Diagnosis and Management of Diabetic Foot Complications

2018

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This publication has been supported by unrestricted educational grants to the American Diabetes Association from Healogics, Inc., and Organogenesis, Inc.

"Diagnosis and Management of Diabetic Foot Complications" is published by the American Diabetes Association, 2451 Crystal Drive, Arlington, VA 22202. Contact: 1-800-DIABETES, professional.diabetes.org.

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Diagnosis and Management of Diabetic Foot Complications

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ABSTRACT | At least half of all amputations occur in people with diabetes, most commonly because of an infected diabetic foot ulcer. A thorough understanding of the causes and management of diabetic foot ulceration is essential to reducing lower-extremity amputation risk. This compendium elucidates the pathways leading to foot ulcers and enumerates multiple contributory risk factors. The authors emphasize the importance of appropriate screening and wound classification and explain when patients should be referred for specialist care, targeted education, or therapeutic shoes or insoles. They provide a comprehensive review of treatment approaches, including devices for foot lesion off-loading and aggressive wound debridement through mechanical, enzymatic, autolytic, biologic, and surgical means. Because infection and peripheral artery disease are key contributors to amputation risk, the authors discuss the diagnosis and management of these conditions in detail. They also review the expanding armamentarium of evidence-based adjunctive treatments for foot ulcers, including growth factors, skin substitutes, stem cells, and other biologics. Because Charcot neuroarthropathy is a serious but frequently missed condition in people with diabetic neuropathy, the authors explain the differential diagnosis of the hot, swollen foot that is a hallmark of this condition. The article ends with an overview of four strategies for maintaining a foot in remission, followed by a brief look at the future of diabetic foot care.

Foot problems in diabetes are common and costly, and people with diabetes make up about half of all hospital admissions for amputations. In the United Kingdom, people with diabetes account for more than 40% of hospitalizations for major amputations and 73% of emergency room admissions for minor amputations. Because most amputations in diabetes are preceded by foot ulceration, a thorough understanding of the causes and management of ulceration is essential.

The annual incidence of foot ulcers in diabetes is approximately 2% in most Western countries, although higher rates have been reported in certain populations with diabetes, including Medicare beneficiaries (6%) and U.S. veterans (5%) (1). Although the lifetime risk of foot ulcers until recently was generally believed to be 15–25%, recent data suggest that the figure may be as high as 34% (1). It was the famous diabetes physician Elliott P. Joslin who, having observed many clinical

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cases of diabetic foot disease, remarked that "diabetic gangrene is not heaven-sent, but earth-born." Thus, foot ulceration is not an inevitable consequence of having diabetes; rather, ulcers develop as a consequence of an interaction between specific lower-limb pathologies and environmental hazards.

This treatise will therefore focus on the pathways that result in foot ulcer development, the importance of regular screening to identify members of the at-risk population, and multiple aspects of novel treatment approaches. Care of the foot in diabetes often falls between specialties, and a team approach is required. Thus, we have assembled a team of experts in the care of diabetes-related foot conditions from a variety of specialties, including endocrinology; dermatology and wound healing; infectious diseases; and podiatric, plastic, and vascular surgery.

The Scottish poet Thomas Campbell wrote, "Coming events cast their shadows before." Although he was not referring to foot ulcers at the time, these words can usefully be applied to the breakdown of the diabetic foot. Ulcers do not occur spontaneously, but rather as a consequence of a combination of factors. These contributory factors are summarized in the next section. This is followed by a discussion of foot screening to identify individuals who are at risk of ulceration. We then describe the importance of wound classification systems and answer the questions of when and where to refer diabetic foot problems.

It is often stated that what you take off a foot ulcer is as important as what is placed on the wound. Therefore, we also include discussions of various methods for off-loading foot lesions and the importance of aggressive wound debridement. Because the combination of infection, foot ulceration, and peripheral artery disease (PAD) often results in amputation, additional sections cover these pivotal areas of management.

The number of available topical treatments for foot ulcers has rapidly increased in recent years. We explore these options in detail, including growth factors, skin substitutes, stem cells, and other biologics.

No treatise on the diabetic foot would be complete without mention of Charcot neuroarthropathy, so our next section is devoted to the differential diagnosis of the hot, swollen foot in diabetes.

It is increasingly recognized that foot ulcer recurrence is common, occurring in up to 50% of cases, and using the term "in remission" has been deemed more appropriate than describing an ulcer as "healed." Thus, in our penultimate section, we describe methods to maintain a foot in

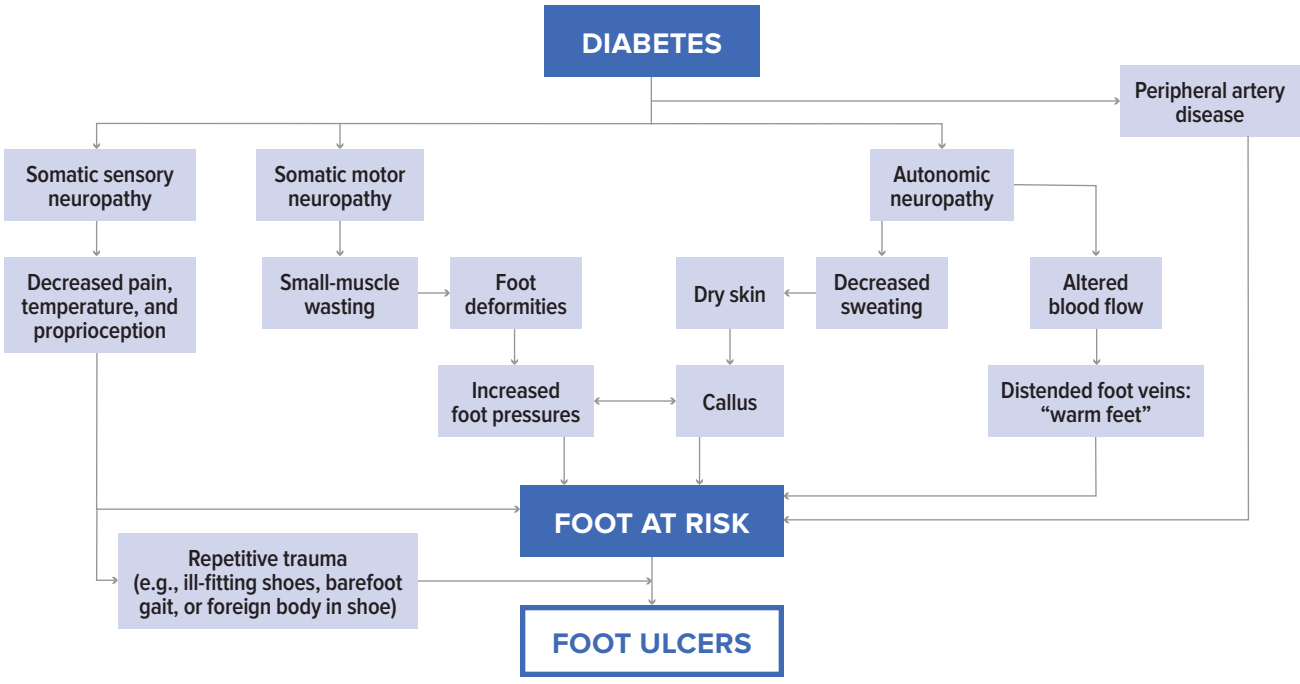


FIGURE 1 Pathways to diabetic foot ulceration.

remission. A brief look into potential future developments in the care of the foot in diabetes brings the monograph to a close.

We hope this succinct monograph will aid health care providers in their efforts to prevent, diagnose, and manage diabetic foot problems.

Pathways to Diabetic Foot Complications

Although evidence is weak that foot care education reduces the risk of first ulceration (2), a thorough understanding of the etiopathogenesis of ulceration is essential if we are to succeed in reducing the incidence of foot lesions and ultimately amputations. The pathways to foot ulceration are summarized in Figure 1, with key contributory factors also listed below.

- **Distal sensorimotor peripheral neuropathy.** This condition is common in diabetes, affecting up to 50% of older people with type 2 diabetes. Small-fiber nerve dysfunction results in loss of pain and temperature perception; patients literally lose the "gift of pain" that normally protects us from tissue damage. Large-fiber dysfunction results in unsteadiness, increasing the risk of trips and falls; recurrent unnoticed minor injuries might increase the risk of Charcot neuroarthropathy. Motor neuropathy contributes to small-muscle wasting and a potential imbalance of flexor and extensor function in the foot.
- **Autonomic neuropathy.** Peripheral sympathetic dysfunction results in decreased sweating (i.e., dry foot skin, increasing the risk of callus formation) and, in the absence of PAD, warm feet due to the release of vasoconstriction. Plantar callus in the neuropathic foot is associated with a marked increase in ulcer risk.
- **PAD.** A major risk factor for foot lesions in diabetes, PAD is discussed in detail beginning on p. 11. Neuropathy and PAD often co-exist and may lead to neuroischemic ulceration.
- **Deformity.** Any deformity occurring in a foot with other risk factors increases ulcer risk. Clawing of the toes is common, leading to increased metatarsal head pressures that, in neuropathic patients, may result in breakdown due to repetitive moderate stress to an insensate area. Other examples include Charcot deformities and hallux valgus.
- **Age, sex, and duration of diabetes.** The risk of ulcers and amputations increases two- to fourfold with both age and duration of disease. In Western countries, male sex is associated with a 1.6-fold increase in foot ulcer risk (3).
- **Ethnicity.** In the United States, ulceration is more common among Hispanics, Native Americans, and individuals of African-Caribbean descent.
- **Repetitive minor trauma.** Such trauma can occur as a consequence of high pressures under a neuropathic foot or from an ill-fitting shoe or a foreign body inside a shoe.
- **Past foot ulceration or amputation**. Both are major risk factors. The annual incidence of ulceration may be as high as 30–50% in people with a history of foot ulcers (1).
- **Other microvascular complications.** Several other conditions are known to be associated with an increased risk of foot ulceration. Visual impairment as a result of retinopathy is an established risk factor for foot lesions. Perhaps the most high-risk group for ulceration is the dialysis population. It can be safely presumed that patients at all stages of nephropathy have increased risk of ulceration. Dialysis treatment is an independent risk factor for foot ulceration.
- **Transplantation.** People with diabetes remain at high risk of foot lesions even after successful kidney, pancreas, or combined pancreas-kidney transplantation.

PATHWAY TO ULCERATION

The combination of two or more of the above risk factors commonly results in ulceration. (See Figure 1.) Examples include:

- **Neuropathy, deformity, and trauma.** Inappropriate footwear is the most common cause of trauma in Western countries.
- **Neuropathy plus chemical trauma.** Inappropriate use of over-the-counter corn treatments on a neuropathic foot can lead to ulceration.

Understanding the many risk factors that increase the chance of foot lesions developing will help to prevent many episodes of foot ulceration if the screening process outlined in the next section is followed. Further details on the pathways to ulceration, together with supporting references, are provided in a forthcoming publication on this topic (4).

TABLE 1 Modified ADA Diabetic Foot Risk Classification

Priority	Indications	Timeline	Suggested Follow-up
URGENT (active pathology)	▸ Open wound or ulcerative area, with or without signs of infection ▸ New neuropathic pain or pain at rest ▸ Signs of active Charcot deformity (red, hot, swollen midfoot or ankle) ▸ Vascular compromise (sudden absent DP/PT pulses or gangrene)	Immediate referral/ consultation	As determined by specialist
HIGH (ADA risk category 3: the diabetic foot in remission)	▸ Presence of diabetes with a previous history of ulcer or lower-extremity amputation ▸ Chronic venous insufficiency (skin color change or temperature difference)	Immediate or "next available" outpatient referral	Every 1–2 months
MODERATE (ADA risk category 2)	▸ PAD ± LOPS ▸ DP/PT pulses diminished ▸ Presence of swelling or edema	Referral within 1–3 weeks (if not already receiving regular care)	Every 2–3 months
LOW (ADA risk category 1)	▸ LOPS ± longstanding, nonchanging deformity ▸ Patient requires prescriptive or accommodative footwear	Referral within 1 month	Every 4–6 months
VERY LOW (ADA risk category 0)	▸ No LOPS or PAD ▸ Patient seeks education on topics such as routine foot care, athletic training, appropriate footwear, or injury prevention	Referral within 1–3 months	At least annually for all people with diabetes

DP, dorsalis pedis; LOPS, loss of protective sensation; PT, posterior tibial. Modified from Diabetes Care 2008;31:1679–1685 (ref. 6), with permission from the American Diabetes Association, ©2008.

Screening for Foot Complications Risk

It is important to assess the neurological, vascular, dermatological, and musculoskeletal status of people with diabetes at least annually. The American Diabetes Association (ADA) developed a Comprehensive Foot Examination and Risk Assessment that can be performed rapidly with minimal equipment (5,6).

After assessment of the foot, Table 1 outlines suggested indications, priorities, and timelines for referral based on ADA guidelines (6). The table shows ADA patient risk categories (i.e., very low, low, moderate, and high risk) and follow-up recommendations.

Patients who present with tissue loss are assigned to a higher risk category. In such cases, the overall degree of limb threat should be assessed.

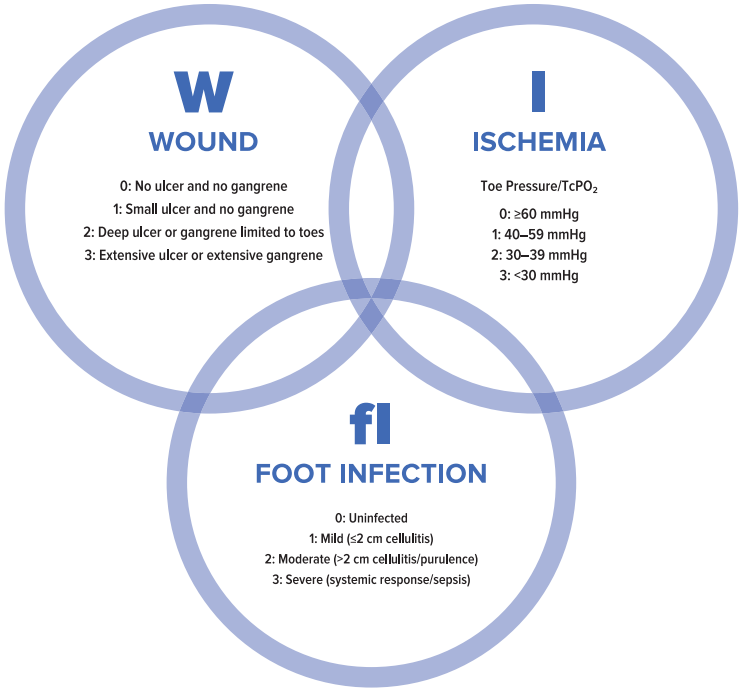
The three key factors associated with limb loss include degree of tissue loss (wound severity), severity of ischemia, and severity of foot infection. The acronym WIfI can be used as short-hand for these factors, which can assist the health care team in describing patients' overall limb threat status (Figure 2) (7,8). Using the Society for Vascular Surgery (SVS) Threatened Limb Classification System (7), patients' wounds, ischemia, and foot infections are graded on a numerical scale from 0 (none) to 3 (severe), and these grades are then translated into an overall "WIfI score" (discussed in more detail in the section on Recognizing and Treating PAD on p. 11).

When and Where to Refer Diabetic Foot Problems

Appropriate patient referral is predicated on a complete history and foot examination. Patients with diabetic foot complications should be referred for preventive services and when acute pathology is identified.

The risk categories shown in Table 1 were adapted from the four-tiered diabetic foot risk classification system recommended by the International Working Group on the Diabetic Foot (9). Patients at the highest risk for ulceration are those who have a history of ulceration, amputation, peripheral vascular surgery, or Charcot neuroarthropathy. These patients are easy to identify from

FIGURE 2 SVS WIfI classification system. $TcPO_2$, transcutaneous oxygen pressure.



history alone and have a very high rate of developing ulceration (9). Of patients who have had an ulcer, 58–83% will develop another ulcer within 1 year if no preventive services are provided (10,11). When therapeutic shoes and insoles are provided, the incidence of ulcer recurrence decreases by 50% to 30–50% annually (1,9).

The next risk tier includes patients with sensory neuropathy and foot deformity or PAD. Evaluation of these patients requires simple sensory testing with a 128-Hz tuning fork or a 10-g Semmes-Weinstein monofilament and clinical assessment of limited joint mobility, hammertoes, hallux valgus, and peripheral perfusion.

High-risk patients need referrals for diabetes education, therapeutic shoes and insoles, and regular foot evaluation and care. Unfortunately, only a small minority of patients receive preventive services (12,13).

For patients with a previous foot complication, diabetes care providers should find an educator who has a strong understanding of and education program specifically focused on diabetic foot complications. Patients need in-depth education about sensory neuropathy, the etiology of ulcers and infections, warning signs, and preventive measures. Providing a "tear sheet" with a vague list of things to do and things to avoid without explaining the rationale behind such recommendations is probably not especially helpful to high-risk patients.

Therapeutic shoes and insoles are mainstays of preventing recurrent diabetic foot ulcers (DFUs). Providers should partner with a podiatrist in their community who is interested in diabetic foot complications. A podiatrist can help evaluate and monitor high-risk patients. They can evaluate patients' biomechanics, structural foot deformities, joint range of motion, sensory neuropathy, and peripheral perfusion and provide a prescription for specific elements of custom insoles and shoes. The prescription will then be sent to a pedorthist or orthotist, who will fabricate the custom insoles and fit the shoes appropriately.

Shoes and insoles should be replaced on a regular basis, so evaluation of shoes, insoles, and the feet of high-risk patients should be a routine part of clinic examinations. Patients with foot ulcers, puncture wounds, ingrown toenails, or infections need prompt referral to a local podiatrist who is experienced in diabetic foot complications or a wound care center with expertise in DFUs.

These patients generally require imaging to evaluate bone infection and vascular testing to determine whether there is adequate perfusion to heal a foot wound. Patients with signs of ischemia or gangrene should be referred to a vascular surgeon, interventional cardiologist, or interventional radiologist for evaluation and treatment. These patients will need arterial Doppler studies and, if these are abnormal, angiography and possibly vascular intervention.

Off-Loading the Diabetic Foot Wound

Off-loading refers to the use of devices or surgeries that remove pressure or reduce the "load" at the site of ulceration to improve healing. DFUs often occur on the sole of the foot at sites of repetitive injury that are unrecognized by patients with diabetic sensory neuropathy. The ulcers are usually at a pressure point on the bottom of the foot where a callus

has formed. If a neuropathic patient continues to walk on an ulcer, every step "crushes" new tissue that is attempting to organize and fill the soft-tissue void. People without sensory neuropathy find it painful to walk on an open wound and will instinctively avoid any weight-bearing forces on a wounded foot; they alter their gait or limp to protect the injured site. However, in people with sensory neuropathy, ulcers are painless and often unrecognized unless they leave a stain on socks or blood on the floor. Because neuropathy blocks the pain response, these patients continue to fully bear weight on the site of injury.

Off-loading devices facilitate healing in several ways. The most effective off-loading strategies reduce pressure and shear forces at the site of ulceration. They reduce motion of the joints of the foot, and they are usually associated with reduced activity. Reducing pressure and shear forces and decreasing the number of steps or loading cycles per day allows healing tissue to bridge the wound without continual damage. Off-loading is one of the most important interventions to facilitate the healing of foot ulcers.

There are a variety of approaches to protecting the site of ulceration from repetitive injury by off-loading the diabetic foot. These include the use of therapeutic shoes and custom insoles (often referred to as "diabetic shoes"), postoperative shoes or sandals, padded dressings, removable cast boots (RCBs), and casting to protect the foot and immobilize the joints of the foot, often referred to as "total contact casts" (TCCs). Randomized controlled trials (RCTs) of the various off-loading methods are summarized in Table 2, and readers are referred to a review by Health Quality Ontario (14) for details on the individual studies discussed here.

TCCs involve a casting technique that uses a minimal amount of cast padding. Plaster of paris or plaster cast material is molded to conform closely to the anatomic structures of the foot and ankle and to limit movement within the cast. Fiberglass cast material is then applied as an outer layer, so the patient can walk on the cast within 30 minutes.

The use of TCCs is one of the most frequently studied techniques for healing DFUs and is regarded by many as the "gold standard" for protecting and off-loading DFUs (15). Numerous RCTs have evaluated TCCs, other casting techniques, modifications of TCCs, and RCBs. Descriptive retrospective cohort studies and RCTs have reported that a high proportion of DFUs (70–100%) heal with an average healing time of approximately 6 weeks (14).

There are challenges involved in using TCCs, and thus the technique is not widely used. The casting technique requires training, and many clinics do not have the skill, staff, or facilities to use the technique effectively. In addition, wearing a TCC may not be well accepted by patients, especially if it impedes driving or in patients with postural instability. TCCs are hot, and they make daily activities such as bathing and walking difficult.

Alternative therapies include RCBs, which were initially de-

TABLE 2 Results of Selected RCTs Evaluating Different Off-Loading Approaches: Proportion of Ulcers That Heal and Time to Healing (2)

MUELLER, et al. Diabetes Care, 1989	TCC 90%, 42 days (*n* = 21)	Shoes 32%, 65 days (*n* = 9)	
CARAVAGGI, et al. Diabetes Care, 2000	Fiberglass 50%, healing time NS (*n* = 26)	Shoes 21%, healing time NS (*n* = 24)	
ARMSTRONG, et al. Diabetes Care, 2001	TCC 90%, 35 days (*n* = 21)	RCB 65%, 50 days (*n* = 21)	Half shoe 58%, 61 days (*n* = 21)
KATZ, et al. Diabetes Care, 2005	TCC 74%, 38 days (*n* = 21)	iTCC 80%, 36 days (*n* = 22)	
ARMSTRONG, et al. Diabetes Care, 2005	RCB 52%, 58 days (*n* = 27)	iTCC 83%, 42 days (*n* = 23)	
PIAGGESI, et al. Diabetes Care, 2007	TCC 95%, 46 days (*n* = 21)	iTCC 85%, 47 days (*n* = 20)	
CARAVAGGI, et al. Diabetes Care, 2007	Cast 82%, 48 days (*n* = 29)	RCB 79%, 71 days (*n* = 29)	
FAGLIA, et al. Diabetes Care, 2010	TCC 74%, 35 days (*n* = 24)	RCB 73%, 40 days (*n* = 24)	
LAVERY, et al. Int Wound J, 2014	TCC 70%, 38 days (*n* = 23)	RCB 22%, 47 days (*n* = 27)	

NS, not stated.

signed to immobilize the foot and ankle to treat fractures. RCBs are safe, easy to use, and require little training or expertise. Patients like them because they can be removed to bathe, clean the foot, and apply new dressings. However, they can be expensive, and often insurance will not pay for RCBs to off-load diabetic foot ulcers. Moreover, because these are not custom-molded devices, they may not fit patients well, and they may need to be replaced every few months.

Several companies have designed modifications of RCBs to meet the needs of patients with foot ulcers. Although not all of these products are equally effective, several companies have designed boots that have been shown in RCTs to be as effective as a TCC in healing DFUs (16,17). However, other studies have shown much lower healing rates with RCBs than TCCs (22–52%) (14).

One of the reasons RCBs may not be as effective as TCCs is that patients can remove them and walk with their injured foot unprotected. Several studies have evaluated boots that can be "locked" on and thus have been deemed "instant TCCs" (iTCCs) (18). The rationale for this approach is that iTCCs, like RBCs, can provide the advantages of easy application without the need for special training or facilities while offering the same pressure reduction and "forced compliance" of TCCs. RCTs by Piaggesi et al. (16) and Katz et al. (19) reported similar healing rates with this approach compared to TCCs.

Other off-loading options include therapeutic shoes and insoles, padded dressings, and postoperative sandals. These have the advantage of being widely accepted by patients. They do not require expertise, special training, or special equipment. Insurance will often pay for therapeutic shoes and insoles, and postoperative sandals and padding are relatively inexpensive. These options do not interfere with normal walking, driving, or bathing. Unfortunately, they are the least effective off-loading strategies. Mueller and Caravaggi reported that only 21–32% of DFUs healed with these techniques during 12-week RCTs (14).

Off-loading is one of the most important treatments for healing DFUs. The evidence clearly indicates that there are significant differences in the proportion of ulcers that heal and the rate of healing based on the type of off-loading employed. Referral to a center that has experience with TCCs should be considered for patients with chronic non-healing ulcers if optimal off-loading is not otherwise available.

Wound Debridement: Surgical or Otherwise

DEBRIDEMENT DEFINED

Debridement is the excision of dead, damaged, or infected tissues to optimize the healing potential of the remaining viable tissues. It is performed in a variety of ways and settings in preparation for closure within the steps of the reconstructive ladder ranging from primary closure to flaps and grafts (20).

ADDITIONAL CONSIDERATIONS FOR WOUND HEALING

Debridement is merely one factor, albeit a vital one, in modern wound bed preparation. The fundamental tenets in the management of most lower-extremity wounds include eradication of infection, optimization of tissue perfusion, and adequate off-loading. Diabetic foot wounds in particular require adherence to a multifactorial algorithm that affords the greatest healing potential while mitigating costs and minimizing recurrence.

Consideration of a variety of factors other than appropriate debridement is essential to obtaining and preserving a healthy wound bed. These factors include a patient's comorbidities, nutrition, glycemic control, smoking status, ambulatory status, wound etiology, access to resources, adherence, and, perhaps most importantly, wound location and topography. Once the patient and wound have been optimized, several options on the reconstructive ladder are available for definitive closure, including secondary intention, primary closure, skin grafting, local tissue transfers, regional tissue transfers, and free tissue transfers (21).

Wound Etiology

Determining the etiology of a patient's wound is of utmost importance to guide decisions regarding the most appropriate course of wound optimization, including the type of debridement performed. It is imperative, however, to understand that debridement type, like wound character, may evolve over time,

especially in the comorbid population, including individuals with diabetes. Consequently, a thoughtful understanding and careful consideration of the patient, wound, and possible methods of debridement are vital to a successful outcome (22).

TYPES OF DEBRIDEMENT

Mechanical

Mechanical debridement is perhaps the oldest form of debridement and involves the use of moist or wet flushes or dressings, which are subsequently removed. This removal and physical wound base disruption causes non-selective debridement of loose tissues and slough. Examples include direct wound irrigation with saline, wet-to-dry dressings, and hydrotherapy, including bath and whirlpool. Dressing changes are simple and can be performed independently by patients in many cases. However, mechanical debridement is considered non-selective in nature and thus may remove or damage healthy tissues if not performed meticulously.

Enzymatic

Enzymatic debridement involves using chemical agents to slough necrotic wound tissue. Collectively, these enzymes are derived from microorganisms such as *Clostridium histolyticum* or from plants, including collagenase, varidase, papain, and bromelain. This method is most useful for debridement of wounds with a large amount of necrotic tissue and poses little risk to healthy tissues.

Autolytic

Autolytic debridement uses the body's own enzymatic processes to debride necrotic tissues and slough. This process interrupts dead and devitalized tissue over time by allowing wound fluids to maintain constant contact in the wound bed to hydrate, soften, and liquefy necrotic tissue and eschar. This method is achieved with the use of occlusive or semi-occlusive dressings with or without the supplementation of hydrocolloids, hydrogels, and transparent films and is suitable for cases in which the amount of dead tissue is not extensive and there is no infection.

Autolytic debridement is selective for necrotic tissues, easy to perform, and virtually painless to patients. However, it is by far the slowest type of debridement, and the wound must be rigorously monitored for signs of infection. For these reasons, this method is usually reserved for patients with poor access to resources or those requiring a break from other debridement methods.

Biologic

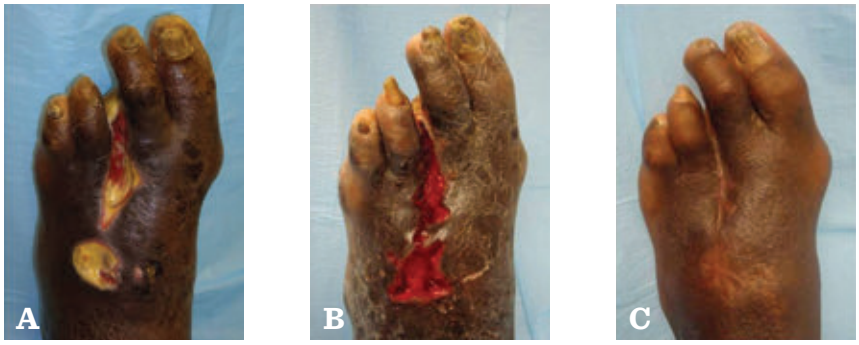
Biologic debridement employs medical maggots that have been grown in a sterile environment. Several young larvae of the green bottle fly (*Lucilia sericata*) are introduced into a wound bed and secured with a dressing. The maggots feed selectively on the necrotic tissue of the host without injuring living tissue and can quite effectively debride a wound in a matter of just a few days. The larvae derive nutrients by secreting a broad spectrum of enzymes that liquefy necrotic tissue for consumption. In an optimum environment, maggots molt twice, increasing in overall size and leaving a clean wound free of necrotic tissue when they are removed.

This method has gained popularity over time, but some patients find it painful, and some patients' aversion to maggots being placed on their body may impede its use. That said, this method has the advantage of being non-surgical in nature and works faster than autolytic or enzymatic debridement with little risk to healthy tissues.

Surgical

Surgical debridement is arguably the most common and varied type of debridement (Figure 3). A myriad of instrumentation and adjuncts are used to physically excise non-viable tissue from the wound bed, either at the bedside, in the clinic, or in an operating room. The surgeon will debride tissue to viability, as determined by tissue character and the presence of vascularity in healthy tissues, using any combination of instruments, such as rongeur, curette, blade, scissors, and forceps.

FIGURE 3 Progression of a diabetic foot ulcer from necrotic wound base (A), to surgical debridement (B), to complete healing (C).



Adjuncts such as the micro water jet device have been developed for even more meticulous and selective debridement.

A novel method used by the authors to ensure a more thorough debridement of wounds, especially those pending closure, is to completely paint the wound with methylene blue immediately before debridement. Sharp debridement sufficient to remove all of the blue-stained tissue provides a clear delineation between more superficial exposed tissues that may harbor bioburden and the healthy tissues below.

Surgical debridement is best suited for progressive or recalcitrant wounds; larger-sized wounds; those in abnormal or precarious locations; grossly infected wounds; and wounds considered to be of an unknown etiology, which necessitate surgical biopsy or resection. Surgical debridement is considered the fastest method of debridement because it is very selective and limited only by the skill and experience of the surgeon. Overall, surgical debridement affords superior control over which tissues and how much of them are removed, is the fastest way to achieve a clean wound bed, and can speed the healing process in most patients with diabetic foot wounds.

Management of Infection

Among patients with diabetes presenting with a foot wound, about half have clinical evidence of infection (23). The development of a diabetic foot infection (DFI), which typically begins in a break in the skin envelope and frequently spreads to deeper soft tissues (often including bone), is a sentinel event. For people with diabetes, DFIs are the most common diabetes-related reason for hospitalizations and for lower-extremity amputations. Recent studies have shown, however, that rapid recognition and appropriate management of DFIs can usually avert these adverse outcomes (23).

DEFINING INFECTION

Because all open wounds will be colonized with microorganisms, we define DFIs by the presence of classic signs and symptoms of inflammation. Because these findings may be altered in patients with peripheral neuropathy or PAD (present in most cases), some clinicians accept "secondary" signs, such as friable granulation tissue or wound undermining, as evidence of infection.

Classifying the severity of infection using standardized criteria helps to define the approach to treatment and the prognosis. Clinicians should probe foot wounds to establish their depth and extent and to seek palpable bone, which is highly suggestive of osteomyelitis. The presence of findings of systemic inflammatory response, especially fever or leukocytosis, defines a severe infection.

For all but the mildest DFIs, clinicians should obtain a complete blood count, as well as plain X-rays to look for foreign bodies, tissue gas, or bone abnormalities. Advanced imaging techniques such as magnetic resonance imaging or radiolabeled scintigraphy may be appropriate for some patients in whom initial evaluations suggest osteomyelitis (24). Definitively diagnosing bone infection requires collecting a bone specimen that has a positive culture or histological evidence of inflammation and necrosis, and preferably both.

CULTURES

It is not necessary to obtain a wound specimen for culture of clinically uninfected diabetic foot wounds (because they do not require antimicrobial therapy), but cultures are indicated for all DFIs. Tissue specimens collected by curettage or biopsy provide more specific and sensitive culture results than swabs. For osteomyelitis, cultures of bone (percutaneous or surgical) more accurately reveal the pathogens than those of soft tissue. Only collect blood cultures for patients with sepsis syndrome. Studies conducted in the past decade using molecular microbiological (genotypic) techniques demonstrate that there are many more microorganisms, of many more species (especially anaerobes), than identified by standard microbiology (phenotypic) (25). But, it remains unclear whether it is clinically beneficial to direct antimicrobial therapy to all of these identified organisms.

TREATMENT

While awaiting the results of cultures (and any additional diagnostic studies), clinicians should initiate *empiric* antibiotic therapy for DFIs. Base the choice of a regimen on the clinical characteristics and severity of the infection, any clues to the likely pathogens, any history of recent antibiotic therapy, and knowledge of local antibi-

otic resistance patterns. In Western countries, the most common DFI pathogens are aerobic gram-positive cocci, especially *Staphylococcus aureus*. For non-severe infections, in the absence of risk factors for gram-negative pathogens (e.g., previous antibiotic therapy or hospitalization) or obligate anaerobes (ischemia, gangrene), relatively narrow-spectrum (anti-staphylococcal) therapy often suffices. For severe infections, it is safer to initially prescribe a broader-spectrum regimen (26).

Topical antimicrobial therapy may be appropriate for some mild infections, but most DFIs require systemic antibiotic therapy (27). For severe infections, initial parenteral therapy (usually for a few days) is often best; otherwise, oral antibiotic agents with good bioavailability are sufficient.

Clinicians should review the selected empiric treatment regimen and adjust it within a few days, after reviewing the clinical response and the culture and sensitivity results. Select the *definitive* antibiotic regimen based on principles of antimicrobial stewardship: treat with the narrowest-spectrum regimen possible for the shortest duration necessary. A key point is that antibiotics treat infections but do not heal wounds or prevent infections (28). Thus, although a foot wound may take months to heal, antibiotic treatment of 10–14 days is sufficient for most soft-tissue infections, and treatment for 4–6 weeks is adequate for bone infections.

There is no evidence to support recommending any adjunctive treatments (e.g., hyperbaric oxygen therapy) for DFIs. Production of biofilm by causative pathogens appears to contribute to the difficulty in eradicating infections and healing wounds. That said, it is not clear whether any of the currently available agents promoted for their ability to eradicate biofilm are clinically effective.

In addition to antimicrobial therapy, most patients with a DFI require some type of surgical procedure; these range from bedside sharp debridement to more extensive operative soft-tissue and bone resection. The operating surgeon must have a thorough understanding of how to drain infections that may involve several of the compartments in the foot. In general, it is best to perform surgical drainage of deep soft-tissue infection, especially abscesses, as soon as practical, rather than waiting for the infectious process to "cool off" with medical therapy. Because most cases of diabetic foot osteomyelitis are chronic and accompanied by necrotic bone, surgical resection is usually the preferred treatment approach. Most surgical resections can and should be "conservative," removing only necrotic bone and soft tissue, while attempting to spare as much of the foot as possible.

Some cases of osteomyelitis, such as limited forefoot infections, respond to antibiotic therapy alone. Because bone infection recurs in about one-third of patients, often months after apparently successful treatment, clinicians should consider osteomyelitis to be "in remission" until 1 year after treatment, after which it may be considered "cured."

OUTCOME

In addition to the involvement of bone in an infection, factors that appear to decrease the likelihood of successful treatment include isolating antibiotic-resistant pathogens (especially methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, and gram-negative bacilli with extended-spectrum beta-lactamases), the presence of severe PAD, and end-stage renal disease.

Despite the difficulties in diagnosing and treating DFIs, with proper management, clinicians can expect to achieve resolution of such infections in more than 90% of mild and moderate soft-tissue infections. Appropriate treatment can also resolve infections in more than 75% of osteomyelitis cases (often with minor bone resection) and severe infections (usually with surgical debridement). Eliminating the clinical manifestations of infection is the key first step in managing patients with a DFI, but these patients will also need appropriate wound care, often including pressure off-loading, wound healing, and revascularization of an ischemic limb. The best predictor of the development of a DFI is a history of a previous DFI, so clinicians should also teach patients optimal prevention techniques.

Recognizing and Treating Peripheral Artery Disease

Although it has been repeatedly demonstrated that creation of well-organized diabetic foot care teams is a highly effective means of reducing major limb amputations associated with DFUs and PAD, such teams are not the norm

in many parts of the world, including the United States, where management of DFUs is often fragmented. For example, a recently published cross-sectional analysis of approximately 6.7 million patients with DFUs seen in ambulatory care settings from 2007 to 2013 across the United States reported that, compared to ambulatory visits of patients without DFUs, DFU visits were associated with a 3.4 times higher odds of direct emergency department or inpatient admission; double the number of previous visits during the past 12 months; double the odds of referral to another physician; and an outpatient visit length 1.4 times longer (29). In another study of more than 1 million patients presenting with DFUs to emergency departments in the United States from 2006 to 2010, more than 80% were admitted to the hospital. Among those admitted, annual estimated costs were $8.78 billion. Clinical outcomes included a sobering 2.0% mortality rate, 9.6% rate of sepsis, and 10.5% rate of minor or major amputations (30). Outcomes were significantly worse for patients residing in rural locations, Medicaid beneficiaries, and those residing in regions in the lowest quartile for income.

Failure to diagnose and adequately treat underlying PAD is a major cause of amputations in people with diabetes. The prevalence of PAD among people with diabetes has risen steadily throughout the past three decades, and PAD is estimated to be present in as many as 50–60% of patients with DFUs (1).

To improve vascular care for such patients, the Society for Vascular Surgery (SVS) developed and published in 2014 a Threatened Limb Classification System based on grading the three major limb factors associated with amputation risk: Wound, Ischemia, and foot Infection (WIfI) (7). As briefly described in the section on Screening for Foot Complications Risk (p. 4), each of these three factors is graded on a scale from 0 to 3, and the resultant grades are used to classify a given limb into four clinical stages of amputation risk ranging from Stage 1 (very low) to Stage 4 (high) (Table 3). Readers are referred to the original publication for details regarding grading and classification (7).

Although the presence of clearly palpable pedal pulses is reassuring, pulse palpation alone is unreliable to assess ischemia, and the application of WIfI grading mandates measurement of perfusion/hemodynamic status of the threatened limb. Because of the issue with falsely elevated ankle brachial index measurements due to underlying medial calcinosis of the arterial wall, toe waveforms and pressures are the preferred measurements in patients with DFUs. The WIfI classification is intended to stage the limb, much as the American Joint Committee on Cancer/Union for International Cancer Control TNM (Tumor, Nodes, and Metastases) classification is used to stage cancer. Data accumulated to date, as recently summarized in a detailed review of 19 studies that correlated WIfI clinical stage with clinically meaningful outcomes such as major-limb amputation, wound-healing time, hospital costs, and lengths of stay, have confirmed the utility of WIfI staging (31).

One of the principles of WIfI is that limb threat is a spectrum, and the use of an absolute critical level of perfusion or cut-off measure that mandates revascularization is not appropriate. The use of the term "chronic limb-threatening ischemia" (CLTI), has been suggested to avoid confusion and missed opportunities to identify ischemia associated with the

TABLE 3 SVS Threatened Limb Classification System, With Clinical Stages 1–4 Based on Severity of Wound, Ischemia, and foot Infection (WIfI)

	ISCHEMIA: 0				ISCHEMIA: 1				ISCHEMIA: 2				ISCHEMIA: 3			
WOUND: 0	1	1	2	3	1	2	3	4	2	2	3	4	2	3	3	4
WOUND: 1	1	1	2	3	1	2	3	4	2	3	4	4	3	3	4	4
WOUND: 2	2	2	3	4	3	3	4	4	3	4	4	4	4	4	4	4
WOUND: 3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	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

Each of the three WIfI components is graded from 0 to 3. Based on Delphi consensus, the 64 possible combinations were placed into one of four clinical stages based on the estimated baseline risk of amputation. For example, a limb scoring Wound: 1, Ischemia: 3, and foot Infection (fI): 2 would be at high risk for amputation, or clinical Stage 4. Adapted from ref. 7.

anachronistic term "critical limb ischemia" (CLI).

The level of perfusion required to heal a foot ulcer is complicated and depends on a number of factors that include ulcer size, location, and depth; presence and extent of infection; and nutritional status. The amount of blood flow improvement required to heal a small, shallow, non-infected ulcer in a compliant patient with well-controlled diabetes and a toe pressure of 36 mmHg is likely to be less than that in a patient with diabetes in poor control who requires open amputation of multiple toes for wet gangrene and who has an identical toe pressure. In general, most patients with foot ulcers and an ischemia grade of 3 (severe) will require revascularization, but the decision regarding revascularization also depends on the wound stage, the presence or absence of infection, and a variety of patient factors such as functional status, advanced age (>80 years), and oxygen-dependent chronic obstructive lung disease. Importantly, patients with moderate ischemia who do not meet the traditional definition of CLI may also benefit from revascularization, particularly as wound and foot infection grades increase.

WIfI Stage 4 patients uniformly have a higher risk of amputation, even with aggressive revascularization, with a mean 1-year amputation rate of 23.8% (median 32.5%) based on a compilation of 2,939 patients treated at 10 centers (32). In contrast, the mean amputation rate in Stage 1 patients was 3.8% (median 0). Patients at Stages 2 and 3 exhibit intermediate amputation rates of 10–11% at 1 year, suggesting some overlap in these stages and opportunities to improve the classification in intermediate-risk patients.

Increasingly, revascularization may be carried out by an endovascular approach, including more complex techniques such as subintimal angioplasty or retrograde pedal access, as well as surgical bypass. Because patients with diabetes often have PAD below the level of the knee, interventions are frequently required to the tibial arteries and even the pedal level. To date, no prospective trials have been conducted randomizing patients to open versus endovascular revascularization based on WIfI clinical stage. However, in functional patients with available vein conduit presenting with Stage 4 limbs, open bypass may be more effective and durable than endovascular therapy (32), which has been associated with higher rates of failure of wound healing, the need for repeat revascularization, and limb amputation (33).

In summary, studies have shown that identification of PAD in patients with DFUs and aggressive, timely revascularization reduces amputation rates. WIfI is a systematic classification to aid in the identification of PAD and impaired perfusion. Patients with threatened limbs in whom significant ischemia is detected (ischemia grades 2 and 3) and any patient with failure to progress after 4 weeks of proper wound care and off-loading should be referred to a vascular limb salvage specialist for further evaluation and consideration for revascularization. Preferably, vascular specialists should serve as integral components of and routinely participate in diabetic foot and limb salvage teams.

Evidence-Based Adjunctive Therapies for Diabetic Foot Ulcers

DFUs are common and costly (34–36). One of six patients with a DFU undergoes an amputation, accounting for nearly 100,000 amputations each year in the United States and making diabetes the leading cause of non-traumatic amputation. Patients with a DFU or history of a DFU have an increased risk of 5- and 10-year mortality, but it is not yet proven that healing DFUs improves longevity. DFUs and their complications exact a financial cost as well; estimated costs of hospitalizations due to DFUs range from $9 to $13 billion, and $43.5 billion is spent on lower-extremity complications of diabetes each year (37,38).

Standard care includes ensuring good vascular supply, preventing and treating soft-tissue and bone infection, performing initial excisional debridement and maintenance debridement as indicted, and, of crucial importance, adhering to high-quality off-loading. Even in optimal situations, at least 25% of patients fail to heal. Instituting adjunctive therapy early improves outcomes. Typically, standard care is provided for a 4-week period because wounds that do not reduce in size by more than 50% after 4 weeks have a decreased likelihood of healing by 12 weeks. Referral to a wound center, where clinical expertise and access to advanced therapies are available, is often indicated.

Numerous therapies can be applied for these recalcitrant ulcers; however, few have been proven to

improve complete ulcer healing in RCTs and fewer still in high-quality trials. Evidence-based adjunctive therapies include cell- and tissue-based products (CTPs) such as bioengineered cell-based therapies, acellular matrices, and placental-derived membranes; recombinant growth factors; platelet-rich plasma; negative pressure wound therapy; and possibly hyperbaric oxygen, all of which can improve complete healing and some of which may treat biofilm, prevent bone infection and limb loss, and improve patients' quality of life (Table 4). The highest-quality evidence exists for products that have undergone the rigorous approval process of the U.S. Food and Drug Administration (FDA) (as opposed to those that have been "cleared" by the FDA) (39,40). Direct comparison of the clinical trial results (efficacy data) is not possible because of the varying rigor of trial design and analysis, inclusion and exclusion criteria, and sample sizes.

EVIDENCE-BASED TREATMENT OF UNCOMPLICATED REFRACTORY DFUS

Growth Factors

One recombinant growth factor, recombinant human platelet–derived growth factor (rhPDGF; becaplermin [Regranex], Smith & Nephew, Largo, FL) is FDA-approved and is the only drug approved for the treatment of DFUs. Produced by incorporation of the gene for the B-chain of human PDGF into the yeast *Saccharomyces cerevisiae*, becaplermin has biological activities similar to endogenous PDGF. Pivotal trials that led to approval have shown that, at week 20, one-third more ulcers healed in the active group receiving daily rhPDGF than in a placebo control group (41). Effectiveness data support benefit of rhPDGF, and in clinical practice its use appears to reduce the risk of amputation. Autologous platelet-rich plasma (PRP; also called platelet-enriched plasma, platelet-rich concentrate, autologous platelet gel, and platelet releasate), the portion of the plasma fraction of autologous blood having a platelet concentration above baseline, has also been shown to improve healing of DFUs. Platelet gels and releasates are prepared from PRP. The benefit of PRP is supported by a prospective, double-blind, multicenter RCT of 72 DFUs using a per-protocol (as opposed to an intention-to-treat) analysis of 35 patients. This analysis revealed that DFUs treated with PRP gel healed significantly more (81.3 vs. 42.1%) than similar-sized DFUs in a control group using an inert gel ($P = 0.036$) (42).

CTPs: Cell-Based Products

Two cellular constructs are FDA-approved class III devices to treat DFUs. The first, allogeneic bilayered human skin equivalent (HSE; [Apligraf], Organogenesis, Canton, MA), consists of a bovine collagen matrix with neonatal fibroblasts overlaid by a stratified

TABLE 4 Comparison of Evidence-Based Treatments for Refractory Ulcers

	rhPDGF (41) *n* = 382	PRP (42) *n* = 35	HSE (43) *n* = 208	DSS (45) *n* = 245	IDRT (46) *n* = 307	SIS (47) *n* = 82	HADWM (48) *n* = 86	hVWM (38) *n* = 97	dHACM (49) *n* = 40	NPWT (50) *n* = 162	HBOT (52) *n* = 94
HEALED, %	50 vs. 35 at 20 weeks	81 vs. 42 at 12 weeks	56 vs. 38 at 12 weeks	30 vs. 18 at 12 weeks	51 vs. 32 at 16 weeks	54 vs. 32 at 12 weeks	70 vs. 46 at 12 weeks	62 vs. 21 at 12 weeks	95 vs. 35 at 6 weeks	56 vs. 39 at 16 weeks	52 vs. 29 at 1 year
TIME TO CLOSURE, DAYS	86 vs. 127	43 vs. 47	65 vs. 90	Not stated	43 vs. 78	63 vs. 77	40 vs. 48	42 vs. 70	24 vs. 57	N/A	N/A
FDA-APPROVED	+		+	+	+						
STUDY QUALITY	+++	+	+++	+++	+++	++	++	++	+	++	++
ADDITIONAL RCTs	+	+	+	+						+	+
EFFECTIVENESS DATA	+	+	+	+							

Because of differences in study design and quality, caution is warranted regarding direct comparisons. Numbers in parentheses after therapy abbreviations are reference citations. N/A, not applicable.

epithelium containing neonatal keratinocytes. In an RCT, up to five weekly applications of HSE in patients with chronic plantar DFUs resulted in a significantly higher healing rate (P = 0.0042) and shorter time to complete closure (P = 0.0026) than in individuals receiving standard care (43). A second RCT confirmed those results, making HSE the best-studied of all CTP therapies (44).

The second cellular construct, dermal skin substitute (DSS; [Dermagraft], Organogenesis, Canton, MA), consists of human fibroblasts grown in a bioabsorbable polyglactin mesh scaffold. A large RCT found that weekly application produced significantly higher healing rates than in control subjects in patients with DFUs of more than 6 weeks' duration (P = 0.023) with significantly faster time to complete wound healing (P = 0.04). Treated patients were 1.7 times more likely to have complete wound closure at any given time than were control subjects, and ulcer-related adverse events were significantly lower (45). The efficacy results of clinical trials have been confirmed by effectiveness results in clinical practice; these later data suggest that use of DSS may produce the best results in clinical practice.

CTPs: Acellular Products

Three acellular constructs have been shown to improve DFU healing. The highest-quality evidence exists for Integra Dermal Regenerative Template (IDRT; Integra Life Sciences, Plainsboro, NJ), which consists of a dermal replacement layer designed with a controlled porosity and degradation rate made up of a three-dimensional matrix of collagen and the glycosaminoglycan chondroitin-6-sulfate. The temporary epidermal layer is made of silicone to provide mechanical protection and act as a barrier against bacterial contamination. A large RCT demonstrated that complete DFU closure was significantly greater with a single application of IDRT (51%) than with a control treatment (32%, P <0.001) at 16 weeks. Time to closure was 35 days faster for IDRT-treated patients compared to control subjects (46). Use of the second acellular construct, the tri-layer porcine small intestine submucosa (SIS [Oasis], Smith & Nephew, Largo FL), led to a significantly greater proportion of wounds closed by 12 weeks than in a control group (54 vs. 32%, P=0.021) and faster time to closure for ulcers (2 weeks earlier) (47). The third product, human acellular dermal wound matrix (HADWM; [Graftjacket], KCI USA, San Antonio, TX), is processed from screened donated human skin and regulated by the FDA as human tissue for transplantation. Epidermal and dermal cells are removed while dermal structure is preserved, including an intact basement membrane complex. A multicenter RCT compared a single application HADWM to advanced moist wound therapy (AMWT). At 12 weeks, significantly more HADWM patients (P = 0.0289) achieved complete healing than did AMWT patients (70 vs. 46%) (48).

CTPs: Placental/Amnionic/ Chorionic-Derived Products

Two placental/amnionic/chorionic-derived products have been shown in RCTs to heal DFUs. Among these, the highest-quality evidence exists for human viable wound matrix (hVWM [Grafix], Osiris Therapeutics, Columbia, MD), which is designed to preserve the native components of the human placental membrane in a cryopreserved product. The proportion of patients achieving complete wound closure was significantly higher among those who received hVWM compared to control subjects (62 vs. 21%, P = 0.0001), and those in the hVWM group had a faster median time to healing (42 vs. 69.5 days in control subjects, P = 0.019). Additionally, fewer adverse events (44 vs. 66%, P = 0.031) were noted (38).

Dehydrated human amnion/chorion membrane (dHACM [EpiFix], MiMedx Group, Marietta, GA) was tested in a small study in which 20 patients received the product applied, on average, 2–3 times during a 12-week period. Ninety-five percent of dHACM-treated patients healed in 6 weeks compared to 35% of individuals in a control group (49). Effectiveness data have not demonstrated such dramatic results.

Many other acellular matrices and placental/amnionic/chorionic-derived products have been cleared by the FDA, with clinical experience suggesting yet-to-be-proven benefits.

EVIDENCE-BASED TREATMENT OF COMPLICATED REFRACTORY DFUS

For complicated (i.e., deeper, infected) wounds, RCTs suggest that two treatments may be helpful. Negative pressure wound therapy (NPWT; VAC Therapy

System, KCI USA, San Antonio, TX) has been shown beneficial in two large studies using different study designs. In one, patients with DFUs undergoing large surgical debridement or amputations healed better with application of NPWT after surgery than those who did not (50). A second study of more than 300 patients found that NPWT plus investigators' choice of other closure techniques led to improved healing of DFUs; 43% of those using NPWT healed compared to 29% of those not using NPWT throughout 16 weeks of treatment (P <0.007) (51).

The second treatment, hyperbaric oxygen therapy (HBOT), is often used for DFUs complicated by osteomyelitis. Data regarding HBOT use are mixed, and a definitive positive study has not yet been performed. The best study to date involved 94 patients with Wagner grade 2–4 ulcers and reported 52% healing with HBOT versus 29% healing in the placebo group (P = 0.03) (52). The best results were observed in patients completing more than 35 sessions of HBOT. Other studies have not yet confirmed these results (53).

Chronic DFUs are a growing global health concern given the implied high associated morbidity and mortality. Standard care is not sufficient for some ulcers, and adjunctive therapy should be considered no later than 4 weeks after standard care fails to reduce wound size. Many products may work, but many fewer have been proven to do so. The use of evidence-based adjunctive therapies may speed healing, save limbs, and potentially save lives.

The Acute Hot, Swollen Foot: Charcot or Infection?

Primary care providers need to have a high index of suspicion that a red, hot, swollen foot is Charcot neuroarthropathy, especially in patients with sensory neuropathy. Charcot neuroarthropathy is a fracture dislocation process that affects the bones, joints, and ligaments of the foot and ankle in people with peripheral sensory neuropathy (54).

The disease process was originally described in patients with tertiary syphilis and usually presents as a unilateral red, hot, swollen foot and ankle (55). The diagnosis for the hot, swollen diabetic foot is often delayed by weeks or months or missed entirely, resulting in severe deformity, loss of function, ulceration, infection, and lower-extremity amputation.

Perhaps the easiest screening tool is to ask whether a patient has symptoms of neuropathy (i.e., numbness, tingling, formication, and burning) and then to test for sensory neuropathy.

The classic presentation is of a patient with painless unilateral swelling without a history of trauma. Sometimes, the patient will recall an incidental injury such as making a misstep when stepping down from a curb or a slight inversion of the ankle. The foot and ankle are usually swollen, red, and warm to the touch compared to the contralateral foot. The unilateral swelling could have lasted for days, weeks, or even months by the time of presentation. Patients sometimes comment that what brought them to see the doctor was that they could no longer fit their foot into a shoe or that the shape of their foot had changed, rather than that they were in pain.

Diagnosis of Charcot neuroarthropathy is based on medical history, physical examination, and plain radiographs (54,55). The differential diagnosis includes cellulitis, deep venous thrombosis, and trauma. Often, patients are treated with antibiotics, surgery, or amputation for infection, or they have multiple ultrasound examinations for deep vein thrombosis before the correct diagnosis is made.

The duration of the swelling and redness is important to ascertain in attempting to pinpoint the timing of the injury. Musculoskeletal deformity may be absent, or there can be severe deformity at initial presentation (56). Patients with an early presentation often have normal X-rays and a normal musculoskeletal clinical examination. Untreated injuries of longer duration have more severe bone and joint destruction and dislocation. Patients who seek medical care later in the disease process on inspection may have loss of the medial longitudinal arch of the foot compared to the contralateral foot, or their feet do not appear to be symmetrical. The classic "rocker-bottom" foot deformity is an example of end-stage disease with severe fracture dislocation, collapse of the midfoot, dorsal dislocation of the metatarsals, and plantar dislocation of the tarsal bones.

Patients will have a history of neuropathy symptoms with a

symmetrical distribution. Occasionally, patients will say that they feel as if they have a thick stocking on their feet when they are barefoot or that their feet feel cold when they are not. Simply put, if you ask these patients whether they have symptoms of neuropathy, they will often help to make the diagnosis before you do a physical examination (57).

Clinical examination often shows good peripheral pulses and severe sensory loss. Sensory testing can be quickly accomplished with a 128-Hz tuning fork or a 10-g monofilament or by testing light-touch perception. Examination of the joints of the foot and ankle can show abnormal alignment, joint effusion, and dislocations that are painless when examined. Plain X-rays maybe appear normal early in the Charcot process, or the radiographic signs can be subtle. Dislocation at the Lis Franc joint in the midfoot is a common presentation that can be missed even by experienced radiologists unless concerns regarding possible Charcot neuroarthropathy are voiced when imaging is ordered (54,55).

It is uncommon for adults to have infections without a wound. Inspect the skin for ulceration. Charcot patients sometimes also have ulcerations. If there is a wound, fractures and dislocations, and cellulitis, the patient may have both disease processes. Many people with diabetes who have cellulitis do not have leukocytosis, so using this in the decision process will be helpful to confirm infection when there are both leukocytosis and other systemic signs of infection. If there is no leukocytosis, you have not ruled infection out. If there is purulence from the wound or exposed bone when the wound is examined with a sterile probe, there is infection (54,56).

Treatment of Charcot neuroarthropathy requires prompt referral to a podiatric or orthopedic surgeon with experience in treating this complication. Early treatment requires immobilization and non-weight-bearing in a cast or wheelchair until the acute inflammatory process subsides, which may take weeks or months. Late treatment requires reconstructive surgery to repair the deformity and obtain a plantar-grade foot (54,57).

How to Maintain the Foot in Remission

The overall risk for developing a wound in people with diabetes is ~2% per year. This risk increases to 7.5% for patients with neuropathy. However, the risk jumps to 40% in people with a history of ulceration (1). The risk further increases to nearly 60% at 3 years and up to 75% at 5 years (1). In fact, re-ulceration is not only common, it is likely. We therefore use the term "in remission" to refer to this population (58). Our goal is not necessarily to prevent every wound, but to maximize ulcer-free, hospital-free, and activity-rich days (59–61) by making each wound recurrence as uncomplicated as possible.

There are currently four key strategies associated with maximizing ulcer-free days: integrated foot care, self-management, therapeutic footwear, and, as necessary, reconstructive foot surgery. These are summarized in Table 5.

Specifically, integrated foot care focuses on regular visits to podiatrists and other members of the diabetes foot care team as described earlier in this monograph. Self-management involves daily evaluation by patients, family members, or caregivers and the use of thermometry. Therapeutic footwear that off-loads the foot by at least 30% appears to be associated with lower risks of recurrence (62). If these non-surgical methods are problematic, foot surgery appears to provide benefit in reducing the severity of deformity and plantar pressure and therefore reduces the risk of recurrence (63–65).

Conclusions and Future Directions

Diabetic foot complications are, as has often been said, common, complex, and costly. Demographic trends suggest that these complications, including ulcers, infections, PAD, and amputations, will continue to be highly prevalent (29).

Future directions should focus not only on the promising therapeutic advances discussed in this monograph, but also on novel monitoring systems (59,66–71). For example, efforts designed to identify pre-ulcerative inflammation through the past generation have now culminated in home-based monitors that can alert patients up to several weeks in advance of a potential complication (69). Similarly, smart insoles paired with smart watches may be able to identify potentially damaging pressure, which over time can cause blistering or callusing and tissue loss (67).

TABLE 5 Effect Sizes in Studies of Interventions to Reduce the Risk of Foot Ulcer Recurrence

INTERVENTION CATEGORY	EFFECT OF THE INTERVENTION			EFFECT OF ADHERENCE TO TREATMENT	
	Number of Studies	Mean Sample Size, *n* (Range)	Mean Effect Size,* % (Range)	Number of Studies	Mean Effect Size,† %
INTEGRATED FOOT CARE	4‡	179 (53–549)	30.9 (9.1 to 100)	2	76.7
SELF-MANAGEMENT	4	138 (70–225)	54.3 (−5.4 to 90.0)	1	98.0
PATIENT EDUCATION	2	152 (131–172)	−13.4 (−26.3 to −0.5)	2	85.5
THERAPEUTIC FOOTWEAR	9	181 (46–400)	47.2 (−14.6 to 92.9)	2	58.1
FOOT SURGERY	7	73 (40–207)	61.8 (10.4 to 100)	0	—

Adapted from ref. 1, to which readers are referred for details about the individual studies summarized here, as well as a 2015 systematic review of ulcer prevention performed by the International Working Group on the Diabetic Foot that assessed the five categories of preventive interventions. All studies were controlled prospective or retrospective studies (randomized trial, cohort study, or case-control study). Information about the quality of the studies can be obtained from the systematic review.

*The mean effect size is expressed as the percentage reduction in the risk of recurrent foot ulcer in the intervention group compared to the group receiving usual care (control group). Therefore, negative percentages indicate an increase in the risk of recurrent foot ulcer in the intervention group as compared with the control group.

†The mean effect size is expressed as the percentage reduction in the risk of recurrent foot ulcer among patients who adhered to the study treatment compared to those who did not adhere to the study treatment.

‡Studies of integrated foot care include one study that is ongoing; see ref. 1 for details.

Combining the evidence-based and common-sense therapies described here with emerging technologies has the potential to help us maximize ulcer-free, hospital-free, and activity-rich days for our patients.

ACKNOWLEDGMENTS

The authors acknowledge Jayson N. Atves, DPM, CO, for contributions to the section on debridement.

Editorial and project management services were provided by Debbie Kendall of Kendall Editorial in Richmond, VA.

AUTHOR CONTRIBUTIONS

A.J.M.B. and D.G.A. served as co-editors and, as such, co-wrote the introduction and conclusion and reviewed and edited the entire manuscript. A.J.M.B. also wrote "Pathways to Diabetic Foot Complications," and D.G.A. wrote "Screening for Foot Complications Risk" and "How to Maintain the Foot in Remission" and co-wrote "The Acute Hot, Swollen Foot: Charcot or Infection?" C.E.A. co-wrote "Wound Debridement: Surgical or Otherwise." R.S.K. wrote "Evidence-Based Adjunctive Therapies for Diabetic Foot Ulcers." L.A.L. wrote "When and Where to Refer Diabetic Foot Problems" and "Off-Loading the Diabetic Foot Wound" and co-wrote "The Acute Hot, Swollen Foot: Charcot or Infection?" B.A.L. wrote "Management of Infection." J.L.M. wrote "Recognizing and Treating Peripheral Artery Disease." J.S.S. co-wrote "Wound Debridement: Surgical or Otherwise." A.J.M.B. and D.G.A. are the guarantors of this work.

DUALITIES OF INTEREST

A.J.M.B., D.G.A., and J.L.M. have no relevant dualities of interest to disclose. C.E.A. is a consultant for Acelity and Integra. R.S.K. has received honoraria for participation in educational programs for Healogics. L.A.L. has received research grants from Cardinal Health; serves on speakers bureaus for Integra, Osiris, and Smith & Nephew; and is a consultant or advisor to Apilon Medical Users, Boehringer Ingelheim, Harbor MedTech, and Medline Industries. B.A.L. is a consultant for Medimmune, Microbion, and Debiopharm. J.S.S. is a consultant for Integra and Syntactx.

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Suggested citation:
Boulton AJM, Armstrong DG, Kirsner RS, et al. *Diagnosis and Management of Diabetic Foot Complications*. Arlington, Va., American Diabetes Association, 2018