# Guidelines for the treatment of arterial insufficiency ulcers

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An advisory panel of academicians, private practice physicians, nurse clinicians, and research nurses was chosen to develop guidelines (minimum standards) for the treatment of arterial insufficiency ulcers of the lower extremities.

## METHODS

Previous guidelines, meta-analyses, PubMed, MEDLINE, EMBASE, The Cochrane Database of Systematic Reviews, recent review articles of arterial ulcer treatment, and the Medicare/CMS consensus of usual treatment of chronic wounds were all searched and 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:

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| 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 were major differences 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. It was also clear that principles that have been validated for other chronic wound types often are applicable to arterial ulcers. Therefore, evidence was sometimes cited that was not specific for arterial ulcers. Because of these variations, a different system was used to grade the evidence weight supporting a given guideline. The level strength of evidence supporting a guideline is listed as Levels I, II, or III. The guideline levels are:

- *Level I*: Meta-analysis of multiple RCTs or at least two RCTs support 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 is included.
- *Level III*: Suggestive data of proof-of-principle, but lacking sufficient data such as meta analysis, RCT, or multiple clinical series.
- *N.B.* 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 arterial ulcers).

In addition to Level of Evidence, the committee agreed to classify the strength of the recommendation. The purpose is to correlate Level of Evidence with Level of Strength. The Levels of Strength supporting a guideline are listed as Level A, Level B, Level C, or Level D. The guideline levels of strength are:

- *Level A*: Strongly recommended/Likely to be of benefit.
- *Level B*: Recommended.
- *Level C*: Recommended but not essential.
- *Level D*: NOT recommended.

## RESULTS

Guidelines have been formulated in seven categories for the treatment of arterial ulcers of the lower extremities. The categories are:

- Diagnosis
- Surgery

- Infection control
- Wound bed preparation
- Dressings
- Adjuvant therapy (device, systemic, local/topical)
- Long-term maintenance

Each of the guidelines underwent a Delphi consensus among the panel members. Each set was critically evaluated by all panel members. There was a consensus of at least ten panel members on each individual guideline. The majority of the guidelines had unanimous concurrence. The resultant GUIDELINES FOR THE TREATMENT OF ARTERIAL INSUFFICIENCY ULCERS are attached.

These are guidelines for treatment. They are intended to guide wound caretakers in choosing the best available options. They are NOT meant to be standards of care.

## GUIDELINES FOR THE *DIAGNOSIS* OF ARTERIAL INSUFFICIENCY ULCERS

*Preamble*: Peripheral arterial occlusive disease (PAOD) affects approximately 10 million people in the United States and is highly associated with significant morbidity and mortality. Because of its high prevalence and associated co-morbidities, there must be an effort to detect arterial disease in patients with wounds and to select appropriate therapy when arterial insufficiency is identified as a significant or primary etiology for an ulcer. [Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in the primary care. *JAMA* 2001; 286: 1317–24.]

*Guideline # 1.1*: All patients with lower extremity ulcers should be assessed for arterial disease. The following signs and values predict that arterial disease may be present. Suspicion of arterial disease in the context of a patient with a lower extremity ulcer should prompt referral to a vascular specialist. (Level IA)

The ideal way to determine whether a patient requires vascular referral has not been defined by clinical research. Health care providers treating patients with lower extremity ulcers should incorporate these evaluations as appropriate for their particular practice, and should consider patient history in deciding whether a vascular referral is necessary.

Decreased or absent palpable pedal pulses (dorsalis pedis and posterior tibialis).[3,9,10] If patients present with strong DP and PT pulses, they generally do NOT need to be referred. A lack of pulse should usually lead to referral. There can be anatomic variability. The sensitivity of a nondetectable pulse for diagnosis of PAOD can be 17–32%, whereas the specificity is 97–99%.[9] In healthy individuals, DP pulse is not present in 8.1%, PT in 2.9%, and both are absent in $< 2\%$.[14]

- Delay in capillary refill response.[1,12]
- Delay of 10–15 seconds in returning of color when raising the leg to 45° for 1 minute, dependent rubor (Buerger's test).[1,12]
- Ankle Brachial Index (ABI) of $\leq 0.90$. ABI for PAOD vary from $< 0.80$ to $< 0.97$,[9,15,16] and a cutoff value of $< 0.9$ is 97% sensitive for isolated aortoiliac disease and 89% sensitive for femoropopliteal disease. More than 50% of patients with PAOD due to an abnormal ABI may not have limb ischemia, but a decrease in their functional activity limiting their quality of life. Furthermore, for most of the described studies in the last two decades, the screening value for PAOD is defined by a resting ABI $\leq 0.9$.[1–6,12–14,17]

Not all patients with abnormal ABI will require revascularization, but referral for further evaluation should be considered. Sensitivity and specificity are reduced in patients with diabetes or in other patients who may have calcified and thus incompressible vessels. ABI $> 1.2$ should also lead to referral to a vascular specialist, as it is also predictive of angiogram-positive disease.

- Transcutaneous oxygen tension ($TcPO_2$) on the periwound skin $< 40$ mmHg.[7,8,11]

Transcutaneous oximetry is not available in every clinic. It is a valuable modality that should be considered in all patients with lower extremity ulcers where it is available.

A number of studies have demonstrated that periwound $PtcO_2$ below a cutoff of about 40 mmHg is associated with impaired healing due to inadequate oxygen supply. Clearly, arterial insufficiency results in reduced oxygen supply and thus decreased $PtcO_2$. A large number of studies have looked at the ability of $PtcO_2$ to predict healing of an amputation.[17–41] The studies have all been performed in patients scheduled for amputation, and thus, presumably, options for revascularization have been exhausted. These studies specifically assess the relationship between $PtcO_2$ and healing when no effort is made to change $PtcO_2$ (e.g., revascularization). Revascularization would be expected to increase $PtcO_2$ and thus change the predicted outcome.

Wutschert and Bounameaux[38] performed a meta-analysis to determine the ability of $PtcO_2$ to predict amputation level, using studies published from 1985 to 1996. There were a total of 615 lower limb amputations (51% in patients with diabetes) and the reamputation rate was 16.4%. Failure was defined as more proximal amputation or extensive (operative) debridement of the stump. They found that 20 mmHg was the most useful cutoff for failure to heal, with a sensitivity of 82% and a specificity of 64%. The positive predictive value (failed to heal) of the 20 mmHg cutoff was 92% and the negative predictive value was 42%. The accuracy was 79%.

$PtcO_2$ is a more effective marker of disease than Doppler assessment or ankle-brachial indices. Thirty-eight studies since 1982 suggest that hypoxia is defined as $PtcO_2$ below 10–40 mmHg.[43–73]

Fifteen studies (1137 patients) demonstrated that $PtcO_2$ provides better overall predictive capability than Doppler studies measuring ABI and segmental pressures, or laser fluximetry.[42–44,48,49,53,56,58,63,64,68,69] The inability of $PtcO_2$ to provide anatomical information may limit its usefulness for vascular screening.[73] $PtcO_2$ has also been used to assess the success of vascular intervention (surgical or endovascular).[46,61,62,69–73] These data suggest that $PtcO_2$ may be superior to Doppler in screening for vascular disease, predicting healing after amputation, and assessing the success of vascular intervention.

Taken together, these studies suggest that evaluation by a vascular specialist be strongly considered for all patients with periwound $PtcO_2 < 40$ mmHg, and should be routine for patients with periwound $PtcO_2 < 20$ mmHg unless it would clearly be inappropriate (for example, the patient would refuse to consider surgical intervention).

- Doppler arterial waveforms disparities.[1]
- Dampened pulse volume recordings.[11]

*Principle*: Pure arterial ulcers are unusual. Arterial insufficiency frequently contributes to poor healing in ulcers with another primary etiology such as diabetic neuropathy or venous insufficiency.

*Evidence*:


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*Guideline # 1.2*: Patients presenting with risk factors for atherosclerosis (smoking, diabetes, hypertension, hypercholesterolemia, advanced age, obesity, hypothyroidism) who have ulcers are more likely to have arterial ulcers and should be carefully and broadly evaluated. Discuss a more complete workup with the primary care physician. (Level IA)

*Guideline #1.3*: In ischemic-appearing ulcers, look for contributing factors other than atherosclerosis that involve the arterial system (microvascular vs. macrovascular), such as thromboangiitis, vasculitis, Raynaud's, pyoderma gangrenosum, thalassemia, or sickle cell disease. (Level IA)

*Principle*: Patients with ulcers that appear "ischemic" should be evaluated for diseases beyond large vessel occlusive disease if the clinical presentation is not completely consistent with atherosclerotic occlusive disease. This generally requires referral to a specialist.

*Evidence*:

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study of aetiology, wound healing and pain reduction after pinch grafting. *Rheumatology* 2001; 40: 816–20. [CLIN S]
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*Guideline # 1.4*: Patients presenting with rest pain or gangrene should be promptly referred to a vascular specialist. (Level IA)

*Principle*: Ulcers in patients with rest pain and gangrene may progress rapidly, and delay in referral increases the risk of limb loss.

*Evidence*:

1. Adler AJ, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes. *Diabetes Care* 1999; 22: 1029–35. [CLIN S]
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6. Goshima KR, Mils JL, Hughes JD. A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. *J Vasc Surg* 2004; 39: 330–5. [RETRO S]

## GUIDELINES FOR SURGERY OF ARTERIAL INSUFFICIENCY ULCERS

*Preamble*: In patients with arterial insufficiency ulcers, restoration of blood flow by revascularization is the intervention that will most likely lead to healing. [Grey JE, Hardling KG, Enoch S. Venous and arterial leg ulcers. *BMJ* 2006; 332: 347–350.]

*Guideline #2.1*: Prior to revascularization, an anatomic road map should be obtained. (Level IIA)

Options include:

- Angiogram[1–3,5]
- Duplex Angiography,[5] which has a sensitivity of 99% and 80% and a specificity of 94% and 91% for the femoropopliteal and tibial segments, respectively, as compared with arteriography.[6]
- Magnetic Resonance Angiography[4,5]
- Contrast Tomography Angiography[4]

*Principle*: The goal of revascularization (open or endovascular) is to restore in-line arterial blood flow to the ulcer, which may be manifested by a pulse in the foot and/or improved ABI.[1]

*Evidence*:

1. Treiman GS, Oderich GSC, Ashrafi A, Scneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. *J Vasc Surg* 2000; 31: 1110–8. [RETRO S]
2. Toursarkissian B, D'Ayala M, Stefanidis D, Shirreman PK, Harrison A, Schoolfield J, Sykes MT. Angiographic scoring of vascular occlusive disease in the diabetic foot: relevance to bypass graft patency and limb salvage. *J Vasc Surg* 2002; 35: 494–500. [CLIN S]
3. Sieggreen MY, Kline RA. Arterial insufficiency and ulceration—diagnosis and treatment options. *Nurse Pract* 2004; 29: 46–52. [LIT REV]
4. Hingorani A, Ascher E, Markevich et al. A comparison of magnetic resonance angiography, contrast arteriography, and duplex arteriography for patients undergoing lower extremity revascularization. *Ann Vasc Surg* 2004; 18: 294–301. [CLIN S]
5. Gjoannaess E, Morken B, Sandbaek J, et al. Gadolinium-enhanced magnetic resonance angiography, colour duplex and digital subtraction angiography of the lower limb arteries from the aorta to the tibio-peroneal trunk in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2006; 31. [CLIN S]
6. Katsamouris AN, Giannoukas AD, Tstetis D, et al. Can ultrasound replace arteriography in the management of chronic arterial occlusive disease of the lower limb? *Eur J Endovasc Surg* 2001; 21:155–60. [CLIN S]

*Guideline #2.2*: In the presence of an arterial ulceration, the natural history is one of disease progression and eventual limb loss, and the treatment options are revascularization (endovascular or open surgery) or amputation. Adjuvant therapies may improve healing of the ulcer but do not correct the underlying vascular disease. They cannot replace revascularization. Revascularization is not always successful and durable. Thus, adjuvant therapy may improve the outcome if combined with revascularization. (Level IIA)

*Principle*: Approximately 10–20% of patients with PAOD will need revascularization surgery. Bypass surgery has a reported patency rate of 70% for crural-pedal bypass in both diabetics and nondiabetics at five years (in survivors), a limb salvage rate of 80% with a 1–2% amputation rate at two years in both diabetics and nondiabetics (the same in diabetics), and a limb salvage rate of 80% with 1–2% amputation rate at five years.[2,3] Surgical results for distal dorsalis pedis bypass: at five years, the primary patency is 57%, whereas the secondary patency is 63% and limb salvage is 78% (only 49% alive). At ten years, the primary patency is 38%, whereas the secondary patency is 42% and limb salvage is 56% (only 24% alive).[2,3,5] Endovascular results reported an 80% two-year limb salvage (small series).

*Evidence*:

1. Pentecost MJ, Criqui MH, Dorros G, et al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. A statement for health professionals from a special writing group of the councils on cardiovascular radiology,

arteriosclerosis, cardio-thoracic and vascular surgery, clinical cardiology, and epidemiology and prevention, the American heart association. *J Vasc Surg* 2003: 14: S495–515. [STAT]
2. Treiman GS, Copland S, McNamara RM, et al. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. *J Vasc Surg* 2001; 33: 1158–64. [CLIN S]
3. Pomposelli FB, Kansal N, Hamdan AD, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. *J Vasc Surg* 2003; 37: 307–15. [CLIN S]
4. Norman PE, Eikelboom JW, Hankey GJ. Peripheral arterial disease: prognostic significance and prevention of the atherotrombotic complications. *MJA* 2004; 181: 150–4. [STAT]
5. Rhodes JM, Gloviczki P, Bower TC, et al. The benefits of secondary interventions in patients with failing or failed pedal bypass grafts. *Am J Surg* 1999; 178: 151–5. [CLIN S]
6. Treiman GS, Oderich GSC, Ashrafi A, Scneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. *J Vasc Surg* 2000; 31: 1110–8. [RETRO S]
7. Goshima KR, Mils JL, Hughes JD. A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. *J Vasc Surg* 2004; 39: 330–5. [RETRO S]

*Guideline # 2.3*: The risk of surgery should be weighed against the likelihood of success (of revascularization and of healing of the ulcer after revascularization) given a patient's co-morbidities. (Level IIB)

*Principle*: Revascularization does not always result in a perfused foot and does not always lead to adequate inflow of oxygen to guarantee ulcer healing in the foot. For example, patients with heel gangrene and ESRD may be considered for primary amputation (controversial: palpable pedal pulse not indicative of healing, as they have lower rates of limb salvage and higher rates of complications). However, care must be individualized. In some cases, limb preservation may be important to the patient because of issues of body image or in cases where limited function is possible and may still allow the patient to maintain independence with transfers. In addition, the risk of amputation needs to be considered in this complex risk–benefit analysis. Providers should discuss the risks and benefits clearly with the patient and determine the patient preference.

*Evidence*:

1. 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]
2. Treiman GS, Copland S, McNamara RM, et al. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. *J Vasc Surg* 2001; 33: 1158–64. [CLIN S]
3. Treiman GS, Oderich GSC, Ashrafi A, Scneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. *J Vasc Surg* 2000; 31: 1110–8. [RETRO S]
4. Hafner J, Schaad I, Schneider E, Seifert B, Burg G, Cassina PC. Leg ulcers in the peripheral arterial disease (arterial leg ulcers): impaired wound healing above the threshold of chronic limb ischemia. *J Am Acad Dermatol* 2000; 43: 1001–8. [CLIN S]
5. Niinikoski JHA. Clinical hyperbaric oxygen therapy, wound perfusion, and transcutaneous oximetry. *World J Surg* 2004; 28: 307–11. [LIT REV]
6. Arora S, Pomposelli F, Logerfo FW, Veves A. Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization. *J Vasc Surg* 2002: 35: 501–5. [CLIN S]
7. Attinger CE, Ducic I, Neville RF, et al. The relative roles of aggressive wound care versus revascularization in salvage of threatened lower extremity in the renal failure diabetic patient. *Plast Reconstr Surg* 2002; 109: 1281–9. [RETRO S]

## GUIDELINES FOR INFECTION CONTROL OF ARTERIAL INSUFFICIENCY ULCERS (SEE ALSO, VENOUS ULCER GUIDELINES)

*Preamble*: Infection results when the host defense equilibrium is upset in favor of the bacteria. Infection plays various roles in the etiology, healing, operative repair, and complications of arterial and mixed ulcers. Restoration of flow is crucial to infection control in arterial ulcers and must be addressed first.

*Guideline #3.1*: In general, removal of all necrotic or devitalized tissue by sharp, enzymatic, mechanical, biological, or autolytic debridement leads to a more normal wound-healing process. (Level IIA) In arterial ulcers with dry gangrene or eschar, however, debridement should not be used until arterial inflow has been reestablished. (Level IIIA)

(Detailed discussion of debridement is in Wound Bed Preparation Guidelines.)

*Principle*: Necrotic tissue is laden with bacteria. Devitalized tissue impairs the ability to fight infection and serves as a rich environment for bacterial growth.

*Evidence*:

1. Edlich RF, Rodeheaver GT, Thacker JG, et al. Technical factors in wound management. In: Dunphy JE, Hunt 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 Tech Assess* 1999; 3(17 Part 1): 1–78. [STAT]
3. Steed D, Donohue D, Webster M, et al. Effect of extensive debridement and rhPDGF-BB (Becaplermin) 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. *Med Surg 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 MI, Robson, MC, Krizek, TJ, et al. 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, Woolfry G, et al. Exploring debridement options for chronic venous ulcers. *Br J Nurs* 2005; 14: 393–7. [LIT REV]
9. 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: 1–247. [STAT]
10. Schmidt K, Debus ES, St. Jessberger U, Ziegler U, Thiede A. Bacterial population of chronic crural ulcers: Is there a difference between the diabetic, the venous, and the arterial ulcer? *Vasa* Feb 2000; 29: 62–70. [CLIN S]
11. Henke PK, Blackburn SA, Wainess RW. Osteomyelitis of the foot and toe in adults is a surgical disease. *Ann Surg* 2005 June; 241: 885–94. [LIT REV]
12. Bowler PG, Davies BJ. The microbiology of infected and non-infected leg ulcers. *Int J Derm* 1999; 38: 573–8. [CLIN S]

*Guideline #3.2*: Patients with *neuro-ischemic* ulcers should be considered for a short course of systemic antibiotics even when clinical signs of infection are not present. These chronic wounds have a bacterial load that may impede healing before any evidence of clinical signs of infection. However, chronic treatment with systemic antibiotics does not prevent infection and may worsen outcome if infection develops. Therefore, routine use of antibiotics should be avoided, and antibiotics should be stopped if no response occurs. (Level IIC)

*Principle*: The immune system is impaired in diabetic patients, so infection may be present without obvious signs. Lack of response to antibiotics in the absence of clinical signs of infection suggests that other therapies should be investigated. Ischemia in diabetics results from atherosclerosis of the leg vessels, often bilateral, multisegmental, and distal, involving arteries below the knee. Considerable data support the observation that $10^5$ organisms/gram of tissue is necessary for infection and to allow invasive sepsis for most types of bacteria. In a review of treatment of digital osteomyelitis, decreased wound healing was associated with peripheral vascular occlusive disease ($p=0.006$) and prolonged prehospital antibiotic use ($p=0.07$) compared with aggressive surgical debridement (including digit amputation) and selected use of arterial bypass. There is no existing evidence to support use of systemic antibiotics for chronic wound healing,[10] but patients who received intravenous antibiotics (a national-level survey) were less likely to have a major or minor amputation.[11] Prolonged pre-admission antibiotic therapy (mean pre-admission antibiotic duration $5 \pm 2$ months) may decrease the chance of wound healing and is associated with a significantly decreased chance of limb salvage.[10]

*Evidence*:

1. Henke PK, Blackburn SA, Wainess RW, et al. Ostemyelitis of the foot and toe in adults is a surgical disease: Conservative management worsens lower extremity salvage. *Ann Surg* 2005; 241: 885–94. [CLIN S]
2. 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]
3. Schmidt K, Debus ES, St. Jessberger U, Ziegler U, Thiede A. Bacterial population of chronic crural ulcers: is there a difference between the diabetic, the venous, and the arterial ulcer? *Vasa* 2000; 29: 62–70. Comment: *Vasa* 2000; 29:156. [CLIN S]
4. Ramsey SD, Newton K, McCulloch DK, Sandiu N, Reiber GE, Wagner EH. Incidence, outcomes, and cost of foot ulcer in patients with diabetes. *Diabetes Care* 1999; 22: 382–7. [RETRO S]
5. Arora S, Pomposelli F, Logerfo FW, Veves A. Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization. *J Vasc Surg* 2002; 35: 501–5. [CLIN S]
6. Linares-Palomino JP, Gutierrez J, Lopez-Espada C, Luna JD, Ros E, Maroto C. Genomic, serologic and clinical case-control study of *Clamydia pneumoniae* and peripheral artery occlusive disease. [CLIN S]
7. Bowler PG, Davies BJ. The microbiology of infected and noninfected leg ulcers. *International J Dermatol* 1999; 38: 573–8. [CLIN S]
8. 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. [CLIN S]
9. Cerveira JJ, LAl BK, Padberg Jr FT, Pappas PJ, Hobson RW. Methicillin-resistant *Staphylococcus aureus* infection does not adversely affect clinical outcome of lower extremity amputations. *Ann Vasc Surg* 2003; 17: 80–5. [CLIN S]
10. Majewski W, Cybulski Z, Napierala M, Pukacki F, Staniszewski R, Pietkiewicz K, Zapalski S. The value of quantitative bacteriological investigations in the monitoring of treatment of ischaemic ulcerations of lower legs. *Int Angiol* 1995 Dec; 14: 381–4. [CLIN S]
11. Kummer O, Widmer MK, Pluss S, Willenberg T, Vogele J, Mahler F, Baumgartner I. Does infection affect amputation rate in chronic critical leg ischemia? *Vasa* 2003 Feb; 32: 18–21. [RETRO S]

*Guideline #3.3*: Wounds will heal and infection will be better prevented and controlled in an environment that is adequately oxygenated. (Level IA)

*Principle*: Oxygen delivery to the wound will be impaired if tissue perfusion is inadequate. Revascularization is crucial, but other treatments may help to maximize

cutaneous flow, and thus ulcer healing. Dehydration and other factors that increase sympathetic tone such as cold, stress, or pain will all decrease tissue perfusion. Belda et al. (2005) and Greif et al. (2000) in separate studies showed a statistically significant reduction in wound infection risk in colorectal surgery patients given 80% vs. 30% inspired oxygen perioperatively. This appears to pertain to arterial ulcers as well: Faglia et al. (1996) demonstrated a significant reduction in amputation rates in patients with ischemic diabetic ulcers treated with hyperbaric oxygen therapy. Stotts and Hopf (2003) showed increased wound tissue oxygen in patients with pressure ulcers given small amounts of supplemental fluids orally. Puzziferi et al. (2001) demonstrated that gentle topical heating (38 °C) increased transcutaneous wound oxygen and decreased pain in patients with arterial ulcers. Clearly, revascularization is the ideal way to increase wound oxygen delivery, but warmth, correction of dehydration, and increased inspired oxygen can increase impaired flow and improve oxygen delivery.

*Evidence*:


1. Belda FJ, Aguilera L, Asuncion JG, et al. Supplemental perioperative oxygen and the risk of surgical wound infection. *JAMA* 2005; 294: 2035–42. [RCT]
2. Kaye KS, Sands K, Donahue JG, Chan KA, Fishman P, Platt R. Preoperative drug dispensing as predictor of surgical site infection. *Emerg Inf Diseases* 2001; 7: 57–65. [LIT REV]
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. Henke PK, Blackburn SA, Wainess RW, et al. Osteomyelitis of the foot and toe in adults is a surgical disease: conservative management worsens lower extremity salvage. *Ann Surg* 2005; 241: 885–94. [CLIN S]
5. Hopf H, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* 1997; 132: 997–1004. [CLIN S]
6. Jonsson, K, Jensen, JA, Goodson, WH, et al. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. *Ann Surg* 1991; 214: 605–13. [RCT]
7. Faglia E, Favales F, Aldeghi A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care* 1996; 19: 1338–43. [CLIN S]
8. Puzziferri N, West J, Hunt T, Hopf H. Local warming increases oxygenation and decreases pain in ischemic ulcers. *Wound Rep Reg* 2001; 9: 146. [CLIN S]
9. Stotts NA, Hopf HW. The link between tissue oxygen and hydration in nursing home residents with pressure ulcers: preliminary data. *J Wound Ostomy Continence Nurs* 2003; 30: 184–90. [RCT]


*Guideline #3.4*: Topical antimicrobial dressings may be beneficial in management of chronically/heavily colonized wounds, decreasing their bacterial load and aiding wound healing. (Level IIIB)

*Principle*: Chronic wounds are open for a prolonged period of time and have the propensity to become heavily colonized. There is evidence that hypoxia, impaired blood flow, and bacterial load are associated with healing impairment. Therefore, it makes sense to decrease the bacterial load in these wounds by integrating existing therapies like topical antimicrobials. While the results from some studies indicate a positive association between higher bacterial counts and delayed wound healing,[6,7] other studies show no such association.[8,9] The relationship between bacterial colonization and wound healing remains unclear.[6–9] Bacterial proliferation has been shown to be significantly lower under occlusive dressings.[7] Further research is required to clarify the relationship between healing and the colonization or infection of wounds, and to clarify these definitions in terms of chronic wounds.[7]

*Evidence*:


1. Hunt TK, Hopf H. Wound healing and wound infection. What surgeons and anesthesiologists can do. *Surg Clin North Am* 1997; 77: 587–606. [LIT REV]
2. Falanga V. The chronic wound: impaired healing and solutions in the context of wound bed preparation. *Blood Cells, Mol Dis* 2004; 32: 88–94. [LIT REV]
3. Markoishvili K, Tsitlanadze G, Katsarava R, Morris JG, Jr, Sulakvelidze A. A novel sustained-release matrix based on biodegradable poly (ester amides) and impregnated with bacteriophages and an antibiotic shows promise in management of infected venous stasis ulcers and other poorly healing wounds. *Int J Dermatol* 2002; 41: 453–8. [CLIN S]
4. Mooney EK, Lippitt C, Friedman J, et al. Silver dressings. *Plast Reconstr Surg* 2006; 117: 666–9. [LIT REV]
5. Ueno C, Hunt TK, Hopf H. Using physiology to improve wound healing. *Plast Reconstr Surg* 2006; wound healing supplement. [LIT REV]
6. 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: 1–247. [STAT]
7. Schmidt K, Debus ES, St. Jessberger U, Ziegler U, Thiede A. Bacterial population of chronic crural ulcers: is there a difference between the diabetic, the venous, and the arterial ulcer? *Vasa* Feb 2000; 29: 62–70. [CLIN S]
8. Henke PK, Blackburn SA, Wainess RW. Osteomyelitis of the foot and toe in adults is a surgical disease. *Ann Surg* 2005 June; 241: 885–94. [LIT REV]
9. Bowler PG, Davies BJ. The microbiology of infected and noninfected leg ulcers. *Int J Derm* 1999; 38: 573–8. [CLIN S]


## GUIDELINES FOR WOUND BED PREPARATION OF ARTERIAL INSUFFICIENCY ULCERS (SEE ALSO VENOUS ULCER GUIDELINES)

*Preamble*: Wound bed preparation is defined as the management of the wound to accelerate endogenous healing or to 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:

1. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. *Wound Rep Reg* 2003; 11: 1s–23s. [LIT REV]
2. Sibbald RG, Williamson D, Orsted HL. Preparing the wound bed: debridement, bacterial balance, and moisture balance. *Ostomy Wound Manage* 2000; 46: 14–35. [LIT REV]

*Guideline # 4.1*: An arterial ulcer is a component of a pool of diseases. It is paramount to evaluate the patient as a whole, identifying and addressing the causes of tissue damage. This includes observation of systemic diseases and medications, nutrition, tissue perfusion, and oxygenation. (Level IIA)

*Principle* 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 immunosuppresive 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. This information in addition to a detailed history of the wound itself is of benefit.

*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. William DT, Harding K. Healing responses of skin and muscle in critical illness. *Crit Care Med* 2003; 31(8 Suppl.): 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. Vaseliso M, Guaitro E. A comparative study of some anti-inflammatory drugs in wound healing in the rat. *Experientia* 1973; 29: 1250–1. [EXP]
5. Jorgensen LN, Kallehave F, Karlsmark T, et al. Reduced collagen accumulation after major surgery. *Br J Surg* 1996; 83: 1591–4. [CLIN S]
6. Sorensen LT, Nielsen HB, Kharazini A, et al. 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* B: Nutrition must be adequate to provide sufficient protein to support the growth of granulation tissue. Inadequate nutrition, dehydration, and/or weight loss must be corrected through nutrition interventions for a chronic wound to heal.

*Evidence*:

1. Bourdel-Marchasson I, Barateau M, Rondeau V, et al. A multicenter trial of the effects of oral nutritional supplementation in critically ill older inpatients. GAGE Group. Groupe Aquitain Gériatrique d'Evaluation. *Nutrition* 2000; 16: 1–5. [RCT]
2. Lansdown AB. Nutrition 2: 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, 54–55. [LIT REV]
4. Patel GK. The role of nutrition in the management of lower extremity wounds. *Lower Extr Wounds* 2005; 4: 12–22. [LIT REV]
5. American Medical Directors Association. *Dehydration and Fluid Maintenance, Clinical Practice Guideline*. Columbia, MD: American Medical Directors Association 2001; p.12.
6. Barbul A, Lazarou SA, Efron DT, et al. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery* 1990; 108: 331–7. [RCT]
7. Demling R. Involuntary weight loss, protein-energy malnutrition, and the impairment of cutaneous wound healing. *Wounds* 2001; 13 (Suppl. D): 11–12.
8. Demling R, DeSanti L. Involuntary weight loss and the nonhealing wound: the role of anabolic agents. *Adv Wound Care* 1999; 12(1 Supp): 1–14. [LIT REV]
9. Schaffer MR, Tantry U, Ahrendt GM, Wasserkrug HL, Barbul A. Acute protein-calorie malnutrition impairs wound healing: a possible role of decreased wound nitric oxide synthesis. *J Am Coll Surg* 1997; 184: 37–43. [EXP]

*Principle* 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 other factors that increase sympathetic tone such as cold, stress, or pain will all 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 WH, Gottrup F, et al. Direct measurement of wound and tissue oxygen tension in postoperative patients. *Ann Surg* 1983; 197: 470–8. [CLIN S]
2. Knighton 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, et al. 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, et al. Cigarette smoking decreases tissue oxygen. *Arch Surg* 1991; 126: 1131–4. [RCT]
6. Hopf H, Hunt TK, West JM, et al. 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]

*Guideline #4.2*: Debridement of nonviable and noninfected tissue is performed ONLY AFTER the revascularization procedure. Prerevascularization debridement should be indicated only in a septic foot with and without ischemic signs. (Level IIA)

*Principle*: Debridement of an ulcer in the absence of adequate arterial inflow enlarges an ulcer when resources for healing are not available and may worsen ischemia by increasing metabolic demand. Necrotic tissue, excessive bacterial concentration, senescent cells, and cellular debris inhibit wound healing. Adequate debridement removes diseased tissue and promotes turnover of the cells. Aggressive debridement often leads to faster healing. Surgical debridement of osteomyelitis is superior to long-term antibiotics alone after revascularization.

*Evidence*:

1. Treiman GS, Oderich GSC, Ashrafi A, Scneider PA. Management of ischemic heel ulceration and gangrene: An evaluation of factors associated with successful healing. *J Vasc Surg* 2000; 31:1110–8. [RETRO S]
2. Falanga V. Wound healing and its impairment in the diabetic foot. *Lancet* 2005; 366: 1736–43. [LIT REV]
3. Sieggreen MY, Kline RA. Arterial insufficiency and ulceration—diagnosis and treatment options. *Nurse Pract* 2004; 29: 46–52. [LIT REV]
4. Falanga V. The chronic wound: impaired healing and its solutions in the context of wound bed preparation. *Blood cells, Mol, Dis* 2004; 32: 88–94. [LIT REV]
5. Grey JE, Hardling KG, Enoch S. Venous and arterial leg ulcers. *BMJ* 2006; 332: 347–50. [LIT REV]
6. Treiman GS, Copland S, McNamara RM, et al. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. *J Vasc Surg* 2001; 33: 1158–64. [CLIN S]
7. Pomposelli FB, Kansal N, Hamdan AD, et al. A decade of experience with dorsalis pedis artery by pass: analysis of outcome in more than 1000 cases. *J Vasc Surg* 2003; 37: 307–15. [CLIN S]
8. Albrektsen SB, Henriksen BM, Holstein PE. Minor amputations on the feet after revascularization for gangrene: a consecutive series of 95 limbs. *Acta Orthop Scand* 1997 Jun; 68: 291–3. [CLIN S]

*Guideline #4.3*: There are many debriding agents, but there is no consensus about the best agent. (Level IIB)

*Principle*: The method of debridement chosen may depend on the status of the wound, the capability of the healthcare provider, and the overall condition of the patient. However, it is common to combine methods of debridement in order to maximize the healing rates.

*Evidence*:

1. Bradley M, Cullum N, Sheldon, T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999; 3(17 Part I). [STAT]
2. Falanga V. Wound healing and its impairment in the diabetic foot. *Lancet* 2005; 366: 1736–43. [LIT REV]
3. Falanga V. The chronic wound: impaired healing and its solutions in the context of wound bed preparation. *Blood Cells, Mol, Dis* 2004; 32: 88–94. [LIT REV]
4. Steed DL. Debridement. *Am J Surg* 2004; 187(Suppl.): 71s–74s. [LIT REV]
5. Ayello EA, Cuddigan J. Debridement: controlling the necrotic/cellular burden. *Adv Skin Wound Care* 2004; 17: 66–75. [LIT REV]
6. Sieggreen MY, Maklebust J. Debridement: choices and challenges. *Adv Wound Care* 1997; 10: 32–7. [LIT REV]

*Guideline #4.4*: Compression therapy may be beneficial in ulcers of mixed etiologies (venous and arterial). (Level IIIB)

*Principle*: Compression therapy is a useful tool in venous ulcers promoting decrease of edema and improving wound healing. Thus, in cases with peripheral arterial ulcers associated with venous ulcers, with close supervision, compression can also be helpful. Additionally, in postvascular bypass surgery, edema is frequently a significant problem and mild compression is helpful. However, excessive compression may be harmful in patients with arterial disease and research is required to establish guidelines for compression in patients with venous ulcers and a significant arterial compromise and in patients immediately after revascularization surgery.

*Evidence*:

1. Moffatt CJ, Franks PJ, Oldroyd M, et al. Community clinics for leg ulcers and impact on healing. *BMJ* 1992 Dec 5; 305(6866): 1389–92. Comment in: *BMJ* 1993 Jan 16; 306: 205. [CLIN S]
2. Arthur J, Lewis P. When is reduced-compression bandaging safe and effective? *J Wound Care* 2000; 9: 469–71. [CLIN S]
3. Bowering CK. Use of layered compression bandages in diabetic patients. Experience in patients with lower leg ulceration, peripheral edema, and features of venous and arterial disease. Adv. *Wound Care* 1998 May–Jun; 11: 129–35. [CLIN S]

*Guideline # 4.5*: There is evidence that:

(A) autograft and allograft can accelerate the closure of wounds. In refractory ulcers, they act as biological dressings, increasing the chance of wound healing. However, adequate arterial inflow is necessary and further study is required in arterial ulcers. (Level IIIC);

(B) Extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an

adjuvant agent in arterial ulcers, but further study is required. (Level IIIC)

*Principle* A: Closing the arterial ulcer with an autologous skin graft (pinch graft, split-thickness graft, meshed graft, full-thickness graft) or an autologous flap can assist in healing the wound and aid in the preservation of lower limbs. Skin graft survival is dependent on appropriate wound bed preparation and perfusion.

*Evidence*:

1. 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]
2. Ramsey SD, Newton K, McCulloch DK, Sandiu N, Reiber GE, Wagner EH. Incidence, outcomes, and cost of foot ulcer in patients with diabetes. *Diabetes Care* 1999; 22:382–7. [RETRO S]
3. Hafner J, Schaad I, Schneider E, Seifert B, Burg G, Cassina PC. Leg ulcers in the peripheral arterial disease (arterial leg ulcers): impaired wound healing above the threshold of chronic limb ischemia. *J Am Acad Dermatol* 2000; 43: 1001–8. [CLIN S]
4. Oien RF, Hakansson A, Hansen BU. Leg ulcers in patients with rheumatoid arthritis—a prospective study of aetiology, wound healing and pain reduction after pinch grafting. *Rheumatology* 2001; 40: 816–20. [CLIN S]
5. Singer AJ, Clark RAF. Cutaneous wound healing. *N Engl J Med* 1999; 341: 738. [LIT REV]

*Principle* B: Biomaterials like human skin and equivalents accelerate healing in selected diabetic and venous ulcers. They promote temporary wound closure and act as a biological dressing, as well as stimulating or attracting host cytokines to the wound. Extracellular matrix replacement therapy stimulates wound epithelialization, increases angiogenesis in a variety of animal models, and sequesters or provides bioactive components within the wound bed. Despite the existence of animal studies, case series, and a small number of RCTs to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.

*Evidence*:

1. Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999; 3: 17Part I. [STAT].
2. Falanga V. Wound healing and its impairment in the diabetic foot. *Lancet* 2005; 366: 1736–43. [LIT REV]
3. Saap LJ, Donohue K, Falanga V. Clinical classification of bioengineered skin use and its correlation with healing of diabetic and venous ulcers. *Dermatol Surg* 2004; 30: 1095–100. [RETRO S]
4. Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. *Cochrane Database Syst Rev* 2003. [STAT]
5. Bouza C, Munoz A, Amate JM. Efficacy of modern dressings in the treatment of leg ulcers: a systematic review. *Wound Rep Reg* 2005; 13: 218–29. [RETRO S]
6. Mostow EN, Haraway GD, Dalsing M, Hodde JP, King D. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg* 2005; 41: 856–62. [RCT]
7. Niezgoda JA, Van Gils CA, Frykberg RG, Hodde JP. Randomized clinical trial comparing Oasis Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care* 2005; 18: 258–66. [RCT]
8. Carson SN, Travis E, Overall K, Lee-Jahshan S. Using becaplermin gel with collagen products to potentiate healing in chronic leg wounds. *Wounds* 2003; 15: 339–45. [CLIN S]
9. Brown-Etris M, Cutshall WD, Hiles MC. A new biomaterial derived from small intestine submucosa and developed into a wound matrix device. *Wounds* 2002; 14: 150–66. [CLIN S]
10. Hampton S. Oasis: A dressing for the future. *Nurse 2 Nurse* 2002; 2: 2–3. [CLIN S]
11. Benbow M. Oasis: An innovative alternative dressing for chronic wounds. *Br J Nurs* 2001; 10: 1489–92. [CLIN S]

## GUIDELINES FOR DRESSINGS OF ARTERIAL INSUFFICIENCY ULCERS (*SEE ALSO VENOUS ULCER GUIDELINES*)

*Preamble*: There is a developing abundance of choices for topical treatment of arterial ulcers. Many dressings now combine wound bed preparation, i.e., debridement and/or antimicrobial activity, with moisture control. As there is a growing patient population who are not prime candidates for bypass surgery or even interventional surgery and may benefit from appropriate use of a combination of dressings and adjuvant therapy, guidelines are necessary to assist the clinician to make decisions regarding the value and best use of these advanced wound care products.

*Guideline #5.1*: In arterial ulcers with sufficient arterial inflow to support healing, use a dressing that will maintain a moist wound-healing environment. (Level IIA) Dry gangrene or eschar is best left dry until revascularization is successful. (Level IIA)

*Principle*: Although there is no evidence to demonstrate the superiority of any specific type of dressing, moist wound care accelerates the wound-healing process. A moist wound environment physiologically favors cell migration and matrix formation accelerating the healing of wounds. Dry dressings, except over intact skin, are considered injurious. They can cause desiccation of the wound, which reduces new granulation tissue formation, as well as removing granulation tissue during dressing changes.

*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, et al. 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, et al. 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, et al. Wet wound healing. *Plast Reconstr Surg* 2002; 110: 1680–7. [CLIN S]
5. Margolis DJ, Cohen JH. Management of chronic venous ulcers: a literature-guided approach. *Clin Dermatol* 1994; 12: 19–26. [LIT REV]
6. Stacey MC, Jopp-McKay AG, Rashid P, et al. The influence of dressings on venous ulcer healing—a randomized trial. *Eur J Vasc Endovasc Surg* 1997; 13: 174–9. [RCT]
7. Briggs, M, Nelson, EA. Topical agents or dressings for pain in venous leg ulcers. *The Cochrane Database of Systematic Reviews* 2003 Issue 1. CD001177. The Cochrane Collaboration. John Wiley & Sons Ltd. [STAT]

*Guideline #5.2*: Select a dressing that is cost effective and appropriate to the ulcer etiology and the health care provider. Dressing changes once daily or less often should be chosen where possible. (Level IIA)

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

*Evidence*:

1. Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. *Cochrane Database Syst Rev* 2003. [STAT]
2. Bouza C, Munoz A, Amate JM. Efficacy of modern dressings in the treatment of leg ulcers: a systematic review. *Wound Rep Reg* 2005; 13: 218–29. [RETRO S]
3. Falanga V. The chronic wound: impaired healing and its solutions in the context of wound bed preparation. *Blood cells, Mol, Dis* 2004; 32: 88–94. [LIT REV]

## GUIDELINES FOR *ADJUVANT THERAPY* OF ARTERIAL INSUFFICIENCY ULCERS

*Preamble*: The level of evidence concerning most adjuvant therapies for arterial ulcers is limited; it ranges from a few case reports to controlled studies. Significant arterial disease should be revascularized. Revascularization cannot be replaced by adjuvant agents. However, when revascularization is impossible or unsuccessful or when successful revascularization does not result in healing, adjuvant agents may be useful. Adjuvant therapy may also be useful in assuring healing in combination with revascularization. More research is needed to define the proper use (timing, dosage, etc.) of most adjuvant therapies.

### Device (A)

*Guideline # 6.A.1*: Ultrasound therapy has been extensively studied in pressure and venous ulcers. There are few, if any, studies specifically in arterial ulcers. Thus, recommendations for use in arterial ulcers cannot currently be made. Further research should be pursued in this area. (Level IIIC)

*Principle*: Ultrasound may have effects through both thermal and nonthermal properties, including effects on the remodeling phase (thermal) and changing cell membrane permeability (nonthermal). Although there are animal studies and case series that support the efficacy of ultrasound, the lack of RCTs and the variability in settings that have been used in different studies make it difficult to make a recommendation for its use, particularly in arterial ulcers.

*Evidence*:

1. Cullum N, Nelson EA, Fleming K. Systematic review of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess* 2001; 5: 1–247. [STAT]
2. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrotimulation. *Ann Plast Surg* 2003; 51: 210–8. [LIT REV]

*Guideline #6.A.2*: Electrostimulation seems to be promising as an adjuvant therapy in arterial ulcers, based on animal studies and case series. However, definition of the proper settings and RCTs are required to make a definitive recommendation. (Level IIC)

*Evidence*:

1. Kloth LC. Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials. *Lower Extremity Wounds* 2005: 4: 23–44. [LIT REV]
2. Cullum N, Nelson EA, Fleming K. Systematic review of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess* 2001; 5: 1–247. [LIT REV]
3. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrotimulation. *Ann Plast Surg* 2003; 51: 210–8. [LIT REV]

*Guideline #6.A.3*: Spinal cord stimulation (SCS) seems to be promising as an adjuvant therapy in managing lower limb ischemia and ulceration based on animal studies and case series. It is particularly useful in reducing pain. RCTs are required to make a definitive recommendation. Based on one RCT (Klomp et al. *Lancet* 1999; 353: 1040–44) that studied limb survival at two years on patients with critical limb ischemia ($N=120$), SCS was not better than cohort in reducing the risk of amputation. Both SCS and cohort did, however, reduce the level of pain. (Level IIC)

*Principle*: These three (ultrasound, electrostimulation, and spinal cord stimulation) therapies should be investigated further as adjuvant treatment of arterial ulcers, including particularly RCTs that compare standardized settings and use for each and their effects on healing outcomes.

*Evidence*:

1. Klomp HM, Spincemaille GH, Steyerberg EW, Habbema JDF, van Urk H, for the ESES study group. Spinal-cord stimulation in critical limb ischemia: a randomised trial. *Lancet* 1999; 353: 1040–4. [RCT]
2. Richardson RR, Cerullo LJ, Meryer PR. Autonomic hyperreflexia modulated by percutaneous epidural neurostimulation: a preliminary report. *Neurosurgery* 1979; 4: 517–20. [CLIN S]
3. Augustinsson LE, Carlsson CA, Holm J, et al. Epidural electrical stimulation in severe limb ischemia. Pain relief, increased blood flow and possible limb-saving effect. *Ann Surg* 1985; 202:104–10. [CLIN S]
4. Petrakis E, Sciacca V. Prospective study of transcutaneous oxygen tension ($TcPO_2$) measurement in the testing period of spinal cord stimulation in diabetic patients with critical lower limb ischaemia. *Int Angiol* 2000 Mar; 19: 18–25. [CLIN S]
5. Horsch S, Claeys L. Epidural spinal cord stimulation in the treatment of severe peripheral arterial occlusive disease. *Ann Vasc Surg* 1994 Sep; 8: 468–74. [CLIN S]

*Guideline #6.A.4*: Topical negative pressure wound therapy appears to be promising for mixed ulcers. It may have a role as an adjuvant agent in arterial ulcers, but further study is required. (Level IIIC)

*Principle*: Although mechanisms of action are only partially understood, topical negative pressure wound therapy promotes removal of exudate, reduces edema, lowers bacterial counts, and seems to increase wound blood flow. Extensive animal studies, case series, and a few RCTs support its use for traumatic wounds, dehisced surgical wounds, burns, pressure ulcers, diabetic ulcers, and skin grafts. There are no studies specifically in arterial ulcers. Further studies should be pursued in this area.

*Evidence*:

1. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrotimulation. *Ann Plast Surg* 2003; 51: 210–8. [LIT REV]
2. Halter G, Kapfer X, Liewald F, Bischoff M. Vacuum-sealed mesh graft transplantation in chronic cutaneous ulcers of the lower leg. *Vasa* 2003 Aug; 32: 155–8. [CLIN S]
3. DeFranzo AJ, Argenta LC, Merlos MW, et al. The use of vacuum assisted closure therapy for the treatment of lower extremity wounds with exposed bone. *Plast Rec Surg* 2001; 108: 1184–91. [CLIN S]
4. Clare MP, Fitzgibbons TC, McMullen ST, Stice RC, Hayes DF, Henkel L. Experience with the vacuum assisted closure negative pressure technique in the treatment of non-healing diabetic and dysvascular wounds. *Foot Ankle Int* 2002 Oct; 23: 896–901. [RETRO S]

*Guideline #6.A.5*: Intermittent pneumatic leg compression (IPC) increases blood flow and it may be beneficial in limbs with impaired distal perfusion, either before or after revascularization. (Level IIB)

*Principle*: There is some evidence that intermittent pneumatic compression (IPC) has a role in managing patients whose claudication has been previously treated surgically. IPC increases blood flow, promoting distal perfusion in the limbs. Despite the fact that it may have clinical implications for postsurgical rehabilitation and length of hospital stay, further studies that comment on patient selection, regimes, and mode of action are needed.

*Evidence*:

1. Delis KT, Husmann MJW, Niclaides AN, et al. Enhancing foot skin blood flux in peripheral vascular disease using Intermittent Pneumatic Compression: controlled study on claudicants and grafted arteriopaths. *World J Surg* 2002; 26: 861–6. [CLIN S]
2. Abu-Own A, Cheatle T, Scurr JH, et al. Effects of intermittent pneumatic compression of the foot on the microcirculatory function in arterial disease. *Eur J Vasc Surg* 1993; 7: 488–92. [CLIN S]
3. Montori VM, Kavros SJ, Walsh EE, Rooke TW. Intermittent compression pump for nonhealing wounds in patients with limb ischemia. The Mayo Clinic experience (1998–2000). *Int Angiol* 2002 Dec; 21: 360–6. [CLIN S]
4. Kavros SJ, Delis KT, Turner NS, Voll AE, Liedl DA, Rooke TW. Improving limb salvage with intermittent pneumatic compression in patients with critical limb ischemia: the Mayo Clinic experience (1998–2004). *In Press*. [CLIN S]

### Systemic Agents (B)

*Guideline #6.B.1a*: In patients with nonreconstructable anatomy or whose ulcer is not healing despite revascularization, hyperbaric oxygen therapy (HBOT) should be considered as an adjuvant therapy. Selection criteria include ulcers that are hypoxic (due to ischemia) and the hypoxia is reversible by hyperbaric oxygenation. Tissue hypoxia, reversibility, and responsiveness to oxygen challenge are currently measured by transcutaneous oximetry ($TcPO_2$), although other methods are under investigation. The majority of data have been collected in patients with diabetes and arterial ulcers. Studies are required to determine whether these results can be generalized to all ischemic ulcers and whether postrevascularization treatment is of benefit. (Diabetic ischemic ulcers—Level IA; Nondiabetic ischemic ulcers—Level IIB)

*Guideline # 6.B.1b*: HBOT should be investigated in the treatment of ischemia–reperfusion injury after revascularization in patients with arterial ulcers.

*Principle* A: Hyperbaric oxygen is known to (1) increase tissue oxygen in ischemic tissue (given some degree of arterial inflow); (2) increase angiogenesis in hypoxic or injured tissue; this benefit was demonstrated in Wagner Grade 3 ischemia (revascularized when possible) ulcers in patients with diabetes; and (3) increase signal transduction (possibly via nitric oxide) and thereby growth factors and receptors (best studied in diabetes). Most randomized, controlled trials have been performed in diabetic patients with ischemic ulcers, but pure ischemic ulcers appear likely to respond as

well. In an RCT, Faglia et al. (1996) demonstrated a significant reduction in amputation in diabetic patients with significant ischemia treated with HBOT that was associated with a significant increase in transcutaneous oxygen levels in the treatment group. A number of studies have evaluated the value of transcutaneous oximetry in predicting the response to HBOT. Significant wound hypoxia ($< 40$ mmHg), combined with a significant increase when breathing oxygen (usually at pressure), is the best predictor of response.[9]

*Principle* B: The benefits of HBOT presents in the treatment of ischemia reperfusion injury in flaps are well known.

*Evidence*:


1. Kranke P, Bennett M, Roeck-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds (Review). *The Cochrane database of systematic reviews* 2004; Jan: 1–34. [STAT]
2. Roeckl-Wiedmann I, Bennet M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg* 2005; 92: 24–32. [RCT]
3. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrotimulation. *Ann Plast Surg* 2003; 51: 210–8. [LIT REV]
4. Niinikoski JHA. Clinical hyperbaric oxygen therapy, wound perfusion, and transcutaneous oximetry. *World J Surg* 2004; 28: 307–11. [LIT REV]
5. Baroni G. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* 1987; 10:81–6. [RCT]
6. Boykin JV. Hyperbaric oxygen therapy: a physiological approach to selected problem wound healing. *Wounds* 1996; 8: 183–98. [LIT REV]
7. Cianci P, Petrone G. Salvage of the problem wound and potential amputation with wound care and adjunctive hyperbaric oxygen therapy: an economic analysis. *J Hyper Med* 1988; 3: 127–41. [RETRO S]
8. Davis JC. The use of adjuvant hyperbaric oxygen in treatment of the diabetic foot. *Clin Podiatr Med Surg* 1987; 4: 429–37. [LIT REV]
9. Fife CE, Otto G, Walker D, Turner T, Smith L. Healing dehisced surgical wounds with negative pressure wound therapy. *Ostomy Wound Manag* 2004 Apr; 50(4A Suppl.): 28–31. [LIT REV]
10. Faglia E, Favales F, Aldeghi A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. a randomized study. *Diabetes Care* 1996; 19: 1338–43. [RCT]
11. Hadorn DC, Hicks N. Rating the quality of evidence for clinical practice guidelines. *J Clin Epidemiol* 1996; 49: 749–54. [STAT]
12. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. *Plast Reconst Surg* 1994; 93: 829–33. [RCT]
13. Harward TRS, Bernstein EF. Oxygen inhalation-induced transcutaneous $PO_2$ changes as a predictor of amputation level. *J Vasc Surg* 1985; 2: 220–7. [CLIN S]
14. Uhl E, Nylander G. Hyerbaric oxygen improves wound healing in normal and ischemic skin tissue. *Plast Reconstr Surg* 1994; 93: 835–41. [EXP]
15. Siddiqui A, Mustoe TA. Ischemic tissue oxygen capacitance after hyperbaric oxygen therapy: a new physiologic concept. *Plast and Reconstr Surg* 1997 Jan; 99: 148–55. [LIT REV]
16. Zhao LL, Mustoe TA. Total reversal of hypoxic wound healing deficit by hyperbaric oxygen plus growth factors. *Surg Forum* 1992; 43: 711–4. [EXP]
17. Oriani G. Hyperbaric oxygen therapy in diabetic gangrene. *J Hyperbaric Med* 1990; 5: 171–5. [LIT REV]
18. Rohr S, Tempe JD. Effect of hyperbaric oxygen on angiogenesis in rats. 58th Annual meeting of the EUBS 1992 Sep, Basel, Switzerland. [EXP]
19. Smith, BM, Desvigne, LD, Slade, JB, Dooley, JW, Warren, DC. Transcutaneous oxygen measurements predict healing of leg wounds with hyperbaric therapy. *Wound Rep Reg* 1996; 4: 224–9. [CLIN S]
20. Wattel F. Hyperbaric oxygen therapy in chronic vascular wound management. 31st Annual meeting of the International College of Angiology symposium proceedings, Rome, Italy, 1989. Angiology 1990; 41: 59–65. [LIT REV]
21. Zamboni WA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *Undersea Hyper Med* 1997; 24: 175–9.
22. Hopf HW, Gibson J, Angeles A, Constant JS, Feng JJ, Rollins MD, Hussain MZ, Hunt TK. Hyperoxia and angiogenesis. *Wound Rep Reg* 2005; 13: 558–64. [EXP]
23. Fife CE, Buyukcakir C, Otto GH, et al. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. *Wound Rep Reg* 2002 Jul–Aug; 10: 198–207. [RETRO S]


*Guideline #6.B.2*: Pentoxifylline does not improve arterial ulcer healing. (Level ID) The value of cilostazol in arterial ulcers remains to be evaluated. (Level IIIC)

*Principle*: Cilostazol has a better outcome in clinical trials as compared with pentoxifylline and placebo for claudicants. There are no data correlating their use with ulcer healing. Beneficial effects of cilostazol include improvements in functional status, quality of life, and ABI. Studies comparing pentoxifylline and placebo have not shown significant difference.

*Evidence*:


1. CAPRIE steering committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996; 348: 1329–39. [RCT]
2. Clagett GP, Sobel M, Jackson MR, Lip GYH, Tangelder M, Verhaege R. Antithrombotic therapy in peripheral arterial occlusive disease—the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126: 609S–26S. [STAT]

3. Hiatt WR. Pharmacologic therapy for peripheral arterial disease and claudication. *J Vasc Surg* 2002; 36: 1283–91. [LIT REV]

*Guideline #6.B.3*: There is no evidence supporting the use of prostaglandins (PGE-1) in the treatment of arterial ulcers. An RCT conducted by Schuler et al. (*J Vasc Surg* 1984) showed no efficacy for intravenous administration of PGE1 in healing of ischemic ulcers in patients with PAOD. A multicenter RCT conducted in Europe showed benefits of oral use of prostacyclin in the short term, but no benefits at one year (*Eur J Endovasc Surg* 2000). (Level IID)

*Principle*: PGE1 and PGI2 are well known as potent vasodilators and inhibitors of platelet aggregation. Treatment with systemic vasodilators can increase local ischemia by causing vasodilation in nonischemic areas and anticoagulants do not show any benefit; thus, prostaglandin application could be useful. Most previous studies were performed with PGE1 alone. There is lack of data showing benefits, optimal treatment duration, and site of administration. There is a high incidence of side effects with PGE1(50%) such as peptic ulcer disease and peptic ulcer perforation and bleeding.[2] PGE1 could be useful for short-term use and PGI2 could be useful in nondiabetic patients, but further studies are required.

*Evidence*:

1. Schuler JJ, Flanigan P, Holcroft JW, et al. Efficacy of prostaglandin E1 in the treatment of lower extremity ulcers secondary to peripheral vascular occlusive disease. *J Vasc Surg* 1984; 1: 160–70. [RCT]
2. Clagett GP, Sobel M, Jackson MR, Lip GYH, Tangelder M, Verhaege R. Antithrombotic therapy in peripheral arterial occlusive disease—the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126: 609S–26S. [STAT]
3. The oral Iloprost in Severe Leg Ischemia Study Group. Two randomized and placebo-controlled studies of an oral prostacyclin analogue (Iloprost) in severe leg ischemia. *Eur J Endovasc Surg* 2000; 20: 358–62. [RCT]

*Guideline #6.B.3*: An approach to control pain in patients with peripheral arterial ulcer should address the cause and use local, regional, or/and systemic measures. (Level IIIA)

*Principle*: Peripheral arterial disease and ulcers are painful. Pain in peripheral arterial insufficiency may be present at rest, may be alleviated by hanging the foot over the side of the bed, and may be extremely severe. The pain pattern changes as disease progresses; generally, it begins in the distal foot beyond the obstruction as in the ulcers and moves proximally. It can be constant (vascular component) and/or intermittent (dressing changes, debridement, etc.). Therefore, it is important to recognize the trigger cause and treat it correctly. Large doses of pain medication may be required.

*Evidence*:

1. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. *Br Med J* 2006; 332: 347–50. [LIT REV]
2. Briggs M, Ferris FD, Glynn C, et al. Assessing pain at wound dressing-related procedures. *Nurs Times* 2004; Oct12–18; 100: 56–7. [LIT REV]
3. Meaume S, Teot L, Lazareth I, Martini J, Bohbot S. The importance of pain reduction through dressing selection in routine wound management: the MAPP study. *J Wound Care* 2004 Nov; 13: 409–13. [CLIN S]
4. Ryan S, Eager C, Sibbald RG. Venous leg ulcer pain. *Ostomy Wound Manage* 2003 Apr;49 (4 Suppl.): 16–23. [LIT REV]

### Local/ Topical Agents (C)

*Guideline #6.C.1*: Stem cell therapy is a promising and expanding field, but currently is not sufficiently developed for recommendation. (Level IIIC)

*Principle*: Stem cells have the potential to differentiate into a variety of tissues, including fibroblasts, endothelial cells, keratinocytes, etc., and possibly to reconstitute components that are necessary for closure of the ulcers, including arterial inflow for arterial ulcers.

*Evidence*:

1. Falanga V. The chronic wound: impaired healing and its solutions in the context of wound bed preparation. *Blood cells, Mol, Dis* 2004; 32: 88–94. [LIT REV]
2. Badiavas EV, Falanga V. Treatment of chronic wounds with bone-marrow derived cells. *Arch. Derm* 2003; 139: 510. [CLIN S]
3. Lenk K, Adams V, Lurz P, et al. Therapeutical potential of blood-derived progenitor cells in patients with peripheral arterial occlusive disease and critical limb ischemia. *Eur Heart J* 2005; 26: 1903–9. [CLIN S]

*Guideline #6.C.2*: Gene therapy with vascular endothelial growth factor (VEGF) may be of benefit for healing arterial ulcers, especially in patients with critical limb ischemia who are not candidates for revascularization. More studies are needed to clarify its benefits. (Level IIIC)

*Principle*: Gene therapy with VEGF seems to improve the integrity of the tissue in leg ulceration and improve blood flow. However, there are some uncertainties regarding the benefits of VEGF therapy. For example, there is a difference between the amount of VEGF necessary for healing in different ethnic groups and experimental studies with high doses of VEGF-induced formation of angiomas.

*Evidence*:

1. Hochberg I, Hoffman A, Levy AP. Regulation of VEGF in diabetic patients with critical limb ischemia. *Annals of Vascular Surgery* 2001; 15: 288. [CLIN S]
2. Shyu KG, Chang H, Wang BW, Kuan P. Intramuscular vascular endothelial growth factor gene therapy in patients with chronic critical leg ischemia. *Am. J. Med* 2003; 114: 85–92. [CLIN S]
3. McLaren M, Newton DJ, Khan F, Belch JJ. Vascular endothelial growth factor in patients with critical limb ischemia before and after amputation. *Int Angiol*. 2002 Jun; 21: 165–8. [CLIN S]

*Guideline #6.C.3*: Topical oxygen therapy has been advocated for ischemic wound healing. Further study is required to clarify its benefits. (Level IIIC)

*Principle*: It has long been recognized that oxygen is required for wound healing and that hypoxic wounds (tissue oxygen tension $< 40$ mmHg) demonstrate impaired healing, or in extreme cases ($PO_2 < 20$ mmHg) failure to heal. Substantial evidence demonstrates the critical role of perfusion, that is, local blood supply, in delivering oxygen to wounds. Because oxygen is so crucial for wound healing, it is logical to consider the potential role of externally supplied (topical) oxygen delivery in modulating wound healing. The ability of oxygen to penetrate intact skin is clearly limited. The ability of oxygen to penetrate injured skin—that is, an open wound—also appears to be quite limited. The best data to date suggest a penetration of 100 μm or less into the wound when oxygen is applied topically, regardless of the method used to apply it to the wound. A number of routes for providing topical oxygen have been devised, including as a pure gas (within a plastic chamber or plastic bag, via continuous introduction by a battery-operated system within a bandage, and from an oxygen reservoir within the bandage), or as a gas dissolved within saline, a gel, or foam (in some cases as a supersaturated gas). The concept of topical oxygen (diffusion of oxygen into the wounds) is attractive; provision of supplemental oxygen at the wound surface has been shown to enhance cytokine production and wound healing in normal animal studies. A number of case studies and clinical series suggest a benefit of topical oxygen in the treatment of a variety of ulcers. Superficial ulcers such as venous ulcers have demonstrated the best response rate. Several of these clinical series include arterial ulcers. Nonetheless, the only true randomized, controlled trial to evaluate topical oxygen (in diabetic ulcers) demonstrated no benefit (Leslie, 1988). The methods used in the study have been criticized (the oxygen may have been applied in a manner that caused dessication of the wound, which would itself impair healing, for example). However, the use of topical oxygen cannot be advocated for arterial ulcers without further rigorous studies.

The literature often presents a confusing picture on topical oxygen, citing literature that demonstrates the value of systemic hyperbaric oxygen (HBO) in treating arterial insufficiency ulcers. This literature does not pertain to topical oxygen, because the route of delivery and mode of action are different with the two therapies; i.e., topical and hyperbaric oxygen are distinct, separate entities, despite their common use of the word oxygen. Topical oxygen may indeed be effective, although this remains to be proven, but it is important to distinguish the two modalities to clarify discussion of efficacy. Some topical devices do produce transient, slight elevations in ambient pressure applied to the wound (as high as 1.03 ATA). The degree of pressure that can be applied is significantly limited by the possibility of occluding arterial inflow or venous outflow with high pressure. In contrast, HBO (systemic) is defined medically as the application of pressures greater than atmospheric to a patient who is entirely enclosed within the pressurized chamber, at pressures of 1.5–6 ATA (generally 2–3 ATA for wound-healing indications). See Section 6.B.1 for a full discussion of the evidence supporting the use of HBO in arterial ulcers.

*Evidence*:


1. Kalliainen LK, Gordillo GM, Shlanger R, Sen SK. Topical oxygen as an adjunct to wound healing: a clinical case series. *Pathophysiology* 2003; 9: 81–87. [CLIN S]
2. Leslie CA, Sapico FL, Ginunas VJ, Adkins RH. Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. *Diabetes Care* 1988; 11: 111–5. [RCT]
3. Fries RB, Wallace WA, Roy S, Kuppusamy P, Bergdall V, Gordillo GM, Melvin WS, Sen CK. Dermal excisional wound healing in pigs following treatment with topically applied pure oxygen. *Mut Res* 2005; 579: 172–81. [EXP]
4. Diamond E, Forst MB, Hyman SA, Rand SA. The effect of hyperbaric oxygen on lower extremities ulcerations. *J Am Podiatry Assoc* 1982; 72: 1180–5. [CLIN S]
5. Upson AV. Topical hyperbaric oxygenation in the treatment of recalcitrant open wounds: a clinical report. *Phys Ther* 1986; 66: 1408–12. [CLIN S]
6. Heng MCY, Harker J, Bardakjlan VB, et al. Enhanced healing and cost effectiveness of low pressure oxygen therapy in healing necrotic wounds: a feasabilty study of technology transfer. *Ostomy Wound Manage* 2000; 46: 52–62. [CLIN S]
7. Heng MCY, Pilgrim JP, Beck FWJ. A simplified hyperbaric oxygen technique for leg ulcers. *Arch Dermatol* 1984; 120: 640–5. [CLIN S]
8. Ignacio DR, Pavot AP, Azer RN, et al. Topical oxygen therapy treatment of extensive leg and foot ulcers. 1985; 75: 196–9. [CLIN S]


## GUIDELINES FOR THE LONG-TERM MAINTENANCE OF ARTERIAL INSUFFICIENCY ULCERS

*Preamble*: Patients with peripheral arterial disease may often be asymptomatic and yet present with significant cardiovascular alterations. The risk of mortality due to peripheral arterial disease increases with age and severity of arterial insufficiency, with a 10-year mortality of approximately 60%. Therefore, management of reducing the risks has a significant impact in morbidity and mortality reduction. [Mohler III ER. Peripheral arterial disease: identification and implications. *Arch Intern Med* 2003; 163: 2306–14.]

*Guideline #7.1*: Risk factor reduction is the most significant issue to be addressed. It includes cigarette smoking cessation, control of diabetes mellitus, elevated homocysteine levels, hyperlipidemia, and hypertension. (Level IA)

*Principle*: Any attempt to reduce these risk factors may reduce the risk of arterial ulcer development and recurrence, as well as cardiovascular complications such as stroke and myocardial infarct.

*Evidence*:

1. Criqui MH, Langer RD, Froneck A, et al. Mortality over a period of 10 years in patients with peripheral disease. *N Engl J Med* 1992; 326: 381–6. [CLIN S]
2. Norman PE, Eikelboom JW, Hankey GJ. Peripheral arterial disease: prognostic significance and prevention of the atherotrombotic complications. *MJA* 2004; 181: 150–4. [STAT]
3. Mohler III ER. Peripheral arterial disease: identification and implications. *Arch Intern Med* 2003; 163: 2306–14. [STAT]
4. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease. Associations with the ankle brachial index and leg symptoms. *JAMA* 2004; 292: 453–61. [CLIN S]
5. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in the primary care. *JAMA* 2001; 286: 1317–24. [CLIN S]
6. Sieggreen MY, Kline RA. Arterial insufficiency and ulceration—diagnosis and treatment options. *Nurse Pract* 2004; 29: 46–52. [LIT REV]

*Guideline #7.2*: Antiplatelet therapy should be advocated. Vasodilation and antiplatelet effects of certain drugs could theoretically improve fibrinolytic activity, improving arterial insufficiency and minimizing ulceration. Further studies are required. (Level IIB)

*Principle* A: Clinical trials as CAPRIE showed that aspirin is less effective than clopidogrel and ticlopidine. (But aspirin and dipiridamole combined presented with positive effects.) On the other hand, the CHARISMA study shows no difference in the primary end point of cardiovascular death, MI, and stroke in patients randomized to aspirin plus clopidogrel vs. aspirin and placebo.

*Principle* B: Low-molecular-weight heparin may play a role in the wound-healing process of PAOD (hemorheological disturbance: high plasma fibrinogen), increasing the fibrinolytic activity and stimulating angiogenesis.

*Evidence*:

1. Ouriel K, Kaul AF, Leonard MC. Clinical and economic outcomes in thrombolytic treatment of peripheral arterial occlusive disease and deep venous thrombosis. *J Vasc Surg* 2004; 40: 971–7. [RETRO S]
2. CAPRIE steering committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996; 348: 1329–39. [RCT]
3. Clagett GP, Sobel M, Jackson MR, Lip GYH, Tangelder M, Verhaege R. Antithrombotic therapy in peripheral arterial occlusive disease—the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126: 609S–26S. [STAT]
4. Fiessinger JN, Schafer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangeitis obliterans. *Lancet* 1990; 335: 555–7. [RCT]
5. Kalani M, Apelqvist J, Blomback M, et al. Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2003; 26: 2575–80. [RCT]
6. Bhatt DL, Fox KA, Hacke W, et al. A global view of atherothrombosis: baseline characteristics in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Am Heart J* 2005; 150: 401. [RCT]

*Guideline #7.3*: Exercise to increase arterial blood flow has been demonstrated to be helpful in long-term maintenance and arterial ulcer prevention. (Level IA)

*Principle*: Exercise rehabilitation therapy is one of the most effective measures for patients with claudication. It also offers improvement in glucose metabolism, cholesterol levels, and cardiovascular benefits.

*Evidence*:

1. Norman PE, Eikelboom JW, Hankey GJ. Peripheral arterial disease: prognostic significance and prevention of the atherotrombotic complications. *MJA* 2004; 181:150–4. [CLIN S]
2. Mohler III ER. Peripheral arterial disease: identification and implications. *Arch Intern Med* 2003; 163: 2306–14. [STAT]
3. Sieggreen MY, Kline RA. Arterial insufficiency and ulceration—diagnosis and treatment options. *Nurse Pract* 2004; 29: 46–52. [LIT REV]
4. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease. Associations with the ankle brachial index and leg symptoms. *JAMA* 2004: 292: 453–61. [CLIN S]
5. Criqui MH, Langer RD, Froneck A, et al. Mortality over a period of 10 years in patients with peripheral disease. *N Engl J Med* 1992; 326: 381–6. [CLIN S]
6. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in the primary care. *JAMA* 2001; 286: 1317–24. [CLIN S]

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