Diabetic foot ulcers are a significant health care problem. Complications of foot ulcers are a leading cause of hospitalization and amputation in patients with diabetes mellitus. In response to a request from the Wound Healing Society, a panel of advisers, including physicians from academia and private practice, nurses, a podiatrist, a pedorthist, and a representative from industry, was selected to develop guidelines for the treatment of diabetic ulcers of the lower extremity.

METHODS
The approach used to develop guidelines was similar to that used by the Venous Ulcer Panel, also convened at the request of the Wound Healing Society. Those guidelines were presented on October 3, 2005, at a conference at the National Institutes of Health (NIH). Previous guidelines, meta-analyses, PubMed, MEDLINE, EMBASE, The Cochrane Database of Systematic Reviews, recent reviews of diabetic ulcer treatment, and the Medicare/CMS consensus of usual treatment of chronic wounds were reviewed for evidence. Guidelines were formulated, the underlying principle(s) enumerated, and evidence references listed and coded. The code abbreviations for the evidence citations were as follows:

STAT Statistical analysis, meta-analysis, consensus statement by commissioned panel of experts
RCT Randomized clinical trial
LIT REV Literature review
CLIN S Clinical case series
RETO S Retrospective series review
EXP Laboratory or animal study
TECH Technique or methodology description
PATH S Pathological series review

There was a major difference between our approach to evidence citations and past approaches to evidence-based guidelines. Most past approaches relied only on publications regarding clinical human studies. Laboratory or animal studies were not cited. We have used well-controlled animal studies that present proof of principle, especially when a clinical series corroborated the laboratory results. Because of this variation, a different system was used to grade the weight of evidence supporting a given guideline. The strength of evidence supporting a guideline is listed as Level I, Level II, or Level III. The guideline levels are:

- **Level I**: Meta-analysis of multiple RCTs or at least two RCTs supporting the intervention of the guideline. Another route would be multiple laboratory or animal experiments with at least two clinical series supporting the laboratory results.
- **Level II**: Less than Level I, but at least one RCT and at least two significant clinical series or expert opinion papers with literature reviews supporting the intervention. Experimental evidence that is quite convincing, but not yet supported by adequate human experience.
- **Level III**: Suggestive data of proof of principle, but lacking sufficient data such as meta-analysis, RCT, or multiple clinical series.

*Note*: The suggestion in the guideline can be positive or negative at the proposed level (e.g., meta-analysis and two RCTs stating intervention is not of use in treating diabetic ulcers).

RESULTS
Guidelines have been formulated in eight categories for the treatment of diabetic ulcers of the lower extremities. The categories are:

- Diagnosis
- Offloading
- Infection control
- Wound bed preparation
- Dressings
- Surgery
- Adjuvant agents (topical, device, systemic)
- Prevention of recurrence
GUIDELINES FOR THE DIAGNOSIS OF LOWER EXTREMITY DIABETIC ULCERS

Preamble: Ulcers of the lower extremity may be caused by a variety of conditions, including neuropathy, ischemia, venous hypertension, and pressure. Patients with diabetes develop wounds secondary to neuropathy with or without biomechanical abnormalities, peripheral vascular disease with ischemia, or both. There are 20 million people in the United States with diabetes, of whom 10–15% are at risk for ulceration. It is imperative that the etiology be established to provide for proper therapy.

Guideline #1.1: Clinically significant arterial disease should be ruled out by establishing that pedal pulses are clearly palpable or that the ankle:brachial index (ABI) is > 0.9. An ABI > 1.3 suggests noncompressible arteries. In elderly patients or patients with an ABI > 1.2, a normal Doppler-derived waveform, a toe:brachial index of > 0.7, or a transcutaneous oxygen pressure of > 40 mmHg may help to suggest an adequate arterial flow. Color duplex ultrasound scanning provides anatomic and physiologic data confirming an ischemic etiology for the leg wound. (Level I)

Guideline #1.2: The presence of significant neuropathy can be determined by testing with a 10 gram (5.07) Semmes–Weinstein monofilament. (Level II)

Principle: Diabetic ulcers can result from arterial insufficiency or neuropathy. Although clinical history and physical examination can be very suggestive of an ischemic etiology of the lower extremity diabetic ulcers, a definitive diagnosis must be established. When significant arterial disease is present, successful treatment requires that arterial insufficiency be addressed.

Evidence:


Evidence:


GUIDELINES FOR OFFLOADING FOR TREATMENT OF DIABETIC ULCERS

Preamble: Diabetic ulceration may result from an increase in pressure on the diabetic foot because of foot deformity, limited joint mobility, and neuropathy. Offloading the area of high pressure has been the mainstay to prevent these problems.

Guideline #2.1: Protective footwear should be prescribed in any patient at risk for amputation (significant arterial insufficiency, significant neuropathy, previous amputation, previous ulcer formation, preulcerative callus, foot deformity, evidence of callus formation). (Level II)

Principle: The incidence of ulceration in diabetic patients at risk for ulceration can be reduced by using protective footwear.

Evidence:

Guideline #2.2: Acceptable methods of offloading include crutches, walkers, wheelchairs, custom shoes, depth shoes, shoe modifications, custom inserts, custom relief orthotic walkers (CROW), diabetic boots, forefoot and heel relief shoes, and total contact casts. (Level I)

Principle: Relieving pressure on the diabetic wound is necessary to maximize healing potential.

Evidence:

GUIDELINES FOR INFECTION CONTROL IN THE TREATMENT OF DIABETIC ULCERS

Preamble: Infection results when the bacteria : host defense equilibrium is upset in favor of the bacteria.
plays various roles in the etiology, healing, operative repair, and complications of diabetic ulcers.

**Guideline #3.1:** Remove all necrotic or devitalized tissue by surgical, enzymatic, mechanical, biological, or autolytic debridement. (Level II; detailed discussion of debridement is in Wound Preparation Guidelines.)

**Principle:** Necrotic tissue is laden with bacteria while devitalized tissue impairs the body's ability to fight infection and serves as a culture medium for bacterial growth.

**Evidence:**


**Guideline #3.2:** If there is suspected infection in a debrided ulcer, or if epithelialization from the margin is not progressing within two weeks of debridement and initiation of offloading therapy, determine the type and level of infection in a debrided diabetic ulcer by tissue biopsy or by a validated quantitative swab technique. (Level II)

**Principle:** High levels of bacteria \( \geq 1 \times 10^6 \) CFU/g of tissue or a tissue level of beta hemolytic streptococci impede the various wound-healing processes and have been demonstrated to impede spontaneous healing and surgical closure of diabetic ulcers. Cultures should be performed to isolate both aerobic and anaerobic bacteria.

**Evidence:**


**Guideline #3.3:** For ulcers with \( \geq 1 \times 10^6 \) CFU/g of tissue or any tissue level of beta hemolytic streptococci following adequate debridement, decrease the bacterial level with a topical antimicrobial agent. Once in bacterial balance, discontinue the use of the topical antimicrobial agent to minimize any possible cytotoxic effects due to the antimicrobial agent or emergence of bacterial resistance to the agent. (Level I)

**Principle:** Systemically administered antibiotics do not effectively decrease bacterial levels in granulating wounds, whereas topically applied antimicrobials can be effective.

**Evidence:**

Guideline #3.4: For acute diabetic foot infections not confined to the granulating wound, systemic antibiotics are effective. (Level II)

**Principle:** Systemic antibiotics have been demonstrated in most trials to be helpful in treating acute diabetic foot infections. Although the most frequent infections are due to aerobic Gram-positive cocci, aerobic Gram-negative organisms, and anaerobic organisms are often isolated. Deep tissue cultures are most helpful in determining antibiotic usage.

**Evidence:**

**Guideline #3.5:** Cellulitis (inflammation and infection of the skin and subcutaneous tissue most commonly due to streptococci or staphylococci) surrounding the ulcer should be treated with systemic Gram-positive bactericidal antibiotics. (Level II)

**Principle:** Edema fluid (plasma) neutralizes the fatty acids of sebum and inactivates the normal bactericidal properties of skin. This renders the skin and subcutaneous tissue susceptible to infection by streptococci and staphylococci.

**Evidence:**

**Guideline #3.6:** If osteomyelitis is suspected, appropriate diagnostic measures include probing the wound with a sterile cotton-tipped applicator, serial x-rays, MRI, CT, and radionucleid scan. (Level II)

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

**Evidence:**

**Guideline #3.7:** Osteomyelitis is best treated by removal of the infected bone, followed by 2–4 weeks of antibiotics. However, when this is not practical, osteomyelitis underlying a diabetic ulcer can be effectively treated with prolonged antibiotic therapy. (Level II)

**Principle:** Osteomyelitis underlying a diabetic ulcer, like osteomyelitis elsewhere, is most effectively treated by debridement of the infected bone. When debridement has been adequate, a 2–4-week course of antibiotics is adequate. If the infected bone is not totally resected, a longer course (at least 6 weeks) is usually required.

**Evidence:**

**Guideline #3.8**: Minimize the tissue level of bacteria, preferably to ≤10^2 CFU/g of tissue with no beta hemolytic streptococci in the ulcer before attempting surgical closure by skin graft, skin equivalent, pedicled, or free flap. (Level II)

**Principle**: “A wound containing contaminated foci with greater than 10^2 organisms per gram of tissue cannot be readily closed, as the incidence of wound infection that follows is 50–100%” Tobin (1984).

**Evidence**:

**GUIDELINES FOR WOUND BED PREPARATION IN THE TREATMENT OF DIABETIC ULCERS**

(Detailed discussions of infection control, dressings, and tissue engineering/growth factors are in Infection Control Guidelines, Dressings Guidelines, and Adjuvant Agents [Topical, Device, and Systemic] Guidelines.)

**Preamble**: Wound bed preparation is defined as the management of the wound to accelerate endogenous healing or facilitate the effectiveness of other therapeutic measures.


**Guideline #4.1**: Examination of the patient as a whole is important to evaluate and correct causes of tissue damage. This includes factors such as: (A) systemic diseases and medications, (B) nutrition, and (C) tissue perfusion and oxygenation. (Level I)

**Principle**: (4.1.A) A general medical history, including a medication record, will help in identifying and correcting systemic causes of impaired healing. The presence of a major illness or systemic disease and drug therapies such as immunosuppressive drugs and systemic steroids will interfere with wound healing by alterations in immune functioning, metabolism, inflammation, nutrition, and tissue perfusion. Autoimmune diseases such as rheumatoid arthritis, uncontrolled vasculitis, or pyoderma gangrenosum can all delay healing and may require systemic steroids or immunosuppressive agents before local wound healing can occur. Patients undergoing major surgery have a diminished wound-healing capacity as do chronic smokers. Smoking is associated with impaired wound healing and increased risk of infection.

**Evidence**:

**Principle**: (4.1.B) Nutrition must be adequate to provide sufficient protein to support the growth of granulation tissue. The patient’s weight, prealbumin level (reflecting recent protein consumption), and serum albumin (reflecting...
long-term protein consumption) are useful in identifying patients who are outside the norms. Although most diabetic ulcer patients are ambulatory and not at the extremes of nutrition, nutritional support is required if an individual is undernourished.

Evidence:

Principle: (4.1.C) Wounds will heal in an environment that is adequately oxygenated. Oxygen delivery to the wound will be impaired if tissue perfusion is inadequate. Dehydration and factors that increase sympathetic tone such as cold, stress, or pain will decrease tissue perfusion. Cigarette smoking decreases tissue oxygen by peripheral vasoconstriction. For optimal tissue perfusion, these factors must be eliminated or minimized.

Evidence:

Guideline #4.2: Initial debridement is required to remove the obvious necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells. Maintenance debridement is needed to maintain the appearance and readiness of the wound bed for healing. The health care provider can choose from a number of debridement methods including surgical, enzymatic, mechanical, biological, or autolytic. More than one debridement method may be appropriate. (Sharp surgical debridement is preferred; Level I.)

Principle: Necrotic tissue, excessive bacterial burden, senescent cells, and cellular debris can all inhibit wound healing. The method of debridement chosen may depend on the status of the wound, the capability of the health provider, the overall condition of the patient, and professional licensing restrictions.

Evidence:


**Guideline #4.3:** Wounds should be cleansed initially and at each dressing change using a neutral, nonirritating, nontoxic solution. Routine wound cleansing should be accomplished with a minimum of chemical and/or mechanical trauma. (Level III)

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

**Evidence:**


**Guideline #4.4:** There should be an ongoing and consistent documentation of wound history, recurrence, and characteristics (location, size, base, exudates, condition of the surrounding skin, staging, and pain) to evaluate wound bed preparation. The rate of wound healing should be evaluated to determine whether treatment is optimal. (Level II)

**Principle:** Ongoing evaluations of wound bed preparation are necessary; if the ulcer is not healing at the expected rate, interventions for wound bed preparation need to be reassessed. The longer the duration of the ulcer, the more difficult it is to heal. If an ulcer is recurrent, etiology, patient education, or issues of prevention and long-term maintenance need to be reassessed.

**Evidence:**


**Guideline #4.5:** Patients who fail to show a reduction in ulcer size by 40% or more after four weeks of therapy should be reevaluated and other treatments should be considered. (Level II)

**Principle:** Percent change in wound area of diabetic foot ulcers over four weeks of treatment is a good predictor of effectiveness of therapy and likelihood of healing.

**Evidence:**

1. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003; 26: 1879–82. [CLIN S]


**Guideline # 4.6:** Optimizing glucose control improves wound healing. (Level III)

**Principle:** Wound healing is more likely to be optimal in the setting of good diabetes management. Abnormal glucose levels also affect the character of infection.

**Evidence:**


2. Rai NK, Suryabhan, Ansari M, Kuma M, Shukla VK, Tripathi K. Effect of glycaemic control on apoptosis


**GUIDELINES FOR DRESSINGS IN THE TREATMENT OF DIABETIC ULCERS**

**Preamble**: There is a plethora of choices for topical treatment of diabetic ulcers. Many dressings now combine wound bed preparation, i.e., debridement and/or antimicrobial activity, with moisture control. Guidelines are necessary to help the clinician make decisions regarding the value and best use of these advanced wound care products. Most dressings will be used in combination with offloading and protection of the foot.

**Guideline #5.1**: Use a dressing that will maintain a moist wound-healing environment. (Level III)

**Principle**: A moist wound environment physiologically favors cell migration and matrix formation while accelerating healing of wounds by promoting autolytic debridement. Moist wound healing also reduces pain.

**Evidence**:


**Guideline #5.2**: Use clinical judgment to select a moist wound dressing. (Level III)

**Principle**: Wet-to-dry dressings are not considered continuously moist. Continuously moist saline gauze dressings are as effective as other types of moist wound healing in terms of healing rate.

**Evidence**:


**Guideline #5.3**: Select a dressing that will manage the wound exudates and protect the peri-ulcer skin. (Level I)

**Principle**: Peri-wound maceration and continuous contact with wound exudates can enlarge the wound and impede healing.

**Evidence**:


**Guideline #5.2**: Use clinical judgment to select a moist wound dressing. (Level III)

**Principle**: Wet-to-dry dressings are not considered continuously moist. Continuously moist saline gauze dressings are as effective as other types of moist wound healing in terms of healing rate.

**Evidence**:


**Guideline #5.3**: Select a dressing that will manage the wound exudates and protect the peri-ulcer skin. (Level I)

**Principle**: Peri-wound maceration and continuous contact with wound exudates can enlarge the wound and impede healing.

**Evidence**:


**Guideline #5.4:** Select a dressing that stays in place, minimizes shear and friction, and does not cause additional tissue damage. (Level II)

**Principle:** Wound location, peri-wound skin quality, and patient activity can all affect the choice of dressing.

**Evidence:**

**Guideline #5.5:** Select a dressing that is cost effective. (Level I)

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

**Evidence:**


**Guideline #5.6:** Selectively use adjuvant agents (topical, device, and/or systemic) after evaluating a patient and their ulcer characteristics and when there is a lack of healing progress in response to more traditional therapies. (Detailed discussions of these alternatives are in Adjuvant Agents [Topical, Device, Systemic] Guidelines; Level I)

**Principle:** Emerging therapies through recombinant technologies and cell-based devices may offer benefit and increase healing in selected patients or difficult wounds. These therapies are quite diverse and are discussed in detail in the Adjuvant Agents Guidelines.

**Evidence:**
Evidence references are detailed in the Adjuvant Agents (Topical, Device, Systemic Guidelines).


GUIDELINES FOR THE USE OF ADJUVANT AGENTS (TOPICAL, DEVICE, AND SYSTEMIC) IN THE TREATMENT OF DIABETIC ULCERS

Preamble: Many agents have been suggested to be used as adjuvants to dressings and offloading therapy in the treatment of diabetic ulcers. These adjuvant agents can be divided into topical agents to be applied to the ulcer, devices aimed at accelerating ulcer healing, and systemic drugs to treat the patient. Several of these agents have enough evidence to allow guidelines regarding their use.

TOPICAL AGENTS

Guideline #7.1.1: Platelet-derived growth factor (PDGF) is effective in treating diabetic neurotrophic foot ulcers. (Level I)

Principle: Cytokine growth factors are messengers/mediators in wound healing.

Evidence:


5. Robson MC, Payne WG, Garner WL, Biundo J, Giacalone V, Cooper D, Ouyang P. Integrating the results of Phase IV (postmarketing) clinical trial with four previous trials reinforces the position that Regranex (becaplermin) gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcers. J Appl Res 2005; 5: 35–45. [STAT]

Guideline #7.1.2: Other cytokine growth factors do not yet have enough data on efficacy to recommend any of them for treatment of diabetic ulcers, although isolated reports suggest their potential usefulness. (Level I)

Principle: Cytokine growth factors are messengers/mediators in wound healing.

Evidence:


11. Gough A, Clapperton M, Rolando N, Foster AV, Philpott-Howard J, Edmonds ME. Randomised placebo-controlled trial of granulocyte-colony...


**DEVICE**

**Guideline #7.2.1:** Negative pressure wound therapy (NPWT) may be of benefit in treating nonhealing diabetic wounds. (Level I)

**Principle:** NPWT treatment may improve wound healing by reducing edema, removing bacterial products, and drawing together the edges of the wound, and should be considered when other treatments are not effective.

**Evidence:**


**Guideline #7.2.2:** Living skin equivalents may be of benefit in healing diabetic foot ulcers. (Level I)

**Principle:** Healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.

**Evidence:**


**Guideline #7.2.3:** Electrical stimulation may be of benefit in healing diabetic foot ulcers. (Level I)

**Principle:** Application of electric current to wounds may affect protein synthesis, cell migration, and bacterial growth.

**Evidence:**


**SYSTEMIC AGENTS**

**Guideline #7.3.1:** Hyperbaric oxygen therapy may be of benefit in reducing the amputation rate in patients with ischemic diabetic foot ulcers. (Level I)

**Principle:** Hyperbaric oxygen therapy may increase the amount of oxygen delivered to a wound in diabetic patients and thereby improve healing.
Evidence:

GUIDELINES FOR PREVENTION OF RECURRENCE OF DIABETIC FOOT ULCERS

Preamble: Diabetic ulcers of the lower extremity are a chronic problem. Recurrence rates are 8–59%. Therefore, long-term maintenance must be addressed even for healed ulcers.

Guideline #8.1: Patients with healed diabetic ulcers should use protective footwear to prevent recurrence. (Level II)

Principle: Most treatments do not eliminate the underlying increased pressure on the foot, so offloading is necessary long term.

Evidence:

Guideline #8.2: Good foot care and daily inspection of the feet will reduce the recurrence of diabetic ulceration. (Level II)

Principle: Good foot care including proper bathing, nail trimming, and wearing proper footwear will reduce ulceration in diabetic feet.

Evidence:

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