Wound healing society 2014 update on guidelines for arterial ulcers

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The Wound Healing Society guidelines for the treatment of arterial insufficiency ulcers were originally published in 2006. These guidelines provided recommendations, along with their respective levels of evidence on seven categories: diagnosis, surgery, infection control, wound bed preparation, dressings, adjuvant therapy, and long-term maintenance. Over the last 7 years, a great deal of literature regarding these aspects of arterial ulcer management has been published. An advisory panel comprised of academicians, clinicians, and researchers was chosen to update the 2006 guidelines. Members included vascular surgeons, internists, plastic surgeons, anesthesiologists, emergency medicine physicians, and registered nurses, all with expertise in wound healing. The goal of this article is to evaluate relevant new findings, upon which an updated version of the guidelines will be based.

METHODS

Data sources and searches

We sought to capture the highest quality of literature available regarding arterial insufficiency ulcer diagnosis and treatment using a key word search of PubMed, Embase, and Cochrane Library databases. Similarly, the citations of relevant articles were examined by hand. Key terms were generated from the existing guidelines. The search was limited to meta-analyses, systematic reviews, randomized controlled trials (RCTs), retrospective series reviews, clinical case series, and expert panel recommendations published between January 2006 and 2013. It was further limited to only English publications, and review articles and case reports were excluded.

The findings of these articles have been divided into one or more of the appropriate categories (diagnosis, surgery, infection control, wound bed preparation, dressings, adjuvant therapy, and long-term maintenance) as performed in the original guideline.

GUIDELINES FOR DIAGNOSIS OF ARTERIAL INSUFFICIENCY ULCERS

Guideline 1.1: The reliability of capillary refill time as an indicator of tissue perfusion is questionable.

Principle: Using the capillary refill test with finger pressure on the dorsum of the dependent foot to measure microcirculatory supply has not been validated. Skin perfusion pressure is a good indicator of lower extremity microcirculation and transcutaneous oxygen tension (TcPO2) is a good indicator for critical limb ischemia (CLI).[1–8]

Evidence:

1. Faglia E, Clerici G, Clerissi J, Mantero M, Caminiti M, Quarantiello A, et al. When is a technically successful peripheral angioplasty effective in preventing above-the-ankle amputation in diabetic patients with critical limb ischaemia? *Diabet Med* 2007; 24: 823–9.
2. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985; 71: 516.
3. Lepantalo M, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F, et al. Chapter V: Diabetic foot. *Eur J Vasc Endovasc Surg* 2011; 42 (Suppl. 2): S60–74.
4. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med* 1998; 158: 1357–64.
5. Holloway GA. Arterial ulcers: assessment, classification, and management. In: Krasner DL, Rodeheaver GT, Sibbald RD, eds. Chronic Wound Care: A Clinical Source Book for Healthcare Professionals. 4th ed. Malvern, PA: HMP Communications, 2007: 443–9.

6. Faglia E, Clerici G, Caminiti M, Quarantiello A, Curci V, Somalvico F. Evaluation of feasibility of ankle pressure and foot oximetry values for the detection of critical limb ischemia in diabetic patients. *Vasc Endovasc Surg* 2010; 44: 184–9.
7. Faglia E, Clerici G, Mantero M, Caminiti M, Quarantiello A, Curci V, et al. Incidence of critical limb ischemia and amputation outcome in contralateral limb in diabetic patients hospitalized for unilateral critical limb ischemia during 1999-2003 and followed-up until 2005. *Diabetes Res Clin Pract* 2007; 77: 445–50.
8. Kawarada O, Yokoi Y, Higashimori A, Waratani N, Fujihara M, Kume T, et al. Assessment of macro- and microcirculation in contemporary critical limb ischemia. *Catheter Cardiovasc Interv* 2011; 78: 1051–8.

Guideline 1.2: Audio handheld Doppler waveforms are diagnostic of peripheral arterial disease (PAD) and triphasic pulse is reliable to rule out significant PAD.

Principle: Audible Doppler signal sounds are effective for the detection or exclusion of PAD compared with the ankle brachial pressure index (ABI). Triphasic waveforms from audio handheld Doppler can rule out PAD in asymptomatic low risk patients.[1–3]

Evidence:

1. Alavi A, Nebavizadeh R, Valei F, Coutts P, Sibbald GR. Audible Doppler alone is comparable to ankle brachial index for detection of significant peripheral arterial disease. *J Vasc Surg* In press.
2. Khandanpour N, Armon MP, Jennings B, Clark A, Meyer FJ. The association between ankle brachial pressure index and pulse wave velocity: clinical implication of pulse wave velocity. *Angiology* 2009; 60: 732–8.
3. Tsai CY, Chu SY, Wen YW, Hsu LA, Chen CC, Peng SH, et al. The value of Doppler waveform analysis in predicting major lower extremity amputation among dialysis patients treated for diabetic foot ulcers. *Diabetes Res Clin Pract* 2013; 100: 181–8.

Guideline 1.3: Pulse wave velocity may be useful in screening and evaluating the severity of PAD.

Principle: Nondiabetic vascular patients can have significant arterial stiffness independent of an impaired ABI. Increased pulse-wave velocity reflecting upon arterial stiffness shows an excellent correlation with decreased values of brachial artery flow-mediated dilation.[1–4]

Evidence:

1. Qasem A, Avolio A. Determination of aortic pulse wave velocity from waveform decomposition of the central aortic pressure pulse. *Hypertension* 2008; 51: 188–95. [CLIN S]
2. Jadhav UM, Kadam NN. Non-invasive assessment of arterial stiffness by pulse-wave velocity correlates with endothelial dysfunction. *Indian Heart J* 2005; 57: 226–32. [CLIN S]
3. Haiden M, Kimura Y, Miyasaka Y, Aota Y, Dote K, Takada A, et al. New index of regional arterial stiffness assessed by tissue Doppler imaging. *Acta Cardiol* 2008; 63: 603–8. [CLIN S]
4. Khandanpour N, Armon MP, Jennings B, Clark A, Meyer FJ. The association between ankle brachial pressure index and pulse wave velocity: clinical implication of pulse wave velocity. *Angiology* 2009; 60: 732–8. [CLIN S]

Guideline 1.4: Diagnosis of PAD by manual palpation of lower limb pulses is a reliable method when resources are limited.

Principle: Primary care physicians are not well versed with the use of Doppler for diagnosis of PAD. Initial cost of the equipment is another adverse factor in low-income countries. Detection of ankle systolic pressure by palpatory method may offer a cheap, simple and useful alternative approach in office care settings for early detection of PAD. However, a palpable pulse does not rule out PAD, particularly in diabetic patients with medical calcinosis. Given the common occurrence of medial calcinosis in patients with diabetes, Toe-Brachial-Pressure-Index is the recommended screening test.[1–7]

Evidence:

1. Schaper NC, Andros G, Apelqvist J, Bakker K, Lammer J, Lepantalo M, et al. Specific guidelines for the diagnosis and treatment of peripheral arterial disease in a patient with diabetes and ulceration of the foot 2011. *Diabetes Metab Res Rev* 2012; 28 (Suppl. 1): 236–7. [STAT]
2. Akhtar B, Siddique S, Khan RA, Zulfiqar S. Detection of atherosclerosis by ankle brachial index: evaluation of palpatory method versus ultrasound Doppler technique. *J Ayub Med Coll Abbottabad* 2009; 21: 11–6. [CLIN S]
3. Migliacci R, Nasorri R, Ricciarini P, Gresele P. Ankle-brachial index measured by palpation for the diagnosis of peripheral arterial disease. *Fam Pract* 2008; 25: 228–32. [CLIN S]
4. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985; 71: 516–22.
5. Lepantalo M, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F, et al. Chapter V: Diabetic foot. *Eur J Vasc Endovasc Surg* 2011; 42 (Suppl. 2): S60–74.
6. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med* 1998; 158: 1357–64.
7. Holloway GA. Arterial ulcers: assessment, classification and management. 2007.

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.[1–3]

Evidence:

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45 (Suppl. S): S5–67.
2. Brownrigg JR, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence-based management of PAD & the diabetic foot. *Eur J Vasc Endovasc Surg* 2013; 45: 673–81.
3. Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Friederichs S, Lammer J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. *Diabetes Metab Res Rev* 2012; 28 (Suppl. 1): 179–217.

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

Options include:

- Digital subtraction angiogram[1–4]
- Duplex angiography,[4] 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.[5]
- Magnetic resonance angiography[4,6,7]
- 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.
2. Toursarkissian B, D'Ayala M, Stefanidis D, Shirreman PK, Harrison A, Schoolfield J, et al. 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.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45 (Suppl. S): S5–67.
4. Gjoannaess E, Morken B, Sandbaek G, Stranden E, Slagsvold CE, Jørgensen JJ, 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: 53.
5. Katsamouris AN, Giannoukas AD, Tstetis D, Kostas T, Petinarakis I, Gourtsoyiannis N. Can ultrasound replace arteriography in the management of chronic arterial occlusive disease of the lower limb? *Eur J Endovasc Surg* 2001; 21: 155–60.
6. Hingorani A, Ascher E, Markevich N, Kallakuri S, Schutzer R, Yorkovich W, 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.
7. Koelemay MJ, Lijmer JG, Stoker J, Legemate DA, Bossuyt PM. Magnetic resonance angiography for the evaluation of lower extremity arterial disease: a meta-analysis. *JAMA* 2001; 285: 1338–45.

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 II).

Principle: Approximately 10–20% of patients with peripheral arterial occlusive disease will need revascularization surgery. Bypass surgery has a reported patency rate of 70% for crural-pedal bypass in both diabetics and nondiabetics at 5 years (in survivors), a limb salvage rate of 80% with a 1–2% amputation rate at 2 years in both diabetics and nondiabetics (the same in diabetics), and a limb salvage rate of 80% with 1–2% amputation rate at 5 years.[1–3] Surgical results for distal dorsalis pedis bypass: at 5 years, the primary patency is 57%, whereas the secondary patency is 63% and limb salvage is 78% (only 49% alive). At 10 years, the primary patency is 38%, whereas the secondary patency is 42% and limb salvage is 56% (only 24% alive).[2–4] Endovascular results reported an 80% 2-year limb salvage (small series).

Evidence:

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45 (Suppl. S): S5–67.
2. Treiman GS, Copland S, McNamara RM, Yellin AE, Schneider PA, Treiman RL. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. *J Vasc Surg* 2001; 33: 1158–64.
3. Pomposelli FB, Kansal N, Hamdan AD, Belfield A, Sheahan M, Campbell DR, 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.
4. Rhodes JM, Gloviczki P, Bower TC, Panneton JM, Canton LG, Toomey BJ. The benefits of secondary interventions in patients with failing or failed pedal bypass grafts. *Am J Surg* 1999; 178: 151–5.

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 comorbidities. (Level II).

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 end-stage renal disease 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.[1–5]

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.
2. Treiman GS, Copland S, McNamara RM, Yellin AE, Schneider PA, Treiman RL. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. *J Vasc Surg* 2001; 33: 1158–64.
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.
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.
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.

Guideline #2.4: The role of endovascular therapy in revascularization of the leg is established but not clearly understood in its comparison with open surgical procedures. The vascular surgeon can use judgment, expertise and local resources to consider the open or the endovascular approach.

Principle: The BASIL trial was a landmark randomized prospective study examining patients treated with either bypass or a balloon angioplasty approach to revascularization; this study found no significant different in either amputation-free survival or overall survival between the groups, but for patients who survived at least 2 years after randomization, a bypass-first approach was associated with increased survival.[1] The bypass-first strategy was associated with a modest increase in costs as well as an insignificant increase in quality of life.[2] Smaller reports document both good success with endovascular approaches as well as inferiority to open surgery; local expertise is often a determinant of treatment strategy.[3]

Evidence:

1. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg* 2010; 51 (5 Suppl.): 5S–17S.
2. Forbes JF, Adam DJ, Bell J, Fowkes FG, Gillespie I, Raab GM, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. *J Vasc Surg* 2010; 51 (5 Suppl.): 43S–51S.
3. Reekers JA, Lammer J. Diabetic foot and PAD: the endovascular approach. *Diabetes Metab Res Rev* 2012; 28 (Suppl. 1): 36–9.

Guideline #2.5: A multidisciplinary approach is recommended for patient care when revascularization is performed.

Principle: Current guidelines are poorly understood and adhered to, with many different treatment strategies and algorithms varying between areas of the world.[1] Treatment appears to be optimized when a multidisciplinary team is involved.[2,3]

Evidence:

1. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale study, a prospective cohort study. *Diabet Med* 2008; 25: 700–7.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45 (Suppl. S): S5–67.
3. Brownrigg JR, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence-based management of PAD & the diabetic foot. *Eur J Vasc Endovasc Surg* 2013; 45: 673–81.

Guideline #2.6: The role of revascularization of the angiosome is currently unknown, with additional studies needed to determine its importance.

Principle: Initial reports documented enthusiasm to treat the angiosomes of the foot.[1–3] However, these results have not been consistently reproducible.[4,5]

Evidence:

1. Neville RF, Attinger CE, Bulan EJ, Ducic I, Thomassen M, Sidawy AN. Revascularization of a specific angiosome for limb salvage: does the target artery matter? *Ann Vasc Surg* 2009; 23: 367–73.
2. Alexandrescu V, Vincent G, Azdad K, Hubermont G, Ledent G, Ngongang C, et al. A reliable approach to diabetic neuroischemic foot wounds: below-the-knee angiosome-oriented angioplasty. *J Endovasc Ther* 2011; 18: 376–87.
3. Iida O, Soga Y, Hirano K, Kawasaki D, Suzuki K, Miyashita Y, et al. Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions. *J Vasc Surg* 2012; 55: 363–70.
4. Azuma N, Uchida H, Kokubo T, Koya A, Akasaka N, Sasajima T. Factors influencing wound healing of critical ischaemic foot after bypass surgery: is the

angiosome important in selecting bypass target artery? *Eur J Vasc Endovasc Surg* 2012; 43: 322–8.
5. Söderström M, Albäck A, Biancari F, Lappalainen K, Lepäntalo M, Venermo M. Angiosome-targeted infrapopliteal endovascular revascularization for treatment of diabetic foot ulcers. *J Vasc Surg* 2013; 57: 427–35.

Guideline #2.7: The role of stem cell therapy as an alternative method of limb revascularization is promising but currently undefined.

Principle: Stem cell therapy is a promising treatment modality for small vessel revascularization with initial success in the TACT trial as well as other small series.[1–3] Recent reports of success have now been documented in small randomized trials.[4] Additional studies are needed to define the role of this therapy in appropriate populations of patients.[5]

Evidence:

1. Tateishi-Yuyama E, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet* 2002; 360: 427–35.
2. Higashi Y, Kimura M, Hara K, Noma K, Jitsuiki D, Nakagawa K, et al. Autologous bone-marrow mononuclear cell implantation improves endothelium-dependent vasodilation in patients with limb ischemia. *Circulation* 2004; 109: 1215–8.
3. Miyamoto K, Nishigami K, Nagaya N, Akutsu K, Chiku M, Kamei M, et al. Unblinded pilot study of autologous transplantation of bone marrow mononuclear cells in patients with thromboangiitis obliterans. *Circulation* 2006; 114: 2679–84.
4. Powell RJ, Marston WA, Berceli SA, Guzman R, Henry TD, Longcore AT, et al. Cellular therapy with Ixmyelocel-T to treat critical limb ischemia: the randomized, double-blind, placebo-controlled RESTORE-CLI trial. *Mol Ther* 2012; 20: 1280–6.
5. Brenes RA, Bear M, Jadlowiec C, Goodwin M, Hashim P, Protack CD, et al. Cell based interventions for therapeutic angiogenesis: review of potential cell sources. *Vascular* 2012; 20: 360–8.

UPDATE ON GUIDELINE FOR TREATMENT OF ARTERIAL ULCERS: ADJUVANT AGENTS

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.

While a number of studies have been published in this area since 2006, by and large they do not change the recommendations made in the 2006 Guidelines. For each of the previous guidelines, new studies are briefly described, along with their impact on the previous recommendations.

DEVICES (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 III)

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.

New evidence: In a RCT of a noncontact, low-intensity, low-frequency ultrasound therapy treatment (MIST Therapy; $n = 35$) plus "standard care" vs. "standard care" alone ($n = 35$) in patients with ischemic ulcers, the ultrasound group had a significantly higher rate of greater than 50% healing at 12 weeks (63% vs. 29% of subjects respectively; $p < 0.001$). Although this is a weak outcome measure, the study does provide some evidence of benefit specifically in arterial ulcers. The level of evidence remains III.[1]

1. Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound: the Mayo clinic experience, 2004-2006. *Adv Skin Wound Care* 2007; 20: 221–6.

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 in patients with CLI (N5120), SCS was not better than cohort in reducing the risk of amputation. Both SCS and cohort did, however, reduce the level of pain. (Level II).

New evidence: A meta-analysis of six RCTs that enrolled 444 patients found an 11% reduction in lower extremity amputation rates and reduced analgesic use in participants treated with SCS vs. standard care. The study also identified transcutaneous oxygen (PtcO2) 10–30 mmHg as a useful range for patient selection. The level of evidence remains II.[1]

1. Ubbink DT, Vermeulen H. Spinal cord stimulation for critical leg ischemia: a review of effectiveness and optimal patient selection. *J Pain Symptom Manage* 2006; 31: S30–35.

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 III).

New evidence: Two case series have been published looking at outcomes in patients with ischemic wounds treated with negative pressure therapy ($n = 3$ and $n = 121$, respectively). This demonstrates that negative pressure wound therapy may be safe, although it does not allow conclusions about outcome. The level of evidence remains III.[1,2]

1. Kasai Y, Svensson S, Björck M, Acosta S. Vacuum assisted wound closure in patients with lower extremity arterial disease. The experience from two tertiary referral-centres. *J Plast Reconstr Aesthet Surg* 2012; 65: 395–8.
2. Nordmyr J, Svensson S, Björck M, Acosta S. Application of low-pressure negative pressure wound therapy to ischaemic wounds. *Int Angiol* 2009; 28: 26–31.

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 II).

New evidence: In a case series (Sultan et al.)[1], 171 patients with nonrevascularizable vessels were given 3 months treatment with IPC. Treatment was associated with increased toe pressure and popliteal flow as well as good limb outcomes. There were no control patients. In a retrospective comparison (Kavros) of 48 patients with nonhealing foot wounds and CLI, below knee amputation was required in 83% of "standard care" patients and 42% in IPC plus "standard care" treated patients. PtcO2 was higher in the IPC patients. Short stretch compression did not impair toe pressure in patients with mixed arterial-venous ulcers (Top). The level of evidence remains IIB.[1–3]

1. Sultan S, Hamada N, Soylu E, Fahy A, Hynes N, Tawfick W. Sequential compression biomechanical device in patients with critical limb ischemia and nonreconstructible peripheral vascular disease. *J Vasc Surg* 2011; 54: 440–7.
2. Kavros SJ, Delis KT, Turner NS, Voll AE, Liedl DA, Gloviczki P, et al. Improving limb salvage in critical ischemia with intermittent pneumatic compression: a controlled study with 18-month follow-up. *J Vasc Surg* 2008; 47: 543–49.
3. Top S, Arveschoug AK, Fogh K. Do short-stretch bandages affect distal blood pressure in patients with mixed aetiology leg ulcers? *J Wound Care* 2009; 18: 439–42.

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 (PtcO2), 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)

New evidence: A systematic review by Goldman found HBOT decreased the chance of amputation (odds ratio [OR] 0.242, 95% CI: 0.137–0.428) (seven studies) and increased the chance of healing (OR 9.992, 95% CI: 3.972–25.132) (six studies) in patients with diabetic foot ulcer (DFU). Efficacy correlated with HBOT-induced hyperoxygenation of at-risk tissue (seven studies) as measured by transcutaneous oximetry. A systematic review by Kranke evaluated HBOT for chronic wounds (not limited to arterial ulcers or DFU). They concluded that HBOT significantly improves ulcer healing in the short term, but not the long term and more studies are required to evaluate the benefit in chronic wounds.

A double blind, RCT in 94 patients with Wagner Grade 2–4 diabetic foot ulcers (Löndahl) demonstrated a significantly higher rate of complete healing at one year in participants treated with HBOT vs. placebo (61 vs. 27%, respectively; $p = 0.009$). In a RCT (Duzgun) in 100 patients with Wagner Grade 2–4 diabetic foot ulcers, patients treated with HBOT were more likely to heal and underwent fewer amputations and more distal amputations. The trial was not limited to patients with ischemic DFU.

In a retrospective database analysis (Fife) of 1144 patients who underwent HBOT for DFU (most Wagner Grade 3), 75% improved. In chamber PtcO2 > 200 mmHg predicted a higher rate of response to treatment. Patients with renal failure and who smoked were much less likely to respond to treatment. In another retrospective database analysis (Chen), patients who received more than 10 HBO treatments had better outcomes.

A comparative effectiveness study (Margolis) using a large, community-based, for-profit wound clinic database demonstrated no apparent benefit of HBOT. Such studies cannot determine whether guidelines were followed in patient selection, whether compared populations were equivalent, and whether there was bias in treatment or inclusion. The results are not in concert with the outcomes of most RCTs, suggesting that further research is required to determine which patients should be treated with HBOT for arterial insufficiency ulcers.[1–7]

1. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. *PM&R* 2009; 5: 471–89.
2. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2012; 4: CD004123.
3. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010; 33: 998–1003.
4. Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *J Foot Ankle Surg* 2008; 47: 515–9.
5. Fife CE, Buyukcakir C, Otto G, Sheffield P, Love T, Warriner R 3rd. Factors influencing the outcome

of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy. *Wound Repair Regen* 2007; 15: 322–31.
6. Chen CE, Ko JY, Fong CY, Juhn RJ. Treatment of diabetic foot infection with hyperbaric oxygen therapy. *Foot Ankle Surg* 2010; 162: 91–5.
7. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, Glick HA, Thom SR, et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. *Diabetes Care* 2013; 36: 1961.

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

New evidence: In a retrospective study of 618 patients with CLI (Soga) who underwent endovascular treatment, patients who received cilostazol postoperatively had an 87% rate of limb salvage at 5 years, while control patients had a 75% rate of limb salvage. There was no difference in repeat operation between the groups. One case series demonstrated a good outcome with cilostazol (Shalhoub), while another demonstrated increased SPP (Miyashita). The level of evidence remains IIIC.[1–3]

1. Soga Y, Iida O, Hirano K, Suzuki K, Kawasaki D, Miyashita Y, et al. Impact of cilostazol after endovascular treatment for infrainguinal disease in patients with critical limb ischemia. *J Vasc Surg* 2011; 54: 1659–67.
2. Shalhoub J, Davies AH, Franklin IJ. Cilostazol may improve outcome in critical limb ischemia. *J Int Angiol* 2009; 28: 363–6.
3. Miyashita Y, Saito S, Miyamoto A, Iida O, Nanto S. Cilostazol increases skin perfusion pressure in severely ischemic limbs. *Angiology* 2011; 62: 156.

Guideline #6.B.3: There is no evidence supporting the use of prostaglandins (PGE-1) in the treatment of arterial ulcers (Level II).

New evidence: A Cochrane review supports no benefit. The level of evidence remains IID.[1]

1. Ruffolo AJ, Romano M, Ciapponi A. Prostanoids for critical limb ischaemia. *Cochrane Database Syst Rev* 2010:CD006544.

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 III).

New evidence: An RCT in patients with arterial ulcers demonstrated that topical morphine is not effective. An RCT in mixed venous/arterial ulcers demonstrated that topical local is more effective than nitrous oxide. The level of evidence remains III.[1,2]

1. Jansen MM, van der Horst JC, van der Valk PG, Kuks PF, Zylicz Z, van Sorge AA. Pain-relieving properties of topically applied morphine on arterial leg ulcers: a pilot study. *J Wound Care* 2009; 18: 306–11.
2. Claeys A, Gaudy-Marqueste C, Pauly V, Pelletier F, Truchetet F, Boye T, et al. Management of pain associated with debridement of leg ulcers: a randomized, multicentre, pilot study comparing nitrous oxide-oxygen mixture inhalation and lidocaïne-prilocaïne cream. *J Eur Acad Dermatol Venereol* 2011; 25: 138–44.

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

New evidence: A nonrandomized, nonblinded trial in 28 patients with DFU demonstrated an 82 vs. 45% healing rate in the topical oxygen vs. silver dressing group. The level of evidence remains IIIL.[1]

1. Blackman E, Moore C, Hyatt J, Railton R, Frye C. Topical wound oxygen therapy in the treatment of severe diabetic foot ulcers: a prospective controlled study. *Ostomy Wound Manage* 2010; 56: 24.

GUIDELINES FOR WOUND BED PREPARATION

1. Wound bed preparation starts with identification of wound etiology and improving associated medical conditions (nutrition, blood flow, awareness).

Address general medical condition involves control of diabetes, hypertension, evaluation of immunosuppressive drugs, improvement of nutritional status, stop smoking and determine if the wound has adequate blood flow (revascularization, angioplasty, regenerative medicine, and others).[1–8]

Level I:

1. Schultz SG, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; 11: 1–28. [STAT]
2. Attinger CE, Janis JE, Steinberg J, Schwatz J, Al-Attar A, Couch K. Clinical approach to wounds: Debridement and wound bed prepaparation including the use of dressings and wound healing adjuvants. *Plast Reconstr Surg* 2006; 117 (Suppl.): 72S–109S. [LIT REV]
3. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. *BMJ* 2006; 11: 347–50. [LIT REV]
4. Chiriano J, Bianchi C, Teruya TH, Mills B, Bishop, V, Abou-Zamzam AM Jr. Management of lower extremity wounds in patients with peripheral arterial disease: a stratified conservative approach. *Ann Vasc Surg* 2010; 24: 1110–6. [CLIN S]
5. Hess CT. Meeting the goal: wound bed preparation. *Adv Skin Wound Care* 2008; 21: 344. [LIT REV]
6. Ohno T, Kaneda H, Nagai Y, Fukushima M. Regenerative medicine in critical limb ischemia – current and future directions. *J Atheroscler Thromb* 2012; 19: 883–89. [STAT]
7. Ueno C, Hunt TK, Hopf HW. Using physiology to improve surgical wound outcomes. *Plast Reconstr Surg* 2006; 117: 59S–71S. [LIT REV]

8. Howard MA, Asmis R, Evans KK, Mustoe TA. Oxygen and wound care: a review of current therapeutic modalities and future direction. *Wound Repair Regen* 2013; 21: 501–11. [LIT REV]

Debridement is the basis of wound bed preparation. It involves understanding basic concepts as showed by TIME (nonviable Tissue; Infection/ uncontrolled Inflammation; excessive Moisture; migrating Epithelial edge). There are multiple strategies for wound debridement: chemical, mechanical, surgical.

Level I: 2a. Nonsurgical debridement involves use of autolytics (liquefies tissue promoting degradation by host enzymes—hydrogels, hydrocolloids), enzymes (remove devitalized tissue and can cause local irritation, proteolytic/collagenase, papain or fibrinolytic), mechanical (induce separation of tissue and remove debris, may macerate normal skin and remove newly formed tissue—wet to dry dressings, whirlpool, ultrasound, wound irrigation,-polyacrylate moist therapy,. . .), larval therapy (Lucilia sericata—produce enzyme that breaks down dead tissue and removes all bacteria harboring wound).[1–8]

1. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake R. Extending the TIME concept: what have we learned in the past 10 years? *Int Wound J* 2012; 9 (Suppl. 2): 1–19. [STAT]
2. Kravitz SR, McGuire J, Zinszer K. Management of skin ulcers: Understanding the mechanism and selection of enzymatic debriding agents. *Adv Skin Wound Care* 2008; 21: 72–4. [LIT REV]
3. Attinger CE, Janis JE, Steinberg J, Schwatz J, Al-Attar A, Couch K. Clinical approach to wounds: debridement and wound bed prepaparation including the use of dressings and wound healing adjuvants. *Plast Reconstr Surg* 2006; 117 (Suppl.): 72S–109S. [LIT REV]
4. Schultz SG, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; 11: 1–28. [STAT]
5. Callam MJ, Harper DR, Dale JJ, Ruckley CV, Prescott RJ. A controlled trial of weekly ultrasound therapy in chronic leg ulceration. *The Lancet* 1987; 2:204–5. [RCT]
6. Soares MO, Iglesias CP, Bland JM, Cullum N, Dumville JC, Nelson EA, et al. Cost effectiveness analysis of larval therapy for leg ulcers. *BMJ* 2009; 33: 1–8. [RCT]
7. Fleck CA, Chakravarthy D. Newer debridement methods for wound bed preparation. *Adv Skin Wound Care* 2010; 23: 313–15. [LIT REV]
8. Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, Part 1: normal and chronic wounds: biology, causes and approaches to care. *Adv Skin Wound Care* 2012; 25: 304–14. [STAT]

2b. Surgical debridement involves excision of necrotic/ fibrotic tissue to a normal, well-vascularized tissue and removal of infected tissue.[1–4]

1. Sibbald SG, Goodman L, Woo KY, Krasner DL, Smart H, Triq G, et al. Special considerations in wound bed preparation 2011: an update. *Adv Skin Wound Care* 2011; 24: 415–38. [STAT]
2. Schultz SG, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; 11: 1–28. [STAT]
3. Attinger CE, Janis JE, Steinberg J, Schwatz J, Al-Attar A, Couch K. Clinical approach to wounds: debridement and wound bed prepaparation including the use of dressings and wound healing adjuvants. *Plast Reconstr Surg* 2006; 117 (Suppl.): 72S–109S. [LIT REV]
4. Granick M, Boykin J, Gamelli R, Schultz G. Toward a common language: surgical wound bed preparation and debridement. *Wound Repair Regen* 2006; 14: S1–10. [STAT]

3. Approach to exudative wound bed.

A moist wound contributes to a healing environment; however, an exudative wound with copious amounts of fluid can be detrimental to healing since it harbors substances that will impede cell proliferation (high levels of proteases (MMP) and pro-inflammatory cytokines). It can progress to an infected wound.

It can be treated with: hydrocolloids (autolytic debridement, occlusive or semi-occlusive, mild exudates), foam dressings (absorb mild to moderate exudates, insulate wound, prevents maceration of normal skin and keep a health moisture in the wound bed); alginates (absorb moderate exudates, antibacterial, hemostatic and biodegradable), negative wound pressure therapy (absorbs large amount of exudates, but indicated only in clean wound bed).[1–3]

Level II:

1. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake, R. Extending the TIME concept: what have we learned in the past 10 years? *Int Wound J* 2012: 9 (Suppl. 2): 1–19. [STAT]
2. Attinger CE, Janis JE, Steinberg J, Schwatz J, Al-Attar A, Couch K. Clinical approach to wounds: debridement and wound bed prepaparation including the use of dressings and wound healing adjuvants. *Plast Reconstr Surg* 2006; 117 (Suppl.): 72S–109S. [LIT REV]
3. Vuerstaek JDD, Vainas T, Wuite J, Nelemans P, Neumann MHA, Veraart JCJM. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J. Vasc. Surg* 2006; 44: 1029–38. [RCT]

4. Approach to infected wound bed.

Infected wounds (elevated bacterial concentration with quantitative count $>$ 105 organisms per gram of tissue determine by biopsy of wound) should be suspected when wounds fail to heal, become more painful, deteriorate or progress to a systemic infection and sepsis.

Treatment involves control of medical conditions, debridement of devitalized tissue and topical antimicrobials (antiseptics—iodine, peroxide, acetic acid, Dakin's solution, hypochlorous acid (VASHE therapy), chlorhexidine, boric acid,. . . and antimicrobials—silver sulfadiazine, honey (peroxide activity and osmolarity—non-favorable),. . .) with coverage for multiorganisms.[1–8]

Level II:

1. Sibbald RG, Woo K, Ayello EA. Increased bacterial burden and infection: the story of NERDS and STONES. *Adv Skin Wound Care* 2006; 19: 447–61. [LIT REV]
2. Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, Part 1: normal and chronic wounds: biology, causes and approaches to care. *Adv Skin Wound Care* 2012; 25: 304–14. [STAT]
3. Black CE, Costerton JW. Current concepts regarding the effect of wound microbial ecology and biofilms on wound healing. *Surg Clin North Am* 2010; 90: 1147–60. [LIT REV]
4. Attinger CE, Janis JE, Steinberg J, Schwatz J, Al-Attar A, Couch K. Clinical approach to wounds: debridement and wound bed prepaparation including the use of dressings and wound healing adjuvants. *Plast Reconstr Surg* 2006; 117 (Suppl.): 72S–109S. [LIT REV]
5. Niezgoda JA, Sordi PJ, Hermans MHE. Evaluation of Vashe wound therapy in the clinical management of patients with chronic wounds. *Adv Skin Wound Care* 2010; 23: 352–7. [CLIN S]
6. Kavros SJ, Liedl DA, Boon AJ, Miller JL, Hobbs JA, Andrews KL. Expedited wound healing with noncontact, low frequency ultrasound therapy in chronic wounds: a retrospective analysis. *Adv Skin Wound Care* 2008; 21: 46–23. [RETRO S]
7. Rodgers AB, Jull A, Walker N. Honey as a topical treatment for wounds. *Cochrane Rev* 2009; 4: 1–48. [STAT]
8. Granick M, Boykin J, Gamelli R, Schultz G. Toward a common language: surgical wound bed preparation and debridement. *Wound Repair Regen* 2006; 14: S1–10. [STAT]

5. Education in management of wound bed.

It is important to establish a sense of team effort with patients, caregivers and healthcare providers from the implementation of an action plan, education to an agreement on adherence to treatment.[1,2]

Level II:

1. Sibbald SG, Goodman L, Woo KY, Krasner DL, Smart H, Triq G, et al. Special considerations in wound bed preparation 2011: an update. *Adv Skin Wound Care* 2011; 24: 415–38. [STAT]
2. Schultz SG, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; 11: 1–28. [STAT]

6. A knowledge of the different dressings (from simple dry gauze to tissue engineering) and that different dressings may be required throughout the healing process depending on wound bed characteristics is important to improve wound healing. Dry wound needs moisture, exudative wound needs absorption, infected wound needs antimicrobial/ antiseptics, necrotic wound needs debridement.[1–6]

Level II:

1. Moore RA, Liedl DA, Jenkins S, Andrews KL. Using a silver-coated polymeric substrate for the management of chronic ulcerations: the initial Mayo Clinic experience. *Adv Skin Wound Care* 2008; 21: 517–20. [RETRO S]
2. Romanelli M, Dini V, Bertone MS. Randomized comparison of OASIS wound matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care* 2010; 23: 34–8. [RCT]
3. Sibbald SG, Goodman L, Woo KY, Krasner DL, Smart H, Triq G, et al. Special considerations in wound bed preparation 2011: an update. *Adv Skin Wound Care* 2011; 24: 415–38. [STAT]
4. Attinger CE, Janis JE, Steinberg J, Schwatz J, Al-Attar A, Couch K. Clinical approach to wounds: debridement and wound bed prepaparation including the use of dressings and wound healing adjuvants. *Plast Reconstr Surg* 2006; 117 (Suppl.): 72S–109S. [LIT REV]
5. Vuerstaek JDD, Vainas T, Wuite J, Nelemans P, Neumann MHA, Veraart JCJM. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum – assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg* 2006; 44: 1029–38. [RCT]
6. Schultz SG, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; 11: 1–28. [STAT]

Evidence reference:

STAT	Statistical analysis, meta-analysis, consensus
RCT	Randomized clinical trial
CLIN S	Clinical series
LIT REV	Literature review