Guidelines for the treatment of diabetic ulcers

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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
RETRO 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

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Each of the separate guidelines is undergoing a Delphi consensus among the panel members. Not all panel members thought they had sufficient expertise to critique all of the separate sections of the guidelines. However, each set of guidelines was critically evaluated by at least ten panel members.

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)

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:

1. Sahli D, Eliasson B, Svensson M, Blohme G, Eliasson M, Samuelsson P, Ojbrandt K, Eriksson J. Assessment of toe blood pressure is an effective screening method to identify diabetes patients with lower extremity arterial disease. *Angiology* 2004; 55: 641–51. [CLIN S]
2. Teodorescu V, Chen C, Morrissey N, Faries P, Marin M, Hollier L. Detailed protocol of ischemia and the use of noninvasive vascular laboratory testing in diabetic foot ulcers. *Am J Surg* 2004; 187 (5A): 75S–80. [LIT REV]
3. Hirsch A, Criqui M, Treat-Jacobson D, Regensteiner J, Creager M, Olin J, Krook S, Hunninghake D, Comerota A, Walsh M, McDermott M, Hiatt W. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; 286: 1317–24. [CLIN S]
4. Ascher E, Hingorani A, Markevich N, Yorkovich W, Schutzer R, Hou A, Jacob T, Nahata S, Kallakuri S. Role of duplex arteriography as the sole preoperative imaging modality prior to lower extremity revascularization surgery in diabetic and renal patients. *Ann Vasc Surg* 2004; 18: 433–439. [CLIN S]
5. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WRC, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease). American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/pad/index.pdf. [STAT]
6. Padberg FT, Back TL, Thompson PN, Hobson RW. Transcutaneous oxygen (TcPO2) estimates probability of healing in the ischemic extremity. *J Surg Res* 1996; 60: 365–9. [CLIN S]

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: Neuropathy leads to foot deformity with abnormal pressure on the foot, especially the plantar surface. Lack of protective sensation allows ulceration in areas of high pressure. Autonomic neuropathy may increase the likelihood of skin breakdown.

Evidence:

1. Singh N, Armstrong D, Lipsky B. Preventing foot ulcers in patients with diabetes. *JAMA* 2005; 293: 217–28. [LIT REV]
2. Kamei N, Yamane K, Nakanishi S, Yamashita Y, Tamura T, Ohshita K, Watanabe H, Fujikawa R, Okubo M, Kohno N. Effectiveness of Semmes–Weinstein monofilament examination for diabetic peripheral neuropathy screening. *J Diab Complications* 2005; 19: 47–53. [CLIN S]
3. Foltz K, Fallat L, Schwartz S. Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. *J Foot Ankle Surg* 2004; 43: 87–92. [CLIN S]
4. Jirkovska A, Boucek P, Woskova V, Bartos V, Skibova J. Identification of patients at risk for diabetic foot: a comparison of standardized noninvasive testing with routine practice at community diabetes clinics. *J Diab Complications* 2001; 15: 63–68. [CLIN S]
5. Mayfield J, Sugarman J. The use of the Semmes–Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. *J Fam Pract* 2000; 49 (Suppl. 11): S17–29. [LIT REV]
6. Pham H, Armstrong D, Harvey C, Harkless L, Giurini J, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000; 23: 606–11. [CLIN S]

7. Smieja M, Hunt D, Edelman D, Etchells E, Cornuz J, Simel D. Clinical examination for the detection of protective sensation in the feet of diabetic patients. International Cooperative Group for Clinical Examination Research. *J Gen Intern Med* 1999; 14: 418–24. [CLIN S]
8. Kumar S, Fernando D, Veves A, Knowles E, Young M, Boulton A. Semmes–Weinstein monofilaments: a simple, effective and inexpensive screening device for identifying diabetic patients at risk of foot ulceration. *Diab Res Clin Pract* 1991; 13: 63–7. [CLIN S]
9. Holewski J, Stess R, Graf P, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. *J Rehabil Res Dev* 1988; 25: 1–10. [CLIN S]
10. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JC. Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Int Med* 1998; 158: 157–62. [CLIN S]
11. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. *Diabetes Care* 2003; 26: 1069–73. [CLIN S]

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:

1. Janisse D. The Therapeutic Shoe Bill: medicare coverage for prescription footwear for diabetic patients. *Foot Ankle Int* 2005; 26: 42–5. [CLIN S]
2. Pinzur M, Slovenkai M, Trepman E, Shields N. Diabetes Committee of American Orthopaedic Foot and Ankle Society. Guidelines for diabetic foot care: recommendations endorsed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society. *Foot Ankle Int* 2005; 26: 113–9. [LIT REV]
3. Reiber GE, Smith DG, Wallace C, Sullivan K, Hayes S, Vath C, Maciejewski ML, Yu O, Heagerty PJ, LeMaster J. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. 2002; *JAMA* 287: 2552–8. [RCT]
4. Maciejewski ML, Reiber GE, Smith DG, Wallace C, Hayes S, Boyko EJ. Effectiveness of diabetic therapeutic footwear in preventing reulceration. *Diabetes Care* 2004; 27: 1774–82. [LIT REV]
5. Chantelau E, Kushner T, Spraul M. How effective is cushioned therapeutic footwear in protecting diabetic feet? A clinical study. *Diabetes Med* 1990; 7: 355–9. [CLIN S]
6. Chantelau E, Haage P. An audit of cushioned diabetic footwear: relation to patient compliance. *Diabetes Med* 1994; 11: 114–6. [CLIN S]
7. Uccioli L, Faglia E, Monticone G, Favales F, Durola L, Aldeghi A, Quarantiello A, Calia P, Menzinger G. Manufactured shoes in the prevention of diabetic foot ulcers. *Diabetes Care* 1995; 18: 1376–8. [RCT]

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:

1. Katz I, Harlan A, Miranda-Polma B, Prieto-Sanchez L, Armstrong D, Bowker J, Mizel M, Boulton A. A randomized trial of two irremovable off-loading devices in management of plantar neuropathic diabetic foot ulcers. *Diabetes Care* 2005; 28: 555–9. [RCT]
2. Armstrong D, Nguyen H, Lavery L, van Schie C, Boulton A, Harkless L. Off-loading the diabetic foot wound: A randomized clinical trial. *Diabetes Care* 2001; 24: 1019–22. [RCT]
3. Hartsell H, Brand R, Frantz R, Saltzman C. The effects of total contact casting materials on plantar pressures. *Foot Ankle Int* 2004; 25: 73–8. [Clin S]
4. Ha Van G, Siney H, Hartmann-Heurtier A, Jacqueminet S, Greau F, Grimaldi A. Nonremovable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety and compliance. *Diabetes Care* 2003; 26: 2848–52. [CLIN S]
5. Piaggesi A, Viacava P, Rizzo L, Naccarato G, Baccetti F, Romanelli M, Zampa V, Del-Prato S. Semiquantitative analysis of the histopathologic features of the neuropathic foot ulcer: effects of pressure relief. *Diabetes Care* 2003; 26: 3123–8. [CLIN S]
6. Ulbrecht J, Cavanagh P, Caputo G. Foot problems in diabetes: an overview. *Clin Infect Dis* 2004; 39 (Suppl. 2): S73–82. [LIT REV]
7. Birke JA, Pavich MA, Patout CA, Horswell R. Comparison of forefoot ulcer healing using alternative offloading methods in patients with diabetes mellitus. *Adv Skin Wound Care* 2002; 15: 210–5. [RETRO S]
8. Helm P, Walker S, Pullium G. Total contact casting in diabetic patients with neuropathic foot ulcerations. *Arch Phys Med Rehabil* 1984; 65: 691–3. [CLIN S]

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. Infection

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:

1. Edlich RF, Rodeheaver GT, Thacker JG, et al. Technical factors in wound management. In: Dunphy JE, Hun TK, editors. *Fundamentals of Wound Management in Surgery*. South Plainfield, NJ: Chirurgecom, 1977. [EXP]
2. Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1993; 3: 1–78. [STAT]
3. Steed D, Donohue D, Webster M, Lindsley L and the Diabetic Ulcer Study Group. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. *J Am Coll Surg* 1996; 183: 61–4. [RCT]
4. Witkowski JA, Parrish LC. Debridement of cutaneous ulcers: medical and surgical aspects. *Clin Dermatol* 1992; 9: 585–91. [LIT REV]
5. Falanga V. Wound bed preparation and the role of enzymes: a case for multiple actions of therapeutic agents. *Wounds* 2002; 14: 47–57. [LIT REV]
6. Hamer ML, Robson MC, Krizek TJ, Southwick W. Quantitative bacterial analyses of comparative wound irrigations. *Ann Surg* 1975; 181: 819–22. [EXP]
7. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Rep Reg* 2002; 10: 354–9. [RCT]
8. Davies CE, Turton G, Woolfrey G, Elley R, Taylor M. Exploring debridement options for chronic venous leg ulcers. *Br J Nurs* 2005; 14: 393–7. [LIT REV]

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:

1. Robson MC, Stenberg, BD, Heggers, JP. Wound healing alterations caused by infection. *Clin Plast Surg* 1990; 17: 485–92. [LIT REV]
2. Robson MC. Wound infection: a failure of wound healing caused by an imbalance of bacteria. *Surg Clin North Am* 1997; 77: 637–50. [LIT REV]
3. Browne AC, Vearncombe M, Sibbald RG. High bacterial load in asymptomatic diabetic patients with neurotrophic ulcers retards wound healing after application of dermagraft. *Ostomy/Wound Manage* 2001; 47: 44–9. [RCT]
4. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. *Lancet* 2005; 366: 1725–35. [LIT REV]
5. Tobin GR. Closure of contaminated wounds: biologic and technical considerations. *Surg Clin North Am* 1984; 64: 639–52. [LIT REV]
6. Heggers JP. Variations on a theme. In: Heggers JP, Robson MC, editors. *Quantitative Bacteriology: Its Role in the Armamentarium of the Surgeon*. Boca Raton: CRC Press, 1991. [TECH]
7. Levine NS, Lindberg RB, Mason AD, Pruitt B. The quantitative swab culture and smear: a quick, simple method for determining the number of viable aerobic bacteria on open wounds. *J Trauma* 1976; 16: 89–94. [TECH]
8. Nystrom PO. The microbiological swab sampler: a quantitative experimental investigation. *Acta Pathol Microbiol Scand* 1978; 86B: 361–7. [TECH]
9. Volenec FJ, Clark GM, Mani MM, Humphrey LJ. Burn wound biopsy bacterial quantitation: a statistical analysis. *Am J Surg* 1979; 138: 695–7. [STAT]
10. Stephens P, Wall I, Wilson MJ, Hill K, Davies C, Hill C, Harding K, Thomas D. Anaerobic cocci populating the deep tissues of chronic wounds impair cellular wound healing responses in vitro. *Br J Dermatol* 2003; 148: 456–66. [CLIN S]
11. Gerding DN. Foot infections in diabetic patients: the role of anaerobes. *Clin Infect Dis* 1995; 20 (Suppl. 2): S283–8. [LIT REV]
12. Schraibman IG. The significance of beta-haemolytic streptococci in chronic leg ulcers. *Ann R Coll Surg Engl* 1990; 72: 123–4. [CLIN S]
13. Lookingbill DP, Miller SH, Knowles RC. Bacteriology of chronic leg ulcers. *Arch Dermatol* 1978; 114: 1765–8. [RCT]

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:

1. Robson MC. Wound infections: a failure of wound healing caused by an imbalance of bacteria. *Surg Clin North Am* 1997; 77: 637–50. [LIT REV]
2. Fumal I, Braham C, Paquet P, Pierard-Franchimont C, Pierard G. The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora: a proof-of-concept study. *Dermatology* 2002; 204 (Suppl. 1): 70–4. [RCT]

3. Robson MC, Mannari RJ, Smith PD, Payne WG. Maintenance of wound bacterial balance. *Am J Surg* 1999; 178: 399–402. [RCT]
4. Schraibman IG. The significance of beta-haemolytic streptococcus in chronic leg ulcers. *Ann R Coll Surg Engl* 1990; 72: 122–4. [CLIN S]
5. White RJ, Cooper R, Kingsley A. Wound colonization and infection: the role of topical antimicrobials. *Br J Nurs* 2001; 10: 563–78. [LIT REV]
6. Lookingbill DP, Miller SH, Knowles RC. Bacteriology of chronic leg ulcers. *Arch Dermatol* 1978; 114: 1765–8. [RCT]

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:

1. Lipsky B. International Consensus Group on Diagnosing and Treating the Infected Diabetic Foot: a report from the international consensus on diagnosing and treating the infected diabetic foot. *Diabetes Metab Res Rev* 2004; 20 (Suppl. 1): S68-77. [STAT]
2. O'Meara S, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. *Health Technol Assess* 2000; 4: 1–237. [STAT]
3. Lipsky BA, Berendt AR. Principles and practice of antibiotic therapy of diabetic foot infections. *Diabetes Metab Res Rev* 2000; 16 (Suppl. 1): S42–6. [LIT REV]
4. Lipsky BA, Armstrong DG, Citron DM, Tice A, Morgenstern D, Abramson M. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. *Lancet* 2005; 366: 1695–703. [RCT]

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:

1. Rickets LR, Squire JR, Topley E, et al. Human skin lipids with particular reference to the self-sterilizing power of the skin. *Clin Sci Mol Med* 1951; 10: 89–93. [EXP]
2. Baddour LM. Cellulitis syndromes: an update. *Int J Antimicrob Agents* 2000; 14: 113–6. [LIT REV]
3. Chiller K, Selkin BA, Murakawa GJ. Skin microflora and bacterial infections of the skin. *J Invest Dermatol Symp Proc* 2001; 6: 170–4. [LIT REV]
4. Guay DR. Treatment of bacterial skin and skin structure infections. *Expert Opin Pharmacother* 2003; 4: 1259–75. [LIT REV]
5. Edlich RF, Winters KL, Britt LD, Long W. Bacterial diseases of the skin. *J Long Term Eff Med Implants* 2005; 15: 499–510. [LIT REV]
6. Dall L, Peterson S, Simmons T, Dall A. Rapid resolution of cellulites in patients managed with combination antibiotic and anti-inflammatory therapy. *Cutis* 2005; 75: 177–80. [RCT]

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:

1. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. *JAMA* 1995; 273: 721–3. [CLIN S]
2. Mader JT, Ortiz M, Calhoun JH. Update on the diagnosis and management of osteomyelitis. *Clin Podiatr Med Surg* 1996; 13: 701–24. [LIT REV]
3. Stengel D, Bauwens K, Sehouli J, Ekkernkamp A, Porzsolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. *Lancet Infect Dis* 2001; 1: 175–88. [STAT]
4. Heller WA, Gottlieb LJ, Zachary LS, Finn H. The use of quantitative bacteriologic assessment of bone. *Plast Reconstr Surg* 1997; 100: 397–401. [CLIN S]

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:

1. Stengel D, Bauwens K, Sehouli J, et al. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. *Lancet Infect Dis* 2001; 1: 175–88. [STAT]

2. Lipsky BA, Berendt AR. Principles and practice of antibiotic therapy of diabetic foot infections. *Diabetes Metab Res Rev* 2000; 16 (Suppl. 1): S42–46. [LIT REV]
3. Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? *Int J Infect Dis* 2005; 9: 127–38. [LIT REV]
4. Swiontkowski MF, Hanel DP, Vedder NB, Schwappach J. A comparison of short- and long-term intravenous antibiotic therapy in the postoperative management of adult osteomyelitis. *J Bone Jt Surg Br* 1999; 81: 1046–50. [RCT]
5. Mader JT, Ortiz M, Calhoun JH. Update on the diagnosis and management of osteomyelitis. *Clin Podiatr Med Surg* 1996; 13: 701–24. [LIT REV]

Guideline #3.8: Minimize the tissue level of bacteria, preferably to $\leq 10^5$ 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 10^5 organisms per gram of tissue cannot be readily closed, as the incidence of wound infection that follows is 50–100%" Tobin (1984).

Evidence:

1. Edlich RF, Rodeheaver GT, Thacker JG, Winn H, Edgerton M. Management of soft tissue injury. *Clin Plast Surg* 1977; 4: 191–8. [LIT REV]
2. Liedberg NC, Reiss E, Artz CP. The effect of bacteria on the take of split thickness skin grafts in rabbits. *Ann Surg* 1955; 142: 92–7. [EXP]
3. Krizek TJ, Robson MC, Ko F. Bacterial growth and skin graft survival. *Surg Forum* 1968; 18: 518–9. [RCT]
4. Murphy RC, Robson MC, Heggers JP, Kadowaki M. The effect of contamination on musculocutaneous and random flaps. *J Surg Res* 1986; 41: 75–80. [EXP]
5. Tobin GR. Closure of contaminated wounds: biologic and technical considerations. *Surg Clin North Am* 1984; 64: 639–52. [LIT REV]
6. Browne AC, Vearncombe M, Sibbald RG. High bacterial load in asymptomatic diabetic patients with neurotrophic ulcers retards wound healing after application of Dermagraft. *Ostomy/Wound Manage* 2001; 47: 44–9. [RCT]

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. The aim of wound bed preparation is to convert the molecular and cellular environment of a chronic wound to that of an acute healing wound. The principles of wound bed preparation have been enumerated: Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. *Wound Rep Reg* 2003; 11: 1s–23s; Sibblad, RG, Williamson, D, Orsted, HL. Preparing the wound bed: debridement, bacterial balance, and moisture balance. *Ostomy/Wound Manage* 2000; 46: 14–35.

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:

1. Lazarus GS, Cooper DM, Knighton DR, Margolis D, Pecoraro R, Rodehaver G, Robson M. Definitions and guidelines for assessment of wounds and evaluation of healing. *Arch Dematol* 1994; 130: 489–93. [STAT]
2. Williams DT, Harding K. Healing responses of skin and muscle in critical illness. *Crit Care Med* 2003; 31 (Suppl. 8): 547s–57s. [LIT REV]
3. Beer HD, Fassler R, Werner S. Glucocorticoid-regulated gene expression during cutaneous wound repair. *Vitam Horm* 2000; 59: 217–39. [EXP]
4. Velasco M, Guaitero E. A comparative study of some anti-inflammatory drugs in wound healing of the rat. *Experientia* 1973; 29: 1250–1. [EXP]
5. Jorgensen LN, Kallehave F, Karlsmark T, Gottrup F. Reduced collagen accumulation after major surgery. *Br J Surg* 1996; 83: 1591–4. [CLIN S]
6. Sorensen LT, Nielsen HB, Kharami A, Gottrup F. Effect of smoking and abstention on oxidative burst and reactivity of neutrophils and monocytes. *Surgery* 2004; 136: 1047–53. [RCT]
7. Mustoe T. Understanding chronic wounds: a unifying hypothesis on their pathogenesis and implications for therapy. *Am J Surg* 2004; 187 (5A): 65s–70s. [LIT REV]

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:

1. Bourdel-Marchasson I, Barateau M, Rondeau V, Dequae-Merchadou L, Salles-Montaudon N, Emeriau J, Manciet G, Dartigues J. A multi-center trial of the effects of oral nutritional supplementation in critically older inpatients. GAGE Group. Groupe Aquitain Gériatrique d'Evaluation. *Nutrition* 2000; 16: 1–5. [RCT]
2. Lansdown A. Nutrition II: a vital consideration in the management of skin wounds. *Br J Nurs* 2004; 13: 1199–210. [LIT REV]
3. Himes D. Protein-calorie malnutrition and involuntary weight loss: the role of aggressive nutritional intervention in wound healing. *Ostomy/Wound Manage* 1999; 45: 46–51. [LIT REV]

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:

1. Chang N, Goodson W, Gottrup F, Hunt T. Direct management of wound and tissue oxygen tensions in postoperative patients. *Ann Surg* 1983; 197: 470–8. [CLIN S]
2. Nighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance. *Arch Surg* 1986; 121: 191–5. [EXP]
3. Hunt TK, Hopf HW. Wound healing and wound infection. What surgeons and anesthesiologists can do. *Surg Clin North Am* 1997; 77: 587–606. [LIT REV]
4. Jonsson K, Jensen JA, Goodson WH, Scheuenstuhl H, West J, Hopf H, Hunt T. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. *Ann Surg* 1991; 214: 605–13. [RCT]
5. Jensen JA, Goodson WH, Hopf HW, Hunt TK. Cigarette smoking decreases tissue oxygen. *Arch Surg* 1991; 126: 1131–4. [RCT]
6. Hopf H, Hunt TK, West JM, Blomquist P, Goodson W, Jensen J, Jonsson K, Paty P, Rabkin J, Upton R, von Smitten K, Whitney J. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* 1997; 132: 997–1004. [CLIN S]
7. Gottrup F. Oxygen in wound healing and infection. *World J Surg* 2004; 28: 312–5. [LIT REV]
8. Hunt TK, Aslam RS. Oxygen 2002: Wounds. *Undersea Hyperb Med* 2004; 31: 147–53. [LIT REV]
9. Greif R, Akca O, Horn E, Kurz A, Sessler D. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. *N Engl J Med* 2000; 342: 161–7. [RCT]

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:

1. Steed DL, Donohoe D, Webster MW, Lindsley L, and the Diabetic Ulcer Study Group. Effect of extensive debridement on the healing of diabetic foot ulcers. *J Am Coll Surg* 1996; 183: 61–4. [RCT]
2. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Rep Reg* 2002; 10: 354–9. [RCT]
3. Mulder GD. Cost-effective managed care: gel versus wet-to-dry for debridement. *Ostomy/Wound Manage* 1995; 41: 68–70. [RCT]
4. Alvarez OM, Fernandez-Obregon A, Rogers RS, et al. A prospective, randomized, comparative study of collagenase and papain-urea for pressure ulcer debridement. *Wounds* 2002; 14: 293–301. [RCT]
5. Steed DL. Debridement. *Am J Surg* 2004; 187 (Suppl. 5A): 71s–4s. [LIT REV]
6. Ayello EA, Cuddigan JE. Debridement: controlling the necrotic/cellular burden. *Adv Skin Wound Care* 2004; 17: 66–75. [LIT REV]
7. Sieggreen MY, Maklebust J. Debridement: choices and challenges. *Adv Wound Care* 1997; 10: 32–7. [LIT REV]
8. Sibbald RG, Williamson D, Orsted HL, Campbell K, Keast D, Krasner D, Sibbald D. Preparing the wound bed—debridement, bacterial balance, and moisture balance. *Ostomy/Wound Manage* 2000; 46: 14–35. [LIT REV]
9. Mosher BA, Cuddigan J, Thomas DR, Boudreau DM. Outcomes of 4 methods of debridement using a decision analysis methodology. *Adv Wound Care* 1999; 12: 81–8. [TECH]
10. Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999; 3 (17 Part 1): 1–17. [STAT]
11. Alvarez OM, Mertz PM, Eaglstein WH. The effect of occlusive dressings on collagen synthesis and re-epithelialization in superficial wounds. *J Surg Res* 1983; 35: 142–8. [EXP]
12. Falanga V. Wound bed preparation and the role of enzymes: a case for multiple actions of the therapeutic agents. *Wounds* 2002; 14: 47–57. [LIT REV]

13. Rao DB, Sane PG, Georgiev EL. Collagenase in the treatment of dermal and decubitus ulcers. *J Am Geriatr Soc* 1975; 23: 22–30. [CLIN S]
14. Capasso VA, Munro BH. The cost and efficacy of two wound treatments. *AORN J* 2003; 77: 984–1004. [RETRO S]
15. Piaggesi A, Schipani E, Campi F, Romanelli M, Baccetti F, Arvia C, Navalesi R. Conservative surgical approach versus non-surgical management for diabetic neurotrophic foot ulcers: a randomized trial. *Diabetic Med* 1998; 15: 412–7. [RCT]
16. Jensen JL, Seeley J, Gillin B. Diabetic foot ulcerations. A controlled, randomized comparison of two moist wound healing protocols: Carrasyn hydrogel wound dressing and wet-to-moist saline gauze. *Adv Wound Care* 1998; 11 (Suppl. 7): 1–4. [RCT]

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:

1. Rodeheaver GT. Wound cleansing, wound irrigation, wound disinfection. In: Krasner, D, Kane, D, editors. *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. Wayne, PA: Health Management Publications Inc., 1997: 97–108. [LIT REV]
2. Morris EJ, Dowlen S, Cullen B. Early clinical experience with topical collagen in vascular wound care. *J Wound Ostomy Continence Nurs* 1994; 21: 247–50. [CLIN S]
3. Rodeheaver GT, Kurtz L, Kircher BJ, Edilich RF. Pluronic F-68: a promising new skin wound cleanser. *Ann Emerg Med* 1980; 9: 572–6. [EXP]
4. Hamer MI, Robson MC, Krizek TJ, et al. Quantitative bacterial analysis of comparative wound irrigations. *Ann Surg* 1975; 181: 819–22. [EXP]

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:

1. Lazarus GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. *Arch Dermatol* 1994; 130: 489–93. [STAT]
2. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Rep Reg* 2002; 10: 354–9. [RCT]
3. Krasner D. Wound Healing Scale, version 1.0: a proposal. *Adv Wound Care* 1997; 10: 82–5. [TECH]
4. Robson MD, Hill DP, Woodske ME, Steed DL. Wound healing trajectories as predictors of effectiveness of therapeutic agents. *Arch Surg* 2000; 135: 773–7. [STAT]

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]
2. Robson MC, Hill DP Woodske ME, Steed DL. Wound healing trajectories as predictors of effectiveness of therapeutic agents. *Arch Surg* 2000; 135: 773–7. [CLIN S]
3. Robson MC, Steed DL, Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. *Current Prob Surg* 2001; 38: 61–140. [LIT REV]
4. Van Rijswijk L. Full thickness leg ulcers: patient demographics and predictors of healing. Multi-center Leg Ulcer Study Group. *J Fam Prac* 1993; 36: 625–32. [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:

1. Rubinstein A, Pierce CE. Rapid healing of diabetic foot ulcers with a meticulous blood glucose control. *Acta Diabetol Lat* 1988; 25: 25–32. [CLIN S]
2. Rai NK, Suryabhan, Ansari M, Kuma M, Shukla VK, Tripathi K. Effect of glycaemic control on apoptosis

in diabetic wounds. *J Wound Care* 2005; 14: 277–81. [CLIN S]
3. Robson MC, Heggers JP. Variables in host resistance pertaining to Septicemia. I. Blood glucose level. *J Am Geriatr Soc* 1969; 17: 991–6. [CLIN S]
4. Robson MC. A new look at diabetes mellitus and infection. *Am J Surg* 1970; 120: 681–2. [EXP]
5. Follak N, Kloting I, Merk H. Influence of diabetic metabolic state on fracture healing in spontaneously diabetic rats. *Diabetes Metab Res Rev* 2005; 21: 288–96. [EXP]
6. Duckworth WC, Fawcett J, Reddy S, Page JC. Insulin-degrading activity in wound fluid. *J Clin Endocrinal Metab* 2004; 89: 847–51. [EXP]
7. Beam HA, Parsons JR, Lin SS. The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. *J Ortho Res* 2002; 20: 1210–6. [EXP]
8. Verhofstad MH, Hendriks T. Complete prevention of impaired anastomatic healing in diabetic rats requires preoperative blood glucose control. *Br J Surg* 1996; 83: 1717–21. [EXP]
9. Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T, Wertheimer E. Glucose effects on skin keratinocytes: implications for diabetes skin complications. *Diabetes* 2001; 50: 1627–35. [EXP]
10. Greenhalgh DG. Wound healing and diabetes mellitus. *Clin Plast Surg* 2003; 30: 37–45. [LIT REV]
11. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999; 22: 1408–14. [CLIN S]

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:

1. Winter GD, Scales JT. Effect of air drying and dressings on the surface of a wound. *Nature* 1963; 197: 91–2. [EXP]
2. Breuing K, Eriksson E, Liu P, Miller DR. Healing of partial thickness porcine skin wounds in a liquid environment. *J Surg Res* 1992; 52: 50–8. [EXP]
3. Svensjo T, Pomahac B, Yao F, Slama J, Eriksson E. Accelerated healing of full-thickness skin wounds in a wet environment. *Plast Reconstr Surg* 2000; 106: 602–12. [EXP]
4. Vranckx JJ, Slama J, Preuss S, Perez N, Svensjo T, Visovatti S, Breuing K, Bartlett R, Pribaz J, Weiss D, Eriksson E. Wet wound healing. *Plast Reconstr Surg* 2002; 110: 1680–7. [CLIN S]

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:

1. Geronemus RG, Robins P. The effect of two new dressings on epidermal wound healing. *J Derm Surg Oncol* 1982; 8: 850–2. [EXP]
2. Blair SD, Jarvis P, Salmon M, McCollum C. Clinical trial of calcium alginate Haemostatic swabs. *Br J Surg* 1990; 77: 568–70. [RCT]
3. Sayag J, Meaume S, Bohbot S. Healing properties of calcium alginate dressings. *J Wound Care* 1996; 5: 357–62. [RCT]
4. Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D. Systematic reviews of wound care management: (2) dressings and topical agents used in the healing of chronic wounds. *Health Technol Assess* 1999; 3 (17 Part 2): 1–35. [STAT]
5. Donaghue VM, Chrzan JS, Rosenblum BI, Giurini JM, Habershaw GM, Veves A. Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers. *Adv Wound Care* 1998; 11: 114–9. [CLIN S]

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:

1. Bucalo, B, Eaglstein WH, Falanga V. Inhibition of cell proliferation by chronic wound fluid. *Wound Rep Reg* 1993; 1: 181–6. [EXP]
2. Trengove NJ, Stacey MC, Mac Auley S, Bennett N, Gibson J, Burslem F, Murphy G, Shultz G. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. *Wound Rep Reg* 1999; 7: 442–52. [EXP]
3. Yager DR, Zhang LY, Liang HX, Diegelmann RF, Cohen IK. Wound fluids from human pressure ulcers contain elevated matrix metalloproteinase levels and activity compared to surgical wound fluids. *J Invest Derm* 1996; 107: 743–8. [EXP]
4. Sayag J, Meaume S, Gohbot S. Healing properties of calcium alginate dressings. *J Wound Care* 1996; 5: 357–62. [RCT]

5. Lalau JD, Bresson R, Charpentier P, Coliche V, Erlher S, Ha Van G, Magalon G, Martin J, Moreau Y, Pradines S, Rigal F, Wemeau J, Richard J. Efficacy and tolerance of calcium alginate versus Vaseline gauze dressings in the treatment of diabetic foot lesions. *Diabetes Metab* 2002; 28: 223–9. [RCT]

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:

1. Sasseville D, Tennstedt D, Lachapelle JM. Allergic contact dermatitis from hydrocolloid dressings. *Am J Contact Dermat* 1997; 8: 236–8. [CLIN S]

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:

1. Ohlsson P, Larsson K, Linkholm C, Moller M. A cost-effectiveness study of leg ulcer treatment in primary care. Comparison of saline-gauze and hydrocolloid treatment in a prospective, randomized study. *Scand J Prim Health Care* 1994; 12: 295–9. [RCT]
2. Harding K, Price P, Robinson B, et al. Cost and dressing evaluation of hydrofiber and alginate dressings in the management of community-based patients with chronic leg ulcerations. *Wounds* 2001; 13: 229–36. [RCT]
3. Bolton L, van Rijswijk L, Shaffer F. Quality wound care equals cost-effective wound care: a clinical model. *Adv Wound Care* 1997; 10: 33–8. [LIT REV]

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).

1. Brem H, Sheehan P, Boulton AJ. Protocol for treatment of diabetic foot ulcers. *Am J Surg* 2004; 187 (5A): S1–10. [LIT REV]

GUIDELINES FOR *SURGERY* IN THE TREATMENT OF DIABETIC ULCERS

Preamble: The mainstays of dressings and offloading are not successful in healing all diabetic ulcers. Over the years, multiple surgical procedures have been attempted to treat diabetic ulcers with varying degrees of success. True randomized clinical trials comparing operative techniques are difficult, but data are available supporting surgery in selected patients.

Guideline #6.1: Achilles tendon lengthening may improve healing of diabetic forefoot wounds. (Level II)

Principle: Lengthening the Achilles tendon reduces pressure on forefoot plantar ulcers in patients with limited dorsiflexion and may be of benefit in healing certain diabetic foot ulcers.

Evidence:

1. Mueller M, Sinacore D, Hastings M, Strube M, Johnson J. Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. *J Bone Jt Surg* 2003; 85-A: 1436–45. [RCT]
2. Nishimoto G, Attinger C, Cooper P. Lengthening the Achilles tendon for the treatment of diabetic plantar forefoot ulceration. *Surg Clin North Am* 2003; 83: 707–26. [LIT REV]
3. Armstrong DG, Stacpoole-Shea S, Nguyen H, Harkless L. Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. *J Bone Jt Surg* 1999; 81-A: 535–8. [CLIN S]
4. Lin SS, Lee TH, Wapner KL. Plantar forefoot ulceration with equinus deformity of the ankle in diabetic patients: the effect of tendo-Achilles lengthening and total contact casting. *Orthopedics* 1996; 19: 465–75. [CLIN S]
5. Maluf KS, Mueller MJ, Strube MJ, Engsberg JR, Johnson JE. Tendon Achilles lengthening for the treatment of neuropathic ulcers causes a temporary reduction in forefoot pressure associated with changes in plantar flexor power rather than ankle motion during gait. *J Biomech* 2004; 37: 897–906. [CLIN S]

Guideline #6.2: Patients with ischemia should be considered for a revascularization procedure.

Principle: In patients with inadequate arterial inflow, improvement in blood supply is associated with an increase in oxygenation, nutrition, and wound healing.

Evidence:

1. Jeffcoate WJ, Price P, Harding KG. International Working Group on Wound Healing and Treatments for People with Diabetic Foot Ulcers. *Diabetes Metab Res Rev* 2004; 20: 578–89. [LIT REV]
2. Sumpio BE, Lee T, Blume PA. Vascular evaluation and reconstruction of the diabetic foot. *Clin Podiatr Med Surg* 2003; 20: 689–708. [LIT REV]
3. Wolfle K, Bruijmen H, Loeprecht H, et al. Graft patency and clinical outcome of femoro-distal arterial reconstruction in diabetic and non-diabetic patients: results of multicentre comparative analysis. *Eur J Vasc Endovasc Surg* 2003; 25: 229–34. [CLIN S]

4. Faglia E, Mantero M, Caminiti M, et al. Extensive use of peripheral angioplasty, particularly infrapopliteal in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentre study of 221 consecutive diabetic subjects. *J Intern Med* 2002; 252: 225–32. [CLIN S]
5. Akbari CM, Pomposelli FB, Gibbons GW, Campbell DR, Pulling MC, Mydlarz D, LoGerfo F. Lower extremity revascularization in diabetes: late observations. *Arch Surg* 2000; 135: 452–6. [CLIN S]
6. Pomposelli FB, Marcaccio EJ, Gibbons GW, Campbell DR, Freeman DV, Burgess AM, Miller A, LoGerfo FW. Dorsalis pedis arterial bypass: durable limb salvage for foot ischemia in patients with diabetes mellitus. *J Vasc Surg* 1995; 21: 375–84. [CLIN S]

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:

1. Steed D, Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet derived growth factor for the treatment of lower extremity diabetic ulcers. *J Vasc Surg* 1995; 21: 71–81. [RCT]
2. Wieman J, Smiel J, So Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a Phase III randomized, placebo-controlled double-blind study. *Diabetes Care* 1998; 21: 822–7. [RCT]
3. d'Hemecourt PA, Smiell JM, Karim MR. Sodium carboxymethylcellulose aqueous-based gel versus becaplermin gel in patients with non-healing lower extremity ulcers. *Wounds* 1998; 10: 69–75. [RCT]
4. Smiell JM, Wieman J, Steed DL, Perry BH, Sampson AR, Schwab BH. Efficacy and safety of becaplemin (recombinant human platelet-derived, growth factor-BB) in patients with non-healing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Rep Reg* 1999; 7: 335–46. [STAT]
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 (becaplemin) 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:

1. Steed DL, Goslen BG, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. *Diabetes Care* 1992; 15: 1598–604. [RCT]
2. Holloway G, Steed D, DeMarco M, Matsumoto T, Moosa H, Webster M. A randomized, controlled multicenter, dose response trial of activated platelet supernatant, topical CT-102 in chronic, non-healing, diabetic wounds. *Wounds* 1993; 5: 198–206. [RCT]
3. Atri S, Misra J, Bisgt D, et al. Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers. *Surgery* 1990; 108: 508–12. [RCT]
4. Knighton D, Ciresi K, Fiegel V, et al. Classification and treatment of chronic nonhealing ulcers using platelet-derived wound healing formula. *Surg Gynecol Obstet* 1986; 170: 26–30. [RCT]
5. Knighton D, Ciresi K, Fiegel V, Schumerth S, Butler E, Cerra F. Stimulation of repair in chronic, non-healing, cutaneous ulcers using platelet-derived wound healing formula. *Surg Gynecol Obstet* 1990; 170: 50–60. [RCT]
6. Richard JL, Purer-Richard C, Daures JF, et al. Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot. A pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care* 1995; 18: 64–9. [RCT]
7. Robson MC, Steed DL, McPherson JM, Prett BM. Effects of transforming growth factors B2 on wound healing in diabetic foot ulcers. *J Appl Res* 2002; 2: 133–45. [RCT]
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stimulating factor in diabetic foot infection. *Lancet* 1997; 350: 855–9. [RCT]
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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:

1. Eginton M, Brown K, Seabrook G, Towne J, Cambria R. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003; 17: 645–9. [RCT]
2. McCallon S, Knight C, Valiulus J, Cunningham M, McCulloch J, Farinas L. Vacuum-assisted closure versus saline-moistened gauze in the healing of post-operative diabetic foot wounds. *Ostomy/Wound Manage* 2000; 46: 28–34. [RCT]
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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:

1. Marston WA, Hanft JR, Norwood P, Pollak R. Dermagraft Diabetic Foot Ulcer Study Group: the efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003; 26: 1701–5. [RCT]
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6. Curran MP, Plosker GL. Bilayered bioengineered skin substitute (Apligraf): a review if its use in the treatment of venous leg ulcers and diabetic foot ulcers. *Biodrugs* 2002; 16: 439–55. [LIT REV]
7. Marston WA. Dermagraft, a bioengineered human dermal equivalent for the treatment of chronic nonhealing diabetic foot ulcers. *Expert Rev Med Devices* 2004; 1: 21–31. [LIT REV]

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:

1. Kloth LC. Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials. *Int J Low Extrem Wounds* 2005; 4: 23–44. [LIT REV]
2. Houghton P, Kincaid C, Lovell M, Campbell K, Keast D, Woodbury M, Harris K. Effect of electrical stimulation on chronic leg ulcer size and appearance. *Phys Ther* 2003; 83: 17–28. [RCT]
3. Lundeberg T, Eriksson S, Malm M. Electrical nerve stimulation improves healing of diabetic ulcers. *Ann Plast Surg* 1992; 29: 328–31. [RCT]
4. Thawer HA, Houghton PE. Effects of electrical stimulation on the histological properties of wounds in diabetic mice. *Wound Rep Reg* 2001; 9: 107–15. [EXP]
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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:

1. Wang C, Schwaitzberg S, Berliner E, Zarin D, Lau J. Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg* 2003; 138: 272–9. [LIT REV]
2. Abidia A, Laden G, Kuhan G, Johnson B, Wilkinson A, Renwick P, Masson E, McCollum P. The role of hyperbaric oxygen therapy in ischemic diabetic lower extremity ulcers: a double-blind randomised controlled trial. *Eur J Vasc Endovasc Surg* 2003; 25: 513–8. [RCT]
3. Abidia A, Kuhan G, Landen G, Battia H, Johnson B, Wilkinson A. Role of hyperbaric oxygen therapy in ischaemic, diabetic, lower-extremity ulcers: a double blind study. *Br J Surg* 2001; 88: 744–9. [RCT]
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7. Kessler L, Bilbault P, Ortega F, Grasso C, Passemard R, Stephan D, Pinget M, Schneider F. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomised study. *Diabetes Care* 2003; 26: 2378–82. [RCT]
8. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2005: 1–18. [STAT]
9. Wunderlich RP, Peters EJ, Lavery LA. Systemic hyperbaric oxygen therapy: lower extremity wound healing and the diabetic foot. *Diabetes Care* 2000; 23: 1551–5. [LIT REV]

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:

1. Maciejewski M, Reiber G, Smith D, Wallace C, Hayes S, Boyko E. Effectiveness of diabetic therapeutic footwear in preventing reulceration. *Diabetes Care* 2004; 27: 3024–5. [LIT REV]
2. Cavanagh PR. Therapeutic footwear for people with diabetes. *Diabetes Metab Res Rev* 2004; 20 (Suppl. 1): S51–5. [LIT REV]
3. Boulton AJ. Pressure and the diabetic foot: clinical science and off-loading techniques. *Am J Surg* 2004; 187 (5A): 17S–24S. [LIT REV]
4. Pinzur MS, Dart HC. Pedorthic management of the diabetic foot. *Foot Ankle Clin* 2001; 612: 205–14. [LIT REV]
5. Lobmann R, Kayser R, Kasten G, Kasten U, Kluge K, Neumann W, Lehnert H. Effects of preventive footwear on foot pressures as determined by pedibarography in diabetic patients: a prospective study. *Diabet Med* 2001; 18: 314–9. [RCT]
6. Uccioli L, Faglia E, Monticone G, Favales F, Durola L, Aldeghi A, Quarantiello A, Calia P, Menzinger G. Manufactured shoes in the prevention of diabetic foot ulcers. *Diabetes Care* 1995; 18: 1376–8. [RCT]
7. Colagiuri S, Marsden L, Naidu V, Taylor L. Use of orthotic devices to correct planter callus in people with diabetes. *Diabetes Res Clin Pract* 1995; 28: 29–34. [CLIN S]
8. Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP 3rd, Drury DA, Rose SJ. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. *Diabetes Care* 1989; 12: 384–8. [CLIN S]

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:

1. Pinzur M, Slovenkai M, Trepman E, Shields N. Diabetes Committee of American Orthopaedic Foot and Ankle Society. Guidelines for diabetic foot care: recommendations endorsed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society. *Foot Ankle Int* 2005; 26: 113–9. [LIT REV]
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3. Pinzur M. The diabetic foot. *Compr Ther* 2002; 28: 232–7. [LIT REV]
4. Suico JG, Marriott DJ, Vinicor F, Litzelman DK. Behaviors predicting foot lesions in patients with non-insulin dependent diabetes mellitus. *J Gen Intern Med* 1998; 13: 482–4. [STAT]
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6. Humphrey AR, Dowse GK, Thoma K, Zimmet PZ. Diabetes and nontraumatic lower extremity amputations. Incidence, risk factors, and prevention—a 12 year study in Nauru. *Diabetes Care* 1996; 19: 710–4. [CLIN S]

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