplished by culture of a specimen using standard or selective growth media, along with antimicrobial sensitivity testing informed by local, national or international prescribing policies. Traditional microscopy and staining techniques, such as the Gram-stained smear (133), can provide additional organism characterisation. In principle, these processes are relatively cost-effective and low in complexity to perform and interpret. The organisms most often reported as causing infections include most aerobic gram-positive cocci (e.g., staphylococci, streptococci) and gram-negative rods (e.g., Enterobacteriaceae,





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Pseudomonas aeruginosa) and common obligate anaerobes (e.g., peptostreptococci, *Bacteroides*). Disadvantages of these techniques include the fact that they take at least a couple of days to process, miss some facultative organisms, and are less useful in patients taking antibiotic therapy.

Genotypic analysis

Genotypic (molecular) analysis is a more sophisticated approach to identify pathogens, where various techniques help to define the genetic makeup of an organism or group of organisms with reference to a single, or set of, trait(s). The most commonly used methods in clinical laboratories include polymerase chain reaction (PCR) (134), real-time (RT) PCR and sequencing technologies (Sanger or next generation) (135). These techniques are currently relatively more complex than phenotypic testing, but their sensitivity and specificity is considerably higher and they can produce results within hours. Thus, they offer the opportunity to rapidly and reliably detect the presence of genetic material encoding for various features used for identification, characterisation, determination of virulence and potentially antibiotic resistance of pathogens (136). While these methods detect many more organisms than phenotypic analysis, especially obligately anaerobic and fastidious species, the clinical significance of these additional isolates is not yet clear (137).

Interpreting wound culture results

Sole or predominant bacterial species identified on culture of a good quality specimen (and seen, where available, on Gram-stained smear) are likely true pathogens. If multiple organisms are isolated, especially from superficial ulcers, it can be difficult to determine which are pathogens. Clinical microbiology services must work closely with clinicians and report results in a manner that is easily understood by the recipients. Targeting antibiotic treatment against likely colonisers (e.g., coagulase-negative staphylococci, corynebacteria) may be unnecessary. These species can, however, sometimes be true pathogens, especially if they grow repeatedly or from reliable specimens. In most centres, *S. aureus* is the most frequently isolated, and perhaps most virulent, pathogen, whether alone or in combination. Streptococci (various groups of -haemolytic and others) are also important pathogens. Enterococci are relatively frequent isolates but usually of secondary clinical importance.

Infections requiring hospitalisation are often polymicrobial and may include various types of aerobes and anaerobes (30,138). Gram-negative bacilli (mainly Enterobacteriaceae, sometimes *P. aeruginosa*, or other gram negative species) are usually isolated in conjunction with gram-positive cocci from patients with chronic or previously treated infections; they are often, but not always, true pathogens. Many recent studies have reported that gram-negative organisms (especially *P. aeruginosa*) are the most frequent isolates in DFIs occurring





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in patients in warm climates, especially in Asia and Africa (139-142). It is unclear if this is related to environmental factors, footwear, personal hygiene, antimicrobial pre-treatment or other factors. Obligate anaerobic species are most frequently isolated from ischaemic or necrotic wounds or those that involve deep tissues; they are rarely the sole pathogen and most often are part of a mixed infection with aerobes (143).

Multidrug-resistant organisms, especially MRSA, are more often isolated from patients who have recently received antibiotic therapy, have been previously hospitalized or reside in a chronic care facility or who have had a previous amputation (144,145). After the prevalence of MRSA dramatically increased in many countries starting in the late 1990s, it has recently begun to decline in most countries, concomitant with improved hospital infection control measures (146-148). DFIs caused by MRSA have been thought to be associated with more severe infections, but a recent review found that they had a similar clinical presentation and outcomes to other pathogens (127). The previously useful distinction of community-acquired (less likely to be resistant to other antibiotics and often more virulent) versus healthcare-associated strains has become less reliable in recent years. In the past decade, other multidrug-resistant organisms, especially gram-negatives with extended-spectrum β -lactamases (ESBL) (149,150), and even carbapenemases (151,152) have been reported to cause DFIs. Vancomycin-resistant enterococci are occasionally recovered from infections of the foot in persons with diabetes, but are rarely a clinically significant pathogen. Most cases of infection with the very rare, but truly dreaded superbug, vancomycin-resistant *S. aureus*, have been from patients with diabetic foot infections (153,154).

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Surgical

Recommendation 16:

Consult a surgical specialist in selected cases of diabetic foot infections that are moderate, and in all cases that are severe, (Weak; Low)

Recommendation 17:

Perform urgent surgical intervention is necessary in most cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (Strong; Low)

Recommendation 18:

Consider surgical intervention is usually advisable in cases of osteomyelitis accompanied by: spreading soft tissue infection; destroyed soft tissue envelope; progressive bone destruction on X-ray; or, bone protruding through the ulcer (Strong; Low)

Rationale 16 – 18:

Surgery is the cornerstone of treating many deep soft tissue infections (125) and early intervention may be associated with better outcomes (47,155-157). Emergent surgery, however, is only needed in specific circumstances, such as gas gangrene or necrotizing fasciitis, compartment syndrome or systemic sepsis. The treating clinician should consider the need for surgery in every infection, which may range from minor debridement or drainage to extensive resections, revascularisation or major amputation. When the wound has a dry eschar, especially in an ischemic foot, it is often best to avoid debriding the necrotic tissue; often these will resolve with autoamputation. Major amputation should, and usually can, be avoided unless the limb is: non-viable; affected by a potentially life-threatening infection (e.g., gas gangrene or necrotizing fasciitis); or, is functionally useless. Revascularisation (either endovascular or open bypass) may be needed for a severely ischaemic infected limb. In many non-urgent infections the initial surgical intervention should be limited to incision and drainage, with further resection needed only if the patient is not responding.



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Figure 2 shows an algorithmic overview of the approach to treating a patient with diabetes and a foot infection. Operative treatment of a DFI should be carried out by surgeon with thorough knowledge of the anatomy of the foot and the ways in which infection spreads through its fascial planes (see Figures 3, 4)(47,158). The aim of surgical treatment is to drain any deep pus and to minimise tissue necrosis by decompressing foot compartments and to removing devitalized and infected tissue. There is a relationship between the point of entry of an infection and the compartment in which the infection spreads: those arising from the great toe and first metatarsal head usually spread through the medial compartment; those arising in the second, third and fourth toes and metatarsal heads spread through the central compartment; and, those arising from the fifth toe and fifth metatarsal head spread through the lateral compartment (47,159). The dorsal compartment may be involved in infections arising in web spaces or in advanced infections of a plantar ulcer, either by involving a metatarsal head or via an interosseus compartment. Acute infections often spread along the tendons, as they are the path of least resistance and run within the compartments, and infected tendons must be widely removed.

Bone resection and amputation is often necessary when there is extensive soft tissue necrosis or to provide a more functional foot. A specimen of bone should be obtained at the time of surgery for analysis by culture and histopathology. Some data suggest that if there is a “clear margin,” i.e., uninfected bone by culture at the site of resection, antibiotic therapy can be safely reduced from several weeks to just days, and the rate of clinical cure is significantly higher than when the margin is culture-positive (160). Surgical procedures in the infected diabetic foot should be conducted as part of an interdisciplinary approach, as it must be accompanied by proper wound care, treatment of any co-morbid medical conditions, and appropriate revascularization (when needed).

Once any necessary surgical drainage and debridement have been performed and infection is under control, the long-term function of the foot is a key issue. Patients who have undergone previous surgeries or amputations may have biomechanical consequences that can potentially result in an unstable foot, or lead to a foot prone to re-ulceration. The surgeon should consider these concerns when contemplating any ablative forefoot operation and balance preservation of tissue with a transmetatarsal amputation (161).



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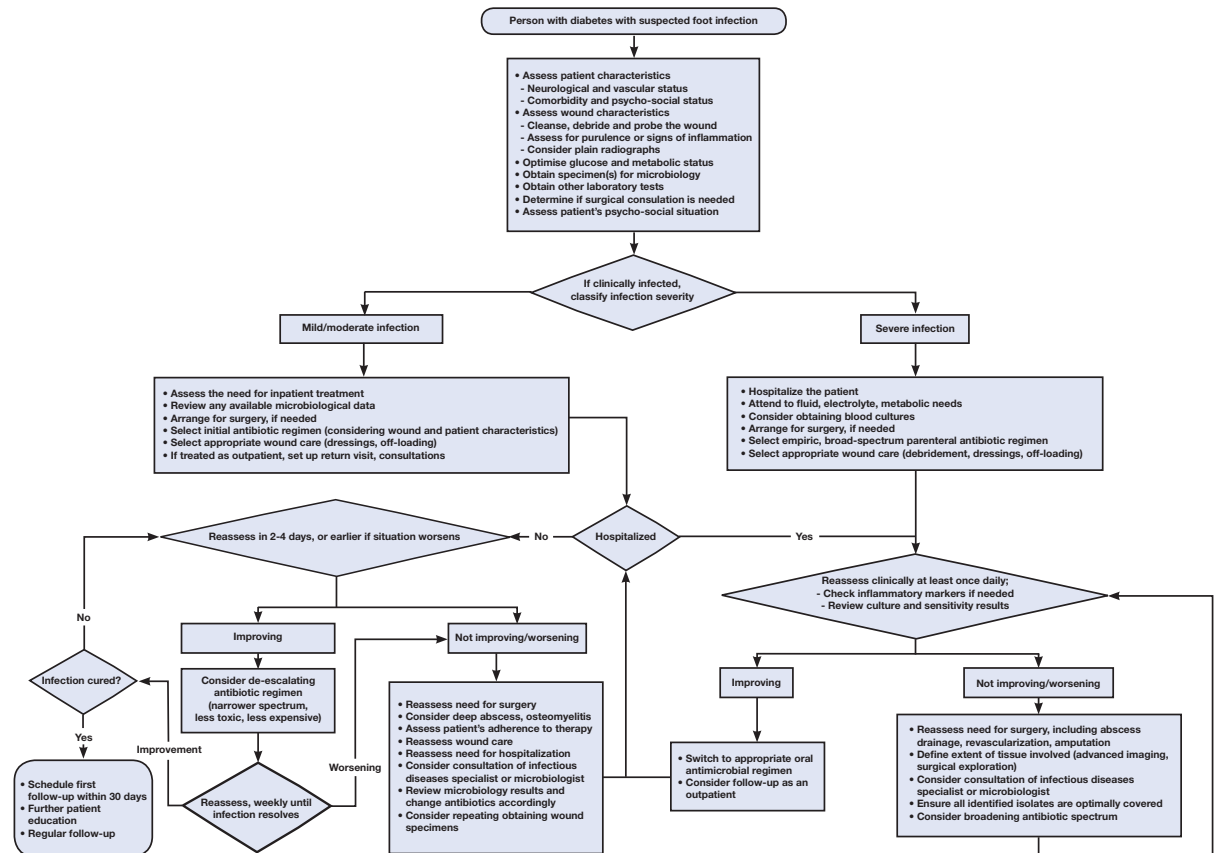
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Figure 2. Algorithm overview of the approach of the patient with diabetes and a foot infection



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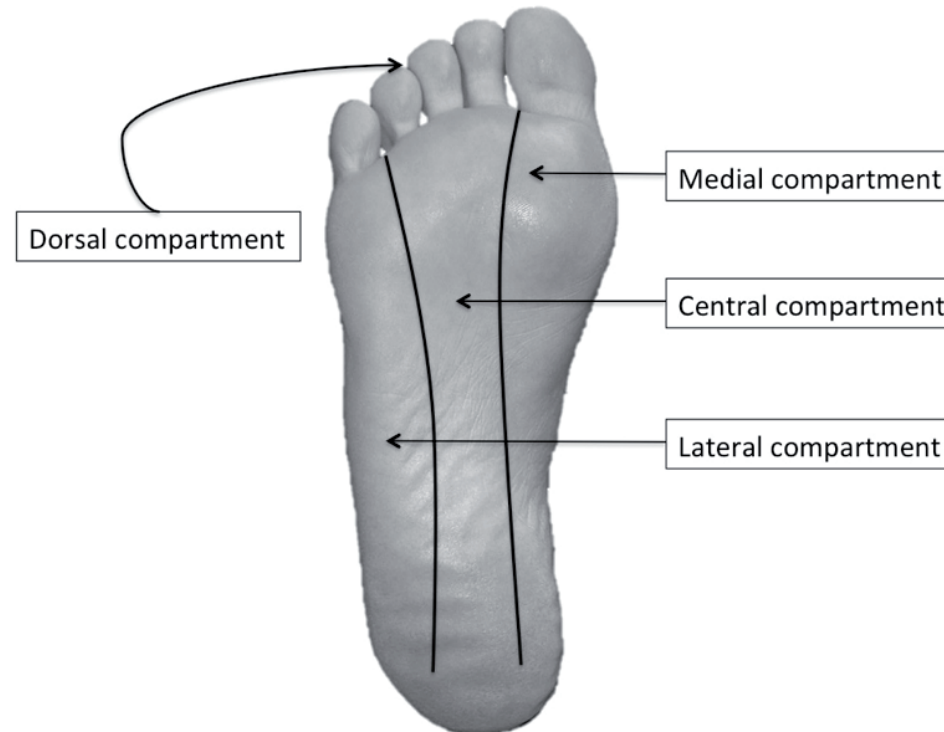
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Figure 3. Longitudinal view of compartments of the foot



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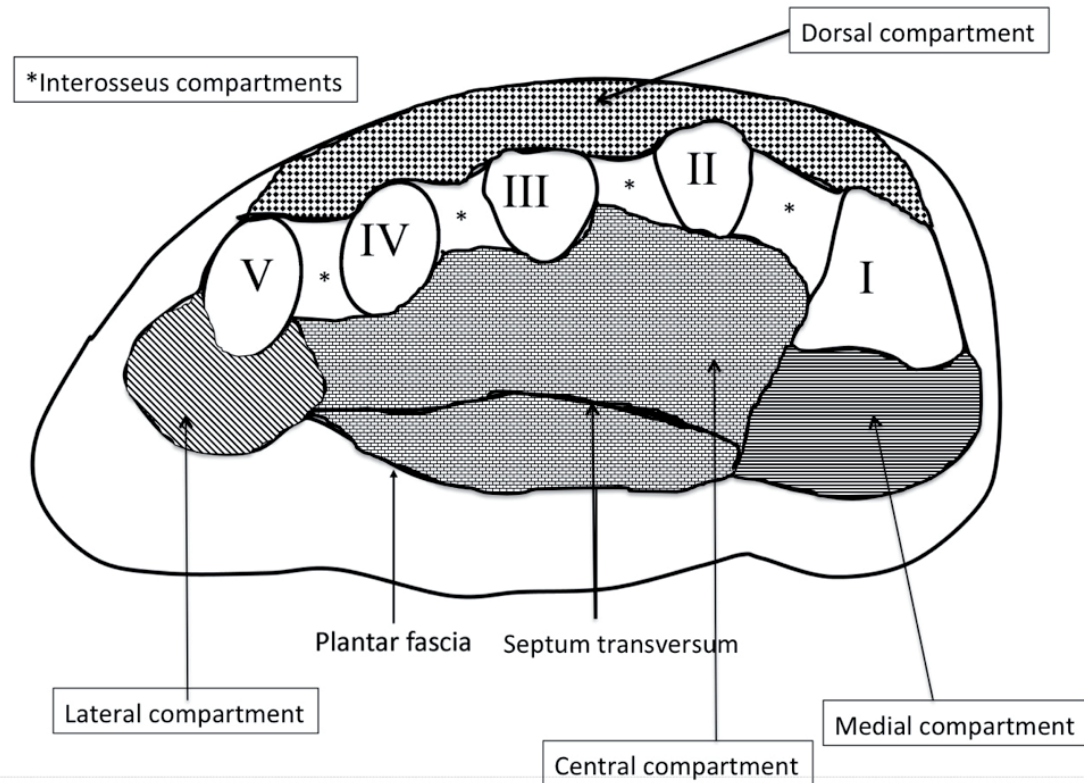
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Figure 4. Transversal view of compartments of the foot





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Antimicrobial therapy

Recommendation 19:

While virtually all clinically infected diabetic foot wounds require antimicrobial therapy, do not treat clinically uninfected diabetic foot wounds with antimicrobial therapy (Strong; Low)

Recommendation 20:

Select specific antibiotic agents for treatment based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, and evidence of efficacy for DFI and costs (Strong; Moderate)

Recommendation 21:

A course of antibiotic therapy of 1-2 weeks is usually adequate for most soft tissue diabetic foot infections (Strong; High)

Rationale 19 - 21 - Indications for therapy:

Failure to treat an infected diabetic foot wound with antimicrobial therapy is usually associated with progressive tissue destruction and poor wound healing. However, antibiotic therapy is also associated with frequent adverse effects, financial costs, and increasing the risk of antibiotic resistance (144), so it should be reserved for treating wounds that are infected. Treatment with antimicrobials has not been proven to be beneficial for managing clinically uninfected skin wounds, irrespective of theoretical considerations of the bacterial “bioburden” (a poorly defined concept) of chronic wounds (162-166). There is no published evidence that antimicrobial therapy either accelerates wound healing or reduces the likelihood of clinical infection developing. Where the clinical assessment for the presence of infection is equivocal, the clinician must make a decision to treat the wound as either uninfected or as infected (using an infection grading system) and then carefully monitor progress.

Recommendation 22:

Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (Strong; Low)

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Rationale 22 - Route of therapy:

For an antibiotic to reach a therapeutic concentration at the site of infection it must first achieve an adequate serum level (167). Because parenteral antibiotics achieve therapeutic serum levels faster and more reliably, they are recommended for patients who are systemically ill or have a severe infection. They may also be required for those unable to tolerate oral agents or who are infected with pathogens insensitive to available oral agents. After the patient's clinical condition has stabilized and the infection is responding, most can switch to oral therapy. Where available, consider outpatient intravenous antibiotic therapy for those requiring prolonged parenteral treatment, for example, for some cases of osteomyelitis or infections with organisms found resistant to available oral agents.

Compared with parenteral therapy, treatment with oral antibiotic agents is more convenient, not associated with infusion-related complications, and generally less expensive. Gastrointestinal absorption of oral antibiotics (bioavailability), while variable, is excellent for several agents, such as fluoroquinolones, clindamycin, rifampin, trimethoprim/sulfamethoxazole, linezolid, and doxycycline (168). Fluoroquinolones in particular achieve high tissue concentrations in diabetic foot infections (167,169,170), even in patients with gastroparesis (171), but most other currently used oral antibiotics also achieve adequate serum and tissue levels (168). Unfortunately, fluoroquinolones are also associated with an increased risk of adverse effects, including *Clostridium difficile* disease, and failure with one of these agents may cause resistance to others (172). No data are currently unavailable to determine if adequate tissue levels predict successful clinical outcome (173). Newly marketed agents generally have an expanded spectrum of activity, greater activity against antibiotic-resistant gram-positive cocci, a longer half-life (allowing for less frequent dosing) or good oral bioavailability. However, they are generally considerably more expensive and have a shorter track record for safety evaluations. Virtually all comparisons of different antibiotic regimens for DFI have reported no clinically significant differences between them, and no specific agents have emerged as being preferred. One new agent, tigecycline (which has broad-spectrum activity, including against MRSA) when compared to ertapenem (with or without vancomycin) was found in a recent large, multicentre, randomised controlled trial to be significantly inferior in clinical outcomes and to have a significantly higher rate of adverse effects (174).

Peripheral vascular disease, but not diabetes per se, may limit the delivery, and therefore penetration, of antibiotics to infected foot tissues (171,175). Optimally, patients with severe arterial insufficiency should undergo revascularization, but even in an ischemic limb, however, antibiotics play an important role in treating and preventing further spread of infection. Problems with limb arterial insufficiency have led some to experiment



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with novel methods of antibiotic delivery to the lower limb, for example, retrograde intravenous perfusion under pressure (176,177), intra-arterial (e.g., femoral) administration (178), primary closure of debrided wounds with catheter instillation of antibiotics (179), or negative pressure wound therapy with installation of saline, antiseptics or antibiotics (180-184). At this time there is insufficient evidence upon which to recommend any of these approaches.

Using topical antibiotic therapy for a foot wound is appealing, as it allows high concentrations at the site of infection without potentially toxic systemic levels (185,186). It would also allow treatment with agents not available for systemic therapy. There are, however, some theoretical and practical caveats to its use, such as a potentially higher susceptibility to the occurrence of hypersensitivity and limited effectiveness for infection in surrounding intact tissue and possibly a lower threshold for development of antimicrobial resistance (186). A large randomised trial of 835 patients treated for an infected DFU (most of which would meet the current PE-DIS criteria for grade 2, and some grade 3) found that an investigational topical antimicrobial peptide (pexiganan) was as effective as oral therapy with a fluoroquinolone, with clinical improvement rates of 85%-90% (187). Topical antimicrobial therapy may also be used in combination with systemic antibiotic therapy. One trial compared outcomes in patients with a moderately infected DFU who were treated with standard therapy (including levofloxacin) with or without the addition of the daily application of a topical gentamicin-collagen sponge (188). Among 56 randomised patients the clinical cure rate for the sponge group was significantly lower at day 7 (the primary outcome), but was significantly higher at the test of cure visit (2 weeks after discontinuation of therapy, which was up to 28 days).

A limited number of marketed topical antimicrobial agents, as well as antimicrobial impregnated wound dressings [e.g., those containing various forms of silver and iodine] might be useful for preventing, or possibly even treating, mild infections (186). Currently supporting data are too limited to recommend topical antimicrobial therapy, but further research is warranted (186,189-192). For deep surgical wounds, antibiotic impregnated beads, cement, or biodegradable bovine collagen sponges can supply high local antibiotic concentrations (for a few days), and in some instances fill dead space (192,193). A systematic review and an expert opinion paper concluded that the data supporting the use of gentamicin-impregnated beads is too limited to make any recommendations (186,194).

Choice of antibiotics

Selection of an initial antibiotic regimen is usually empirical, i.e., a best guess at what agent(s) will cover the likely pathogen(s). These should be selected to cover the most common infecting organisms, but be modified





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according to infection severity and available clinical or microbiological information. We prefer relatively narrow-spectrum agents for mild infections, with adjustments if clinical response is inadequate, especially if cultures disclose pathogens resistant to the selected agent(s). Initial regimens for many moderate and all severe infections should be broader spectrum and treatment must be delivered promptly. An empirical regimen must also consider factors related to the current infection, the likely pathogen(s), the patient co-morbidities, and potential drug-related issues (see Table 5).



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Table 5. Factors that may influence choices of antibiotic therapy for diabetic foot infections (specific agents, route of administration, duration of therapy)

Infection related

- Clinical severity of the infection (see Table 1)
- History of antibiotic therapy within previous 3 months
- Presence of bone infection (presumed or proven)

Pathogen related

- Likelihood of non-GPC etiologic agent(s) (e.g., GNR, anaerobes)
- History of colonization or infection with MDROs
- Local rates of antibiotic resistance

Patient related

- Allergy to any antibiotics
- Impaired immunological status
- Patient treatment preferences
- Patient adherence to therapy
- Renal or hepatic insufficiency
- Impaired gastrointestinal absorption
- Peripheral arterial disease in affected limb
- High risk of MDROs or unusual pathogens (e.g., hospitalised patients, travel or animal exposure)

Drug related

- Safety profile (frequency and severity of adverse effects)
 - Drug interactions potential
 - Frequency of dosing
 - Formulary availability/restrictions
 - Cost considerations (acquisition and administration)
 - Approval for indication
 - Likelihood of inducing *C. difficile* disease or antibiotic resistance
- Published efficacy data

Note: GPC= gram-positive cocci (aerobic); GNR= gram-negative rods (aerobic); MDRO= multi-drug resistant organism.





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A Gram-stained smear of a wound specimen may help direct empiric antibiotic therapy by informing the clinician of the number and gram-types of pathogens present (195). This simple and inexpensive procedure is particularly useful in regions of limited resources. A recent study from Tanzania found that among 128 diabetic patients with a limb ulcer the positive predictive value of a Gram-stain for bacterial growth was 93% and the predictive value was 75% (15/20) for gram-positive organisms and 82% (31/38) for gram-negative organisms (133).

An empiric regimen should virtually always include an antibiotic usually active against standard strains of staphylococci and streptococci. Consider adding an agent active against MRSA if there is substantial risk of infection with this organism (e.g., a high local prevalence of MRSA, a patient with a recent stay in a health-care institution, recent antibiotic therapy or known MRSA colonization). Patients who have been previously treated with an antibiotic (for whatever reason), or who have a more severe infection, may need extended coverage for common gram-negative bacilli, and perhaps in rare cases for Enterococcus species. Empiric anti-pseudomonal therapy is usually not required unless risk factors for Pseudomonas infection are present, e.g., high local prevalence of Pseudomonas infections, warm climate, or frequent exposure of the foot to water. Empiric anti-anaerobic therapy is appropriate for necrotic, gangrenous, or foul-smelling wounds, which also require debridement. Combination therapy may be appropriate for infections presumed (or proven) to be caused by more than one organism, when the pathogen has a high potential for developing resistance (e.g., Pseudomonas) or when selecting an agent (e.g., rifampi(c)i)n when treating osteomyelitis) to which resistance may quickly develop when used alone. Some DFI pathogens are highly resistant to antibiotics, such as those reported from Italy caused by extensively-resistant *P. aeruginosa* that required treatment with colistin combined with rifamp(c)i) in and imipenem (196).

When culture and sensitivity results are available, consider changing to a more specific regimen that targets just the isolated pathogens. To reduce the likelihood of antibiotic resistance, narrower spectrum agents are preferable, but it is important to assess how the infection has responded to the empirical regimen. If the infection is improving and the patient is tolerating therapy, there may be no reason to change, even if some or all of the isolated organisms are resistant to the agents prescribed (197,198). If the infection is not responding, however, modify treatment to cover all isolated organisms. When the infection is worsening despite the isolated bacteria being susceptible to the selected regimen consider if: surgical intervention is needed; fastidious infecting organisms were not recovered on culture; patient adherence to the treatment regimen has been suboptimal; serum levels of the prescribed antibiotic are inadequate because of decreased intestinal absorption or drug interactions causing more rapid metabolism of the antibiotic.

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Several antibiotic agents have been used successfully (including some for decades) to treat DFIs despite not having been evaluated in prospective comparative studies; these include semisynthetic penicillinase-resistant penicillins (e.g., dicloxacillin, nafcillin, flucloxacillin), cephalosporins (e.g., cefazolin, ceftriaxone, ceftazidime), glycopeptides (teicoplanin, oritavancin, telavancin, dalbavancin), rifampi(c)n, fusidic acid, trimethoprim/sulfamethoxazole, and doxycycline. The following agents that have demonstrated clinical effectiveness, alone or in combination, in published prospective studies that include patients with diabetic foot infections (see Table 6) (8,9):

- Cephalosporins (cephalexin orally; cefoxitin, ceftizoxime, ceftibiprole, ceftaroline (199) parenterally)
- Penicillin/ β -lactamase inhibitor combinations (amoxicillin/clavulanate orally; ampicillin/sulbactam, piperacillin/tazobactam, and ticarcillin/clavulanate parenterally)
- Carbapenems (imipenem/cilastatin and ertapenem, parenterally)
- Fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin, all of which can be administered orally or parenterally)
- Other agents: clindamycin (orally and parenterally); linezolid (orally and parenterally); daptomycin (parenterally); tigecycline (parenterally); and vancomycin (parenterally)

Other agents in the same antibiotic classes as those listed in Table 6 are also likely to be effective. Overall, the clinical and microbiological response rates have been similar in published trials with various antibiotics, and there is no one preferred agent or combination (8,30,52,173,201-203). Understanding the principles of antibiotic therapy is more important than knowing the specific agents currently in favour, especially as new antibiotics are introduced and some older ones are made obsolete by emergence of resistance or newly appreciated toxicities or adverse interactions (195,202,204,205). In the absence of a compelling reason to choose a specific antibiotic, the one with the lowest acquisition cost is preferred, even though antibiotics account for only a small portion of the treatment costs for a foot infection (206). There is an urgent need for comparative trials and economic analyses of various anti-infective regimens for DFIs (8,30,207,208). Suggested empirical antibiotic regimens, by type of infection, are given in Table 5. Fungi are occasional pathogens in DFI, most often as part of a mixed infection (209)

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Table 6. Selecting an empiric antibiotic regimen for diabetic foot infections

Infection Severity	Additional Factors	Usual Pathogen(s)	Potential Empirical Regimens ^a
Mild	No complicating features	GPC	S-S pen; 1st gen ceph
	β -lactam allergy or intolerance	GPC	Clindamycin; FQ; T/S; macrolide; doxy
	Recent antibiotic exposure	GPC + GNR	β -L-ase-1; T/S; FQ
	High risk for MRSA	MRSA	Linezolid; T/S ; doxy; macrolide; FQ
Moderate and Severe ^b	No complicating features	GPC ± GNR	β -L-ase 1; 2nd /3rd gen ceph
	Recent antibiotics	GPC ± GNR	β -L-ase 2; 3rd gen ceph, group 1 carbapenem (depends on prior therapy; seek advice)
	Macerated ulcer, warm climate	GNR, including Pseudomonas	β -Lase-2; S-S pen + ceftazidime, S-S pen + cipro, group 2 carbapenem
	Ischemic limb/ necrosis/ gas forming	GPC ± GNR ± anaerobes	β -L-ase 1 or 2; group 1 or 2 carbapenem; 2nd /3rd gen ceph + clindamycin or metronidazole

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Table 6. Selecting an empiric antibiotic regimen for diabetic foot infections

Infection Severity	Additional Factors	Usual Pathogen(s)	Potential Empirical Regimens ^a
	MRSA risk factors	MRSA	Consider addition of, or substituting with, glycopeptides; linezolid; daptomycin; fusidic acid; T/S ($\pm$ rif)*; doxycycline; FQ
	Risk factors for resistant GNR	ESBL	carbapenems, FQ, aminoglycoside, colistin

Note: GPC = gram positive cocci (staphylococci and streptococci); GNR = gram negative rod; MRSA = methicillin-resistant *Staphylococcus aureus*; ESBL = extended spectrum beta lactamase producing organism; S-S pen = semisynthetic penicillinase-resistant penicillin; β -L-ase = β -lactam, β -lactamase inhibitor; β -L-ase 1 = amoxicillin/clavulanate, ampicillin/sulbactam; β -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; T/S ($\pm$ rif) = trimethoprim/sulfamethoxazole with or without *rifampin (200) (for now we think rifampin should only be used for osteomyelitis).

^a Given at usual recommended doses for serious infections. Modify doses or agents selected for azotaemia, liver dysfunction, etc. Recommendations based upon theoretical considerations and available clinical trials.

^b Oral antibiotic agents should generally not be used for severe infections, except as follow-on (switch) after initial parenteral therapy.



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Another factor that appears to impair response to antibiotic therapy in DFI is the presence of biofilm. These slime-enclosed aggregates of sessile bacteria adhering to surfaces are present in many chronic infections, and the majority of DFIs, and demonstrate great resistance to most antibacterial agents as well as to host defences (210,211). Eradicating bacteria in a biofilm usually requires physical removal, often combined with high doses of an antimicrobial agent found to be more active against these organisms. These include topical agents such as hypochlorous acid (212), cadexomer iodine (213) and systemic agents such as fluoroquinolones, rifamp(c)in, daptomycin, or fosfomycin (214,215).

Duration of therapy.

The optimal durations of antibiotic therapy for diabetic foot infections involving skin and soft tissue or bone are unknown. Based on data from available studies, for mild to moderate skin and soft tissue infections 1 to 2 weeks is usually effective (9,131,173), while for more serious skin and soft tissue infections 3 weeks is usually sufficient (9,173,197,198,216,217). Antibiotic therapy can generally be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed—as the antibiotics are employed to treat infection, not to heal wounds. More extended treatment may be needed for immunocompromised patients, for wounds that are poorly perfused, deep, large or necrotic, or for osteomyelitis (vide infra), but this decision should be accompanied by clinical re-evaluations to support the treatment strategy. In the occasional instances in which prolonged parenteral therapy is needed, outpatient therapy should be considered (218). The necessary duration of therapy may be shortened by adequate debridement, resection or amputation of infected tissue. Some patients who cannot (or refuse to) undergo surgical resection, or who have an implanted foreign body at the infection site, may require prolonged or intermittent suppressive antibiotic therapy.

Wound care

Recommendation 23:

Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection, or improving its outcome (Strong; High)

Rationale 23:

For treating DFIs, antibiotics (and often surgery) are necessary, but not sufficient to overcome inadequate vascular supply, poor glycaemic control, persistent wound trauma or improper wound care (219,220). Most DFUs need



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to be carefully cleaned and debrided to remove devitalized tissue that may impede wound healing and foster infection. No prospective studies have evaluated the optimal frequency or type of debridement for diabetic foot ulcers, but post hoc evaluations of clinical studies in non-infected DFUs suggest that more frequent debridement is associated with a higher healing rate (221,222). Systematic reviews of various wound dressings and topical antimicrobials have found no evidence that any specific type of therapy is better than others (223,224). For example, simple gauze dressings have performed as well for healing DFUs as silver dressings, hydrogels, alginates, and foam dressings. In general, DFUs with heavy exudate need a dressing that absorbs moisture, while dry wounds need topical treatments that add moisture. Dressings should optimally be changed at least daily, both to apply a clean wound covering and to allow careful examination of the wound for infection. Applying a total contact cast makes it difficult for the clinician and patient to visualise the wound for evaluation of response to treatment between changes, and is generally not appropriate for infected wounds. For further discussion of wound care the reader is referred to the IWGDF guidance document on wound care.

Treating osteomyelitis

Recommendation 24:

For diabetic foot osteomyelitis we recommend 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic therapy if all infected bone is resected. (Strong; Moderate)

Rationale 24:

While many cases of DFO require, or benefit from, surgical debridement or resection of bone, some can be treated successfully by medical therapy alone. Several published retrospective series have shown that DFO can be arrested (or even apparently cured) with antibiotic therapy in the absence of surgical intervention in about two-thirds of cases (111,119,225-229). In these reports, clinicians have generally employed the higher recommended daily doses of antibiotics given for at least two (and usually 3–6) months. Unfortunately, available studies do not provide information to inform which types of DFO cases may be successfully treated without surgery (111,119,225-229). In some cases, limited surgery (resection of infected and necrotic bone without amputation) combined with antibiotic therapy may be most appropriate (157,230-233). A retrospective study from four centres in France and Spain compared outcomes of patients with bone culture-proven *S. aureus* DFO who were treated by either “medical” (just antibiotic therapy, other than soft tissue debridement at the bedside) or “surgical” (operative treatment combined with prolonged antibiotic therapy) (234). Outcomes were similar for the



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two groups (favourable in 80% in the surgical group and 87% in the medical group), but significant differences between patients in the medical group compared to the surgical group were that they were less frequently hospitalized (49% versus 94%), had a shorter length of hospital stay (17 versus 12 days), had a slightly longer course of antibiotic therapy (11 versus 10 weeks) and more treatment related side effects (33% versus 9%).

Recently the first published prospective, randomized trial was published that compared the outcomes of the treatment of DFO in patients who received exclusively antibiotic therapy (for up to 90 days) versus those who underwent limited resection of the osteomyelitic bone (accompanied by ~10 days of antibiotic therapy) (235). The primary end point was foot wound healing, which occurred in 18 antibiotic-treated patients compared with 19 predominantly surgically treated patients (75% versus 86.3% healing rates, respectively, $p=0.33$). There was no significant difference in median time to healing (6-7 weeks), the need for surgery (first or repeat procedure, including minor amputations), reulceration (up to 12 weeks after healing) or treatment related complications. This study suggests that the short-term results of therapy with either antibiotics alone or predominantly surgical treatment (with some antibiotic therapy) are similar in patients who have neuropathic forefoot ulcers complicated by osteomyelitis, but without ischemia or necrotizing soft tissue infections. Noteworthy aspects of this trial were that the number of enrolled patients was relatively small, only about a third of the patients they evaluated for the study were eligible for inclusion and the duration of follow-up was rather short (236). Table 7 summarises factors potentially favouring selecting either primarily antibiotic or surgical treatment for diabetic foot osteomyelitis.

The IWGDF produced a full systematic review of, and guidelines for, the treatment of DFO in 2008 (52), and updated the review for all types of DFI in 2012 and 2015 (9,173). Recently a non-systematic review provided guidance on selecting systemic antibiotic therapy for chronic osteomyelitis (237). Among the important factors to consider when treating osteomyelitis are the following: the anatomic site of infection, the local vascular supply, the extent of both soft tissue and bone destruction, the presence of any systemic signs of infection and the patient's preferences for treatment. The choice of an antimicrobial agent for treating osteomyelitis should optimally be based on the results of a bone culture, especially because of the need for long-duration therapy (49,119). If empiric therapy is necessary, the regimen should usually cover *S. aureus* as it is the most common pathogen, but the patient's history or culture results may suggest a need for broader coverage. Some antibiotics may not penetrate well into infected bone, but the unreliability of measuring bone levels limits the value of published data on this issue. Furthermore, the association between high bone levels of an antibiotic and improved outcome has not yet been studied. Although treatment of osteomyelitis has traditionally been

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parenteral (at least initially) and prolonged (at least 4 weeks), these recommendations are not based on strong data. Many patients can probably be switched to oral therapy after about a week of parenteral treatment to complete their treatment course. Any oral antibiotics selected should have good bioavailability [e.g. fluoroquinolones, rifampi(c)i(n) (always combined with another agent), clindamycin, linezolid, fusidic acid or trimethoprim-sulfamethoxazole]. If all of the infected bone is surgically removed a shorter course of antibiotic therapy (i.e. 2–14 days) may be sufficient, depending on the status of the soft tissues (9). Extending post-debridement antibiotic therapy beyond six weeks, or giving IV treatment longer than one week, does not appear to increase the remission rate. A recent randomised controlled trial that compared 6 versus 12 weeks of antibiotic therapy for non-surgically treated DFO in 40 patients found no significant difference in the remission rate (60% versus 70%), but significantly fewer adverse effects with the shorter treatment (238,239).

For some patients with apparently incurable infection, long-term suppressive therapy, or intermittent short courses of treatment for recrudescence symptoms, may be the most appropriate approach. When there are clinical signs of persistent or recurrent infection the clinician should strongly consider a percutaneous bone biopsy for culture to determine if there is persistent infection or any changes in the pathogens or their antibiotic susceptibilities. Antibiotic impregnated beads (192), sponges (188), cement or orthopaedic implants have been used successfully to treat DFO in a few small studies (193).

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Table 7. Factors potentially favouring selecting either primarily antibiotic or surgical resection for diabetic foot osteomyelitis

Medical

- Patient is too medically unstable for surgery
- Poor postoperative mechanics of foot is likely (e.g., with mid- or hind-foot infection)
- No other surgical procedures on foot are needed
- Infection is confined to small, forefoot lesion
- No adequately skilled surgeon is available
- Surgery costs are prohibitive for the patient
- Patient has a strong preference to avoid surgery

Surgical

- Foot infection is associated with substantial bone necrosis or exposed joint
- Foot appears to be functionally nonsalvageable
- Patient is already nonambulatory
- Patient is at particularly high risk for antibiotic-related problems
- Infecting pathogen is resistant to available antibiotics
- Limb has uncorrectable ischemia (precluding systemic antibiotic delivery)
- Patient has a strong preference for surgical treatment

Note: Modified from Lipsky, 2014, *Diabetes Care* (236).



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Adjunctive therapies

Recommendation 25:

We suggest not using any adjunctive treatments for diabetic foot infection [Weak; Low]

Rationale 25:

Several studies have reported the results of additional approaches (beyond antibiotics and surgery) to help resolve infection, accelerate wound healing or improve host response. These include negative pressure wound therapy (NPWT), systemic hyperbaric oxygen therapy (HBOT), granulocyte colony stimulating factors (G-CSF) and larval (maggot) therapy (9,240). While NPWT is often used for infected cardiothoracic, traumatic and orthopaedic wounds, we know of no studies that have specifically investigated the role of NPWT to treat infected diabetic foot wounds. A randomized controlled study of patients with chronic diabetic foot wounds after partial amputation reported a nonsignificantly higher rate of infection in those treated with NPWT than in the controls (16.8% versus 9.4%) (241). One retrospective cohort study reported a higher proportion of healed or surgically closed wounds and shorter periods of hospitalisation in infected diabetic patients treated with NPWT with simultaneous irrigation with an antiseptic solution (182). One controlled trial of treatment of diabetic foot wounds included a group of 130 patients randomized after surgical debridement of an infected open minor amputation to either NPWT or a semi-occlusive silver dressing (242). The authors reported that the NPWT group had a significantly “more rapid development of granulation tissue covering exposed bone” and “better and more rapid control of infections” and reduced time to complete close of the wound. We find it difficult to interpret these endpoints and await further prospective trials of this therapy for infected wounds.

Several randomized clinical trials evaluated HBOT for treating DFUs and some have shown an increased likelihood or faster rates of wound healing and fewer major amputations (243-246). Most of these studies included Wagner 3 ulcers, which can include patients with osteomyelitis, but none presented any subanalyses of patients with infected DFUs or specifically reported on infection related outcome measures. To date, there are no data to support using HBOT to treat either soft tissue infection or osteomyelitis.

A meta-analysis of five studies with a total of 167 patients with DFIs found that therapy with various types of investigational G-CSF treatments was associated with significantly fewer surgeries and amputations and shorter hospital stays, but did not increase the likelihood of resolving infection, healing wounds or shortening the duration of systemic antibiotic therapy (9,247,248). Maggot debridement, or larval biotherapy, has been shown





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to have antibacterial effects (249). A recent systematic review of its value for chronic wounds, including DFUs, reported that in one study there was a significantly longer antibiotic-free time period in patients who received maggot therapy than in those who did not, but in two studies the proportion of antibiotic use was similar for those who did and did not receive maggot therapy (250,251).

Outcome of treatment

With appropriate treatment the signs and symptoms of mild DFIs almost always resolve without need for amputation. When infection involves deep soft tissue structures or bone, the outcome is often less favourable; many require surgical debridement, bone resection or partial amputations. With extensive infection, or in medical centres with limited expertise or resources, lower extremity amputation rates may reach 50–60% (9,252). For hospitalized patients, poor outcomes (mostly amputations) occur in almost half, even in expert centres (126). A recent study from the US found that of 57 hospitalized DFI patients who were discharged to an outpatient parenteral antibiotic therapy program, 93% were considered a treatment success on discharge, but only 64% had resolution of the DFI at 6 months follow-up (39). Not surprisingly, treatment success was significantly higher with moderate compared to severe infections (79% vs 21%, $p=0.04$). Regrettably, in this small, retrospective study, adherence to the IDSA diabetic foot infection guidelines was suboptimal, and did not correlate with clinical outcome. Another recent US study found that of 234 patients with a DFI hospitalised in three different types of university-affiliated centres, only 17% of wounds healed and the amputation rate was 42% (253). Independent risk factors for amputation were the presence of gangrene or osteomyelitis and a wound area of >5 cm².

In the hands of an experienced surgeon, most amputations can be foot sparing (i.e., below the malleoli), and long-term control of infection is achieved in over 80% of cases (114). The presence of limb or foot ischemia has an important adverse effect on the outcome, synergising with infection to worsen the prognosis (254). Unfortunately, having had one foot infection is associated with an increased likelihood of another; foot infection recurs in 20% to 30% of diabetic patients, especially those with underlying osteomyelitis (255). It is difficult to know when osteomyelitis is cured, but clinical experience suggests that evidence of remission includes a drop in the erythrocyte sedimentation rate (and to a lesser extent, the C-reactive protein level), reconstitution of destroyed bone on plain radiograph and healing of any overlying soft tissue wound. While not recommended for this purpose, a negative nuclear medicine scan makes active ongoing infection unlikely. A negative culture of the bone margin left after operative resection of infected bone is associated with a lower incidence of recrudescence of infection than if the bone margin is culture-positive.(256) Because DFO recurrences are common, it is best to consider apparent treatment success a “remission” for at least a year,





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before calling it a cure. Factors that predict healing include the absence of any exposed bone, palpable pedal pulses, blood pressure in the toe of >45 mmHg or in the ankle of >80 mmHg, peripheral white blood cell count of $<12\,000/\text{mm}^3$ and a lower extremity transcutaneous oxygen tension of >40 mmHg (13,257). There is no convincing evidence that clinical outcome is related to the specific infecting organism, even multidrug resistant (e.g., MRSA) strains (127), including in cases involving bone (258). Because of the risk of reinfection, it is crucial to educate patients who have a DFI about prevention techniques and the need for prompt consultation for any future foot problems.

Issues of particular importance in developing (low-income) countries

Recommendation 26:

When treating a diabetic foot infection, assess for use of traditional remedies, previous antibiotic use and consider local bacterial pathogens and their susceptibility profile. [Strong; Low]

Rationale 26:

These guidelines must, of course, be adapted to the local circumstances in which a healthcare provider sees patients. Many aspects of the management of DFIs may differ in developing (or low income), compared with more developed (higher income), countries. In resource constrained regions infections are often a consequence of wounds caused by the diabetic person wearing footwear that is not sufficiently protective (e.g., sandals) or poorly fitting, or wearing none at all. Poor hygiene may be associated with risk of rat bites (259) and increases the risk of ulcer infection and may enable larval infestation (myiasis) (260). Persons with foot wounds may delay seeing a healthcare provider because they lack health-related education, nearby healthcare services or financial resources (261). During this period of delay the person may attempt to treat the infection with various traditional remedies, including plants or other locally accepted treatments (262-264), seek treatment from a faith or herbal healer, or have to be referred from primary to district to regional health centres (265). In a recent questionnaire study of patients with a DFI in the West Indies, 382 who had sought medical attention soon after detecting the infection were compared to 313 who voluntarily chose to delay medical therapy in favour of home remedies (266). The home remedy group had significantly worse outcomes for duration of hospitalization (16.3 versus 8.5 days) and number of (and need for operative) debridements. They also had a non-significant trend toward more major amputations (9.3% versus 5.2%) and an estimated increase cost for their treatment of \$10,821 (US). Furthermore, in developing countries people can often buy antibiotics without a prescription; thus, they may have treated themselves, occasionally with the advice of a local pharmacist or other trusted but non-licensed persons,





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before presenting to a physician. This unsupervised treatment, sometimes with generic drugs of questionable quality, expired medications or at inadequate doses, is likely to result in infections caused by more antibiotic-resistant organisms (262,267).

Healthcare providers in developing or low-income countries may also face a lack of access to a microbiology laboratory, so cannot determine the identity and antibiotic susceptibility of foot pathogens infecting an individual patient, or of current isolates and susceptibilities in the community. Recent studies have demonstrated substantial variations in the causative pathogens of DFIs in different regions of the world (268). In contrast to Western countries, studies from Asia and Africa have reported that aerobic gram-negative organisms (especially *P. aeruginosa*) are more common. Similarly, many clinicians will not have access to even basic (not to mention more sophisticated) imaging equipment or to specialist consultants with adequate knowledge of foot anatomy and the available conservative management methods for treating DFIs. Even when a patient sees a physician and receives an antibiotic prescription, indigent patients may be unable to afford the full course of therapy, or may be prescribed inexpensive but potentially more toxic or less effective agents.

Adverse social situations for many patients in these regions may also impair proper treatment. Home or work circumstances may make it difficult for them to stay off the affected foot, or to afford or be able to purchase or use an off-loading device. Furthermore, they may have travelled a long distance to see a physician and cannot easily return for follow-up visits. Understandably, patients and providers in low-income countries do not want “second-class,” or “best we can afford,” medical care. Improving management of DFIs in developing countries will likely require a combination of education (for patients, pharmacists and healthcare providers) and funding (for diagnostic, therapeutic and preventative services) (263,269,270).

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1. How should we monitor treatment 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 osteomyelitis?
Since bone infection is more difficult to cure than just soft tissue involvement, and the duration of antibiotic therapy is more prolonged for osteomyelitis than soft tissue infection, this is a key issue.
3. How should we 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 crucial to improve outcomes.
4. When, and which, imaging studies should we order for a patient with a DFI?
Imaging studies can be expensive and time-consuming and awaiting their results may delay appropriate therapy. Especially with the advent of new technologies, evaluating their cost-effectiveness to optimise use would improve management.
5. When should we select primarily medical versus surgical treatment for osteomyelitis?
This has been a controversial and simmering issue for some time, addressed by several retrospective studies but to date only one prospective one. An additional large, well-designed prospective study could largely answer the question.
6. Is there a definition 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 standardising the definition could help industry develop useful products and clinicians know which to employ.
7. What is the value and proper interpretation of molecular (genotypic) microbiological testing for DFI?
The era of molecular microbiology is inexorably approaching, but it is crucial for clinicians to understand when to order and how to interpret the results of these tests in deciding on antibiotic therapy.





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Prepared by the IWGDF Working Group on Wound Healing

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1. Clean ulcers regularly with clean water or saline, debride them when possible in order to remove debris from the wound surface and dress them with a sterile, inert dressing in order to control excessive exudate and maintain a warm, moist environment in order to promote healing. (GRADE strength of recommendation: Strong; Quality of Evidence: Low)
2. In general remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contra-indications such as severe ischemia into account. (Strong; Low)
3. Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)
4. Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. (Strong; Moderate)
5. Consider the use of systemic hyperbaric oxygen therapy, even though further blinded and randomised trials are required to confirm its cost-effectiveness, as well as to identify the population most likely to benefit from its use. (Weak; Moderate)
6. Topical negative pressure wound therapy may be considered in post-operative wounds even though the effectiveness and cost-effectiveness of the approach remains to be established. (Weak; Moderate)
7. Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care. (Strong; Low)
8. Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care. (Strong; Low)
9. Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care. (Strong; Low)

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There is a clear need for evidence to substantiate the use of particular interventions in the management of chronic ulcers of the foot in diabetes. Following the completion of the latest of three systematic reviews undertaken over the last ten years for the International Working Group on the Diabetic Foot (IWGDF) (1-3), the authors have formulated guidance on the use of interventions to enhance the healing of foot ulcers in diabetes, based on the evidence from all three reviews. The guidance is based on the GRADE system of rating both the quality of the evidence and the strength of the recommendations¹. Recommendations can be made to support an intervention, but also against the use of a particular intervention if there is no strong supporting evidence to justify its adoption. The guidance is divided into ten categories – the same as those used to group different types of intervention in the systematic reviews.

¹ Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (4,5). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence on: the risk of bias of included studies, effect sizes, and expert opinion, and rate the quality of evidence as 'high', 'moderate', or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.

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What is the best way of debriding a diabetic foot ulcer?

Recommendation 1:

Clean ulcers regularly with clean water or saline, debride them when possible in order to remove debris from the wound surface and dress them with a sterile, inert dressing in order to control excessive exudate and maintain a warm, moist environment in order to promote healing. (GRADE strength of recommendation: Strong; Quality of Evidence: Low)

Recommendation 2:

In general remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contra-indications such as severe ischemia into account. (Strong; Low)

Rationale 1 & 2:

The term debridement is here defined as the removal of surface debris, slough, necrotic and infected matter with the aim of leaving clean, viable tissue. Even though professional opinion is united in support of the use of debridement to clean the surface of the wound when possible, the experimental evidence to justify debridement in general and of any particular method of debridement, is not strong. Debridement may be undertaken using physical (eg surgical, sharp or hydro-debridement), biological (larvae), autolytic (hydrogels) or biochemical (enzymes) methods. There is surprisingly little evidence on sharp or surgical debridement with only a single paper included in one of the previous systematic reviews and that being a subgroup analysis from another trial (6). Despite this the majority of national guidelines emphasise that sharp debridement (7,8,9) is an essential part of good wound care, taking relative contra-indications such as severe ischemia into account.

The available evidence from the three systematic reviews undertaken by the IWGDF, as published earlier in this journal, suggest that the use of hydrogels (10,11,12) as a means of debridement may have some benefit in terms of wound healing when compared to saline moistened gauze, but the risk of bias in the published studies was high – a conclusion supported by a Cochrane review (13). Similarly, the use of enzymatic or hydro-debridement cannot be supported by the available evidence, which is limited to one study on each method that qualified for inclusion (14,15). The use of larval therapy is equally unsupported in these three reviews with only four small



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studies identified, each of which had a high risk of bias (16-19). Of interest, two recent large RCTs of the use of larval therapy in venous leg ulcers have failed to demonstrate benefit in terms of healing (20,21).

This does not mean that debridement is ineffective but simply that the studies have not been done that provide robust evidence to support a strong recommendation. In general, however, clinicians should not adopt newer, more expensive, interventions unless they have been shown to have a greater impact on wound healing than existing methods.

What is the best dressing to use?

Recommendation 3:

Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)

Recommendation 4:

Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. (Strong; Moderate)

Rationale 3 & 4:

The three systematic reviews performed have looked at a number of different topical preparations designed to improve the healing of ulcers of the foot in diabetes. In general, the evidence to support the adoption of any particular intervention is poor, because the available studies are small and at high risk of bias.

The results of an earlier positive study on a carboxymethylcellulose dressing (22) were not born out by a more recent large single blind RCT with low risk of bias (23).

There is increasing interest in the use of surface antiseptics or antimicrobials and although healing may not be the most obvious outcome measure to evaluate these agents, it is important that it is assessed in order to demonstrate the contribution it may make to the healing process. A single study reporting the use of antibiotic beads after transmetatarsal amputation found that this intervention had no impact on the incidence of wound healing (24).

Honey has been used for centuries as an antimicrobial agent and its appeal as a potential target for the management of chronic wounds is obvious. There is, however, little evidence to support its use for either the



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promotion of healing or the prevention of secondary infection. Over the three systematic reviews, only three small controlled studies on the use of honey were identified and none showed convincing evidence of benefit when compared with an iodine-containing dressing (25-27). A Cochrane review of honey based dressings in all wound types (28) concluded that health services may wish to consider avoiding routine use of honey dressings until sufficient evidence of effect is available – a conclusion that is endorsed by the results of the current review.

Other topical antimicrobials, such as silver or iodine based dressings and applications, are also used frequently. Only one controlled trial of a silver based dressing was identified in all three systematic reviews (29) and this demonstrated no convincing evidence of benefit. Similarly, a recent Cochrane review found no evidence of benefit from the use of antiseptic preparations in terms of either healing or secondary infection in any studies of infected or contaminated wounds (30). Similarly a single large high scoring multicentre RCT which compared a non-adherent dressing with an iodine impregnated dressing and a carboxymethylcellulose hydrofibre dressing was reported in the 2012 review. This showed no difference between the three products either in terms of wound healing or the incidence of new infection (23).

The conclusion for the whole group of topical interventions is that there was either insufficient or no evidence to justify the use of any of the preparations considered in preference to any other. In the absence of any specific indication, practitioners should use the dressing/application with the lowest acquisition cost, but which supports moist wound healing whilst controlling any exudate.

Does systemic hyperbaric oxygen therapy (HBOT) hasten wound healing in diabetic foot ulcers?

Recommendation 5:

Consider the use of systemic hyperbaric oxygen therapy, even though further blinded and randomised trials are required to confirm its cost-effectiveness, as well as to identify the population most likely to benefit from its use. (Weak; Moderate)

Rationale 5:

In our systematic reviews we reported two RCTs (31,32) of methodologically good quality on systemic HBOT. The larger study (32), which included patients both with and without (severe) peripheral arterial disease, demonstrated a significantly improved outcome in the intervention group, who were more likely to heal within 12

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months. In a post-hoc analysis ulcer healing in the patients treated with HBOT was associated with baseline trans cutaneous oxygen pressure (TcPO₂) levels, but not with ankle:brachial index (ABI) or toe blood pressure (33). Of note, the second RCT that also observed improved wound healing (31) included only patients with non-reconstructable critical limb ischemia. It remains therefore to be determined which group of patients will benefit most from systemic HBOT. This is underscored by a large retrospective cohort study of patients treated in 83 centres located in 31 states of the USA (34). Data were included if patients had been treated according to reimbursement guidelines from Centers for Medicare and Medicaid Services which require that patients have “an adequate lower-extremity arterial flow” as determined by the clinician. Using propensity score-adjusted models, the authors concluded that HBOT did not appear to be useful for the prevention of amputation and did not improve the likelihood that a wound would heal in these patients. Although the design and inclusion criteria of this study have been criticised, it highlights the need for further studies to determine which patient group might benefit most from this treatment and to establish cost-effectiveness.

Does topical negative pressure wound therapy (NPWT) hasten healing in diabetic foot ulcers?

Recommendation 6:

Topical negative pressure wound therapy may be considered in post-operative wounds even though the effectiveness and cost-effectiveness of the approach remains to be established. (Weak; Moderate)

Rationale 6:

NPWT is a technique for applying continuous or intermittent negative pressure to wounds via a material that fills the wound. Optimal use of this technique requires knowledge of the influence of different pressure levels, the different materials that can be put in the wound and the interface materials (those in direct contact with the wound surface). One theory behind the use of NPWT is that by extracting wound exudate, the frequency of dressing changes can be reduced and, wounds can therefore be kept cleaner, and with reduced malodour. Moreover, NPWT appears to stimulate granulation tissue formation (35,36) and contraction of the wound (35). It is also suggested that NPWT may increase tissue perfusion by mechanical means and may also encourage off-loading by making ambulation difficult (35). NPWT is generally useful in stimulating the healing process, but does not result in complete epithelialisation. Potential adverse effects of NPWT have been described, including wound maceration, retention of dressings and wound infection (36).



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A number of other potential contraindications to its use have been listed elsewhere (37). Given the relative complexity of this technique and its risks, it requires skills and organization.

There are two distinct types of wounds in which NPWT has been studied in the management of ulcers of the foot in diabetes; the post surgical and the chronic non-surgical wound.

Post-surgical wounds:

In earlier systematic reviews we reported on two large RCTs and a small RCT which suggested in post-operative wounds a significant benefit of NPWT in both the time to healing and the proportion of wounds healed (38,39,40). However, there were methodological issues in these studies rendering them subject to bias.

One small study was reviewed in the latest review which compared the use of NPWT on the success of split skin grafting (41). Although apparently improving the number of split skin grafts which took successfully when compared to usual care, the study was of poor methodological quality. A small randomised but single blind study has shown that the qualitative but not quantitative assessment of the graft take improved when NPWT was used in addition to split skin grafting (42) but this was not undertaken in diabetic foot ulcers.

Non-surgical ulcers:

Three small RCTs and one cohort study have been identified on the use of NPWT in chronic DFUs from all three systematic reviews (43-46). All had methodological flaws but showed NPWT was associated with decreased wound volume and depth (43), and decreased time to ulcer healing (44), but these studies were subject to bias and there is, in addition, considerable publication bias in this area (35). It is not possible to make a recommendation on the use of NPWT in non-surgical wounds because of the lack of available evidence.

Is there a place for the use of other topically applied treatments?

Recommendation 7:

Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care. (Strong; Low)

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Rationale 7:

Four studies of collagen/oxidised regenerated cellulose dressing were identified in the three systematic reviews (47-50). The largest of these failed to show an effect on healing (49). Small, poor quality studies have reported the use of an acellular dermal regenerative matrix and an acellular bioproduct from pig intestine but they provided no good data to support the use of these products in routine care (51-53).

The latest search also identified a single study of perilesional injections of polydeoxyribonucleotide (54). Although a high scoring RCT, there are concerns about the poor healing rate in the control arm, the lack of detail concerning offloading and lack of health economic data. Earlier reports have suggested promise of some other agents (acellular bioproduct derived from the porcine small intestinal submucosa, acellular dermal regenerative tissue matrix, talactoferrin, chrysalin) that alter wound biochemistry and cell biology. The studies identified have provided no firm evidence to justify the use of any intervention listed.

Platelet concentrates and platelet derived growth factors have been of interest as a therapeutic target for a number of years. The earliest study identified was of autologous platelet factor (55) but was limited by being undertaken in both leg and foot ulcers and not all patients had diabetes. A later study on platelet concentrate (56) reported an apparent improvement in wound healing but was marred by a high number of drop-outs and the use of per protocol analysis. The problem of the volume of blood required for the preparation of autologous platelet gel or fluid was overcome in a later RCT by the use of blood bank derived platelets (57). Although the study reported positive results, few details were provided on study inclusion criteria. As this product was used in uninfected, non-ischemic, non-necrotic wounds, this represents a minority of patients with foot ulcers. In addition, the use of non-autologous platelets is potentially associated with adverse effects such as infection.

The use of recombinant platelet derived growth factor has also been assessed. Six RCTs were identified (58-63) that either showed no improvement in healing between intervention and control groups or were marred by significant methodological problems. Given the cost of the product, firm data are required for both its effectiveness and its cost effectiveness before it is considered for use in routine care.

Other recombinant growth factors have also been the subject of studies, and these include basic fibroblast growth factor (bFGF), epidermal growth factor vascular endothelial growth factor. Two studies of bFGF (64,65) do not support the use of this agent in clinical practice. Despite the widespread use of EGF in some countries, only



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three moderately to high scoring RCTs have been identified, with conflicting results (66-68). Hence no clear outcomes in terms of healing or area reduction have been demonstrated. One study of intramuscular injections of a plasmid containing the gene for vascular endothelial growth factor (69), has shown some promising results on reduction in wound area but needs confirmation before this therapy could be recommended in clinical practice. There is currently little evidence to suggest that any single growth factor should be considered for adoption in the management of foot ulcers that fail to heal with standard good care.

Several early studies of cultured dermal fibroblasts, keratinocytes or fibroblast/keratinocyte co-culture were marred either by methodological problems or by low healing rates in the control groups (70-74). Only one well designed RCT later reported a significant improvement in healing in a group of patients who were otherwise well managed (75) but the trial was stopped prematurely and the result is that the effectiveness and cost effectiveness of this type of therapy remains to be confirmed. One promising study of co-cultured keratinocytes in combination with fibroblasts followed by epidermal tissue engineered autograft (76) requires confirmation. There are several concerns related to these products such as the complex application process, costs as well as suboptimal quality of the skin after healing and the potential of (slow-virus). For this reason we feel that higher level of evidence is needed to justify its routine use. Split skin grafting is widely used for various kinds of non-infected, non-ischemic, non-necrotic wounds, including diabetic foot ulcers. Surprisingly, only one study of split skin grafting (77) has been identified which for methodological reasons does not provide support for the use of split skin grafting to improve healing of diabetic foot ulcers.

The evidence to justify the use of the various products available has been well reviewed in the three earlier IWGDF reviews, as published earlier, and the evidence to justify the use of any is inconclusive. It is for this reason that the routine use of any such product is not currently recommended.

Is there a place for other local therapies to improve wound healing in the diabetic foot?

Recommendation 8:

Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care. (Strong; Low)

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Rationale 8:

Studies on the use of electrical stimulation (78-80), ultrasound (81), normothermic therapy (82), magnetism (83) and laser therapy (84) have reported no convincing evidence of benefit. Reports of apparent superiority of shockwave therapy over HBO treatment are marred by the use of per protocol analysis and other methodological problems (85,86). There is no evidence to justify the recommendation for the adoption of any reported physical therapies in routine practice.

Is there a place for other systemic therapies, including drugs and herbal therapies, in improving wound healing in the diabetic foot?

Recommendation 9:

Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care. (Strong; Low)

Rationale 9:

Trials of low molecular weight heparin (87), iloprost infusion (88), and of herbal preparations – (administered orally in two studies and intravenously in one) (89-91) were of poor quality and none showed any major improvement in outcome. One recent study of the use of oral vildagliptin (92), reported apparent improvement in healing at 12 weeks in one recent study but the very low incidence of healing in the control group casts doubt on the likely clinical benefit of this product if used in addition to good clinical care. There is no evidence to justify the recommendation for the adoption of any other systemic therapy to enhance the healing of DFUs in routine practice.

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Our recommendations are derived from critical systematic review of all relevant publications but this process has its limitations and these must be borne in mind. The first is that the reviews sought evidence specifically that an intervention may improve healing (and only of foot ulcers complicating diabetes – and not of other wounds, whether acute or chronic). As, however, the process of healing is a highly complex one, involving the interaction of many different cell types and signalling pathways, it is likely that the benefit of the majority of specific interventions is limited to a particular type of wound and to a particular phase in the healing process. As the process tends to last for weeks or months, this means that the impact of any beneficial effect of a therapy may not be apparent. It is also important to consider whether the benefit of a therapy has been demonstrated in people who are also receiving usual best care, including adequate offloading in those with ulcers on weight bearing areas of the foot.

If, however, studies are of insufficient duration to assess complete healing of an ulcer as an outcome measure, it may be possible to use a surrogate measure – such as percentage reduction in wound area over four weeks, which has been shown to correlate with, and to be predictive of, the incidence of eventual healing (93). The adoption of such a surrogate measure will reduce the chance of a short term response to an intervention being obscured by the complexity of the overall healing process. Demonstration of benefit in such short duration studies could then be used as the foundation for further work designed to determine the specific population and circumstances in which the use of the intervention is likely to be beneficial.

Ultimately, however, the clinical endpoint of care is to accelerate complete healing of chronic ulcers of the foot in diabetes and this must be demonstrated if any treatment is to be generally recommended. Hitherto, such recommendation has not been possible because of the limitations both in extent and, in many cases, in quality of reported studies.

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1. Overall low evidence base for the assessment of interventions

With the exception of off-loading (not considered in this review), the field remains blighted by the poor level of evidence to justify the use of any particular therapy in the management of ulcers. There is little evidence that the number of high-quality studies is increasing.

2. The contribution made by difficulties of trial design in the continuing low output of high quality research in the field

One particular aspect of trial design may be having a major impact on the poor evidence base for specific interventions and this relates to the choice of outcome measure for intervention studies. The difficulty derives from the fact that the best measure of efficacy of an intervention in this field is the demonstration of an effect on ulcer healing, and yet ulcer healing may take many weeks. If, however, an intervention is only effective at a particular stage of wound healing or under a particular set of clinical circumstances, then it is difficult to demonstrate its benefit in a conventionally designed trial.

3. Very few data on effectiveness and cost-effectiveness

Even though there are a small number of studies suggesting efficacy of particular interventions, there are very few studies confirming effectiveness (and, thereby, of cost-effectiveness) of any particular intervention in routine care.

Conflict of interest

FG, JA, AH, RH, ML,PP, WJ: None declared relating to the interventions reviewed.

CA: Consultant: Acclity, Integra and Smith and Nephew.

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Systematic review

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Definitions and criteria

Several disciplines are involved in the management of diabetic foot disease and having a common vocabulary is essential for clear communication. Thus, based on a review of the literature, the IWGDF has developed a set of definitions for our documents and that we suggest may be used in daily practice.

General

Foot:	The structure below the malleoli.
Diabetic foot:	Infection, ulceration or destruction of tissues of the foot associated with neuropathy and/or peripheral artery disease in the lower extremity of people with diabetes.
Foot lesion:	Any abnormality associated with damage to the skin, nails or deep tissues of the foot.
Foot ulcer:	Full thickness lesion of the skin of the foot.
A healed ulcer:	Intact skin, meaning complete epithelization of a previously ulcerated site.
Diabetic neuropathy:	The presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes.
Loss of protective sensation:	Inability to sense light pressure, e.g. as applied with a 10 gram Semmes-Weinstein monofilament.
Neuro-ischemic:	The combination of diabetic neuropathy and peripheral artery disease.

Vascular

Peripheral artery disease (PAD):	Obstructive atherosclerotic vascular disease with clinical symptoms, signs or abnormalities on non-invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities.
Ischemia:	Signs or symptoms of reduced arterial supply, verified by clinical examination, with vascular testing if indicated.
Critical limb ischemia:	Persistent rest pain requiring regular analgesia for more than 2 weeks; ulceration or gangrene attributable to objectively proven peripheral artery disease.
Claudication:	Pain in a foot, thigh or calf that occurs during walking and is relieved by rest, due to peripheral artery disease.



Definitions and criteria

Vascular

Rest pain:

Severe and persistent pain localized to the foot due to peripheral artery disease, that can, at least partially, be relieved by putting the foot in a dependent position.

Angioplasty:

The technique to re-establish the patency of an artery by percutaneous transluminal or subintimal procedures.

Ulcer

Superficial ulcer:

Full thickness lesion of the skin not penetrating any structure deeper than the dermis.

Deep ulcer:

Full thickness lesion of the skin penetrating below the dermis to subcutaneous structures, such as fascia, muscle, tendon or bone.

Infection

Infection:

A pathological state caused by invasion and multiplication of microorganisms in tissues accompanied by tissue destruction or a host inflammatory response.

Superficial infection:

An infection of the skin not extending to any structure below the dermis.

Deep infection:

An infection that extends deeper than the dermis, that may include evidence of abscess, septic arthritis, osteomyelitis, septic tenosynovitis or necrotizing fasciitis.

Cellulitis:

An infection of the skin manifested by one or more of the following signs and symptoms: induration, erythema, warmth, pain or tenderness.

Osteitis:

Infection of the bone cortex without involvement of bone marrow.

Osteomyelitis:

Infection of the bone, with involvement of the bone marrow.

Amputation

Amputation:

Resection of a segment of a limb through a bone.

Disarticulation:

Resection of a limb through a joint.

Major amputation/ disarticulation:

Any resection proximal of the ankle.



Definitions and criteria

Amputation

Major amputation levels:

TF. transfemoral amputation
(frequently referred to as 'above knee amputation'),
KD. knee disarticulation
(frequently referred to as 'through knee amputation'),
TT. transtibial amputation
(frequently referred to as 'below knee amputation').

Minor amputation/ disarticulation:

Any resection through or distal of the articulation of the ankle.

Minor amputation levels:

1. toe amputation
2. toe disarticulation
3. distal transmetatarsal amputation
4. proximal transmetatarsal amputation
5. tarso metatarsal disarticulation
6. midtarsal metatarsal disarticulation
7. ankle disarticulation

Primary amputation/ disarticulation:

The first resection in a sequence until a final outcome (healing or death).

First event amputation:

The primary resection within a certain period, irrespective of side and level of amputation.

Re-amputation/ disarticulation:

Repeated resection in the same limb to correct an unhealed previous resection.

New amputation/ disarticulation:

Resection in a limb with a healed previous resection.

Bilateral amputation/ disarticulation:

Simultaneous resection of both lower limbs, irrespective of level.

Second leg amputation/ disarticulation:

Resection in a patient who had a previous resection of the contralateral limb.

Classifications

IWGDF Risk classification:

- 0 - no peripheral neuropathy
- 1 - peripheral neuropathy
- 2 - peripheral neuropathy with peripheral arterial disease and/or a foot deformity
- 3 - peripheral neuropathy and a history of foot ulcer or lower-extremity amputation



Definitions and criteria

Classifications

IWGDF Infection classification:

1 - Uninfected

No systemic or local symptoms or signs of infection.

2 - Mild infection

At least two of the following items are present: local swelling or induration; erythema > 0.5 cm around the wound; local tenderness or pain; local warmth; purulent discharge.
Other causes of an inflammatory response of the skin should be excluded (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).
Any erythema present extends < 2 cm* around the wound.

3 - Moderate infection

No systemic signs or symptoms of infection (see below).
Infection involving structures deeper than skin and subcutaneous tissues (e.g., bone, joint, tendon, muscle) or erythema extending >2 cm* from the wound margin.

4 - Severe infection

No systemic signs or symptoms of infection (see below).
Any foot infection with the systemic inflammatory response syndrome (SIRS), as manifested by ≥ 2 of the following: temperature >38 or <36°C; Heart rate >90 beats/minute; • Respiratory rate >20 breaths/minute or PaCO₂ < 4.3 kPa (32 mmHg); White blood cell count >12,000 or <4,000/mm³, or >10% immature (band) forms.



Definitions and criteria

Classifications

PEDIS:

The IWGDF diabetic foot ulcer classification system for research purposes, with the following categories: Perfusion, Extent/size, Depth/tissue loss, Infection, Sensation. For each category a grading system is provided.

Miscellaneous

Necrosis:

Devitalized (dead) tissue.

Gangrene:

Death of tissue in all tissue layers (cutis, tendon, fascia, muscle) due to insufficient blood supply. Without infection this generally results in dry and black tissue, frequently called dry gangrene; when the tissue is infected, with accompanying putrefaction and surround cellulitis, it is often called wet gangrene.

Edema of the lower extremity:

Swelling of the leg or foot caused by increased interstitial fluid.

Erythema:

A pink or red discoloration that blanches to some degree on compression.

Callus:

Hyperkeratosis caused by excessive mechanical loading.

Debridement:

Removal of callus or dead tissue.

Foot deformity:

Structural abnormalities of the foot such as hammer toes, mallet toes, claw-toes, hallux valgus, prominent metatarsal heads, residuals of neuro-osteoarthropathy, amputations or other foot surgery.

Neuro-osteoarthropathy (Charcot-foot):

Non-infectious destruction of bone and joint associated with neuropathy, in the acute phase associated with signs of inflammation.

Total contact cast:

A well-moulded, minimally padded, below-the-knee non-removable fibreglass or plaster cast that maintains total contact with the entire plantar surface and lower leg. The cast is often worn with an attachable sole to facilitate walking.

Non removable cast walker:

Same as removable cast boot/walker but then with a layer(s) of fibreglass cast material circumferentially wrapped around it rendering it irremovable (also known as “instant total contact cast”).



Definitions and criteria

Miscellaneous

High risk:

Presence of characteristics indicating a greatly increased probability of developing a specific condition or an event.

Low risk:

A low probability of developing a specific condition or event.

