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GUIDELINES

WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines

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1 | BACKGROUND

Globally, it is estimated that at least 536.6 million people are diagnosed with diabetes globally, and it is projected that by 2045, the amount of people with diabetes will increase by 49.6% to a total of 783.2 million individuals.[1] Diabetic foot ulcers (DFUs) are a growing health problem. DFUs are a leading cause of infection, amputation, and hospitalisation in patients with diabetes mellitus.

Guidelines for the treatment of DFUs were published by the Wound Healing Society (WHS) in 2006 and 2016. However, in the past few years new evidence has emerged that has improved our understanding of previous recommendations. The objectives of the WHS DFU guidelines are to systematically evaluate the medical literature to assist clinicians in making health care decisions, identify areas that need additional research, and to clarify controversial diagnosis and treatment strategies. An advisory panel comprised of academicians, clinicians, and researchers was chosen to update the 2016 guidelines.

2 | METHODS

In 2006 and 2016, we published guidelines to improve the information for clinicians with our goal to improve patient care. Even in the absence of high-quality human data, the WHS developed guidelines using a different approach to evidence citations and past approaches to evidence-based guidelines. There is a growing number of randomised clinical trials (RCTs), meta-analysis, and society directed practice guidelines that evaluate diagnoses, treatments, and prevention strategies for patients with DFUs. There is better evidence to support recommendations. The strength of evidence supporting a guideline is listed as Level I, Level II, or Level III.

The strength of evidence used in the previous guidelines has been retained:

Level I: Meta-analysis or at least two RCTs supporting the intervention of the guideline. Another route would be multiple laboratory or animal experiments with at least two clinical series supporting the laboratory results.

Level II: Less than Level I, but at least one RCT and at least two significant clinical series or expert opinion papers with literature reviews supporting the intervention. Experimental evidence that is quite convincing, but not yet supported by adequate human experience.

Level III: Suggestive data of proof of principle, but lacking sufficient data such as meta-analysis, RCT, or multiple clinical series.

3 | DATA SOURCES AND SEARCHES

Since the 2006 and 2016 guidelines, we sought to capture the highest quality of literature available regarding DFU diagnosis using a key

word search of PubMed, Embase, and Cochrane Library databases. Similarly, the citations of relevant articles were examined by hand. Key terms were generated from the existing guidelines. In this search as opposed to the previous data collection prior to 2006, we used human and disease specific data and limited to meta-analyses, systematic reviews, RCTs, retrospective series reviews, clinical case series, and expert panel recommendations published between January 2006 and present. References prior to 2016 supporting the previous guideline recommendations are not included. Therefore, in some cases no additional updated references were included and the support for the guideline recommendation is based on evidence presented in the 2006 guideline. It was further limited to English publications. Any relevant additional references found after the formal search were also included. The findings of these articles have been divided into one or more of the appropriate categories as performed in the original guideline. Each of the separate guidelines has undergone a Delphi consensus among the panel members.

3.1 | Categories

RCT	Randomised controlled trial
STAT	Statistical analysis, meta-analysis, consensus
CER	Comparative effectiveness research: comparing one or more treatments
PCOH	Prospective cohort study
CASE S	Case series of 3–10 patients
RETROS	Retrospective study (>10 patients)
LIT REV	Literature review
EXP	Experimental laboratory or animal study
TECH	Technique or methodology description
PATH S	Pathological series review

REFERENCE

1. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119.

4 | GUIDELINES FOR THE DIAGNOSIS OF LOWER EXTREMITY DIABETIC ULCERS

Preamble: Globally, 9–26 million people develop diabetic foot ulcers annually. The lifetime risk of developing a DFU is thought to be high (19%–34%), and once a patient has had a DFU, ulcer recurrence is 30%–60% a year [1]. Foot ulcers may be caused by various conditions, including neuropathy, ischemia, venous hypertension, limited joint mobility, trauma, and biomechanical pressure. Patients with diabetes develop foot ulcers secondary to neuropathy with or without biomechanical abnormalities, and peripheral arterial disease, or both.

Guideline #1.1: In patients with diabetic foot ulcers, peripheral arterial disease (PAD) should be evaluated with clinical examination and advanced vascular testing. A high index of suspicion for ischemia complicating a DFU is necessary since PAD is quite common. In patients with diabetes with an ankle-brachial index (ABI) between 0.9 and 1.3, a triphasic Doppler-derived waveform, a toe-brachial index (TBI) of >0.75, or a transcutaneous oxygen pressure of >25 mmHg may help to suggest an adequate arterial flow to heal. (Level I – unchanged).

Principle: Diabetic ulcers can result from or be complicated by arterial insufficiency. Although clinical history and physical examination can be very suggestive of an ischemic component in patients with DFUs, when significant PAD is present, successful treatment requires that PAD is diagnosed and treated.

Updated Evidence:

1. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. *J Clin Orthop Trauma*. 2021;17:88-93. [LIT REV].
2. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(1S):S1-S109.e33. [STAT]
3. Forsythe RO, Apelqvist J, Boyko EJ, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3277. [STAT]
4. Casey S, Lanting S, Oldmeadow C, Chuter V. The reliability of the ankle brachial index: a systematic review. *J Foot Ankle Res*. 2019;12:39. [STAT]
5. Wang Z, Hasan R, Firwana B, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. *J Vasc Surg*. 2016;63(suppl 2):29S-36S.e1-2. [STAT]
6. Hinchliffe RJ, Forsythe RO, Apelqvist J, et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3276. [STAT].
7. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69(6S):3S-125S.e40. [STAT].

Guideline #1.2: The presence of sensory neuropathy with loss of protective sensation can be determined by using clinical testing with a 10 g Semmes–Weinstein monofilament, a 128 Hz tuning fork or the Ipswich Touch Test. (Level II – unchanged).

Principle: Diabetic sensory neuropathy creates an environment in which repetitive trauma, injury and infection are unrecognised by the patient. Several simple clinical techniques can be used to identify sensory neuropathy with loss of protective sensation. The presence of sensory neuropathy with loss of protective sensation can be determined by testing with a 10 g Semmes-Weinstein monofilament, or a

128 Hz tuning fork, vibration perception threshold testing or a good neurological clinical examination for sensory loss.

Updated Evidence:

1. Wang F, Zhang J, Yu J, et al. Diagnostic accuracy of monofilament tests for detecting diabetic peripheral neuropathy: a systematic review and meta-analysis. *J Diabetes Res*. 2017;2017: 8787261. [STAT]
2. Dube S, Hulke SM, Wakode SL, et al. Effectiveness of Semmes Weinstein 10 gm monofilament in diabetic peripheral neuropathy taking nerve conduction and autonomic function study as reference tests. *J Family Med Prim Care*. 2022;11(10): 6204-6208. [PCOH]
3. Ziegler D, Tesfaye S, Spallone V, et al. Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: international expert consensus recommendations. *Diabetes Res Clin Pract*. 2022;186:109063. [STAT]
4. Zhao N, Xu J, Zhou Q, et al. Application of the Ipswich touch test for diabetic peripheral neuropathy screening: a systematic review and meta-analysis. *BMJ Open*. 2021;11(10):e046966. [STAT]
5. Hu A, Koh B, Teo MR. A review of the current evidence on the sensitivity and specificity of the Ipswich touch test for the screening of loss of protective sensation in patients with diabetes mellitus. *Diabetol Int*. 2021;12(2):145-150. [STAT]

Guideline #1.3. Diabetic foot ulcerations should be classified by a system that accounts for size, depth, extent and both infection and ischemia. (Level I).

Principle: Ulcer classifications can improve documentation, direct treatment, and be predictive of outcomes. The University of Texas Diabetic Ulcer Classification system, Wagner Ulcer classification and WIfI (Wound, Ischemia, and foot Infection) Classification are widely used and validated.

Updated Evidence:

1. Carro GV, Saurral R, Carlucci E, Gette F, Llanos MLÁ, Amato PS. A comparison between diabetic foot classifications WIfI, saint Elian, and Texas: description of wounds and clinical outcomes. *Int J Low Extrem Wounds*. 2022;21(2):120-130. [PCOH]
2. Mathioudakis N, Hicks CW, Canner JK, et al. The Society for Vascular Surgery Wound, ischemia, and foot infection (WIfI) classification system predicts wound healing but not major amputation in patients with diabetic foot ulcers treated in a multidisciplinary setting. *J Vasc Surg*. 2017;65(6):1698-1705. [PCOH]
3. Vera-Cruz PN, Palmes PP, Tonogan L, Troncillo AH. Comparison of WIFi, University of Texas and Wagner classification systems as major amputation predictors for admitted diabetic foot patients: a prospective cohort study. *Malays Orthop*. 2020;14(3):114-123. [PCOH],
4. Cerqueira LO, Duarte EG, Barros ALS, Cerqueira JR, de Araujo WJB. WIfI classification: the society for vascular surgery lower extremity threatened limb classification system, a literature review. *J Vasc Bras*. 2020;19:e20190070. [LIT REV]
5. Jeon BJ, Choi HJ, Kang JS, Tak MS, Park ES. Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. *Int Wound J*. 2017;14(3):537-545. [RETROS]

5 | GUIDELINES FOR OFF-LOADING FOR TREATMENT OF DIABETIC ULCERS

Guideline #2.1: The most effective methods to off-load plantar DFUs are total contact casts and non-removable cast boots followed by removable cast boots, healing sandals, custom shoes and insoles. Post-operative shoes are least effective at off-loading plantar wounds. (Level I).

Principle: Relieving pressure and shear forces at the site of a diabetic foot ulcer is necessary to maximise healing potential.

Updated Evidence:

1. Okoli GN, Rabbani R, Lam OLT, et al. Offloading devices for neuropathic foot ulcers in adult persons with type 1 or type 2 diabetes: a rapid review with meta-analysis and trial sequential analysis of randomized controlled trials. *BMJ Open Diabetes Res Care*. 2022;10 (3):e002822. [STAT]
2. Lazzarini PA, Jarl G, Gooday C, et al. Effectiveness of offloading interventions to heal foot ulcers in persons with diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3275. [STAT]
3. Health quality Ontario, fibreglass total contact casting, removable cast walkers, and irremovable cast walkers to treat diabetic neuropathic foot ulcers: a health technology assessment. *Ont Health Technol Assess Ser*. 2017;17(12): 1-124. [STAT]
4. Elraiyah T, Prutsky G, Domecq JP, et al. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. *J Vasc Surg*. 2016;63(suppl 2):59S-68S.e1-2. [STAT]

6 | GUIDELINES FOR INFECTION CONTROL AND TREATMENT IN THE MANAGEMENT OF DIABETIC ULCERS

Preamble: All wounds are colonised with microorganisms (Bacteria, Fungi, Archaea, Viruses) but this does not necessarily equate that all wounds will become infected. Infection occurs when microorganisms enter the body, replicate, increase in number, and cause damage to host tissue. Infection plays various roles in aetiology, healing, operative repair, and complications in patients with DFUs. Diabetic foot infections are a major cause of hospital admission and can be limb- and life-threatening.

Guideline #3.1: Evaluation of infection should be based on clinical signs and not based on swab or tissue cultures. (Level II).

Principle: Bacteria (and to a lesser extent fungi) are often identified through microbiological culture in acute and chronic wounds.

The presence of bacteria should not be used as a criterion to define infection but as a guide to target antibiotic therapy where clinical infection is present. Infection involves characteristics of the host's immunity and the presence, quantity, and virulence of bacterial pathogens. Therefore, clinical examination is recommended as the basis for diagnosing clinical infection. Diabetic foot infection is established by ≥2 classic findings of inflammation or purulence. Infections should be classified according to the International Working Group on the Diabetic Foot infection classification: mild (superficial and less than 2 cm of erythema), moderate (deeper tissue infected or more than 2 cm of erythema, with or without osteomyelitis) or severe (accompanied by sepsis, with or without osteomyelitis).

Updated Evidence:

1. Norman G, Shi C, Westby MJ, et al. Bacteria and bioburden and healing in complex wounds: a prognostic systematic review. *Wound Repair Regen*. 2021;29(3):466-477. [STAT]
2. Commons RJ, Charles J, Cheney J, Lynar SA, Malone M, Raby E. Australian guideline on management of diabetes-related foot infection: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res*. 2022;15(1):47. [STAT]
3. Lipsky BA, Senneville É, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3280. [STAT]

Guideline #3.2: Microorganisms can become organised into multicellular, not very metabolically active aggregates in a glycocalyx, commonly referred to as biofilm. Biofilms are identified in many (34% to 78.2%) [1] but certainly not all chronic DFUs, where they may play a role as a cause of infection. Wound biofilms have often been observed as being polymicrobial and tolerant to the host immune system and to various treatments. The scientific evidence for commonly used topical wound antimicrobials is poor [2]. There are limited DFU studies that measure biofilm (or the total amount of microorganisms) pre- and post-treatment to demonstrate that; 1. Biofilm was present before interventions and 2. Anti-biofilm interventions eradicated or changed the biofilm and improved clinical infection or wound healing. (Level II).

Principle: Biofilm has been suggested to impede wound healing through inducing localised infection. In animal studies biofilm has been associated with poor healing and infection. There are small proof of concept studies which have set out to determine the effectiveness of topical wound dressings against biofilm in vivo. However, there is an absence of high-level evidence to support that therapies directed at biofilm are effective to improve DFU healing or infection.

Updated Evidence:

1. Malone M, Bjarnsholt T, McBain AJ, et al. The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. *J Wound Care*. 2 2017;26(1):20-25. [STAT]
2. Schwarzer S, James GA, Goeres D, et al. The efficacy of topical agents used in wounds for managing chronic biofilm infections: a systematic review. *J Infect*. 2020;80(3):261-270. [STAT]
3. Pouget C, Dunyach-Remy C, Pantel A, Schuldiner S, Sotto A, Lavigne JP. Biofilms in diabetic foot ulcers: significance and clinical relevance. *Microorganisms*. 2020;8(10). [LIT REV]
4. Afonso AC, Oliveira D, Saavedra MJ, Borges A, Simoes M. Biofilms in diabetic foot ulcers: impact, risk factors and control strategies. *Int J Mol Sci*. 2021;22(15). [LIT REV]

Guidelines #3.3: In the absence of clinical infection, systemic antibiotics do not improve wound healing or reduce the incidence of clinical infections. (Level I – unchanged).

Principle: Systemically administered antibiotics do not remove or reduce all microorganisms present in a wound. In the absence of clinical infection signs and symptoms, systemic antibiotics have not been shown to reduce or prevent clinical infection and/or improve wound healing. However, unnecessary or overuse of systemic antibiotics will increase the risk of developing antibiotic resistant bacteria.

Updated Evidence:

1. Norman G, Shi C, Westby MJ, et al. Bacteria and bioburden and healing in complex wounds: a prognostic systematic review. *Wound Repair Regen*. 2021;29(3):466-477. [STAT]
2. Lipsky BA, Senneville É, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3280. [STAT]
3. Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fiscon M, Xia J. Topical antimicrobial agents for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2017;6(6): CD011038. [STAT]

Guidelines #3.4: Topical antimicrobial and antiseptic therapies may improve wound healing by affecting microorganisms in the wound bed. (Level II).

Principle: Clinical infection may decrease healing. However, there is no evidence that products designed to reduce bioburden translate into a reduction in clinical infections. More wounds may heal when treated with an antimicrobial dressing than with a non-antimicrobial dressing, but the quality of the evidence is not strong.

Updated Evidence:

1. Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fiscon M, Xia J. Topical antimicrobial agents for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2017;6(6): CD011038. [STAT]
2. Jaber D, Younes N, Khalil E, et al. Effect of diluted Dakin's solution versus standard care on diabetic foot ulcer management: a randomized controlled trial. *J Am Podiatr Med Assoc*. 2022;112 (1). [RCT]
3. Woo K, Dowsett C, Costa B, Ebohon S, Woodmansey EJ, Malone M. Efficacy of topical cadexomer iodine treatment in chronic wounds: systematic review and meta-analysis of comparative clinical trials. *Int Wound J*. 2021;18(5):586-597. [STAT]

Guideline #3.5: For acute diabetic foot infections, surgical incision and drainage of abscess or debridement of infected tissue is often necessary and performed in combination with systemic antibiotics. Cellulitis and soft tissue infection should be stratified by severity and initially treated empirically with systemic antibiotics. Cultures of wound bed biopsies or curettages are the preferred culture method to define pathogens of infection and to implement culture directed therapy. (Level II – unchanged).

Principle: Systemic antibiotics have been demonstrated to be effective in treating acute diabetic foot infections. Cultures of wound bed biopsies or curettages are more helpful than wound swabs in determining pathogens of infection and thus in directing antibiotic therapy.

Updated Evidence:

1. Truong DH, Bedimo R, Malone M, et al. Meta-analysis: outcomes of surgical and medical management of diabetic foot osteomyelitis. *Open forum Infect Dis*. 2022;9(9):ofac407. [STAT]
2. Lipsky BA, Senneville E, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3280. [STAT]
3. Peters EJG, Lipsky BA, Senneville E, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3282. [STAT]

Guideline #3.6: If osteomyelitis is suspected, appropriate diagnostic measures include bone biopsy, probing the wound area to the bone with a sterile instrument, serial plain radiographs, MRI, CT, radionuclide scans, 18F-fluorodeoxyglucose (FDG) PET/CT, and Tc99m white blood cell labelled SPECT/CT. (Level II – unchanged).

Principle: Bone underlying a diabetic ulcer may become infected. Biopsy of the bone gives a definitive diagnosis, but less invasive techniques can be useful in establishing a diagnosis with a high degree of specificity and sensitivity.

Updated Evidence:

1. Senneville E, Lipsky BA, Abbas ZG, et al. Diagnosis of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3281. [STAT]
2. Lam K, van Asten SA, Nguyen T, La Fontaine J, Lavery LA. Diagnostic accuracy of probe to bone to detect osteomyelitis in the diabetic foot: a systematic review. *Clin Infect Dis*. 2016;63 (7):944-948. [STAT]
3. Llewellyn A, Kraft J, Holton C, Harden M, Simmonds M. Imaging for detection of osteomyelitis in people with diabetic foot ulcers: a systematic review and meta-analysis. *Eur J Radiol*. 2020;131: 109215. [STAT]
4. Lauri C, Tamminga M, Glaudemans AWJM, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. *Diabetes Care*. 2017;40 (8):1111-1120. [STAT]
5. Treglia G, Sadeghi R, Annunziata S, et al. Diagnostic performance of Fluorine-18-fluorodeoxyglucose positron emission tomography for the diagnosis of osteomyelitis related to diabetic foot: a systematic review and a meta-analysis. *Foot* (*Edinb*). 2013;23 (4):140-148. [STAT]

Guideline #3.7: In patients with osteomyelitis, determine the bacterial pathogens and resistance patterns to antibiotics by bone culture. (Level II – unchanged).

Principle: Culture-directed antibiotic treatment seems to provide better clinical outcomes than empiric therapy. If diabetic foot osteomyelitis (DFO) is suspected, bone specimens should be obtained to identify the bacterial pathogens and to direct antibiotic therapy. The specimens should be taken with aseptic measures through sterilised skin adjacent to the wound or during a surgical procedure to prevent contamination.

Updated Evidence:

1. Commons RJ, Charles J, Cheney J, Lynar SA, Malone M, Raby E. Australian guideline on management of diabetes-related foot infection: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res*. 2022;15 (1):47. [STAT]
2. Lipsky BA, Senneville E, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3280. [STAT]
3. Uddin A, Russell D, Game F, Santos D, Siddle HJ. The effectiveness of systemic antibiotics for osteomyelitis of the foot in adults with diabetes mellitus: a systematic review protocol. *J Foot Ankle Res*. 2022;15(1):48. [STAT]

Guideline #3.8: Osteomyelitis can be treated with antibiotics alone or with surgery to excise the infected bone. When there is residual osteomyelitis following minor amputation to treat osteomyelitis, 3 weeks of additional antibiotic therapy is recommended. When chosen for antibiotic therapy alone, 6 weeks of therapy is recommended. (Level III).

Principle: Osteomyelitis underlying a diabetic ulcer, can be treated medically or surgically. Comparable results have been reported with both approaches. It is widely accepted that diabetic foot osteomyelitis should be treated with 6 weeks of antibiotics. However, no clear evidence exists on the duration of treatment. Two recent randomised clinical studies have demonstrated that there was no difference in patients treated with 6 versus 12 weeks of antibiotic therapy and three versus 6 weeks of antibiotic therapy for diabetic foot osteomyelitis.

Updated Evidence:

1. Senneville É, Albalawi Z, van Asten SA, et al. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023. *Diabetes Metab Res Rev*. 2023; e3687. [STAT]

2. Commons RJ, Charles J, Cheney J, Lynar SA, Malone M, Raby E. Australian guideline on management of diabetes-related foot infection: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res*. 2022;15(1):47. [STAT]
3. Truong DH, Bedimo R, Malone M, et al. Meta-analysis: outcomes of surgical and medical management of diabetic foot osteomyelitis. *Open forum Infect Dis*. 2022;9(9):ofac407. [STAT]
4. Gariani K, Pham TT, Kressmann B, et al. Three weeks versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: a prospective, randomized, noninferiority pilot trial. Clin Infect Dis. 2021;73(7):e1539-e1545. [RCT]
5. Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes Care 2015;38:302-307. *Diabetes Care*. 2015;38(4):735-735. [RCT]

7 | GUIDELINES FOR WOUND BED PREPARATION IN THE TREATMENT OF DIABETIC ULCERS

Preamble: Wound bed preparation is defined as the management of the wound to accelerate endogenous healing or facilitate the effectiveness of other therapeutic measures. The aim of wound bed preparation is to convert the biological and cellular environment of a chronic wound to that of an acute healing wound and to remove nonviable tissue and bacteria.

Guideline #4.1: A holistic examination of the patient is important to evaluate and correct causes of poor healing. This includes factors such as: systemic diseases, medications, and nutrition. (Level III).

Principle: A general medical history will help to identify systemic causes of impaired healing. The presence of a major illness or systemic disease and drug therapies such as immunosuppressive drugs and systemic steroids will interfere with wound healing by alterations in immune functioning, metabolism, inflammation, nutrition, and tissue perfusion. Autoimmune diseases such as rheumatoid arthritis or vasculitis can all delay healing and may require systemic steroids or immunosuppressive agents before local wound healing can occur.

Updated Evidence:

1. Jalilian M, Ahmadi Sarbarzeh P, Oubari S. Factors related to severity of diabetic foot ulcer: a systematic review. *Diabetes Metab Syndr Obes*. 2020;13:1835-1842. [STAT]
2. Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. *PLoS One*. 2020;15(9):e0239236. [STAT]
3. Liu M, Zhang W, Yan Z, Yuan X. Smoking increases the risk of diabetic foot amputation: a meta-analysis. *Exp Ther Med*. 2018;15 (2):1680-1685. [STAT]

Guideline #4.2: The evidence for nutritional interventions from RCTs to increase the incidence of DFU healing and reduce complications is not clear. (Level I).

Principle: Some studies show a correlation between poor nutritional status and impaired wound healing. However, the operational definitions used to determine the state of being malnourished are variable. The studies are small and use different nutritional interventions and different definitions for wound healing. It is also uncertain whether there is a difference in outcomes and complications between groups treated with nutritional interventions and no interventions.

Updated Evidence:

1. Apergi K, Dimosthenopoulos C, Papanas N. The role of nutrients and diet characteristics in the management of diabetic foot ulcers: a systematic review. *Int J Low Extrem Wounds*. 2023:15347346231153531. [STAT], 153473462311535.
2. Moore ZE, Corcoran MA, Patton D. Nutritional interventions for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2020;7(7):CD011378. [STAT]
3. Lauwers P, Dirinck E, van Bouwel S, et al. Malnutrition and its relation with diabetic foot ulcer severity and outcome: a review. *Acta Clin Belg*. 2022;77(1):79-85. [LIT REV]
4. Daher GS, Choi KY, Wells JW, Goyal N. A systematic review of Oral nutritional supplement and wound healing. *Ann Otol Rhinol Laryngol*. 2022;131(12):1358-1368. [STAT]
5. Bechara N, Gunton JE, Flood V, Hng TM, McGloin C. Associations between nutrients and foot ulceration in diabetes: a systematic review. *Nutrients*. 2021;13(8). [STAT]

Guideline #4.3: Cessation of smoking and the use of other nicotine products should be prioritised in lifestyle recommendations. Patients need to be educated on the negative impact on tissue oxygenation, wound healing, and limb amputation and offered assistance or referred to a cessation program. (Level I – unchanged).

Principle: Tissue oxygenation is a central tenet of wound healing. Macro and Microvascular disease is common in people with DFUs, and PAD is one of the most important risk factors for poor healing and amputation. Smoking decreases the oxygen delivery to the tissue and causes peripheral vasoconstriction and local wound hypoxia in the short-term and decreasing overall blood flow by causing PAD in the long-term. Smoking is also a major risk factor for amputation in patients with DFUs, quitting smoking reduces the risk of amputation. For optimal tissue perfusion, patients with a wound (if not all persons) should be advised to stop smoking.

Updated Evidence:

1. Liu M, Zhang W, Yan Z, Yuan X. Smoking increases the risk of diabetic foot amputation: a meta-analysis. *Exp Ther Med*. 2018;15 (2):1680-1685. [STAT]
2. Forsythe RO, Apelqvist J, Boyko EJ, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3278. [STAT]
3. Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. *Diabetes Metab Res Rev*. 2019;35 (7):e3165. [STAT]

4. Jalilian M, Ahmadi Sarbarzeh P, Oubari S. Factors related to severity of diabetic foot ulcer: a systematic review. *Diabetes Metab Syndr Obes*. 2020;13:1835-1842.
5. Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. *PLoS One*. 2020;15(9):e0239236. [STAT]

Guideline #4.4: Debridement is required to remove non-viable or necrotic tissue, microorganisms, and cellular burden of dead and senescent cells. The health care provider can choose different debridement methods including surgical, sharp conservative, enzymatic, mechanical, biological, or autolytic. Limited evidence has identified that more frequent debridement reduces the time to wound healing. More than one debridement method may be appropriate. Sharp surgical debridement is preferred. The evidence for other debridement techniques is limited. (Level III).

Principle: Non-viable tissue, necrotic tissue, excessive microbial burden, senescent cells, and cellular debris can all inhibit wound healing. The debridement method may depend on the wound's status, the health provider's capability, the patient's overall condition, and professional licensing restrictions.

Updated Evidence:

1. Mohd Zubir MZ, Holloway S, Mohd Noor N. Maggot therapy in wound healing: a systematic review. *Int J Environ Res Public Health*. 2020;17(17). [STAT]
2. Dayya D, O'Neill O, Habib N, Moore J, Iyer K, Huedo-Medina TB. Debridement of diabetic foot ulcers: public health and clinical implications—a systematic review, meta-analysis, and meta-regression. *BMJ Surg Interv Health Technol*. 2022;4(1): e000081. [STAT]
3. Shoham Y, Shapira E, Haik J, et al. Bromelain-based enzymatic debridement of chronic wounds: results of a multicentre randomized controlled trial. *Wound Repair Regen*. 2021;29 (6):899-907. [RCT]
4. Nube VL, White JM, Brewer K, et al. A randomized trial comparing weekly with every second week sharp debridement in people with diabetes-related foot ulcers shows similar healing outcomes: potential benefit to resource utilization. *Diabetes Care*. 2021;44 (12):e203-e205. [RCT]

Guideline #4.5: Wounds should be cleansed initially and at each dressing change. The type of cleansing agents should be based on the wound presentation. Dirty (contaminated/foreign bodies) or infected wounds with excessive slough may require more aggressive mechanical cleaning with surfactant and/or antiseptic solutions. There is little evidence that the cleaning approach impacts wound healing or prevents infection. (Level III – unchanged).

Principle: Irrigating and cleansing the wound removes loose impediments to wound healing. Sterile saline or water is usually recommended. Tap water should only be used if the water source is reliably clean. Experimental data suggest that a nontoxic surfactant may be useful as may fluid delivered by increased intermittent pressure.

Updated Evidence:

1. Rajhathy EM, Meer JV, Valenzano T, et al. Wound irrigation versus swabbing technique for cleansing noninfected chronic wounds: a systematic review of differences in bleeding, pain, infection, exudate, and necrotic tissue. *J Tissue Viability*. 2022;32:136-143. [STAT]
2. Malone M, Radzieta M, Schwarzer S, Jensen SO, Lavery LA. Efficacy of a topical concentrated surfactant gel on microbial communities in non-healing diabetic foot ulcers with chronic biofilm infections: a proof-of-concept study. *Int Wound J*. 2021;18 (4):457-466. [STAT]

Guideline #4.6: There should be an ongoing and consistent documentation of wound history, recurrence, and characteristics (location, size, base, exudates, condition of the surrounding skin, staging, and pain) to evaluate wound bed preparation. The rate of wound healing should be evaluated to determine whether treatment is optimal. (Level III).

Principle: Ongoing evaluation of wound is necessary to evaluate changes in wound characteristics, monitor infection, and evaluate the effectiveness of therapies. Risk factors for poor healing include the duration, size, and depth of the wound.

Updated Evidence:

1. Chen P, Carville K, Swanson T, et al. Australian guideline on wound healing interventions to enhance healing of foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res*. 2022;15(1):40. [STAT]
2. Rayman G, Vas P, Dhatariya K, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3283. [STAT]
3. Vas P, Rayman G, Dhatariya K, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3284. [STAT]

Guideline #4.7: Patients who fail to show a reduction in ulcer size by 50% or more after 4 weeks of therapy should be reevaluated and other treatments, disease processes, and adherence should be considered. (Level II).

Principle: Percent change in wound area of DFUs over 4 weeks of treatment is a good predictor of effectiveness of therapy and likelihood of healing.

Updated Evidence:

1. Gwilym BL, Mazumdar E, Naik G, Tolley T, Harding K, Bosanquet DC. Initial reduction in ulcer size as a prognostic indicator for complete wound healing: a systematic review of diabetic foot and venous leg ulcers. *Adv Wound Care* (*New Rochelle*). 2022. [STAT]

Guideline #4.8: Optimising glucose control improves wound healing. (Level II – unchanged).

Principle: Wound healing is more likely to be optimal in the setting of good diabetes management. Patients benefit from a team-approach which includes tight glucose control.

Updated Evidence:

1. Rayman G, Vas P, Dhatariya K, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1): e3283. [STAT]
2. Vas P, Rayman G, Dhatariya K, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3284. [STAT]
3. Boyko EJ, Zelnick LR, Braffett BH, et al. Risk of foot ulcer and lower-extremity amputation among participants in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care*. 2022;45(2):357-364. [RETROS]

8 | GUIDELINES FOR WOUND CARE DRESSINGS OR THERAPIES IN THE TREATMENT OF DIABETIC ULCERS

Preamble: There are many topical therapies available for DFUs. Most dressings are used in combination with off-loading, debridement, and infection control. It is thought that a moist wound environment physiologically favours cell migration and matrix formation. There are several criteria that should be considered when selecting a dressing including the cost, potential for iatrogenic injury, and wound exudate management. First, dressings should not damage the wound. Wound dressings or therapies should also not impede the cellular or biological phases of wound healing, which can occur if a dressing or therapy proves to be cytotoxic to host cells. Furthermore, a dressing should be used for its intended purpose otherwise issues may arise such as If the wound and surrounding tissue have continuous contact with wound exudate, the local tissue can become macerated and impede healing. Likewise, dressings that are not secure can cause friction injuries to the surrounding skin or wound bed. The cost of health care provider time, healing rate, and the unit cost of dressings should be considered when determining cost efficacy.

Guideline #5.1: Use a dressing that will maintain a moisture-balanced wound-healing environment, absorbs excess exudate and protects the peri-ulcer skin. (Level III – unchanged).

Principle: A moist wound environment physiologically favours cell migration and matrix formation while accelerating healing of wounds by promoting autolytic debridement. Wet-to-dry dressings are not considered continuously moist. Continuously moist saline gauze dressings are as effective as other types of moist wound healing in terms of healing rate.

Updated Evidence:

1. Rayman G, Vas P, Dhatariya K, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3283. [STAT]
2. Game FL, Attinger C, Hartemann A, et al. IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*. 2016;32(suppl 1):75-83. [STAT]

Guideline #5.2: Select a dressing that is cost effective. (Level II).

Principle: Because of their low unit cost, moist saline gauze dressings are often viewed as the least expensive and, therefore, the most cost-effective dressing. However, when determining cost efficacy, it is important to consider the care provider's time, ease of use, and healing rate, and the unit cost of the dressing.

Updated Evidence:

1. Blunck D, Schoffski O. Hyaluronic acid treatment versus standard of care in chronic wounds in a German setting: cost-effectiveness analysis. *Health Sci Rep*. 2023;6(1):e969. [CER]
2. Lobmann R, Augustin M, Lawall H, et al. Cost-effectiveness of TLC-sucrose octasulfate versus control dressings in the treatment of diabetic foot ulcers. *J Wound Care*. 2019;28(12):808-816. [CER]
3. Maunoury F, Oury A, Fortin S, Thomassin L, Bohbot S, Explorer S. Cost-effectiveness of TLC-NOSF dressings versus neutral dressings for the treatment of diabetic foot ulcers in France. *PLoS One*. 2021;16(1):e0245652. [CER]

9 | GUIDELINES FOR SURGERY IN THE TREATMENT OF DIABETIC ULCERS

Preamble: Even with optimal care of a DFU (debridement, dressings, and offloading), successful healing of diabetic ulcers may not occur. Even with robust prevention services, the incidence of re-ulceration is high. Multiple surgical procedures have been attempted to treat diabetic foot ulcers with varying degrees of success. RCTs comparing operative techniques are difficult, but data are available supporting surgery in selected patients. The focus of elective surgery is to increase range of motion or correct structural deformity to reduce pressure at the site of foot ulcers. In selected patients these types of procedures have been shown to be safe and effective to heal ulcers and prevent re-ulceration.

Guideline #6.1: Achilles tendon lengthening improves healing of diabetic forefoot wounds. (Level II) Lengthening the Achilles tendon reduces pressure on forefoot plantar ulcers in patients with limited dorsiflexion of the ankle joint. Achilles tendon lengthening has been associated with a reduction in ulcer recurrence. (Level I – unchanged).

Principle: Limited joint mobility of the toes, metatarsophalangeal joints and ankle contribute to increased forefoot pressures and ulceration. Specific procedures to lengthen tight tendons or correct structural deformities can reduce pressure and shear forces on forefoot plantar ulcers.

Updated Evidence:

1. Meshkin DH, Fagothaman K, Arneson J, et al. Plantar foot ulcer recurrence in neuropathic patients undergoing percutaneous

Tendo-Achilles lengthening. *J Foot Ankle Surg*. 2020;59 (6):1177-1180. [RETROS]
2. van Bael K, van der Tempel G, Claus I, et al. Gastrocnemius fascia release under local anaesthesia as a treatment for neuropathic foot ulcers in diabetic patients: a short series. *Acta Chir Belg*. 2016;116 (6):367-371. [CASE S]
3. Imaoka S, Kudou G, Minata S, Furukawa M, Higashi T. Changes in physical function and ambulatory state after Achilles tendon lengthening for diabetic foot ulcers. *J Phys Ther Sci*. 2023;35 (1):51-54. [CASE S]
4. Searle A, Spink MJ, Ho A, Chuter VH. Association between ankle equinus and plantar pressures in people with diabetes. A systematic review and meta-analysis. *Clin Biomech* (*Bristol, Avon*). 2017;43:8-14. [STAT]

Guideline #6.2: Flexor tenotomy for hammertoe correction improves healing for ulcers on the tip of digits and reduces the risk of re-ulceration. (Level II).

Principle: Ulcers on the tip of patient's toes are often due to hammertoes associated with tight flexor tendons. Lengthening the tendon or cutting the tendon corrects the deformity and allows the DFU to heal.

Updated Evidence:

1. Scott JE, Hendry GJ, Locke J. Effectiveness of percutaneous flexor tenotomies for the management and prevention of recurrence of diabetic toe ulcers: a systematic review. *J Foot Ankle Res*. 2016;9:25. doi:10.1186/s13047-016-0159-0. [STAT]
2. Bonanno DR, Gillies EJ. Flexor tenotomy improves healing and prevention of diabetes-related toe ulcers: a systematic review. *J Foot Ankle Surg*. 2017;56(3):600-604. [STAT]
3. Schmitz P, Scheffer R, De Gier S, Krol RM, van der Veen D, Smeets L. The effect of percutaneous flexor tenotomy on healing and prevention of foot ulcers in patients with claw deformity of the toe. *J Foot Ankle Surg*. 2019;58(6):1134-1137. [RETROS]

Guideline #6.3: Arthroplasty of the great toe increases the incidence of plantar hallux ulcer healing and reduces the incidence of infection and recurrent ulcers compared to offloading alone. (Level III).

Principle: Ulcers on the interphalangeal joint of the great toe are often associated with limited motion of the first metatarsophalangeal joint. Resection of the base of the proximal phalanx of the great toe increases the first metatarsophalangeal joint range of motion, and it reduces pressures on the interphalangeal joint of the great toe. This allows these ulcers to heal and reduces the risk of re-ulceration.

Updated Evidence:

1. Periasamy M, Muthukumar V, Mali Reddy R, Asokan K, Sabapathy SR. Outcomes of Keller gap arthroplasty for plantar hallux interphalangeal joint ulcers in patients with diabetes mellitus. *Foot Ankle Int*. 2023. [RETROS]
2. Yammine K, Assi C. A meta-analysis of the outcomes of resectional arthroplasty of resistant hallucal diabetic ulcers. *J Foot Ankle Surg*. 2021;60(4):795-801. [STAT]

Guideline #6.4: For isolated ulcers under a metatarsal head, metatarsal head resection increases the incidence of ulcer healing and reduces the incidence of infection and recurrent ulcers compared to offloading alone. (Level I).

Principle: Isolated ulcers on the ball of the foot are associated with dislocated metatarsophalangeal joints, resecting the metatarsal head eliminates high pressure areas on the sole of the foot, so DFU can heal.

Updated Evidence:

1. Yammine K, Kheir N, Assi C. A meta-analysis of the outcomes of metatarsal head resection for the treatment of neuropathic diabetic foot ulcers. *Adv Wound Care* (*New Rochelle*). 2021;10 (2):81-90. [STAT]
2. Sanz-Corbalan I, Tardaguila-Garcia A, Garcia-Alamino JM, Garcia-Alvarez Y, Alvaro-Afonso FJ, Lazaro-Martinez JL. Metatarsal head resections in diabetic foot patients: a systematic review. *J Clin Med*. 2020;9(6). [STAT]

Guideline #6.5: For ulcers under the metatarsal heads, pan-metatarsal head resection surgery may increase the incidence of ulcer healing and reduce the incidence of infection and recurrent ulcers compared to standard ulcer treatments (Level I).

Principle: When ulcers on the ball of the foot are associated with dislocated metatarsophalangeal joints, resecting the metatarsal heads eliminates high pressure areas on the sole of the foot, so DFUs can heal.

Updated Evidence:

1. Yammine K, Kheir N, Assi C. A meta-analysis of the outcomes of metatarsal head resection for the treatment of neuropathic diabetic foot ulcers. *Adv Wound Care* (*New Rochelle*). 2021;10(2):81-90. [STAT]
2. Sanz-Corbalan I, Tardaguila-Garcia A, Garcia-Alamino JM, Garcia-Alvarez Y, Alvaro-Afonso FJ, Lazaro-Martinez JL. Metatarsal head resections in diabetic foot patients: a systematic review. *J Clin Med*. 2020;9(6). [STAT]

10 | GUIDELINES FOR THE USE OF ADJUNCTIVE AGENTS AND TOPICAL DEVICES IN THE TREATMENT OF DIABETIC FOOT ULCERS

Preamble: Many agents or devices have been suggested to be used as adjuvants to debridement and off-loading therapy to treat DFUs. These adjuvant agents can be divided into topical agents to be applied to the ulcer, devices aimed at accelerating ulcer healing, and systemic drugs to treat the patient. Several of these agents have enough evidence to allow guidelines regarding their use.

10.1 | Topical agents

Guideline #7.1: Topical growth factors such as platelet-derived and recombinant human epidermal growth factor have been shown to

increase the incidence of ulcer healing and reduce the time to heal. (Level I – unchanged).

Principle: Growth factors are messengers/mediators in wound healing. Diabetic foot wounds are often deficient in growth factors. Addition of growth factors to non-healing wounds can therefore accelerate wound healing.

Updated Evidence:

1. Sridharan K, Sivaramakrishnan G. Growth factors for diabetic foot ulcers: mixed treatment comparison analysis of randomized clinical trials. *Br J Clin Pharmacol*. 2018;84(3):434-444. [CER]
2. Mahdipour E, Sahebkar A. The role of recombinant proteins and growth factors in the management of diabetic foot ulcers: a systematic review of randomized controlled trials. *J Diabetes Res*. 2020;2020:6320514. [STAT]
3. Yang S, Geng Z, Ma K, Sun X, Fu X. Efficacy of topical recombinant human epidermal growth factor for treatment of diabetic foot ulcer: a systematic review and meta-analysis. *Int J Low Extrem Wounds*. 2016;15(2):120-125. [STAT]
4. Yang Q, Zhang Y, Yin H, Lu Y. Topical recombinant human epidermal growth factor for diabetic foot ulcers: a meta-analysis of randomized controlled clinical trials. *Ann Vasc Surg*. 2020;62:442-451. [STAT]
5. Zhao DY, Su YN, Li YH, Yu TQ, Li J, Tu CQ. Efficacy and safety of recombinant human epidermal growth factor for diabetic foot ulcers: a systematic review and meta-analysis of randomised controlled trials. *Int Wound J*. 2020;17(4):1062-1073. [STAT]
6. Bui TQ, Bui QVP, Nemeth D, et al. Epidermal growth factor is effective in the treatment of diabetic foot ulcers: meta-analysis and systematic review. *Int J Environ Res Public Health*. 2019;16 (14). [STAT]

Guideline #7.2: The evidence is uncertain for the efficacy of therapy with platelet-rich plasma as studies report mixed results regarding the benefits of this therapy. (Level I).

Principle: Several growth factors that are secreted by platelets are involved in wound healing such as vascular endothelial growth factor and insulin-like growth factor-1. Treatment with autologous platelet rich plasma is thought to support cell growth and stimulate wound healing by reducing inflammatory cytokines and increasing growth factors.

Updated Evidence:

1. Martinez-Zapata MJ, Marti-Carvajal AJ, Sola I, et al. Autologous platelet-rich plasma for treating chronic wounds. *Cochrane Database Syst Rev*. 2012;10:CD006899. [STAT]
2. Dai J, Jiang C, Sun Y, Chen H. Autologous platelet-rich plasma treatment for patients with diabetic foot ulcers: a meta-analysis of randomized studies. *J Diabetes Complications*. 2020;34 (8):107611. [STAT]
3. Del Pino-Sedeno T, Trujillo-Martin MM, Andia I, et al. Platelet-rich plasma for the treatment of diabetic foot ulcers: a meta-analysis. *Wound Repair Regen*. 2019;27(2):170-182. [STAT]

Guideline #7.3: NPWT (Negative Pressure Wound Therapy) in patients with complex diabetic foot wounds has been shown to increase the proportion of wounds that heal, the time to heal, and reduce the incidence of amputations compared with standard wound care in diabetic lower extremity wounds. NPWT has not been shown to reduce the incidence of infection. (Level I – unchanged).

Principle: NPWT may improve wound healing by reducing edema, removing bacterial products, and acerating granulation tissue, and should be considered for large or deeper defects. The addition of continuous or intermittent irrigation with saline or antiseptics was hypothesized to reduce infection and accelerate healing.

Updated Evidence:

1. Wang N, Li SS, Liu YP, Peng YY, Wang PF. Comparison of negative pressure wound therapy and moist wound care in patients with diabetic foot ulcers: a protocol for systematic review and meta-analysis of randomized controlled trials. *Medicine* (*Baltimore*). 2022;101(31):e29537. [STAT]
2. Liu Z, Dumville JC, Hinchliffe RJ, et al. Cochrane Wounds Group Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2018;10 (10):CD010318. [STAT]
3. Chen L, Zhang S, Da J, et al. A systematic review and meta-analysis of efficacy and safety of negative pressure wound therapy in the treatment of diabetic foot ulcer. *Ann Palliat Med*. 2021;10 (10):10830-10839. [STAT]

Guideline #7.4: NPWT with irrigation or instillation has not been shown to improve wound healing or clinical infection in complex DFUs (Level I).

Principle: The existing literature does not provide clear evidence of NPWT with irrigation improving wound healing or decreasing the risk of infection in diabetic foot ulcers.

Updated Evidence:

1. Kim PJ, Lavery LA, Galiano RD, et al. The impact of negative-pressure wound therapy with instillation on wounds requiring operative debridement: pilot randomised, controlled trial. *Int Wound J*. 2020;17(5):1194-1208. [RCT]
2. Lavery LA, Davis KE, La Fontaine J, et al. Does negative pressure wound therapy with irrigation improve clinical outcomes? A randomized clinical trial in patients with diabetic foot infections. *Am J Surg*. 2020;220(4):1076-1082. [RCT]
3. Davis KE, La Fontaine J, Farrar D, et al. Randomized clinical study to compare negative pressure wound therapy with simultaneous saline irrigation and traditional negative pressure wound therapy for complex foot infections. *Wound Repair Regen*. 2020;28 (1):97-104. [RCT]

Guideline #7.5: Cellular, bioengineered skin substitutes increase the incidence of healing and decrease the time to heal. (Level I – unchanged).

Principle: A growing number of cellular, acellular, and synthetic dermal matrix products have been introduced with variable individual claims, but likely have generalizable data as a class-effect, which increase the incidence of ulcer healing, accelerate healing time, and reduce adverse events. Some of these products include stem cells, growth factors and/or provide a scaffold for cell migration. Biologic products are sourced from both human and animal tissues.

Updated Evidence:

1. Ontario H. Skin substitutes for adults with diabetic foot ulcers and venous leg ulcers: a health technology assessment. *Ont Health Technol Assess Ser*. 2021;21(7):1-165. [CER]
2. Santema TB, Poyck PP, Ubbink DT. Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: highlights of a Cochrane systematic review. *Wound Repair Regen*. 2016;24(4):737-744. [STAT]
3. Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: a systematic review and meta-analysis. *Int J Surg*. 2017;40:1-7. [STAT]

Guideline #7.6: Acellular dermal matrix products have been shown to increase the incidence of healing and decrease the time to heal. (Level I – unchanged).

Principle: Extracellular matrix from acellular dermal matrix products provide a scaffold for the ingrowth of cells and growth factors to stimulate wound healing. These types of products have been developed from human, porcine, equine, and bovine models.

Updated Evidence:

1. Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: a systematic review and meta-analysis. *Int J Surg*. 2017;40:1-7. doi:10.1016/j.ijsu.2017.02.008. [STAT]
2. Alvaro-Afonso FJ, Garcia-Alvarez Y, Lazaro-Martinez JL, Kakagia D, Papanas N. Advances in Dermoepidermal skin substitutes for diabetic foot ulcers. Curr Vasc Pharmacol 2020;18(2):182-192. [CER]

Guideline #7.7: Human amniotic tissue membranes have been shown to increase the incidence of healing and decrease the time to heal. (Level I).

Principle: Amniotic tissue has pluripotent stem cells, growth factors, and extracellular matrix proteins to accelerate wound healing.

Updated Evidence:

1. Huang W, Chen Y, Wang N, Yin G, Wei C, Xu W. Effectiveness and safety of human amnion/chorion membrane therapy for diabetic foot ulcers: an updated meta-analysis of randomized clinical trials. *Wound Repair Regen*. 2020;28(6):739-750. [STAT]
2. Mohammed YA, Farouk HK, Gbreel MI, et al. Human amniotic membrane products for patients with diabetic foot ulcers. Do they help? A systematic review and meta-analysis. *J Foot Ankle Res*. 2022;15(1):71. [STAT]
3. Wong AYW, Ong BSY, Lee A, et al. Topical biological agents as adjuncts to improve wound healing in chronic diabetic wounds: a systematic review of clinical evidence and future directions. *Cureus*. 2022;14(7):e27180. [STAT]
4. Lakmal K, Basnayake O, Hettiarachchi D. Systematic review on the rational use of amniotic membrane allografts in diabetic foot ulcer treatment. *BMC Surg*. 2021;21(1):87. [STAT]

Guideline #7.8: Synthetic skin equivalents have been shown to increase the incidence of healing and decrease the time to heal. (Level II).

Updated Evidence:

1. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of integra template for diabetic foot ulcer treatment. *Wound Repair Regen*. 2015;23(6):891-900. [RCT]
2. Kuang B, Pena G, Cowled P, et al. Use of biodegradable temporising matrix (BTM) in the reconstruction of diabetic foot wounds: a pilot study. *Scars Burn Heal*. 2022;8:205951312211222. [PCOH]
3. Gordon AJ, Alfonso AR, Nicholson J, Chiu ES. Evidence for healing diabetic foot ulcers with biologic skin substitutes: a systematic review and meta-analysis. *Ann Plast Surg*. 2019;83(4S suppl 1):S31-S44. [STAT]

Guideline #7.9: Topical oxygen has been shown to increase the incidence of healing and decrease the time to heal. (Level I).

Principle: Oxygen is essential to promote wound healing. Topical oxygen diffuses oxygen into the ulcer wound bed. The rationale for topical oxygen is to eliminate hypoxia and stimulate growth factors that contribute to angiogenesis such as *Transforming growth factor beta*, Tumour necrosis factor-alpha, Vascular endothelial growth factor, and IGF-1 Insulin growth factor.

Updated Evidence:

1. Connaghan F, Avsar P, Patton D, O'Connor T, Moore Z. Impact of topical oxygen therapy on diabetic foot ulcer healing rates: a systematic review. *J Wound Care*. 2021;30(10):823-829. [STAT]
2. Carter MJ, Frykberg RG, Oropallo A, et al. Efficacy of topical wound oxygen therapy in healing chronic diabetic foot ulcers: systematic review and meta-analysis. *Adv Wound Care* (*New Rochelle*). 2023;12(4):177-186. [STAT]
3. Frykberg RG, Franks PJ, Edmonds M, et al. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO_2 study. *Diabetes Care*. 2020;43(3):616-624. [RCT]
4. Niederauer MQ, Michalek JE, Armstrong DG. A prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to sham therapy in the treatment of diabetic foot ulcers. *J Diabetes Sci Technol*. 2017;11(5):883-891. [RCT]
5. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot

ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *J Wound Care*. 2018;27(suppl 9):S30-S45. [RCT]

Guideline #7.10: Electrical stimulation has been shown to increase the proportion of healed ulcers and the time to heal. (Level I – unchanged).

Principle: Application of electric current to DFUs increases local tissue perfusion and may affect protein synthesis, cell migration, and bacterial growth to improve wound healing.

Updated Evidence:

1. Melotto G, Tunprasert T, Forss JR. The effects of electrical stimulation on diabetic ulcers of foot and lower limb: a systematic review. *Int Wound J*. 2022;19(7):1911-1933. [STAT]
2. Chen Z, Chen ZY, Liu WH, Li GS. Electric stimulation as an effective Adjunctive therapy for diabetic foot ulcer: a meta-analysis of randomized controlled trials. *Adv Skin Wound Care*. 2020;33 (11):608-612. [STAT]
3. Avendano-Coy J, Lopez-Munoz P, Serrano-Munoz D, Comino-Suarez N, Avendano-Lopez C, Martin-Espinosa N. Electrical microcurrent stimulation therapy for wound healing: a meta-analysis of randomized clinical trials. *J Tissue Viability*. 2022;31 (2):268-277. [STAT]

Guideline #7.11: Extracorporeal shockwave therapy increases the incidence of healing and reduces the time to heal. (Level I – unchanged).

Principle: Extracorporeal shockwave therapy has been used in clinical applications for fracture repair, tendon injuries and wound healing. Extracorporeal shockwave therapy can be used as additional treatment for patients with DFUs, as it can increase the healing rate and healing pace.

Updated Evidence:

1. Huang Q, Yan P, Xiong H, et al. Extracorporeal shock wave therapy for treating foot ulcers in adults with type 1 and type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Can J Diabetes*. 2020;44(2):196-204.e3. [STAT]
2. Hitchman LH, Totty JP, Raza A, et al. Extracorporeal shockwave therapy for diabetic foot ulcers: a systematic review and meta-analysis. *Ann Vasc Surg*. 2019;56:330-339. [STAT]
3. Snyder R, Galiano R, Mayer P, Rogers LC, Alvarez O, Sanuwave Trial I. Diabetic foot ulcer treatment with focused shockwave therapy: two multicentre, prospective, controlled, double-blinded, randomised phase III clinical trials. *J Wound Care*. 2018;27 (12):822-836. [STAT]

Guideline #7.12: Hyperbaric oxygen therapy as an adjunct, increases the rate of healing and reduces the risk of major amputation in Wagner Grade III diabetic foot ulcers. (Level I – unchanged).

Principle: Hyperbaric oxygen therapy (HBOT) uses 100% oxygen at greater than atmospheric pressures which causes hyperoxia of tissues and improves wound healing in patients with Wagner Grade III diabetic foot ulcers. HBOT has additional, related uses in ischemia, and skin graft and flap failure.

Updated Evidence:

1. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. *Ont Health Technol Assess Ser*. 2017;17(5):1-142. [LIT REV]
2. Moreira DACDL, Oliveira-Pinto J, Mansilha A. The role of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers: a systematic review with meta-analysis of randomized controlled trials on limb amputation and ulcer healing. *Int Angiol*. 2022;41 (1):63-73. [STAT]
3. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2015;2015(6):CD004123. [STAT]
4. Sharma R, Sharma SK, Mudgal SK, Jelly P, Thakur K. Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. *Sci Rep*. 2021;11(1):2189. [STAT]

11 | GUIDELINES FOR PREVENTION OF RECURRENCE OF DIABETIC FOOT ULCERS

Preamble: Diabetic foot ulcerations are most commonly a result of sensory neuropathy and repetitive moderate stress/trauma on pedal skin. Ulcerations are often associated with foot deformities causing moderate to high pressures or limited joint mobility. Off-loading devices reduce pressure on the foot's sole and often reduce the patient's activity level. Off-loading the area of high pressure has been the mainstay to heal and to prevent re-ulceration. After a DFU is healed, the recurrence rates are remarkably high and costly. However, when effective prevention strategies are implemented, the incidence of re-ulceration is cut in half.

Guideline #8.1: Protective footwear should be prescribed in any patient at high-risk for ulceration (end-stage renal disease, previous amputation, previous ulcer, and previous Charcot neuro-osteoarthropathy). Protective footwear results in a reduction of recurrent ulcerations in high-risk patients with a previous foot ulcer or amputation. (Level I – unchanged).

Principle: The aetiology of many foot ulcers involves a biomechanical component. Most treatments do not eliminate the underlying biomechanical aetiology of the ulcer. Abnormal pressure and shear stress is still present, so long-term off-loading and accommodation is necessary. By reducing pressure and shear forces on the sole of the foot, repetitive injury to the foot is reduced, and high-risk areas are protected from recurrent ulcers.

Updated Evidence:

1. van Netten JJ, Raspovic A, Lavery LA, et al. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3270. [STAT]

2. Bus SA, Lavery LA, Monteiro-Soares M, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3269. [STAT]
3. Crawford F, Nicolson DJ, Amanna AE, Smith M. Reliability of the evidence to guide decision-making in foot ulcer prevention in diabetes: an overview of systematic reviews. *BMC Med Res Methodol*. 2022;22(1):274. [STAT]
4. Luo B, Cai Y, Chen D, et al. Effects of special therapeutic footwear on the prevention of diabetic foot ulcers: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes Res*. 2022;2022:9742665. [STAT]

Guideline #8.2: Good foot care and daily inspection of the feet will not reduce the recurrence of diabetic ulceration alone. (Level I – unchanged).

Principle: There is contradictory data regarding the effectiveness of good foot care including proper bathing, nail trimming will reduce ulceration in diabetic feet. Self-care behaviours such as good foot care, proper bathing and nail care should be included as part of a comprehensive care program that includes professional foot care, education and therapeutic shoes and insoles.

Updated Evidence:

1. Kaminski MR, Golledge J, Lasschuit JWJ, et al. Australian guideline on prevention of foot ulceration: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res*. 2022;15(1):53. [STAT]
2. Bus SA, Lavery LA, Monteiro-Soares M, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(suppl 1):e3269. [STAT]

Guideline #8.3: Preventative programs which utilise home monitoring of foot temperatures reduce re-ulceration risk. (Level I – unchanged).

Principle: Local areas of increased temperature are a sign of inflammation and deep tissue injury that precede the development of ulceration. By daily assessment of foot temperature with the calculation of asymmetry between feet, an early warning of tissue inflammation can occur up to 1 month before re-ulceration. Interventions such as activity reduction, footwear modification, and off-loading, can avert the development of ulceration which can result in a reduction of hospitalizations and significant savings to the system.

Updated Evidence:

1. Ena J, Carretero-Gomez J, Arevalo-Lorido JC, Sanchez-Ardila C, Zapatero-Gaviria A, Gomez-Huelgas R. The association between elevated foot skin temperature and the incidence of diabetic foot ulcers: a meta-analysis. *Int J Low Extrem Wounds*. 2021;20(2):111-118. [STAT]
2. Bus SA, Aan de Stegge WB, van Baal JG, Busch-Westbroek TE, Nollet F, van Netten JJ. Effectiveness of at-home skin temperature monitoring in reducing the incidence of foot ulcer recurrence in people with diabetes: a multicenter randomized controlled trial (DIATEMP). *BMJ Open Diabetes Res Care*. 2021;9(1). [RCT]
3. Lavery LA, Petersen BJ, Linders DR, Bloom JD, Rothenberg GM, Armstrong DG. Unilateral remote temperature monitoring to predict future ulceration for the diabetic foot in remission. *BMJ Open Diabetes Res Care*. 2019;7(1):e000696. [PCOH]
4. Frykberg RG, Gordon IL, Reyzelman AM, et al. Feasibility and efficacy of a smart mat technology to predict development of diabetic plantar ulcers. *Diabetes Care*. 2017;40(7):973-980. [PCOH]

CONFLICT OF INTEREST STATEMENT

LAL, MAS, CEA, GEK, PAC, EJP, LER have no disclosures. MM is employment with molnlycke healthcare post completion of the guidelines.

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