COMPREHENSIVE INVITED REVIEW

Management of Diabetic Wounds: Expert Panel Consensus Statement

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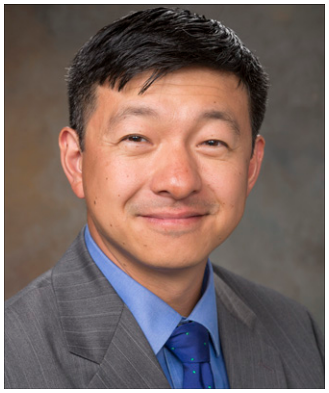

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Significance: The Wound Healing Foundation recognized the need for consensus-based unbiased recommendations for the treatment of wounds. Consensus statements on the treatment of chronic wounds and acute wounds have been developed and published previously. The current publication on diabetic wounds represents the next step in this process. Diabetic wounds constitute a major problem. Population-based and meta-analytic studies indicate that the presence of foot wounds in patients with diabetes increases their mortality risk by more than twofold. The management of diabetic wounds requires consistent and evidence-driven intervention to achieve optimal clinical outcomes. This consensus statement provides the clinician with the necessary foundational approaches to the causes, diagnosis, and therapeutic management of diabetic wounds. Presented in a structured format, this is a useful guide for clinicians and learners in all patient care settings.

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Recent Advances: Continuous glucose monitoring and other new tools have facilitated better diabetes management and the management of associated wounds. Diabetic limb salvage should focus on achieving and optimizing function for the patient with diabetes rather than preserving limb tissue at all costs.
Critical Issues: Successful management of diabetic wounds requires a multidisciplinary approach encompassing comprehensive assessment, timely intervention, and collaborative care by the wound clinician with providers who can address critical aspects to achieve healing, including careful management of blood glucose levels, optimization of off-loading and physical therapy, assessment and treatment of limb ischemia, control and prevention of wound infection, and optimal pain management.
Future Directions: Emerging treatments offer hope and promise, but the heterogenicity of diabetic wounds poses a challenge to performing good studies, which will be necessary to advance new treatments for diabetic wounds.

Keywords: diabetic wound, management, comprehensive, expert

SCOPE AND SIGNIFICANCE

This body of work is intended to be a guide for clinicians in the treatment of diabetic wounds. The scope of topics includes diabetes pathophysiology, clinical diabetes management, epidemiology, neuropathic conditions, infections, peripheral vascular disease, diabetic limb salvage, management of pain and wound dressings, and surgical and adjunct treatments, including emerging treatments.

TRANSLATIONAL RELEVANCE

This body of work does not focus on bench research or its translation to clinical practice.

CLINICAL RELEVANCE

The intended purpose of this expert consensus statement is to provide clinicians with practical guidance for the bedside treatment of diabetic wounds. As such, the focus is purely on clinical application. In serving as a guide for the practicing clinician, the included consensus statements were required to have at least an 80% agreement rate among the experts who participated in the panel. The content is broad and intended to be comprehensive to aid clinicians and learners caring for the broad spectrum of diabetic wounds encountered in any clinical care setting.

BACKGROUND

All areas of wound care benefit from consensus-based unbiased treatment recommendations supported by the best available objective data. The Wound Healing Foundation has previously organized consensus panels on chronic wounds in general,[1] and acute wounds.[2] The consensus panel on diabetic wounds was convened on October 21, 2023, and included many of the most prominent experts on diabetic wounds. Each participant had been given a topic which was presented virtually at the meeting. The topics included diabetes pathophysiology, clinical diabetes management, epidemiology of diabetic wounds, neuropathic conditions in diabetic wounds, infections, peripheral vascular disease, surgical and adjunct treatment, diabetic limb salvage, management of pain and wound dressings, and emerging treatment modalities.

Diabetic wounds constitute a major problem. Every year 1 million patients with diabetes in the United States develop a foot ulcer, and over their lifetime 6–7 million will. Many of these ulcers will eventually lead to amputation. Treatment strategies include a multidisciplinary approach with careful management of diabetes and prompt optimal care of the wound and the extremity once it occurs.

METHODS

The editors (the three first authors) outlined the various topics and subsequently the experts were invited. Everybody who had been invited agreed to participate, and no one (editors or invited experts) received compensation for their work. The methodology was very similar to the one used for the peer-reviewed publications "Chronic Wounds: Treatment Consensus" and "Acute Wounds: Treatment Consensus"[1,2] and only key parts are included here. Diversity in terms of clinical specialty (plastic surgery, internal medicine, diabetes care, dermatology, podiatry, microbiology, vascular surgery, wound care nursing, and general surgery) as well as practice location (hospital, wound care clinic) and geography was attempted to make the consensus as broadly applicable as possible. The structured format facilitated discussion and consensus-building among panel members during the consensus panel session, fostering a collaborative effort toward enhanced patient care and improved clinical outcomes.

After each presentation, a thorough discussion ensued until consensus was reached. A number of statements were made, and each had a better than 80% concurrence by the panel members. This article is the result of the contributions by panel members who are listed among the authors in addition to other individuals who provided important contributions to its writing and editing (see the Acknowledgments section).

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DISCUSSION

The multidisciplinary approach to successfully managing diabetic wounds encompasses comprehensive assessment, timely intervention, and collaborative care. Wound clinicians need to be in contact and work in collaboration with providers having the appropriate expertise to effectively manage key aspects of care that will directly impact successful healing, including off-loading and physical therapy as well as nutrition and glucose control. The recommendations laid out in this document aim to provide a robust framework for wound clinicians in navigating the complex landscape of diabetic wounds, ensuring the delivery of holistic, patient-centered care.

DIABETES PATHOPHYSIOLOGY

Impaired wound healing in diabetes mellitus is caused by multiple factors including macrovascular disease and microvascular disease (MVD) that lead to tissue hypoxia, peripheral neuropathy, low-grade systemic inflammation, and hyperglycemia that results in increased accumulation of advanced glycation end-products (AGEs).[3] These factors greatly impair the ability of skin tissues to mount a proper healing response, especially in the foot and lower extremity, where the majority of diabetic wounds occur.[4] More specifically, normal acute wound healing can be divided into the following three phases: coagulation–inflammation, proliferation, and remodeling with linear progression from one phase to the next.[5] The coagulation–inflammation phase is characterized by rapid blood clot formation followed by intense infiltration by inflammatory cells, such as neutrophils and macrophages, while the proliferation phase is marked by angiogenesis, deposition of extracellular matrix (ECM), and keratinocyte migration. Finally, the remodeling phase includes ECM remodeling and the development of a scar.[6,7] In diabetic wounds, there is a lack of linear progression from one phase to the next as seen in normal healing. Furthermore, there is persistence of the inflammatory phase, although progression to the proliferation phase may be sporadically present in certain wound areas.[5,8]

Diabetic foot wounds tend to occur mainly in patients with type 2 diabetes (T2DM), which has been characterized as promoting a state of chronic inflammation within wounds.[9] A recent study compared wound tissue and peripheral blood monocyte cells (PBMCs) sampled from patients with diabetes whose wounds healed ("healers") with samples from patients who failed to heal over 12 weeks ("nonhealers").[10] PBMCs from healers consisted mostly of nondifferentiated or naive lymphocytes, while PBMCs from nonhealers consisted of natural killer T lymphocyte cells commonly associated with an inflammatory state. Furthermore, inflammation-associated master regulator genes such as nuclear factor-kappa B and transforming growth factor-beta and pathways including interleukin-6 (IL-6) and IL-8 were all activated in nonhealers, suggesting that in nonhealers, there exists a state of increased systemic inflammation compared with healers.

In the skin wound tissue samples, single-cell RNA sequencing analysis revealed that contrary to expectations, healers had more M1 macrophages rather than M2 macrophages, with 195 differentially expressed genes. Furthermore, the activated genes in healers were mainly acute inflammatory genes associated with M1 macrophages such as IL-1β and S100 calcium-binding protein A1, while in nonhealers, the activated genes were associated with M2 macrophages. In addition, a previously unreported cell type called a healing enhancing (HE) fibroblast was identified. HE fibroblasts overexpress the matrix metalloproteinases MMP-1 and MMP-3, which are involved in ECM remodeling. These cells also overexpress chitinase-3 like-protein-1, which is a secreted glycoprotein that is also associated with acute inflammation and ECM remodeling.[11] HE fibroblasts also overexpress tumor necrosis factor-alpha (TNF-α)-induced protein-6, which is associated with ECM stability, cell migration, and acute inflammation.[12] When examining pathway expression in HE fibroblasts, changes similar to macrophages were found, namely, that compared with nonhealers, healers had overexpression of pathways associated with acute inflammation such as IL-6.

Moreover, most of the master gene regulators that were activated in tissue samples from healers were acute inflammatory genes such as TNF-α, IL-6, and nuclear factor-kappa B. Special transcriptomic analyses performed in different areas

of the wound (center of the wound, edge of the wound, and the periwound tissue) revealed that in nonhealers, the area in the wound center showed major differences compared with areas at the edge of the wound or within the periwound tissue, suggesting that the healing process is not uniform across the region. Similar but less pronounced differences were found in tissue samples from healers; however, through immunofluorescence staining techniques, HE fibroblasts were noted in healers to be present mainly in the wound itself and not in the periwound tissue. Activated genes in tissue from the center of the wound were also different between healers and nonhealers, with tissue from healers showing activated genes associated with M1 macrophage function and inflammatory pathways, while tissue from nonhealers showing activated genes associated with M2 macrophages. Finally, it was found that in healers there is the activation of cellular response to TNF. In summary, nonhealing diabetic foot wounds have molecular and cellular signatures associated with chronic low-grade inflammation, while healing diabetic foot wounds have signatures associated with acute inflammation. These findings suggest that in diabetic foot ulcers (DFUs), conversion of chronic low-grade inflammation to an intense inflammatory response has the potential to lead to progression to the next phase, the proliferative one, and improve wound healing. This may also explain why treatments with factors that act in the proliferative phase, such as growth factors, have been largely inefficient in the presence of the nonprogressing low-grade inflammation that characterizes chronic nonhealing DFUs.

Key Consensus Point:

- Nonhealing diabetic wounds are associated with chronic low-grade inflammation that can hinder overall progressive healing.

CLINICAL DIABETES MANAGEMENT

Successful management of diabetic wounds requires a multidisciplinary approach, and the clinician managing a wound in a patient with diabetes should be in contact with the physician who is managing the diabetes, usually a primary care physician (PCP) or an endocrinologist, to discuss a plan for tight glucose control that may involve multiple modalities including diet, exercise, and medication to maintain hemoglobin A1C (HbA1c) <7%. Patients with diabetes are prone to complications, the most important of which is renal failure followed by gastroparesis and other gastrointestinal disturbances, that can have a major impact on the patient's nutritional goals. Therefore, a plan to meet the nutritional needs of the patient with diabetes should also be discussed with the patient's PCP or endocrinologist, which may involve the services of a dietitian and other providers with nutrition expertise. While the wound provider is usually not directly involved in clinical diabetes management, there have been several important recent advances in this area that the wound provider should be aware of and are reviewed here.

The introduction of new glycemic monitoring tools made it possible to achieve better diabetes management. In 2023, HbA1c monitoring became just part of the full picture of optimal diabetes control after the introduction of continuous glucose monitoring (CGM).[13] Several new parameters are currently used,[13] including percentage glucose time in range, which should be >70%; glucose variability (GV), ideally <36%; glucose management indicator, a reciprocal of HbA1c and should be <7%; overall average glucose; and percentage time in hyperglycemia and in hypoglycemia. If using CGM, time below range (<70 mg/dL) is ideally <4% and time <54 mg/dL recommended to be <1%. For those with frailty or at high risk of hypoglycemia, a percentage glucose time in range of >50% with <1% time below range is recommended.[13] Currently, CGM is suggested for all patients with type 1 diabetes (T1-DM)[13–15] and patients with T2DM on insulin,[16–18] whether it is long-acting insulin, multiple daily injection, or an insulin infusion pump.

At present, greater emphasis is directed toward mitigating cardiovascular disease (CVD)[19] and chronic kidney disease[18] through pharmacological interventions in the management of T2DM. It is evident that several glucagon-like-peptide-1 receptor agonists (GLP-1RAs) and all sodium–glucose cotransporter-2 (SGLT-2) inhibitors reduce major cardiovascular adverse events among T2DM patients with established history of atherosclerotic CVD.[13,18,20,21] It is also evident that SGLT-2 inhibitors reduce hospital admission for congestive heart failure and reduce progression to end-stage renal disease.[20,21] The cardiovascular benefits of SGLT-2 inhibitors or GLP-1RAs are not contingent upon HbA1c lowering[13,19–21]; therefore, initiation can be considered in people with T2DM and CVD independent of the current HbA1c or HbA1c goal or metformin therapy. Based on these considerations, the following two strategies are currently recommended[13]: (1) If patient is already on dual therapy or multiple glucose-lowering therapies and not on an SGLT-2 inhibitor or GLP-1RA, switching to or

adding one of these agents with proven cardiovascular benefit is recommended. (2) Introduce SGLT2 inhibitors or GLP-1RAs in people with CVD at HbA1c goal (independent of metformin) for cardiovascular benefit, independent of baseline HbA1c or individualized HbA1c target.

For patients with diabetes admitted to the hospital,[22–24] insulin therapy should be initiated for the treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (checked on two occasions). Once insulin therapy is started, a target glucose range of 140–180 mg/dL is recommended for most critically ill and noncritically ill patients.[24] More stringent goals, such as 110–140 mg/dL or 100–180 mg/dL,[24] may be appropriate for selected patients and are acceptable if they can be achieved without significant hypoglycemia. To reduce surgical risk in people with diabetes, the following approach may be considered[22]: the HbA1c target for elective surgeries should be <8% whenever possible, the target range for blood glucose in the perioperative period should be 100–180 mg/dL within 4 h of surgery, metformin should be held on the day of surgery, SGLT-2 inhibitors must be discontinued 3–4 days before surgery, oral glucose-lowering agents must be held on the morning of surgery or procedure, and half of neutral protamine Hagedorn insulin dose or 75–80% doses of long-acting analog should be considered. There are no data on the use and/or influence of GLP-1RA or ultralong-acting insulin analogs on glycemia in perioperative care. People with diabetes who are competent to safely use diabetes devices such as insulin pumps and CGM[13,22] should be supported to continue using them in an inpatient setting or during outpatient procedures once competency is established and proper supervision is available. It is recommended that blood glucose be monitored at least every 2–4 h while the individual takes nothing by mouth and dose with short- or rapid-acting insulin as needed.

The current standards recommend[25] increased focus on the prevention of amputations with an emphasis on screening for vascular disease as a means of detecting problems early. Initial screening for vascular disease should include several simple assessment tests and checks, including lower extremity pulses, capillary refill time, venous filling time, and other checks of blood flow. As a preventive measure, a comprehensive foot evaluation should be done at least annually and at every visit in individuals with evidence of sensory loss, prior ulceration, or a prior amputation.[25]

Key Consensus Point:

- CGM and other new tools have facilitated better diabetes management, and the wound clinician should be in contact with the patient's PCP or endocrinologist to discuss a plan that includes these new tools in addition to traditional strategies optimizing nutrition and exercise.

Epidemiology of diabetic wounds

Epidemiology entails the comprehensive investigation of disease incidence, prevalence, and burden, as well as the natural progression of ailments. Through epidemiological research, considerable advancements have been made in enhancing our comprehension of the natural course, diagnosis, management, and therapeutic interventions for chronic wounds, which represent notable medical concerns. A recent study examining Medicare beneficiaries revealed a concerning escalation in the prevalence of chronic wounds across the United States, with a notable 13% increase observed between 2014 and 2019, rising from 14.5% to 16.4%.[26] The study's investigators identified a substantial cohort of 8.2 to 10.5 million Medicare beneficiaries afflicted with chronic wounds.[26] The financial impact of managing these individuals, whose primary diagnosis was a chronic wound, imposed a significant burden on Medicare, ranging from 24.7 billion to 33.6 billion dollars annually.[26] Notably, the study highlighted a specific subgroup affected by DFUs, with the prevalence escalating from 406,000 beneficiaries in 2014 to 507,000 in 2019.[26]

Lower extremity complications among those with diabetes are an international problem.[27–30] The epidemiological significance of DFUs is underscored by the profound impact they impose on individuals with diabetes, particularly due to their association with lower extremity amputation (LEA). As LEA constitutes a surgical intervention, its documentation within administrative data necessitates adherence to a specific set of International Classification of Diseases and Current Procedural Terminology codes, which are essential for reimbursement purposes. The Centers for Disease Control and Prevention (CDC) also disseminates publicly accessible data concerning diabetes and its consequential severe complications, including LEA.[31]

When trying to understand the burden of an illness to a population, epidemiologists rely on several key terms such as incidence and prevalence, which are often misrepresented or perhaps misinterpreted by nonepidemiologists. Incidence is the frequency of new cases of a disease or other outcomes among those who are at risk of the disease

or outcome of interest within a specified time-period (*e.g.,* new cases divided by number of people at risk for a disease in a year). Prevalence is the frequency of a disease or other outcome of interest over a given period (*e.g.,* the number of people with an illness divided by the total population in a year). In this setting, the "at-risk population" mainly refers to individuals with diabetes who have lower extremity limbs but could be defined differently. It does not refer to individuals at highest risk for a DFU or LEA (*e.g.,* individuals with previous DFU, end-stage renal disease). Prevalence can be measured as point prevalence (*i.e.,* does an individual have a DFU today), yearly prevalence (*i.e.,* does an individual have a DFU during a 12-month period), their lifetime prevalence, or any other given period of interest, and is a measure of disease burden.

The definition of diabetes, which affects the denominator for incidence and prevalence estimates, changed dramatically between 1997 and 2010.[32–34] These changes occurred around 1997, 2003, and 2008, were related to the criteria used to diagnose diabetes, and included lowering the fasting blood sugar value and decreasing the magnitude of the glycemic index from a glucose tolerance test (or eliminating the need for this test) to make a diabetes diagnosis as well as the acceptance of HbA1c as a diagnostic test.[32–37] The decision to lower the fasting glucose criteria in 2003 stemmed from observations indicating that individuals with fasting glucose levels below the diagnostic threshold, often categorized as "prediabetes," nonetheless proceeded to develop diabetes-associated complications, whereas early treatment for diabetes could potentially have prevented these complications.[35,37] These changes markedly increased the number of individuals with a diagnosis of diabetes.[35,38] DFUs, typically manifesting at least 6 years following the diagnosis of diabetes—where the risk of DFU escalates with prolonged diabetes duration—often precede LEAs. By enlarging the pool of at-risk individuals earlier in their diabetes trajectory, proactive interventions could substantially mitigate the incidence and prevalence of both DFUs and the subsequent LEAs.[39,40]

The global prevalence of DFUs was recently estimated to be about 6.3% per year.[41] The prevalence rates exhibited regional disparities, with North America recording the highest prevalence at 13.0%, while Oceania reported the lowest prevalence at 3.0%.[41] By country, the highest prevalence was in Belgium (16.6%) and the lowest in Australia (1.5%).[41] Other studies have estimated that the prevalence of DFU varies from 1.2% to 20% for patients with diabetes evaluated in the hospital, and from 0.02% to 10% for patients with diabetes in the community.[27,42,43] In the U.S. Medicare population, the yearly prevalence of DFU among Medicare beneficiaries older than 65 years was 8.0 and 8.1 per 100 between 2006 and 2008, again with significant variation by geographic location.[43,44] DFUs stand as a prominent contributor to LEA, contingent upon factors such as lower extremity arterial blood flow and neuropathy.[39]

A global review and meta-analysis from 2023 reported a worldwide incidence of minor LEA at 1.40 per 1,000 individuals with diabetes and 0.95 per 1,000 for major amputations.[30] Overall, LEA rates varied from a low in Italy of 0.22 per 1,000 to a high in the United States of 6.11 per 1,000 with diabetes.[30] In a study of the U.S. Medicare population with diabetes between 2006 and 2008, the prevalence of LEA associated with diabetes was 1.8 per 100 enrolled in Medicare with diabetes and the incidence was about 0.5 per 100.[44,45] Rates varied widely by state and within states.[44–47] A recent analysis of the Veterans Health Administrative Services in the United States revealed that between 2008 and 2018, the rate of LEA increased from 12.89 per 10,000 persons treated in the Veterans Health Administrative Services system (in- or outpatient) to 18.12 per 10,000, representing a net increase of 5.23%.[48] The largest increase was for toe amputations (3.24%), which accounted for 62% of the overall increase, and trans-metatarsal amputations (1.54%), with below the knee increasing only 0.81% during this time frame.[48] In the United States using CDC data, the incidence of new cases of diabetes increased dramatically after the diabetes diagnostic changes and the incidence of LEA decreased dramatically in the first part of this century (Fig. 1). More recently, the incidence of new cases of diabetes has decreased, the prevalence of diabetes has plateaued, and the incidence of LEA has increased (Fig. 1). The recent increased incidence of LEA was at first associated with toe amputations but is now also associated with foot amputations. These changes may have been associated with the changes in the diagnosis of diabetes and including individuals in the risk pool with earlier disease.[28,31–33] Within the context of DFU progression, it is paramount to recognize that DFU represents the primary cause of LEA, with the decision for such surgical intervention contingent upon patient-specific clinical management.[49] However, a recent meta-analysis noted that for individuals who originally had LEA associated with DFU, the reamputation rates were about 20%, 30%, and 46% at 1, 3, and 5 years postsurgery.[40] This rate

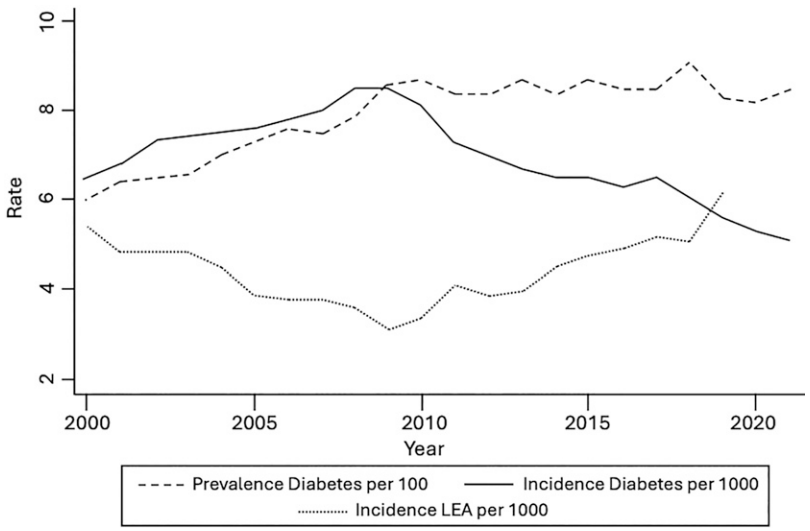

Figure 1. Incidence and prevalence data for diabetes and amputations. According to the Centers for Disease Control and Prevention (CDC) data, in recent years in the United States, the incidence of new cases of diabetes has decreased, the prevalence of diabetes has plateaued, while the incidence of lower extremity amputations (LEAs) has increased (courtesy of David J. Margolis).

is consistent with previous studies stating that 25–34% of individuals who had an LEA will have a second amputation within 6–12 months on the same limb and some minor amputations will become major amputations.[50–52]

Both DFUs and LEAs are associated with elevated mortality rates compared with individuals with diabetes who did not experience either DFU or LEA.[27,29,51,53–56] A recent report equated the 5-year mortality associated with LEA to the risk of death from cancer in general, and found it more than three times that of breast cancer.[57] In a study conducted in the United Kingdom, individuals with diabetes who underwent any form of LEA exhibited a 3.02-fold increased risk of mortality compared with those without LEA, with an overall 5-year mortality rate of 27.2%.[58] The increased risk of death among those with diabetes and a DFU is approximately 2.5 times the risk of death for those with diabetes and no foot ulcer.[55,59] For both LEA and DFU, the risk of mortality remained unchanged after statistical adjustments for various factors potentially linked to LEA and mortality, including renal disease, glycemic control, history of cerebrovascular disease, vascular disease, and myocardial ischemia—suggesting that the risk of mortality subsequent to a DFU or LEA is distinct from the risks associated with these comorbidities.[55,58]

Key Consensus Point:

- The presence of a foot ulcer is a prominent contributor to the risk of LEA and increases the mortality risk for patients with diabetes by more than twofold.

Neuropathic conditions in diabetic wounds

Lower extremity complications of diabetes, including DFUs and Charcot arthropathy, pose a significant health challenge, often exacerbated by neuropathy. The intertwined relationship between neuropathy and diabetic wound healing necessitates a multidisciplinary approach for effective management. Neuropathy in diabetes manifests as sensory, motor, and autonomic neuropathy, all playing significant roles in the development and hindrance of healing in DFUs. Sensory neuropathy leads to a loss of protective sensation, rendering individuals unaware of trauma or pressure on the foot. Motor neuropathy results in foot deformity and biomechanical abnormalities, promoting callus formation and altered weight distribution. Autonomic neuropathy causes viscoelastic changes in the skin and dryness, predisposing to skin breakdown and ulceration.[56,60] These combined neuropathic effects underscore the complexity of DFUs and highlight the importance of comprehensive management strategies in diabetic foot care.

In patients with diabetes, routine neuropathy screening is essential in initial screening, often conducted using tools such as the Semmes–Weinstein monofilament examination. Once protective sensation is lost, attention can be better focused on managing additional risk factors to reduce the likelihood of ulceration, reulceration, infection, and limb loss.[61,62] The Wound, Ischemia, Foot Infection (WIfI) classification system integrates wound assessment, ischemia, and foot infection to accurately gauge the risk of limb loss.[63,64] By identifying and communicating the severity of diabetic foot ulceration, this

classification system facilitates the organization of rapid multidisciplinary clinical care. A higher WIfI score is associated with LEA and morbidity, guiding decisions regarding the necessity for revascularization.

Charcot arthropathy significantly elevates DFU risk, especially in the midfoot and ankle/hindfoot regions.[65–67] A unilateral red, hot, swollen foot may indicate Charcot arthropathy. Aggressive protection through casting, custom walkers such as a Charcot Restraint Orthotic Walker, or surgical intervention as warranted is crucial for preventing further deformity and promoting healing.[65]

In managing diabetic wounds, various strategies can be used to facilitate healing and prevent complications. Regular debridement is crucial to eliminate nonviable tissue, with weekly sessions demonstrating a significant increase in healing rates.[56] Off-loading devices, such as total contact casts or knee-high walkers, play a pivotal role in reducing pressure on ulcerated areas,[58,68] promoting optimal healing conditions. Ideally, irremovable devices (such as the total contact cast) should be considered first to improve adherence, moving to alternates depending on the location of the wound and functional considerations.[69] Selection of wound dressings should be tailored to the wound characteristics, aiming to maintain a moist environment conducive to healing.[56,70] In cases where standard care proves ineffective, advanced therapies such as negative pressure wound therapy (NPWT), biologics/immune modulators, and topical oxygen therapy (TOT) may be considered.[70] Continued assessment of the wound healing trajectory is essential in guiding treatment decisions and ensuring optimal outcomes for patients with diabetic wounds.[64]

Infection management is paramount in diabetic wound care to mitigate the risks of hospitalization and amputation. Early intervention is critical to effectively treat infections and prevent further complications.[64] In addition, addressing underlying vascular disease is vital for promoting tissue healing. Revascularization procedures play a key role in restoring arterial flow, with timely intervention linked to improved wound healing outcomes.[71,72] By prioritizing early infection management and timely revascularization, health care providers can optimize patient outcomes and minimize the risks associated with DFUs.

Key Consensus Point:

- The use of orthotic devices to optimize off-loading and neuropathy screening is essential in patients with diabetes to minimize wound development and deterioration and risk of further complications.

Infections

As a breach in the skin barrier, all wounds are inherently contaminated with microbes and thus vulnerable to infection. Wounds acquire microorganisms from a number of potential sources, including normal microbiota of the periwound skin,[73] microbiota from other body sites, and the environment. As defined by a wound infection continuum,[74] contamination leads to colonization in which the open wound provides a suitable environment for microbes to proliferate, but not in sufficient levels or virulence so as to provoke an immune response. Colonizing microbes move deeper into the wound tissue during early local infection but are still localized to the skin. In the later stages of localized infection, more pronounced clinical symptoms such as erythema, purulence, and delayed wound closure become evident. If uncontrolled, the infection can spread beyond the initial wound affecting nearby structures, including deeper and surrounding tissues. Immune responses to infection also become apparent beyond the wound itself. When microbes from the wound proliferate and disseminate through the vascular or lymphatic systems, systemic infection ensues.

Patients with chronic, uncontrolled T2DM often exhibit impaired wound healing. This impairment is associated with multiple effects stemming from chronically elevated blood glucose levels, including nonenzymatic glycosylation of key proteins or AGEs. AGEs regulate various processes in wound healing, influencing inflammation, cell proliferation, and migration, as well as the formation of granulation tissue and scar tissue.[75] Therefore, in patients with chronic, uncontrolled T2DM, acute skin wounds in the lower extremity tissues frequently result in impaired function of the innate immune system, leading to reduced capacity for rapid and effective recognition and elimination of contaminating bacteria and fungi. In this scenario, the microbial bioburden is permitted to advance to clinically significant levels of infection, exacerbating the impediment to healing. This is facilitated by the induction of chronic inflammation, characterized by markedly elevated levels of proteases and reactive oxygen species (ROS), which degrade essential proteins necessary for the healing process.[76]

Diagnosis of diabetic wound infections primarily relies on clinical evaluation. The presence of two or more clinical signs is indicative of infection, such as erythema, swelling, pain/tenderness, warmth, and purulence.[64] In cases where such signs are

absent, the necessity of obtaining a wound culture lacks substantial data support.

Contemporary understanding suggests that diabetic wounds typically host polymicrobial communities; however, *Staphylococcus aureus* predominates as the most frequently identified organism, as evidenced by both culture-based methods and molecular diagnostics.[77–79] Other common microorganisms include *Pseudomonas spp*., *Enterococcus spp*., *Escherichia coli*, *Streptococcus spp*., coagulase-negative *Staphylococcus spp*., and *Proteus spp*.[80] While anaerobic bacteria are less frequently recovered by cultures, molecular methods have indicated that these bacteria may be more frequent than previously appreciated in infected and even uninfected diabetic wounds.[81,82] Moreover, the prevalence of anaerobic organisms, particularly gram-positive anaerobic cocci such as *Peptoniphilus* and *Peptostreptococcus*, within the diabetic wound microbiome has been associated with unfavorable clinical outcomes.[78,83,84]

Typical pathogenic bacteria and fungi identified in DFUs exist in two distinct phenotypes.[85] The most abundant type (viable colony forming units) is the single, nonattached, rapidly metabolizing and proliferating planktic bacteria. Planktonic bacteria have the capability to initiate local wound infection, and if left unchecked may propagate to disseminated infection and potentially progress to systemic sepsis. The second phenotype of bacteria is the biofilm community consisting of bacteria that are encased in a large, self-produced, complex, exo-polymeric matrix (EPM) that tightly attaches the biofilm community to surrounding structures. The EPM consisting of large, unique polysaccharide chains ($\sim$80%), free extracellular bacterial DNA ($\sim$10%), unique proteins synthesized by the bacteria ($\sim$5%), and host ECM proteins ($\sim$5%).

Individual clinical studies and meta-analyses of published clinical studies of chronic wounds of different etiologies that include biopsies and curettage samples indicate that biofilm communities are present in up to $\sim$80% of chronic wounds.[86] Proliferating planktonic bacteria can be effectively killed in wounds by appropriate antibiotics, unless the strain has developed permanent, genetic resistance. In contrast, many of the bacteria present in mature biofilm communities are metabolically dormant, which provides temporary tolerance to antibiotics that effectively kill only the metabolically active planktonic form of the bacteria.[87] In addition, the microbiocidal efficacy of many common antimicrobial agents to bacteria in mature biofilm communities is significantly reduced due to chemical reaction with components of the EPM (reaction–diffusion problem),[88] ionic binding of the antimicrobial agents to highly charged components of the EPM (negatively charged polysaccharide chains and free extracellular bacterial DNA), or reduced diffusion of large antimicrobial polymers into the dense EPM of the biofilm structure.

Pooling data from various clinical studies indicates a shared molecular pathology frequently implicated in the transition of acute wounds to chronic wounds. In conjunction with prevalent comorbidities such as compromised arterial perfusion, venous insufficiency, persistent tissue pressure or reperfusion injury, and T2DM, the microbial bioburden within both planktonic and biofilm bacteria escalates to levels conducive to chronic inflammation. This inflammatory milieu in the wound bed is characterized by significantly elevated neutrophil and M1-type macrophage activity, which stimulates the release of proteases (including MMPs and neutrophil elastase) and ROS. These inflammatory mediators can reach concentrations several orders of magnitude higher than those observed in healing wounds.[89] The persistently elevated levels of proteases and ROS degrade proteins that are required for healing, thus converting an acute wound into a chronic wound.

In general, all wounds are assumed to be contaminated or infected, and reducing bioburden is considered a critical component of wound bed preparation.[90,91] The prevention and treatment of wound infections encompass several key strategies. Debridement serves as a fundamental approach, aimed at eliminating nonviable tissue from the wound, including necrotic tissue and surface biofilm formation. While various techniques exist for debridement, early, aggressive, sharp debridement followed by weekly sessions is widely endorsed to effectively manage bioburden.[90] Since debridement alone cannot entirely eradicate bacteria, it is recommended to complement it with antimicrobial wound bed preparation to mitigate the risk of reinfection and biofilm formation.[91,92]

Clinically invasive infections, acute infections, and planktonic bacteria are treated with systemic antibiotics. However, bacteria in biofilms, which are thought to form on most chronic wounds,[91] are highly tolerant to systemic antibiotics and topical antiseptics. Topical antimicrobial treatments are often used after debridement to control regrowth of microbes in the wound bed. Antimicrobials may be used in dressings to treat local planktonic infections, and are embedded with agents such as nanocrystalline silver, hypochlorous acid, and iodine,

which are released in various concentrations to the wound surface.[90]

Antimicrobial resistance has been designated a threat to global health by the World Health Organization.[93] The selective pressure exerted by antibiotics results in the elimination or inhibition of susceptible bacteria, allowing naturally resistant or acquired antibiotic-resistant strains to proliferate. The evolution of antibiotic resistance is further exacerbated by both overuse of antibiotics and inadequate adherence to treatment guidelines. Antibiotic resistance is a highly pertinent issue for diabetic wounds, which are often treated with antibiotics and harbor microbes known to evolve resistance. Methicillin-resistant *S. aureus* constitute ~18% of *S. aureus* infections, according to a meta-analysis of 112 studies investigating cultured isolates from DFU infection.[77] Vancomycin-resistant *S. aureus* remain rare, but have been isolated from diabetic wounds.[94,95] More common are vancomycin-intermediate strains, where multiple chromosomal mutations arise *de novo* that influence the cell surface to protect against vancomycin, an inhibitor of cell wall synthesis that acts by binding precursors of peptidoglycan.[96] Infections associated with *Pseudomonas aeruginosa* have shown resistance against the most effective antimicrobials, such as third-generation cephalosporin.[97] Multidrug-resistant nondiphtheritic *Corynebacterium spp*. are now recognized as emerging wound pathogens.[98,99] In *Enterococcus faecalis*, resistance to the last-resort antibiotic daptomycin has been linked to changes in phospholipid metabolism.[100] Whole metagenomic sequence analysis of DFU indicates that >50% of DFU specimens contained resistance genes to the aminoglycoside (*e.g.,* clindamycin), macrolide (*e.g.,* erythromycin), beta-lactam (*e.g.,* amoxicillin), and tetracycline (*e.g.,* minocycline) classes of antibiotics. Thus, resistance to antibiotics is estimated to be widespread and evolving in diabetic wounds and associated infections.

The general treatment strategy for diabetic wound infections includes management of blood glucose levels and the mitigation of concurrent comorbidities. This entails off-loading ulcers located on the plantar surface of the foot and padding regions susceptible to recurrent shear or friction forces. The "Step-Down Then Step-Up" concept as described in the Consensus Guidelines for the Identification and Treatment of Biofilms in Chronic Non-Healing Wounds[101] and the International Wound Infection Institute 2022 update on Wound Infection In Clinical Practice[102] underscores the importance of commencing treatment with a comprehensive "wound cleansing" procedure. This involves meticulous cleansing of the wound bed to remove any loosely adherent wound slough or debris. In addition, these professional societies advocate for further debridement of necrotic tissues and the application of an appropriate topical dressing to the debrided wound bed. Systemic antibiotics should be considered if clinical evidence of local or spreading wound infection is present. This approach effectively targets residual biofilm bacteria, preventing the reformation of mature biofilm, which can occur within less than 3 days.[103] Continuous monitoring of wound healing and frequent debridement with appropriate topical dressing are recommended until the wound exhibits no signs of local infection and inflammation. As the wound progresses toward healing, treatment modalities may transition to maintenance debridement and wound dressings that specifically target planktonic bacteria. However, in cases where the wound healing rate could be enhanced by the use of advanced wound care products such as cell/tissue dressings, growth factors, or skin grafts, the treatment strategy may escalate to incorporate these advanced interventions. This approach is particularly effective when the wound bed has been adequately prepared using the principles of biofilm-based wound care. Four recently published peer-reviewed research journal articles reported that only 17% of 18 chronic wounds with positive staining for biofilms healed after 4 weeks of standard clinical care, whereas 77% of 13 chronic wounds with no biofilm staining healed after 4 weeks.[104]

Finally, phage therapy represents an emerging treatment modality for wound infections, using viruses (phages) to target and eliminate bacterial pathogens. Accumulating evidence from controlled studies conducted in preclinical models of skin and burn infections indicates the efficacy of phage therapy in reducing bacterial burden and enhancing survival rates, particularly in cases of *S. aureus* and *P. aeruginosa* infections.[105] Despite the potential, efficacy of phage therapy has not been demonstrated *via* randomized controlled trials.[106,107]

Key Consensus Points:

- Resistance to antibiotics is widespread and evolving in diabetic wounds and associated infections.
- Successful treatment strategies for diabetic infections include meticulous wound cleansing with removal of biofilm and management of blood glucose levels as well as assessment and treatment for limb ischemia.

Peripheral vascular disease

Macrovascular disease. The global epidemic of diabetes overlaps significantly with the rising prevalence of peripheral artery disease (PAD). Fowkes and colleagues estimated the global incidence of PAD back in the early part of this decade and found that >200 million people are afflicted, and that the increasing prevalence over the last decade is of the order of 25%.[108] The rise in PAD is not unique to any socioeconomic status. In fact, areas of the greatest growth around the world are lower income countries and areas of Southeast Asia. PAD is a huge and growing global health problem, requiring a lot of resources from health care systems as the population in the world ages and diabetes prevalence continues to rise. The Eurodiale observational studies[109–111] demonstrated that the coprevalence of PAD and a DFU is a very worrisome combination in terms of prognosis for the patient. DFUs precede perhaps up to 85% of all nontraumatic limb amputations, and we know that PAD is highly prevalent in patients with diabetes for 10 years or longer.

In Eurodiale, 49% of the patients with an open DFU had PAD, and the presence of PAD was a very strong negative predictor of healing, particularly when compounded with infection.[109] Therefore, it is vitally important to diagnose PAD in all patients with DFUs because it is a major driver of outcomes, and also because the treatment needs to be tailored to the presence and severity of the vascular disease. Work from Armstrong and colleagues[57] has shown that 5-year mortality in patients with DFU is 25%, a somewhat grim statistic greater than or equal to most types of cancers. Even more sobering is the prognosis for those with chronic limb-threatening ischemia (CLTI), the most advanced stage of PAD, in which inadequate perfusion leads to tissue necrosis. Once individuals are diagnosed with CLTI, their annual mortality rate is generally around 10%, exceeding almost every type of cancer, save perhaps lung cancer. If a patient requires a major limb amputation due to advanced vascular disease, there are substantial data demonstrating that both their life is shortened and their quality of life severely reduced.[57]

Turning to diagnosis, it is fairly well accepted that patients with diabetes should have a vascular examination, at least annually, and that they should be asked about the classic symptoms of PAD. However, it is also well-known that classical PAD symptoms may be absent or masked in patients with peripheral neuropathy and in those who have a sedentary lifestyle and do not exercise. Furthermore, patients who have a primarily distal pattern of disease (*e.g.,* involving below knee arteries) often will not have exercise-related claudication but may present *de novo* with frank tissue loss and poor healing. Performing an extensive cardiovascular and particularly vascular history, along with foot pulse examinations, should be a standard of care (SOC) for everyone with diabetes and certainly for those with a prior history of DFU. In patients who have symptoms that are suggestive of PAD with an abnormal vascular examination or an existing foot wound, objective measurement of the severity of vascular disease is critical before surgery or other wound intervention and is a practice guideline measure.

Standard noninvasive arterial studies rely on segmental pressures and Doppler waveforms in the lower leg, ankle, and foot. They include ankle pressure, the ankle brachial index (ABI), toe pressure, toe brachial index (TBI), and the Doppler waveforms, which should be inspected. There are much data concerning this topic, and no single one of these tests is optimal for assessing perfusion in all patients.[112] Moreover, localized perfusion to the wound bed ("angiosome" or "woundosome"[113]) is not always reflected in these measures. Current guidelines reflect that one or more of the tests should be done in conjunction, and the visual inspection of the Doppler waveforms associated with the measured pressures is quite useful. The sensitivity and specificity for any one test still leave significant room for improvement. However, significant PAD is quite unlikely if the ankle index is between the range of 0.9 and 1.4 and/or if the toe index is greater than 0.7 in the presence of a multiphasic Doppler waveform. There are special circumstances that can influence these measurements. Most important is the presence of arterial calcification, particularly medial artery calcification (MAC) in the tibial arteries, that can render the ankle pressures either not measurable or falsely elevated. An ABI >1.4 is considered an unreliable measurement for PAD. Digital artery calcification is less common, although not rare in those with diabetes and renal disease. Accordingly, the toe pressure and TBI may be a better measure of vascular disease in the diabetic population and in those with unmeasurable or inappropriately high ABI. It should be noted, however, that MAC can also affect the pedal arteries and thus even digital pressures may be rendered inaccurate[114,115]; a plain radiograph of the foot (SOC for most DFUs) demonstrates the presence and severity of pedal MAC, which can help the clinician to interpret the noninvasive study results within this context.

Visual examination of the Doppler waveforms can be helpful to determine if the measured pressure is likely accurate. If the waveform is barely pulsatile, the distal pressure value is likely to be an overestimation. Importantly, these tests are noninvasive, fast, and inexpensive in most office settings. In current practice in most parts of the Western world, patients with DFU should have access to vascular testing to quantify the degree of ischemia more routinely and more consistently. Improvement in this area is critical so that patients obtain an accurate diagnosis and treatment; it also provides better epidemiological data.

An algorithm from the Global Vascular Guidelines (GVG)[116] provides guidance on vascular testing (Fig. 2). For patients with a clinical suspicion of advanced limb ischemia such as pain at rest in the foot that has the characteristics of ischemic rest pain, or any degree of tissue loss in the presence of an abnormal vascular examination, it is suggested that ankle pressures, toe pressures, and Doppler waveforms should be done. When the ankle pressure or waveform is abnormal and if there is any tissue loss, toe pressures are preferred because they have a better predictive value for wound healing than ankle pressures alone. Thus, most patients with DFU benefit from toe pressure/TBI measurement.

Limb staging is the next important area to address. There are several systems for vascular staging and wound staging out there, but the only one that combines them both into a single framework is the Society for Vascular Surgery's WIfI staging system that was published in 2014.[63] This scheme provides a TNM-type approach to grade 3 independently critical factors in patients presenting with tissue loss. To use WIfI, the clinician must characterize the extent and depth of the wound, assess the severity of ischemia noninvasively, and the presence and extent of foot infection. These individual grades are combined into four overall WIfI stages for the limb to predict the 1-year risk for major amputation, and to suggest which patients would benefit most from revascularization. An important concept in WIfI is that rather than applying a simple threshold value of perfusion pressure, there is recognition of a gradient of ischemia that may be limb threatening depending on the clinical circumstance. Previous concepts of "critical limb ischemia" were based on a sharp cutoff value (*e.g.,*

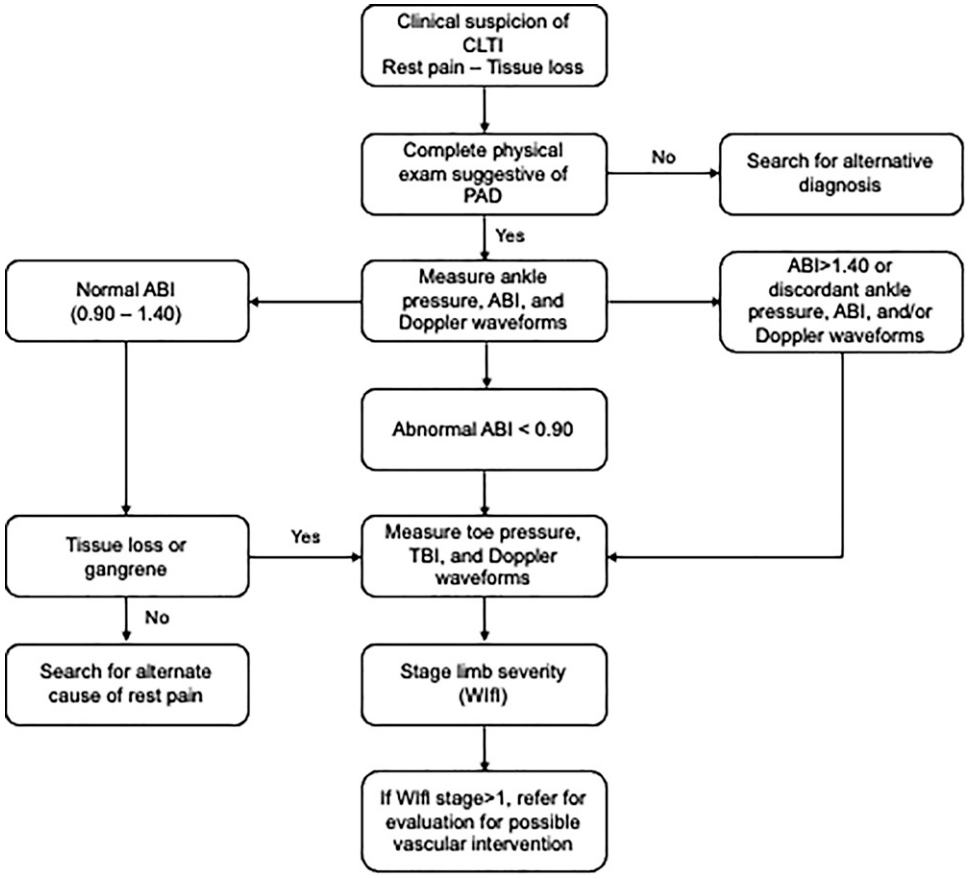

Figure 2. Suggested algorithm for noninvasive vascular testing and evaluation in patient with suspected chronic limb-threatening ischemia (CLTI). ABI, ankle brachial index; PAD, peripheral arterial disease; TBI, toe brachial index; WIfI, Wound, Ischemia, Foot Infection (from Conte et al., 2019[116]).

ABI <0.4 or a toe pressure <30 mm Hg). However, more moderate degrees of ischemia in the presence of an extensive wound or infection may also in fact be "critical." This evolving concept also explains the change in terminology recently to CLTI.

When considering the relationship between blood flow and wound healing, a fundamental observation is that regardless of which measure one uses for perfusion, the relationship to wound healing is an S-shaped curve with a large intermediate range of ischemia that may be most relevant clinically in the setting of an advanced wound or infection. In other words, the degree of ischemia that may be clinically important to impair healing is likely to be quite different depending on the complexity of the wound and the presence of infection.

Review of the WIfI grades and stages (Fig. 3) demonstrates how the system is used for prognosis.[63,117] Each of the three primary components is graded on a 0–3 scale, and then these domains are combined into four overall stages of limb threat. An expert consensus panel developed the scheme, informed by evidence review, and suggested the assignment of the overall stages based on the expected risk of major amputation at 1 year. There have been many subsequent publications that have validated the WIfI staging system largely among cohorts with CLTI, demonstrating that it is quite good at predicting 1-year major amputation risk.[118] However, these studies are primarily retrospective in nature, and largely included patients who got revascularization. WIfI is yet to be validated prospectively in all comers presenting in a longitudinal cohort manner and specifically in the DFU population. The available data demonstrate that patients in WIfI stage 1 have a very low to negligible risk of major limb amputation with good basic foot care. Conversely, those presenting in stage 4, even with aggressive revascularization in all of these series, face about a 20% chance of major limb loss. Stages 2 and 3 seem to overlap in intermediate severity. WIfI staging is meant to be used in a manner similar to TNM in cancer, which means it is not a one-time assessment but is used to gauge trajectory over time. It should be reassessed in any patient whose wound or symptoms are not resolving or worsening.

In practice, one makes an initial assessment about the need for revascularization based on the patient's overall risk, the severity of the ischemia, and clinical presentation of the limb. This defines an initial treatment approach that should include optimal wound care and off-loading. One should then reassess if the wound is not improving after 4 to 6 weeks, including remeasuring the state of any ischemia and restaging that foot.[119] This provides a systematic, data-driven approach to assess

A

Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mmHg)	Toe pressure or $TcPO_2$
	0	≥0.80	> 100	≥60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	<0.40	<50	<30
fI (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

B

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Figure 3. Society for Vascular Surgery Threatened Limb Classification System based on Wound, Ischemia and Foot Infection (WIfI). **(A)** Grades shown in top panel. **(B)** Stages shown in bottom panel correlate with risk of major amputation (adapted from Mills *et al.*, 2014, and Aboyans *et al.*, 2018[117,118]).

the treatment strategy's progress and whether a change is needed, particularly in the domain of revascularization.

Regarding limb revascularization in patients with diabetes, there is a long history of using distal extremity revascularization to prevent limb loss dating back to the middle of the 20th century. Pioneering vascular surgeons in the 1960s demonstrated that you could salvage limbs with vein bypass grafts in patients with advanced peripheral vascular disease, including patients with diabetes. It is important to understand that although the absolute certainty of MVD in the foot of patients with diabetes is well recognized, the notion that one could not effectively treat these patients with a macrovascular approach such as bypass surgery was disproven heartily in the 1980s[120] by Dr. Frank LoGerfo who is credited with bringing this concept to the forefront and removing the nihilistic approach about MVD that suggested revascularization would not be effective in patients with diabetes.

Contemporary strategies for limb revascularization have evolved rapidly due to the increasing availability and success of catheter-based endovascular techniques in addition to traditional open surgery. This, together with better staging, allows us to consider how to approach these patients in a precision medicine way. First of all, in any patient with DFU in whom PAD has been demonstrated or is suspected, evaluation by a vascular specialist is absolutely indicated to consider the severity of ischemia and the potential benefits and risks of revascularization. The WIfI staging system is helpful to define the potential benefits of revascularization in patients across the spectrum of CLTI. When ischemia is severe, such as a toe pressure less than 30 mm Hg or an ankle pressure less than 50 mm Hg, the consultation should be urgent. When ischemia is mild or moderate, the wound clinician can consider focusing on optimizing wound care management and off-loading with frequent visits to assess progress. If the foot or clinical status is deteriorating, a consultation with a vascular specialist should be indicated.

The GVG[116] provide a patient-oriented framework to define the optimal revascularization strategy based on the PLAN concept of Patient risk, Limb threat severity (WIfI), and the ANatomic pattern of PAD in the limb. For anatomical staging, a new integrated approach called the Global Limb Anatomical Staging System (GLASS) was developed. GLASS integrates the complexity of disease in the limb from the groin to the foot based on the selection of a preferred target artery path (selected tibial vessel) from angiographic imaging including the ankle and foot. Technical success and durable patency of a limb revascularization, just as in coronary disease, are highly dependent on how the anatomical pattern plays off disease. Without delving into the fine details of the GLASS, it involves separately grading the disease severity above the knee (femoral and popliteal) and below the knee (tibial and pedal vessels) in separate components based on high-quality angiographic imaging. These grades are then combined into three overall stages for the limb as a whole, based on the understanding that to achieve effective revascularization you need to achieve inline flow to the foot. The resulting stages range from low-complexity disease, which is very amenable to endovascular treatment with good expected results, to high-complexity disease patterns where both the expected technical success and the downstream patency of an endovascular intervention are markedly reduced. The GLASS is increasingly being validated in published studies, including a recent systematic review and meta-analysis.[121]

The GVG recommendations that an optimal revascularization strategy in CLTI patients should be individualized are based on the defined critical elements of PLAN outlined above. In a patient presenting with signs of advanced limb ischemia or tissue loss, it begins with limb staging. If it is initially a low-risk limb presentation, you may start with wound care and surveillance. If the limb is judged to be in immediate or higher risk, the patient is evaluated as an appropriate candidate for limb salvage based on their overall risk and their functional status. For frail or nonambulatory patients, there is an important role for primary limb amputation and palliative wound care. If the patient is a candidate for limb salvage, you should estimate the operative and cardiovascular risk using one of multiple available risk calculators (*e.g.*,[122,123]) and consider the options for revascularization using WIfI and GLASS.

If revascularization appears feasible in a high-risk patient, one may choose to use a catheter-based approach as much as possible. However, in a standard-risk patient with CLTI, choosing between open bypass and endovascular intervention should consider the anatomical complexity and the ability to undergo a vein bypass. The GVG suggested a rubric for average surgical risk patients that is based on WIfI and GLASS, as well as the availability of great saphenous vein for a bypass conduit (Fig. 4). In this scheme, many patients are approached with an endovascular-first approach

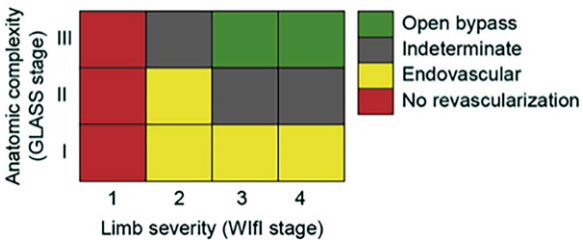

Figure 4. Suggested initial revascularization strategy for average surgical risk CLTI (chronic limb-threatening ischemia) patients with an available great saphenous vein is based on limb severity and anatomical complexity (from Conte *et al.*, 2019[116]).

highlighted in yellow. Those patients who have very complex anatomy and high-risk limbs probably do better with an open bypass (Fig. 4, green). There are many that fall into an indeterminate zone based on current data, and in general a stronger evidence base is needed to guide recommendations.

Very recently, level 1 data have been published comparing the effectiveness of revascularization strategies in CLTI patients. The recently published BEST-CLI randomized trial was conducted primarily in the United States and was funded by the National Institutes of Health over an 8-year period. This is a landmark trial that was published in the *New England Journal of Medicine* in 2022[72]; its results are reflected in the most current International Working Group guidelines on PAD management[124] and likely will be reflected in other upcoming societal guidelines related to the management of CLTI. Investigators in BEST-CLI trial randomized patients with CLTI, who were deemed to be a reasonable surgical risk and who could be treated with either a catheter-based approach or with open bypass surgery. Patients were screened for the presence of an adequate great saphenous vein and placed into two different trial cohorts. Cohort 1 included patients who were deemed to be likely to get a saphenous vein bypass with a single segment of vein. Cohort 2 included subjects likely to require an alternative conduit for bypass based on their preoperative vein mapping. In cohort 1, over 1,400 patients were randomized and followed for nearly 3 years. The majority of these patients had diabetes, more than 70%. The primary endpoint of the trial was the occurrence of major adverse limb events, which included conversion to open bypass surgery, thrombectomy/thrombolysis, and major amputation, or all-cause death. Among patients in cohort 1 after a median of 2.7 years of follow-up, there was a 32% relative risk reduction in the primary endpoint among the patients randomized to open bypass first. This comprised a 65% relative risk reduction in major reinterventions, a 27% relative risk reduction in major limb amputation, and no difference in all-cause mortality or major adverse cardiovascular events. This finding in cohort 1 was robust across nearly every patient subgroup, including those with diabetes, tissue loss, and infrapopliteal disease. There was no significant difference in the primary endpoint in cohort 2 (those lacking an adequate great saphenous vein).

It is important to recognize that similar to any clinical trial, generalizability of the BEST-CLI results is an important question. The trial was designed to focus on CLTI patients who were assessed to be of reasonable surgical risk and had an acceptable anatomy for either type of revascularization. It is unclear at present what percentage of the overall CLTI population this may represent, but it is likely to be a minority. Overall results demonstrated excellent limb salvage and improved quality of life in both treatment arms of the trial. Nonetheless, the results of BEST-CLI strongly suggest that some patients with CLTI should be treated initially with an open bypass for a more effective outcome. There is much more to come from subsequent analyses in this trial. It is also important to note that the BASIL-2 trial from the United Kingdom was also recently reported and presented a contrasting result from a different (and smaller) population.[125] Comparison of these trial populations and outcomes is beyond the scope of this review. However, the much larger scale and inclusive scope of the BEST-CLI trial, combined with the robustness of its findings, have led to renewed enthusiasm for the clinical effectiveness of vein bypass surgery in appropriate patients with CLTI.

In conclusion, it should be clear that the early and accurate diagnosis of PAD in patients with diabetic foot wounds is paramount. Limb staging and restaging are important for prognosis and to define treatment success. More validation studies of the WIfI system are needed with possible modifications going forward based on well-done outcome studies. Revascularization should be considered in any DFU patients with PAD, based on their clinical staging, their clinical trajectory, and on their overall patient risk and goals of care. For some frailer patients, primary amputation and palliation have important roles to play.

Microvascular disease. While macrovascular disease is well known to be associated with the development of and the poor healing-associated DFU, MVD association with DFU remains controversial. MVD is also known as microangiopathy or small-vessel disease and has been associated with a range of

conditions that impact the arterioles, venules, and/or capillaries, in general vessels with diameters of 100 um.[126] Disease that affects these small vessels manifest locally in organ-specific diseases. MVD is associated with T2DM, particularly those patients where uncontrolled blood glucose levels cause chronic cellular stress include retinopathy, nephropathy, coronary microangiopathy, and neuropathy in the peripheral nervous system.[127–130]

As a review, central regulation of skin blood flow balances sympathetic-mediated vasoconstriction and vasodilatation, responsible for most of the blood flow to the skin capillary network, including the foot.[131] Numerous arteriovenous anastomoses allow direct communication between meta-arterioles and venous plexus shunting large volumes of blood to the skin surface for heat dissipation but at the same time bypassing nutrient capillaries. Local regulation of blood flow is mediated mainly by local vascular responses and by neurogenic C-fibers *via* the nerve axon reflex (Lewis triple response) stimulated by noxious stimuli, including mechanical, chemical, and thermal injury. Thus, direct injury (*e.g.,* thermal injury above 42°C) increases blood flow specifically at the site of injury by decreasing the precapillary sphincter tone, a direct vascular mechanism. In contrast, in the surrounding skin there is also an increase in blood flow, the "flare response." Nociceptive C fibers responsible for neural conduction to the thalamus to mediate the pain sensation also simultaneously conduct to the local neural network, resulting in the release of vasoactive substances, including substance P, histamine, and calcitonin gene-related peptide, into the surrounding skin at the site of injury to cause vasodilation.[132–135]

With diabetes, structural changes occur, such as thickening of the capillary basement membrane, diminished capillary luminal size, and pericyte degeneration. These are more pronounced in lower extremities due to gravity-induced hydrostatic pressure and loss of postural vasoconstriction in people with diabetes.[136] Increased capillary pressure increases fluid filtration and probably induces inflammatory responses in the microvascular endothelium, contributing to basement membrane thickening and hyalinosis of the arterioles. These microvascular changes have also been linked to increased glycosylation and formation of nonenzymatic AGEs.[131] As a result, basement membrane thickening can impair normal transport across the capillary wall.

There is controversy regarding the significance of structural changes in the small vessels of the diabetic foot. One study of 152 amputation specimens, of which 92 had diabetes, described endothelial proliferation sufficient to almost occlude the lumen of digital arteries and smaller vessels.[137] Subsequent studies using light microscopy, vascular casting, and physiological studies did not confirm the presence of occlusion.[120] However, a recent study on T2DM found that capillary microangiopathy was present in neuro-ischemic and neuropathic diabetic foot skin, with a predominance of arteriolar occlusions in the neuro-ischemic foot.[138]

Unfortunately, standard vascular tests (ABI and TBI) do not correlate with known clinical diagnoses that support the presence and severity of MVD. These data agree with the notion that ABI and TBI are generally used for evaluation of large-vessel arterial flow, rather than diseases of the small vessels. In practice, most physicians do not directly measure perfusion in the small vessels. More recently, significant improvements to evaluate skin microcirculation have emerged, they are still not used by most clinicians caring for DFU. Among them is capillaroscopy, which is a sensitive and exacting method for estimating the skin's microcirculation at a microscopic level by *in vivo* visualization of the density, morphology, and blood flow in capillaries using a real-time video technique.[139] Laser Doppler flowmetry and imaging noninvasively measure blood flow in the superficial 1 to 1.5 mm of skin and as such include capillaries, superficial meta-arterioles, venous plexuses, and acral areas. Using monochromatic laser light, back-scattered by moving red blood cells, blood flow and velocity can be assessed.[140] Hyperspectral imaging is a technique assessing skin blood flow noninvasively based on the principle that oxy- and deoxy-hemoglobin have different absorption spectra resulting in differences in reflectance of light emitted in specific wavelengths. With the aid of complex imaging algorithms, information regarding the perfusion of tissues.[141,142] Transcutaneous oxygen pressure, often used for patients undergoing hyperbaric oxygen, noninvasively measures the partial pressure of oxygen molecules, diffusing through the skin from the superficial microvasculature. Heating greatly increases perfusion such that the transcutaneous oxygen levels more closely correlate with local perfusion, and thus, transcutaneous oxygen pressure in heated skin has been considered a measure of skin perfusion and included in some vascular units, a measure that will influence vascular intervention.[143–146]

Often MVD in patients with diabetes is clinically defined and the presence of clinically defined

MVD increased peripheral amputation risk independently of PAD (3.7 times higher than no MVD) and worked synergistically with PAD (amputation risk 13.9 times higher than baseline) to yield a 22.7 times higher amputation risk in patients who had both MVD and PAD. MVD has also been shown to correlate with increased rates of DFU development.[147]

Limited high-quality evidence exists to support specific intervention to address or prevent MVD. Glucose control is paramount, and recently, a study evaluating a healthy lifestyle consisting of nonsmoking, having a healthy body weight, vigorous exercise, high-quality diet, and moderate alcohol consumption was published.[148] After multivariable adjustment, a healthy lifestyle before and after the diagnosis of T2DM was associated with a lower risk of developing microvascular complications.

Key Consensus Points:

- Early and accurate diagnosis of PAD in patients with diabetic foot wounds is paramount, and revascularization should be considered in any DFU patient with PAD within the context of overall patient risk and goals of care.
- The presence of clinically defined MVD increases peripheral amputation risk independently of PAD, but limited high-quality evidence exists to support specific intervention to address or prevent MVD.

Diabetic limb salvage

In the United States, 2.4 to 4.5 million people suffer from chronic nontraumatic lower extremity wounds, costing our health system $31.7 billion annually.[149] The incidence of lower extremity wounds is rising due to an aging population and an increased prevalence of risk factors associated with atherosclerotic disease, including T2DM, smoking, and obesity.[150] Use of the WIfI classification system[63] described in previous sections is critical to assessing the severity and risk of infection from diabetic foot ulceration as a higher WIfI score is associated with increased risk of LEA.[56,63] If left untreated, these conditions can lead to a predictable pathway toward amputation, and the WIfI classification system can facilitate timely multidisciplinary clinical care including early patient education and use of orthotic devices to optimize off-loading and prevent deterioration and infection in the wound that would make amputation necessary. In this section, a multidisciplinary, function-based approach to limb salvage and amputations is highlighted.

Limb salvage versus amputation. A successful limb salvage procedure is defined by maximized anatomical limb preservation and the ability to remain ambulatory at a functional level. For patients with diabetic wounds of the lower extremity, limb salvage is generally preferable to amputation. However, regardless of whether a limb can be salvaged, the critical factor for long-term survival is the level of activity where ambulation equals more life years especially with the ability of independent function. If a patient with diabetes exercises three times a week, their chances of increasing their life years increases by 2.4 to 3.6 years and if they exercise daily, then their life years can increase by as much as 5 years.[151–153] The decision between limb salvage and major LEA (MLEA; *e.g.,* below-knee amputation (BKA), above-knee amputation (AKA)) hinges on various factors, including the patient's overall health, wound location and healing potential, and patient goals and preferences. If anatomical limb salvage does not lead to improvement in ambulation and level of activity, then a more functional amputation may be preferable if that will result in increased ambulation through the use of prosthetics. For less active patients who need to manage daily activities, foot level amputations such as Chopart's or Lisfranc's may suffice.[154] These procedures help prevent further soft tissue loss, preserve limb length, and minimize progression toward MLEAs.

However, if the foot cannot be functionally reconstructed to meet a patient's goals, a functional and carefully performed BKA is often recommended. BKAs are particularly suitable for active patients seeking high-functioning limbs, offering quicker recovery and effective functional rehabilitation. Generally, MLEAs are considered a last resort due to their association with depression, reduced quality of life, and high 5-year mortality.[155] BKA ambulation rates, ranging from 16% to 77%, highlight the importance of careful patient selection based on overall health, surgical technique, rehabilitation, and social support.[156]

MLEA 5-year mortality rates exceed 60%, with BKA mortality surpassing 68.0%, largely due to worsening comorbidities.[53] Diabetes independently increases 1- and 5-year mortality rates by up to 1.4 times. The pooled 5-year mortality rate for all cancers is 31%, similar to 30.5% for DFU alone. The 5-year mortality of minor and major amputations was 46.2% and 56.5%, respectively.[57] The highest mortality occurs in patients who are nonambulatory, have renal failure, and have had an AKA. Patients with AKAs are up to four times less

likely to regain ambulatory function compared with those with BKAs. This reduced likelihood of walking contributes to the higher mortality rates associated with AKAs.[157] There is a noted bias toward AKAs, despite a recommended BKA:AKA ratio of 2.5:1. This is likely skewed by wound healing complications associated with BKAs. About 90% of AKAs heal, compared with lower healing rates for BKAs, with 50% of unhealed BKAs eventually requiring AKAs.[158,159]

The 5-year mortality rates for BKA and AKA patients at one institution were noted to be 36.3% and 44.0%, respectively, the lowest reported in the literature.[160] This may be attributed to a multidisciplinary approach and careful patient selection aimed at maximizing postoperative ambulatory function, regardless of limb salvage or amputation. The ultimate goal is that ambulation and daily exercise can extend life by up to 5 years.[57] Consequently, a function-based approach is recommended that emphasizes ambulation as crucial to extending life years.

Function-based approach to BKAs. The amputee's ability to ambulate depends on the patient's comorbidities, baseline functional status, social support, and access to prosthetics, physical therapy, and other rehabilitation services. From the surgeon's perspective, efforts to provide a well-padded, pain-free stump in collaboration with prosthetists, physical therapists, and other rehabilitation providers are crucial to optimizing long-term outcomes. Recent studies have found that prosthetic fitting after amputation is associated with improved survival after 3 years[161] and that failure to achieve greater ambulation and mobility through successful prosthetic fitting in these patients is linked to reduced survival in a manner that is not explained by other patient characteristics and comorbidities.[162]

For BKAs, technical considerations include maintaining a minimum clearance of eight inches from the ground to fit a prosthesis and its artificial ankle, with ideal measurements ranging from 12 to 18 cm from the joint line depending on the patient's anatomy. A posterior flap design may be used, which requires an additional 8 to 10 cm of soft tissue distal to the bone cut for the posterior flap. In terms of blood supply, a patent popliteal and tibial peroneal trunk are preferred due to their association with higher healing rates and lower complication rates, although successful outcomes were found with a closed popliteal artery if the sural arteries remain open.[163] At one institution, it was found that 60% of those patients were ambulatory at 9.5 months, and the conversion rate of BKA to AKA was 4%.[163]

Pain is a major factor in limiting ambulation and the level of functional activity after amputation. Notably, residual limb pain after MLEA affects 50% to 80% of patients, with 20% to 50% requiring narcotics, and it has been noted that 14.6% of patients develop symptomatic neuroma, primarily affecting the superficial peroneal and saphenous nerves; however, diabetes and obesity were protective against symptomatic neuroma formation.[164] Preventing neuroma formation is a key strategy to avoid pain, and this has been facilitated by the development of targeted muscle reinnervation (TMR) where a cut sensory nerve such as the superficial peroneal nerve, posterior tibial nerve, or saphenous nerve is connected to a motor nerve branch entering a muscle so that the cut sensory nerve then grows down into the muscle itself and dissipates, preventing formation of a neuroma. This technique has shown a significant reduction in overall pain (41.5% vs. 67.2%; $p = 0.010$).[165]

In addition, myodesis where the peroneal, anterior, and deep posterior muscles are attached directly to the residual tibia can help prevent muscle wasting and atrophy. This surgical approach also helps mitigate the instability that can make it more difficult for the patient to wear a prosthesis and ultimately ambulate.[166] The posterior flap consisting of the superficial posterior compartment muscle and overlying skin is inset by tenodesing the soleus, gastrocnemius muscles, and Achilles tendon to the anterior tibia.[167] Furthermore, shortening the fibula, beveling the tibia, and getting rid of dogears along the incision prepare the limb for immediate postoperative prosthetic fitting. This requires a multidisciplinary collaboration among the surgeon, the prosthetist, and the physical therapist. In cases where infection is present, a two-stage procedure can be used with initial drainage and amputation followed by compression therapy of lymphedema to optimize the leg for amputation and minimize complications.[168]

For the athletic and other active patients with few comorbidities, the Ertl technique, which fuses the tibia and fibula distally using a free or vascularized bone graft to transfer torque directly to the artificial ankle when running, can be utilized to prevent the fibula from moving past the tibia.[167,169,170] It was found that patients who underwent this surgery began using prostheses sooner (2.5 vs. 3.5 months; $p = 0.008$) and began ambulating sooner (2.3 vs. 3.7 months; $p = 0.001$) than their non-Ertl counterparts, with no differences

in postoperative complication rates.[171] Furthermore, the use of the Ertl technique with TMR has been found to result in 92% rate of patients ambulating compared with just 71% in patients who had neither technique performed, with 70% of patients experiencing no pain.[171]

Optimizing the choice of limb salvage options is crucial to maximize the patient's chances of ambulation after amputation. Knowledge of the patient's preoperative medical and surgical status is a key component for success. In the context of the traditional paradigm of LEAs, advances in surgical technique, TMR, Ertl procedure, and prosthetics have evolved BKAs into a functionally well-regarded option. Collaborating with a true multidisciplinary team enables the provision of all necessary resources to heal the wound and prevent recurrence of the wound or a more proximal amputation, allowing a focus to be placed on achieving and optimizing function rather than simply anatomical limb salvage for the sake of limb salvage.

Key Consensus Point:

- Diabetic limb salvage should focus on achieving and optimizing function rather than optimizing tissue preservation, requiring a multidisciplinary approach and collaborative care with prosthetists and physical therapists.

Management of pain and wound dressings

The management of pain and wound dressings for diabetic wounds is similar to management in chronic wounds as described previously.[1] In diabetic wounds, most pain is chronic in nature, often related to neuropathy, which is a common morbidity of diabetes with about 75% of patients with diabetes having distal symmetric polyneuropathy of lower extremities.[172] About 10–20% of patients with diabetes will have peripheral neuropathy at the time of their initial diagnosis of diabetes, rising after 5 years to 26% and after 10 years to 41%. Lifetime prevalence of diabetic peripheral neuropathy (DPN) among patients with diabetes has been estimated to be approximately 50–65%.[172] Therapeutic strategies, both pharmacologic and nonpharmacologic, for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain and improve quality of life.[173] International guidelines recommend testing protective sensation in patients using various modalities, including monofilament sensory testing, vibration sensation, reflexes, pain perception, and review of neurological symptoms.[174] This is important for long-term survival of patients with diabetes as the loss of protective sensation is associated with an increase in the annual incidence of ulcer formation from under 1% to 7% and the presence of an ulcer is associated with an increase in the 3-year mortality rate of patients with diabetes from 13% to 28%.[174]

Pain associated with diabetic wounds is often underestimated and undertreated as there is a common belief that patients with DFUs do not experience pain because of DPN. In reality, studies have shown that 75% of patients with DFUs in fact do experience wound-related pain such as night pain and as a result of triggering stimuli, including walking, standing, and dressing changes.[175] Diabetic wound pain, however, can be difficult to assess and describe as its cause is due to a range of underlying comorbidities, including painful peripheral neuropathy, ischemia, inflammation, edema, and abnormal foot biomechanics such as Charcot-related deformities. No definitive diagnostic tool or clinical guidelines exist specifically to assess wound-related pain in lower limb wounds, which is a significant barrier to management. Sudden onset of wound pain may signal the onset of limb-threatening complications, including critical ischemia or deep infection.[175] Even in the absence of limb-threatening signs, pain associated with DFUs can have significant adverse effects on a patient's quality of life, including fear of amputation, anxiety, depression, decreased mobility, and sleep disturbances.[176] Therefore, early identification and prompt treatment are key to pain management.

A critical component in the care of diabetic foot and DFU is focused attention to foot and wound hygiene.[177] Fluorescence imaging has enabled clinicians to realize the extensive bacteria found in web spaces of the toes and macerated skin, with callus being an even greater harbinger of bacteria.[178]

Regardless of the specific wound dressing regimen used, optimal healing depends on achieving an appropriate moisture balance in the wound bed between desiccation and maceration (Fig. 5). The selection of the appropriate dressing for any wound is based on the comprehensive evaluation of the wound to include location, size and depth, exudate level, tissue types including structures, and presumption of the degree of bacterial load. In addition, the patient's ability to self-apply or access to assistance such as family or home care nursing must be considered as many are unable to reach their feet to adequately apply dressings.

Various dressings are accessible to manage wound moisture, with selection contingent upon the degree of wound exudate and the probability of wound healing.[92] These dressings encompass a

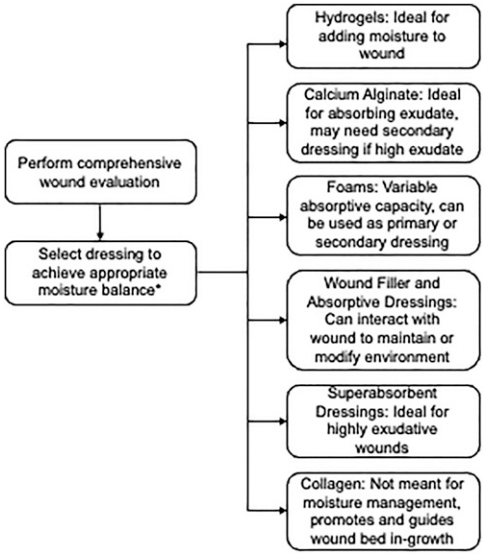

Figure 5. Selection of the appropriate dressing should be based on a comprehensive evaluation of the wound and achieve an appropriate moisture balance in the wound bed between desiccation and maceration. *Clinicians should modify dressing regimen based on other wound and patient factors, including degree of pain, bacterial load, and home support (see text).

spectrum from least to most absorbent. Some dressing categories are not recommended due to their lack of absorptive capacity (transparent film dressings) or high occlusive properties (hydrocolloid dressings) and should be used with caution.

Hydrogels: Water or glycerin-based gels that add moisture to the wound. These should be used only until the ulcer is rehydrated as the potential for maceration is high.

Calcium alginate or gelling fiber dressings: Available in sheets and packing ropes/ribbons, these dressings are ideal for absorbing exudate. The level and manner of absorption vary, reportedly gelling fibers are slightly more absorbent. These require a secondary dressing able to manage the exudate transferred through the primary dressing.

Foams: Absorbent primary or secondary dressings with great variability in capacity. Available with or without border, self-adhering or nonadhesive, acrylic or silicone adhesion, and various anatomical shapes.

Wound filler and absorptive dressings: Dressings with specific mechanisms of action that uniquely interact with the wound bed/wound fluid. Examples include cadexomer iodine, available in a gel or pad. As the cadexomer beads absorb wound fluid, 0.9% iodine is slowly released into the exudate to manage bacteria. Another example is a transforming powder dressing that begins as a powder when placed on the wound bed and upon hydration covers and protects the wound bed.

Superabsorbent dressings: Primary or secondary dressings with increased ability to absorb due to multiple layers structured to lift and move exudate, and absorbent fibers.

Collagen: A category of dressing that is not meant for moisture management, but rather to interact with the wound bed to reduce sequester MMPs, protect growth factors, and guide tissue ingrowth. They are an ideal dressing choice once a wound is clean, to improve wound healing and as a first step before application of human cells, tissues, and cellular- and tissue-based products also referred to as cellular, acellular, and matrix-like products.

All dressing categories are also available with differing degrees and types of antimicrobial agents such as silver, organic pigments, time released iodine, polyhexamethylene biguanide, honey, and copper. These dressings address the bacteria in the exudate without releasing the agent into the wound bed. In addition, there is a pathogen binding mesh coated with a fatty acid derivative, which is hydrophobic, causing bacteria to bind to the construct and are removed from the wound bed with dressing changes.

Large and/or heavily draining DFUs also respond favorably to the use of NPWT, negative pressure wound dressing systems that continuously or intermittently apply subatmospheric pressure *via* a contact layer (reticulating open cell foam) and sealed with an acrylic or hybrid acrylic and silicone drape and attached to a mechanical pump *via* a tube attachment. They are available as a rental durable medical equipment (DME) product, as well as single-use disposable devices, which are mechanically or battery powered and allow more freedom of movement.

Further comprehensive dressing information is readily available at woundsource.com

Key Consensus Points:

- Pain associated with diabetic wounds can be difficult to assess and is often underestimated and undertreated.
- Selection of the appropriate dressing should be based on a comprehensive evaluation of the wound and achieve an appropriate moisture balance in the wound bed between desiccation and maceration while accounting for other patient factors, which include degree of pain, bacterial load, and home support.
- The wound should be regularly monitored for changes in moisture level or other factors that may necessitate a change in dressing regimen to maintain an optimal healing trajectory.

Surgical and adjunct treatments

Biomechanical surgery. Surgical treatment includes wound bed preparation, direct closure methods including flaps or grafts, and biomechanical surgery. Biomechanical surgery takes into account the long-term functional durability of the diabetic foot and may be appropriate when other measures, including orthotic devices, are not effective. Altered biomechanics and foot deformity often precede the development or chronicity of a DFU.[179,180] Repetitive or acute trauma in an insensate or vascularly compromised foot leads to ulcer formation that can lead to infection and/or limb loss. The foot is a high-demand end organ specifically designed to be a mobile adaptor as well as a rigid construct depending on the phase of gait. The patient with diabetes is at high risk due to underlying changes in nerves, arteries, muscles, ligaments, tendon, and bone. The triad that leads to limb loss is peripheral neuropathy, peripheral vascular disease, and bone deformity in the environment of a compromised host. Thus, the surgical approach to DFU management must include a working knowledge of the implications of foot biomechanics.

Procedure selection is determined by the patient's functional capacity and the plane of deformity. The patient's functional capacity has a broad range and needs to be determined to meet the ambulatory demands of the patient. The activity level of a patient with diabetes may be limited to a wheelchair or working daily with frequent and prolonged standing or walking. In the case of a patient resigned to a wheelchair, typically the ulcer location may be where the foot platform of the wheelchair is in constant contact with the foot (*e.g.,* hindfoot). Whereas the ambulatory patient wound location is typically in the midfoot or forefoot. Surgery selection must take into account these factors. The plane of deformity (*i.e.,* sagittal, coronal, transverse) is identified though a biomechanical examination and weightbearing radiographs. The biomechanical examination includes identifying restricted range of motion of joints, which can cause uneven distribution of pressures experienced in the foot.[181,182] The weightbearing radiographs will identify abnormal bone relationships and articulations. The goal of biomechanical surgery is to better balance the foot on the weightbearing surface to redistribute pressure more evenly.

Biomechanical surgical correction of the diabetic foot begins with discriminating between soft tissue and bone limitations, or the combination of both. A tendon or capsule procedure cannot correct a deformity in which the bone or joint is impacted due to their immobility through processes such as end-stage osteoarthritis. If the major deforming force is tendon driven, then tendon release or lengthening is indicated. In patients with long-standing diabetes and poor blood glucose control, there is atrophy of the intrinsic muscles of the foot as well as structural changes to the tendon and capsules.[183,184] This tendon substance thickens and loses its elastic properties leading to joint contracture.[184] This translates to excess forces experienced in isolated areas of the plantar foot rather than being broadly distributed.[182,185]

Tendon procedures include flexor or extensor tenotomy, Achilles tendon lengthening (TAL), tendon transfer of the tibialis anterior or peroneal tendons. Bone reconstruction includes exostectomy (bony prominence removal), arthroplasty (joint resection) and arthrodesis/osteotomy (joint realignment and fusion). A few examples of bone reconstruction include hammertoe arthroplasty, hallux abductor valgus reduction, pes planus correction, and ankle fusion. These types of procedures include the use of internal or external hardware with sometimes prolonged recovery. An extreme example of a bone procedure is for diabetic Charcot neuropathy where there is significant bone destruction, which necessitates the use of multiple robust hardware constructs across multiple joints. Again, the goal for soft tissue and bone procedures is to redistribute pressure experienced on the plantar aspect of the foot. In general, soft tissue corrections are less complex surgeries with quicker recovery.

There is limited peer-reviewed evidence for biomechanical surgery of the diabetic foot. Largely the evidence is relegated to small case series representing a single surgeon or group experience. The most robust evidence for the success of a tendon procedure is for the TAL. Muller *et al*. published a prospective randomized clinical study comparing the TAL plus total contact versus a total contact alone for the treatment of recurrent diabetic forefoot ulcers.[182] They report a 38% recurrence rate at 2 years for the TAL group compared with an 81% recurrence rate for the other group. Andersen *et al*. in a multicenter, randomized controlled trial in diabetic digital preulcers and ulcers report 100% ulcer healing and higher ulcer prevention (1 vs. 7) in the group assigned to flexor tendon tenotomies.[186] A meta-analysis performed by Yammine *et al*. reports the results of metatarsal osteotomies for improving the off-loading of DFUs of 119 patients with a mean follow-up of 10.9 months.[187] This meta-analysis only included four studies with a reported healing rate of 98.7%. A systematic review conducted by Ha *et al*.

compiled studies of 1,089 patients with diabetic Charcot neuropathy reconstruction and report no benefit of one technique over another and also report a 36% complication rate and a 5.5% amputation rate.[188] As mentioned above, there is a lack of robust comparative studies examining the outcomes of biomechanical surgery; results are largely driven by surgeon experience.

Partial foot amputation is a viable surgical treatment option. Again, the goal for diabetic foot surgery is to preserve a functional and durable foot. A properly performed partial foot amputation may be the best option in the right patient. Amputation-level selection is often guided by the extent of soft tissue and bone loss due to infection or ischemia. However, the surgeon must also consider the biomechanical implications of the amputation level selected. As the amputation level progresses proximally (toe, ray, tarsometatarsal, midfoot, hindfoot), the lever arm of the foot reduces. Furthermore, the extensor mechanism responsible for dorsiflexion is lost, thereby increasing flexor dominance. The propulsive ability decreases with more proximal foot amputations. There may also be greater plantar pressures experienced at the distal plantar stump potentially leading to reulceration and reamputation. This initiates the cascade of repeat surgery with more of the foot requiring amputation. Isolated digital or ray amputations have repercussion as this leads to redistribution of pressure to other plantar foot locations, which again will make these areas prone to ulceration and reamputation of 34% (digital) and 10% for ray amputations.[52] After a trans-metatarsal amputation, the reamputation rate is reported to be approximately 30%.[189] The goal of partial foot amputation is to maintain balance to the pressures experienced to the plantar aspect of the remaining foot.

The surgical approach to the DFU includes a thoughtful approach to the biomechanical implications. Closure or coverage of the DFU is not enough. Alterations in the underlying biomechanics of the diabetic foot must be addressed for long-term success. Unlike follow-up of other type of surgical procedures, long-term vigilance and close monitoring are absolutely necessary. This includes the use and exchange of appropriate shoes, orthotics, braces, and prosthetics as well as close collaboration with a multidisciplinary team including physical therapists to optimize long-term functional outcomes.

Wound bed preparation. Wound bed preparation is a fundamental principle to advance wound closure or coverage.[190,191] This includes optimizing the macroenvironment by enhancing host factors such as tightening glucose control and optimizing nutritional support.[192,193] Furthermore, more local factors such as maximizing perfusion through vascular interventions to the targeted angiosome where the wound is located are preferred.[194] Other local factors include eliminating infection and decreasing colonized bacterial load in the wound through appropriate and adequate wound hygiene and topical antimicrobials. Periwound tissue stabilization, as well as joint immobilization, is also important through compression wraps, splinting, casting, orthotics, and other off-loading devices, and fixation using internal and external hardware.

Proper wound bed preparation involves the removal of all nonviable tissue, including necrotic, fibrotic, liquified, and indurated tissue. After sufficient wound bed preparation is performed, the remaining tissue should be bleeding, pliable, and without malodor.[190] The wound perimeter should also be excised because bacteria can harbor in these areas, and in chronic DFUs, the wound edge is often rolled (epibole), or callused, which inhibits epithelization across the wound surface if secondary healing is the goal.[195]

The surgical approach to wound bed preparation includes the use of sharp instrumentation, including scalpel, scissors, rongeur, curette, and/or hydro-surgical scalpel. Surgical-based excisional debridement is different from nonoperating room-based sharp debridement. In the operating room setting, the surgeon can be more precise, more aggressive with the ability to control pain through anesthesia, and control bleeding through multiple methods. Furthermore, particularly in DFUs, there is always a concern for bacteria. DFUs contain not only planktonic bacteria but also biofilm.[196] Thus, full surgical excision of the wound is necessary with the use of adjuncts such as antiseptics and preservatives. The mechanisms of action of antiseptics and preservatives are different than the mechanism of action of antibiotics, and thus can impact biofilm.[197] There are multiple methods of delivering antiseptics and preservatives to the wound bed, including wet-moist dressing changes in preparation for wound closure or coverage, as an irrigation solution during the operation, or as the instillation solution used in conjunction with NPWT with instillation (NPWTi).

Serial or staged excisional debridement may be necessary. This allows for demarcation of infection and nonviable tissue as well as an opportunity to optimize the blood flow and the patient. A patient with a DFU frequently presents with a deep-seated abscess. Thus, the goal of the initial excisional

debridement decompresses the infection and reduces the overall bacterial bioburden before definitive closure or coverage.[52,198] The use of NPWT can be an effective method to bridge between operations. The goal of NPWT is to remove exudate, promote granulation tissue, increase local perfusion, and to decrease bacterial contamination.[199,200] Armstrong *et al*. report that in a prospective, multicenter, randomized clinical trial, the use of NPWT in patients hospitalized for a diabetic partial foot amputation results in higher rates of complete healing.[201] NPWTi is a modification of traditional NPWT, which has been reported to be superior in the acute-care setting. NPWTi combines the benefits of traditional NPWT with continuous dwelling of topical solution. A meta-analysis performed by Gabriel *et al*. report that NPWTi results in a decreased number of operations, faster time to closure or coverage, decreased bacterial counts, and overall decreased length of therapy compared with other wound care modalities, including traditional NPWT.[202] Further modifications of NPWTi include a large perforated foam design, which has been reported to detach nonviable tissue on the wound surface, essentially hydromechanically debriding the surface of the wound.[203] This innovation can potentially expedite wound bed preparedness for wound closure or coverage.

Wound bed preparation precedes any next step in wound management, whether the goal is wound closure, coverage, or secondary healing. There are clear benefits to surgical excisional debridement. However, factors including surgeon or operating room availability as well as the patient's medical stability and consent may limit this approach. Furthermore, while surgical treatment for DFU is well accepted, the literature supporting common clinical care is not at the highest levels of evidence. Reasons for this are complex and include the difficulty in blinding surgical procedures. In randomized clinical studies, provider and patient bias toward active treatment arms can be substantial. Nevertheless, the best evidence we have is based on randomized controlled clinical trials and meta-analysis and what follows is a review of the current high-level evidence for each of these surgical interventions.

Free tissue transfer. Free tissue transfer (FTT) takes a segment of tissue along with its blood supply and moves this to a debrided ulcer site. In addition to suturing the tissue in place, microvascular anastomosis is a technique used with at least an artery and a vein. Sometimes structures such as a sensory nerve are included. These are highly technical procedures in patients who have substantial comorbid disease. These operations can take several hours to perform and can have a 5% to 10% total failure rate in lower extremity wound cases. As such, these are most often performed in specialized centers with the surgical expertise and the postoperative ability to closely monitor these flaps. Bhat *et al*. recently performed a meta-analysis which suggests that for carefully selected cases, this technique can be valuable, albeit with a substantial risk profile.[204] Kim *et al*.[205] recently performed a registry study of 21 free flaps that were compared with patients treated with a skin substitute product, NPWT, or local flaps. They found comparable outcomes using all of these methods, but presumably the FTT patients had more severe disease.[205] In conclusion, FTT appears to be a reasonable option in a specialized center, although the level of evidence to support this is low.

Local flaps and skin grafts. Local flaps and skin grafts are less technically demanding than FTT but are generally used in smaller areas. In DFU, the clinician needs to make sure there is adequate perfusion to the flap in the setting of a high percentage of patients with vascular disease. Although the amount of tissue available to use as a flap in the foot and ankle is limited, when these are used in conjunction with a skin graft, critical structures such as bone, joint, tendon, and large neurovascular pedicles are optimally closed with a local flap, while the rest of the wound can be treated with a skin graft. This is nicely reviewed by Clemens *et al*.[206] Santema *et al*.[207] performed a 2016 Cochrane review on skin grafting and tissue replacements for the treatment of DFU. They found that these treatments slightly lowered the chance of amputation compared with the SOC. The data available were insufficient to draw conclusions of the effectiveness of different types of skin grafts or tissue replacement therapies.[207]

Products to treat DFUs. There are a large number of skin substitutes available in the market today for clinicians to use. Because many of these require little clinical data before going to market, the number of studies justifying their effectiveness is small. In most cases, the best studies available compare a specific construct to the SOC, which is most often some sort of moist wound healing dressing along with off-loading of the foot. What follows is a review of the highest level of studies for skin substitutes available in the literature, which has also been reviewed by the Centers for Medicare and Medicaid Services.[208]

Placental constructs. Mohammed *et al*.[209] performed a systematic review and meta-analysis for patients with DFUs treated with dehydrated human amnion and chorion allograft (DHACA) compared with SOC. They pooled 11 randomized clinical trials of 655 patients with DFUs, where 328 patients were treated with DHACA and compared this with 327 patients treated with SOC alone. They concluded that DHACA, in addition to SOC enhanced wound healing, reduced the mean time to heal, and diminished adverse events.

Skin substitutes. Santema *et al*. performed a 2016 systematic review and meta-analysis of a variety of skin substitutes, where they looked at 17 trials with 1,655 randomized patients.[207] One of the small trials included an amniotic product, but there were a wide variety of other products, including processed allogeneic and xenogeneic scaffolds and bioengineered skin substitutes. They concluded that in addition to SOC, skin substitutes increase the likelihood of achieving complete wound closure compared with SOC alone. The noted a lack of long-term and cost-effectiveness data. Tchero *et al*. performed a systematic review and network meta-analysis of five regeneration matrices (Integra, Nevelia, Matriderm, Pelnac, and Renoskin), where they looked at 13 studies.[210] They concluded that these products have low failure rates and low ulcer recurrence rates. They called for more studies looking at safety, efficacy, and failure rates.

Regulatory review and studies needed to justify reimbursement. Many advanced products that are novel require complex approval processes from the Food and Drug Administration (FDA), including class 3 medical devices, drug approval, or biological approval. These studies generally require large relatively homogeneous patient populations with carefully designed inclusion and exclusion criteria. Because of the expense of these products, there often is a run-in period where the control dressing is used for some time to make sure that the wound neither greatly expands nor quickly heals. Studies tend to last 6 to 12 weeks and complete healing is very often the primary outcome.

Studies for reimbursement, generally require fewer patients, but need to be done in a comparative manner. To avoid the complex FDA approval studies, many have focused on simpler mechanisms to clear the FDA, including the 510(k) process for medical devices (substantially similar to a predicate product) and 21 CFR 1271 for tissues and biologics. An orphan drug status is a simplified application for drug approval. The 510(k) process and 21 CFR 1271 are much simpler than a typical approval process as little clinical data need to be applied. Clinical data are often required for insurance approval, but this can often be done with a simpler study. As a result, most new products used in wound healing today go through the 510(k) or 21 CFR 1271 process.

DFUs are complex with a heterogenicity of wound sizes, locations, and patient comorbidities. Both surgical technologies and new products to treat these wounds bring new hope to these patients and in a large range of studies have good healing rates that presumably reduce amputations. Because of the heterogenicity of the ulcers and patients involved, doing good studies is challenging. Randomized controlled trials have been regarded as the best method to study these patients, but give only a limited view on how an actual patient is treated in our medical systems. These trials typically have a complex set of inclusion and exclusion criteria and only a fraction of patients with DFUs are included in a trial. Some have advocated for registry studies to further elucidate the effectiveness of these products and surgical techniques. Comparative effectiveness studies would be very helpful but would require large numbers of patients. Because of the expense of these studies, most are funded by industry, and they are often designed to show the safety and efficacy of a specific product. Independent funding and asking more hypothesis-based questions could potentially help move new therapies forward.

Emerging treatments and hyperbaric oxygen therapy. The roles of emerging modalities including adipose-derived stem cells (ASCs) in the treatment of diabetic wounds are still being investigated and currently not approved or recommended for general use in the management of diabetic wounds. Clinical data for the use of ASCs in DFUs have been limited to a handful of studies done outside of the United States.[211–215] A pilot study performed in 2010 in South Korea[211] relied on topical application as did a more recent study from Poland,[212] while other recent studies in Nicaragua, Turkey, and Italy used injections of ASCs directly into the wound bed.[213–215] While these studies had variability in patient selection, cell dose, and the methods by which ASCs were isolated and applied, they generally document the safety of the technique and provide data suggesting that healing rates can be improved using ASCs compared with the current SOC. Other modalities being investigated for use to treat diabetic wounds include miR146a, a regulatory microRNA that targets upstream regulators of inflammatory and oxidative stress pathways, which has been found to be suppressed in

diabetic mouse wounds.[216,217] A form conjugated to cerium oxide nanoparticles is currently under development with clinical studies in humans planned.[218,219]

TOT has been used to enhance the healing of DFUs as an adjunct therapy following treatment with hyperbaric oxygen. Recent evidence for the use of TOT in the treatment of DFUs was reviewed in a meta-analysis by Carter *et al*.[220] Their systematic review identified four randomized controlled trials published from 2017 through 2021.[221–224] The authors concluded that these studies provided a moderate level of evidence to support the use of TOT to treat noninfected, nonischemic DFUs of at least 4-week duration that have not adequately responded to SOC measures such as optimal off-loading and wound care. Further studies are needed to clarify the indications for its use and efficacy in other wound types.

The use of hyperbaric oxygen therapy (HBOT) for the treatment of chronic wounds was recently reviewed by a previous consensus panel.[1] As noted by the consensus panel with regard to diabetic wounds:

"In a meta-analysis of the relevant literature, two separate Cochrane reviews conducted 10 years apart came to significantly different conclusions regarding the usefulness of HBOT in DFUs. The 2004 meta-analysis concluded that HBOT decreased the incidence of major amputations and improved healing at 1 year.[225] However, an updated 2015 metanalysis contradicted this conclusion and found that HBOT improved healing in the short term (6 weeks), but not at 1 year.[226] Since this last Cochrane review, numerous new studies have been conducted, including both randomized controlled studies and newer 'big data' studies based on large data bases derived from the electronic medical record. These newer techniques again yielded conflicting results with one study showing no impact on amputation outcomes[227] while a later study on the same data base demonstrated efficacy in a subset of more severe DFUs (Wagner 3 and 4) in terms of wound closure.[228,229] Clearly, how the analysis is performed and how the questions are asked can skew results in different directions. Unfortunately, since none of these studies is perfect or definitive, this allows the controversy to continue ad infinitum. However, when considering the totality of the existing data, among the potential indications for HBOT in the field of chronic wounds, the strongest evidence exists for ischemic, infected DFUs, that is, Wagner Grade 3 or worse.[230]"

Key Consensus Points:

- Surgical treatment includes a thoughtful approach to the biomechanical implications where closure or coverage of the DFU is not enough. The alterations in the underlying biomechanics of the diabetic foot must be addressed for long-term success where long-term vigilance and close monitoring are absolutely necessary. This includes the use and exchange of appropriate shoes, orthotics, braces, and prosthetics, as well as close collaboration with a multidisciplinary team.
- Emerging treatments offer hope and promise, but the heterogenicity of diabetic wounds poses a challenge to performing good studies, which will be necessary to advance new treatments for diabetic wounds.

Executive summary

Diabetic wounds constitute a major problem. Many of these ulcers will eventually lead to amputation and increased risk of mortality. The multidisciplinary approach to successfully managing diabetic wounds encompasses comprehensive assessment, timely intervention, and collaborative care. Wound clinicians need to be in contact and work in collaboration with providers having the appropriate expertise to effectively manage key aspects of care that will directly impact successful healing, including off-loading and physical therapy as well as nutrition and glucose control. Treatment strategies also include prompt optimal care of the wound and the extremity once they occur as well as ensuring associated conditions such as peripheral vascular disease and limb ischemia are identified and addressed. Achieving and optimizing function should be the focus of diabetic limb salvage rather than maximizing tissue preservation. Patient education and shared decision-making to ensure patients are able to understand and comply with recommended treatments are also key to optimizing outcomes for patients with diabetic wounds.

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TAKE-HOME MESSAGES

- Nonhealing diabetic wounds are associated with chronic low-grade inflammation that can hinder overall progressive healing.
- CGM and other new tools have facilitated better diabetes management, and the wound clinician should be in contact with the patient's PCP or endocrinologist to discuss a plan that includes these new tools in addition to traditional strategies optimizing nutrition and exercise.
- The presence of a foot ulcer is a prominent contributor to risk of LEA and increases the mortality risk for patients with diabetes by more than twofold.
- The use of orthotic devices to optimize off-loading and neuropathy screening is essential in patients with diabetes to minimize wound development and deterioration and risk of further complications.
- Resistance to antibiotics is widespread and evolving in diabetic wounds and associated infections.
- Successful treatment strategies for diabetic infections include meticulous wound cleansing with removal of biofilm and management of blood glucose levels as well as assessment and treatment for limb ischemia.
- Early and accurate diagnosis of PAD in patients with diabetic foot wounds is paramount, and revascularization should be considered in any DFU patient with PAD within the context of overall patient risk and goals of care.
- The presence of clinically defined MVD increases peripheral amputation risk independently of PAD, but limited high-quality evidence exists to support specific intervention to address or prevent MVD.
- Diabetic limb salvage should focus on achieving and optimizing function rather than optimizing tissue preservation, which requires a multidisciplinary approach and collaborative care with prosthetists and physical therapists.
- Pain associated with diabetic wounds can be difficult to assess and is often underestimated and undertreated.
- Selection of the appropriate dressing should be based on a comprehensive evaluation of the wound and achieve an appropriate moisture balance in the wound bed between desiccation and maceration while accounting for other factors, which include degree of pain, bacterial load, and home support.
- The wound should be regularly monitored for changes in moisture level or other factors that may necessitate a change in dressing regimen to maintain an optimal healing trajectory.
- Surgical treatment includes a thoughtful approach to the biomechanical implications where closure or coverage of the DFU is not enough. The alterations in the underlying biomechanics of the diabetic foot must be addressed for long-term success where long-term vigilance and close monitoring are absolutely necessary. This includes the use and exchange of appropriate shoes, orthotics, braces, and prosthetics as well as close collaboration with a multidisciplinary team.
- Emerging treatments offer hope and promise, but the heterogenicity of diabetic wounds poses a challenge to performing good studies, which will be necessary to advance new treatments for diabetic wounds.

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Abbreviations and Acronyms

ABI = ankle brachial index
AGE = advanced glycation end-product
AKA = above-knee amputation
ASC = adipose-derived stem cell
BKA = below-knee amputation
CDC = Centers for Disease Control and Prevention
CGM = continuous glucose monitoring
CLTI = chronic limb-threatening ischemia
CVD = cardiovascular disease
DFU = diabetic foot ulcer
DHACA = dehydrated human amnion and chorion allograft
DPN = diabetic peripheral neuropathy
ECM = extracellular matrix
EPM = exo-polymeric matrix
FDA = Food and Drug Administration
FTT = free tissue transfer
GLASS = Global Limb Anatomic Staging System
GLP-1RA = glucagon like-peptide-1 receptor agonist
GVG = Global Vascular Guidelines
HbA1c = hemoglobin A1C
HBOT = hyperbaric oxygen therapy
IL-1β = interleukin-1 beta
IL-6 = interleukin-6
IL-8 = interleukin-8
LEA = lower extremity amputation
MAC = medial artery calcification
MLEA = major lower extremity amputation
MMP = matrix metalloproteinase
MMP-1 = matrix metalloproteinase-1
MMP-3 = matrix metalloproteinase-3
MVD = microvascular disease
NPWT = negative pressure wound therapy
NPWTi = negative pressure wound therapy with instillation
PAD = peripheral artery disease
PBMCs = peripheral blood monocyte cells
PCP = primary care physician
PLAN = Patient risk, Limb threat, Anatomic disease pattern
RNA = ribonucleic acid
ROS = reactive oxygen species
SGLT-2 = sodium–glucose cotransporter-2
SOC = standard of care
T1DM = type 1 diabetes mellitus
T2DM = type 2 diabetes mellitus
TAL = Achilles tendon lengthening
TBI = toe brachial index