CLINICAL MANAGEMENT extra

Arterial Disease Ulcers, Part 2: Treatment

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This continuing educational activity will expire for physicians on October 31, 2015.

Editor's note: Part 1 of this article series appeared in the September issue of *Advances in Skin & Wound Care*.

PURPOSE:

The purpose of this learning activity is to provide information about therapeutic clinical intervention options based on the pathophysiology of arterial ulcers.

TARGET AUDIENCE:

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:

After participating in this educational activity, the participant should be better able to:

1. Identify assessments needed to guide treatment choices for arterial ulcers.

2. Select treatment options for arterial ulcers under varying clinical circumstances.

ABSTRACT

OBJECTIVES: The objectives of this article are to describe the therapeutic options available and develop an appropriate clinical approach suitable to the individual needs of the patient with arterial insufficiency, based on the wound bed preparation paradigm.[1] This information will also assist in the integration of decision making regarding appropriate clinical intervention in an interprofessional team approach, according to the International Inter-professional Wound Caring Model 2012,[2] with inclusion of patient-centered concerns within the patient's circle of care.

KEYWORDS: arterial disease, hyperbaric oxygen therapy, ischemia, ischemic wounds, amputation

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TREATMENT

From the onset, a holistic, evidence-based, cost-effective, interprofessional, and individualized, patient-centered team approach should be adopted in the management of a patient with an arterial ulcer.[2] The authors recommend that the team apply the wound bed preparation paradigm[1] (Figure 1), which is a consistent framework for assessment, diagnosis, and treatment of wounds along the continuum toward optimal healing. An individualized plan of care should be devised for every patient, taking into consideration his/her unique biopsychosocial needs, including risk factors, physical disability, pain, mental anguish, lack of sleep, comorbidities, quality of life, social needs, support systems, access to care, and personal preferences. The human touch builds the trust and the confidence that heals wounds, people, and lives.[2]

Treatment plans should emphasize correcting the cause by urgent revascularization, if and when required. Not only is the limb at risk, but also the patient's life.[3] Patients with peripheral arterial disease often have coexisting coronary and cerebrovascular atherosclerosis and are twofold to fourfold more likely than patients without peripheral arterial disease to die of cardiovascular disease.[4] A vascular surgeon and physician must be consulted and included in the interprofessional team.[5,6]

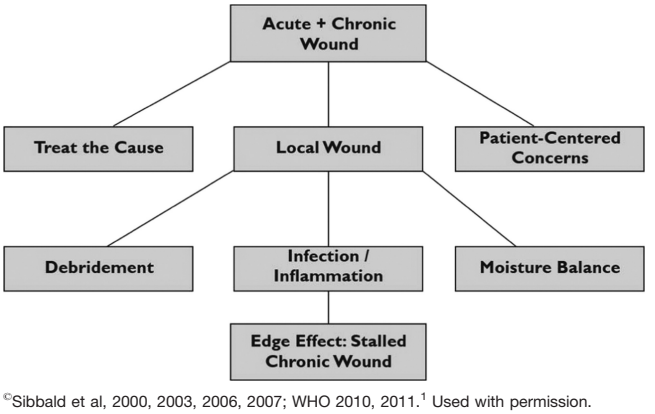
Patient-centered concerns that need to be addressed include pain, quality of life, and activities of daily living (ADLs). Arterial ulcers add the psychological stress of the potential risk of an amputation, which should be emphatically and realistically addressed by the team. Schneider[7] suggests that patients may often be able to discover a positive perspective on their situation within their reality. This helps individuals to achieve peace of mind, appreciation for their experiences, and mobilization for future endeavors. This perspective invites emotions, such as hope, pride, curiosity, and enthusiasm, as powerful motivators.[7]

The clinician's initial contact with the patient is an important event. One should attempt to engage, empathize, educate, and enlist[2,8] the patient in an attempt to create a therapeutic relationship in an environment conducive to healing. A treatment plan that is developed with the patient, and his/her circle of care, will be more likely followed. Success in managing arterial ulcers requires total patient commitment. The management of risk factors and the ulcer are dependent on the patient's activities and his/her understanding of the treatment process. Honest, open, and direct communication between the healthcare professionals and the person with an arterial ulcer, as well as his/her caregivers, will allow all concerns to be considered and contribute to the development of a mutually negotiated treatment plan. An interprofessional patient conference may increase the patient's understanding of the suggested treatment options, especially if more advanced, higher-risk, and costly strategies are being considered. This can further enhance the collaboration between team members, patients, and caregivers and improve coherence of the treatment plan. After a treatment plan has been agreed on, clear communication, flexibility, adaptability, openness, shared leadership, professionalism, and mutual respect will further encourage the team effort.[2]

Negative factors that influence patients' ability to perform ADLs include pain, odor, decreased mobility, finances, and other aspects of living, such as reactive depression and anxiety with a sense of social isolation.[1] Clinicians must be aware that quality of life means different things to different people. The team should pursue a treatment plan that will improve the patient's psychosocial well-being that is within their personal financial and logistic constraints.

The availability of various treatment strategies offers a unique spectrum of potential solutions and risk-benefit choices for patients with arterial ulcers. Unfortunately, methods for reversing hypoxia in chronic wounds are often complex and expensive. Essentially there are 2 strategies: (*a*) improving circulation and (*b*) improving

Figure 1.
WOUND BED PREPARATION PARADIGM FOR HOLISTIC PATIENT CARE



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oxygenation. The reason why many of these interventions work is that intact skin requires very low quantities of oxygen to *survive*, but a transcutaneous oxygen pressure ($TcPo_2$) of at least 30 to 40 mm Hg to *heal*. If oxygen delivery can be maintained to the point of healing, a subsequent return to a lower baseline may not be detrimental. This emphasizes the importance of preventing primary wounding of ischemic tissues and early diagnosis of peripheral arterial disease.[9,10] Prevention is better than cure.

An interprofessional approach protects patients against one specific treatment modality. Enthusiasm should always be tempered by careful consideration of what is really best for the patient. In some situations, the interprofessional team should exercise restraint. If the patient is considered high risk for intervention, or if a treatment modality is contraindicated, a conservative approach may be appropriate. Under these conditions, the patient should be reassessed frequently to ensure appropriate control of the patient's pain, and risk factors and to monitor the wound. The intervention should be reconsidered if the patient's risk factors and medical contraindications have been adequately addressed. The conservative approach may also fail because of propagating sepsis or intractable pain, or if conservative management becomes unacceptable to the patient.

Optimal Medical Treatment

Optimal medical therapy aimed at risk factor reduction is advocated for all patients with arterial disease.[11–13] This may be all that is required to treat mild arterial disease. To reduce risk factors, clinicians should encourage smoking cessation, the lowering of elevated lipids, and controlling hypertension and diabetes, along with antiplatelet therapy. Lipid-lowering therapy should include an HMG-CoA reductase inhibitor (eg, statin) and a low-density lipoprotein goal of less than 70 mg/dL (1.8 mmol/L).[11,13] The target blood pressure for patients with peripheral arterial disease is less than 140/90 mm Hg without diabetes and less than 130/80 mm Hg with diabetes.[11,13] Glucose control therapies that reduce hemoglobin A_{1c} to less than 7% can be effective in reducing microvascular complications and potentially improve cardiovascular outcomes.[11,13] Even if surgery is contemplated, antiplatelet therapy (eg, aspirin) should be started preoperatively and continued as adjuvant pharmacotherapy after the endovascular or surgical procedure.[11,13]

Risk factor reduction lowers the risk of arterial ulcer development and recurrence, as well as cardiovascular complications, such as stroke and myocardial infarction. Coexisting morbidities, including coronary artery disease, chronic renal disease, or cerebrovascular disease should also be addressed when indicated.[11,13] Other cofactors that may impair healing include medications, poor nutrition, low hemoglobin, low blood pressure, congestive heart failure, and impaired liver function.[1]

In patients with vasospastic disorders such as Raynaud phenomenon, peripheral vasodilators such as nifedipine or pentoxifylline may increase the blood flow. Pentoxifylline facilitates red blood cell deformability, which increases perfusion of tissues. Factors that increase sympathetic tone, including stress or pain, will decrease tissue perfusion and should therefore be avoided.

In advanced peripheral arterial disease, pharmacological agents will have very little effect. Current guidelines do not recommend pentoxifylline to improve arterial ulcer healing, but suggest that cilostazol requires further investigation.[12] Despite positive short-term results, current evidence and guidelines do not support the use of prostanoids to promote amputation-free survival.[14,15] There is also no other pharmacotherapy that can be recommended for the treatment of critical limb ischemia.

Gene therapy with vascular endothelial growth factor has demonstrated promising early efficacy, especially in patients with critical limb ischemia who are not candidates for revascularization, but further trials are warranted.[11,13] Short-term results of intra-arterial and intramuscular injections of bone marrow mononuclear cells are also promising in rest pain reduction, ulcer healing, and postponing or avoiding amputation.[16–18] Stem cell therapy is a promising and expanding field but currently is not sufficiently developed for routine clinical practice.[12]

Exercise is recommended (30 minutes per day, 3 times a week) to increase arterial blood flow. Evidence has demonstrated exercise to be helpful in long-term maintenance and arterial ulcer prevention.[9,12] Patient smoking cessation strategies are also helpful and should include educational, pharmacological, and behavioral techniques.[19] Smoking cessation advice and encouragement of cessation efforts should be key components of each office visit.[11,13,20–22] Warmth, correction of dehydration, and increased inspired oxygen can increase impaired blood flow and improve oxygen delivery.[12,23] Lastly, foot protection with soft, conforming, proper-fitting shoes (foot deformity/altered biomechanics), casts, orthotics, and offloading is essential to preventing ulceration by decreasing tissue trauma. The prevention of injury is essential to limb preservation.[9]

Nutritional Support

A low protein intake (or relative deficiency) can prevent the production of granulation tissue. This in turn will contribute to a stalled healing environment for the wound. Because of the fact that patients with arterial ulcers often experience severe pain, appetite might be suppressed to such an extent that formal nutritional support becomes essential. Albumin, prealbumin, and transferrin tests can be performed to assess the extent of nutritional deficiency. Clinicians should be aware that these enzymes are affected by a range of conditions and results should be interpreted accordingly.

Provision of a diet with high protein, micronutrients, and arginine has resulted in improved healing rates and less wound care intensity for the care providers.[24] Inadequate nutrition, dehydration, and weight loss must be corrected through nutritional interventions for a chronic wound to heal.[12] Some authors have in the past advocated the use of oral zinc sulfate; however, this is not supported by current evidence.[25] Dehydration or clinical undetectable underhydration aggravates wound healing and impairs skin microcirculation because of hypoperfusion. Patients' fluid requirements should be assessed and addressed.[23]

Pain Control

For the patient with an arterial ulcer, pain is usually the first priority. In contrast, several international pain surveys have demonstrated that pain is the third to fifth most important component of care for healthcare providers.[26] The management team should use a uniform pain scale to assess pain before, during, and after all patient interactions. The patient's wound should be considered painful until proven otherwise.[27]

The primary pain objective of the wound bed preparation paradigm is to determine and treat the underlying cause.[1] Addressing the cause of the ulcer by improving the blood supply is the most effective way to control pain in a patient with a peripheral arterial ulcer. Increasing pain in patients with arterial ulcers is an indication for revascularization. Once patients develop severe ischemic pain, their decision making becomes severely impaired. Pain intervention strategies should be implemented urgently. Input from the interprofessional team regarding local, regional, and systemic measures for pain control should be a priority.[12]

According to the World Health Organization,[28] there should be prompt oral administration of analgesics in the following order: nonopioids (such as aspirin and acetaminophen); then, if required, mild opioids (such as codeine); followed by strong opioids including morphine or oxycodone, until the patient is free of pain. Higher doses may be required and should be administered under close supervision to avoid systemic complications. To calm fears and anxiety, additional medication such as anxiolytics should be used. To maintain freedom from pain, pain medication can be given at regular intervals (eg, every 3 to 6 hours), rather than on demand. This 3-step approach of administering the right medication in the right dose at the right time is inexpensive and 80% to 90% effective in the treatment of nociceptive pain.

Neuropathic pain (burning, stinging, shooting, stabbing) often responds to tricyclic agents, particularly second-generation agents high in antinoradrenaline activity (nortriptyline and desipramine are often better than amitriptyline). For nonresponders, consider alternate agents such as gabapentin and pregabalin or other antiepileptic agents.[29]

From a nursing perspective, it is important to focus on patient comfort. The patient's leg should be placed in a dependent position to help to increase the arterial flow through collateral vessels. Patients may find benefits from sleeping with an elevated head of the bed.[30] Extremes of temperature should be avoided. The limb should be protected from further harm by using a bed cradle with a high degree of vigilance. The World Union of Wound Healing Societies published a consensus document on *Minimizing Pain at Wound Dressing-Related Procedures*[26] (see Figure 2).

Spinal cord stimulation may be of benefit in reducing the pain associated with ischemic arterial ulcers.[31,32] Prostanoids also appear to give some relief of rest pain.[15] For nonhealable or maintenance wounds, pain and quality of life may be indicated as the primary goals of care. If all adjuvant options have been depleted and a balance between pain control and quality of life cannot be achieved, amputation should be considered.

Local Wound Care

The American College of Cardiology and American Heart Association's guidelines on the management of patients with peripheral arterial disease recommends patients with critical limb ischemia and skin breakdown be referred to healthcare providers with specialized expertise in wound management (class I level B evidence).[13]

An individualized wound care plan should be put in writing as part of the patient's permanent healthcare record. This plan must be made available to all team members. This plan should be routinely evaluated, reevaluated, and updated. The plan should also be updated with any significant change in the patient's general health status.[1]

Local wound care should be initiated to avoid infection and further injury. Optimal local wound care involves carefully cleaning the ulcer, controlling infection and inflammation, and covering it with a nonadherent dressing for moisture balance. Patient participation, including removal of the dressing at dressing change, should be encouraged if clinically appropriate. Dressing changes should be coordinated with the patient's hygiene schedule. This will enable the patient to have a shower before a dressing change. These measures will contribute to the patient's adherence to the treatment plan.[1]

A clean wound, free of dead tissue and wound debris, is necessary for healing to occur. Many commercially available wound cleaners are cytotoxic but have surfactant properties that are often useful. Povidone-iodine, chlorhexidine, hydrogen peroxide, and 0.25% to 1% acetic acid have been shown to interfere with fibroblast formation and epithelial growth. The selective use of these agents, particularly povidone-iodine and chlorhexidine, should be reserved for wounds that have limited ability to heal or for time-limited use in wounds in which bacterial burden is more important than cellular toxicity.

The safest wound cleanser is 0.9% saline solution or water. Wounds should be cleaned with a force just strong enough to dislodge debris but gentle enough to prevent damage to newly growing tissue. Irrigation remains controversial and should be avoided in arterial ulcers.

Figure 2.
PHARMACOLOGICAL AND NONPHARMACOLOGICAL STRATEGIES TO MINIMIZE WOUND-RELATED PAIN

Source: Woo KY, Harding K, Price P, Sibbald G. Minimising wound-related pain at dressing change: evidence-informed practice. Int Wound J 2008;5:144-57.[26]

In general, surgical debridement of an arterial ulcer should be avoided because this will inevitably lead to higher oxygen demands in the adjacent tissue and potentially contribute to further necrosis, enlarging the wound. It could also lead to spread of infection in the already compromised tissue. Irreversible tissue loss (dry gangrene or eschar) should be left dry. Adding moisture to devitalized tissue could create the ideal medium for bacterial growth. The vascular surgeon responsible for the arterial reconstruction will opt to debride the wound just prior to or directly after a revascularization procedure, under appropriate antibiotic cover.

If an arterial ulcer is deemed to be a *healable wound*, careful debridement, infection control, and moisture balance should be implemented. Debridement may include careful sharp surgical debridement and the use of mechanical, enzymatic, or autolytic debridement methods, along with dressings (usually alginates, hydrogels, or hydrocolloids). A clinician should have objective evidence that an arterial ulcer is healable before debridement is performed. Appropriate tests include ankle brachial pressure index (ABPI) greater than 0.5 or $TcPo_2$ greater than 30 to 40 mm Hg.[33] These ulcers are often recalcitrant to healing, and they do not follow the expected trajectory that estimates a wound should be 30% smaller (surface area) at week 4 to heal by week 12. Interventions should be considered if conservative treatment does not improve ulcer healing in 4 to 6 weeks.[34]

Reconstructive bypass surgery or endovascular intervention is not required in all patients with arterial ulcers. Nehler et al[35] observed that a lesion-oriented approach may result in patients undergoing revascularization, when in fact they might have healed with aggressive wound care. Objective parameters (ankle pressure <50 mm Hg, toe pressure <30 mm Hg) were found to predict unfavorable outcome of cutaneous arterial leg ulcers.[36] Chiriano et al[37] also suggested that $TcPo_2$ greater than 30 mm Hg and ankle Doppler pressures should be used as objective measures in selecting patients for conservative management. Marston et al[38] suggested that ischemic ulcers should be treated in a dedicated wound program and that interventions designed to improve outcomes in critical limb ischemia should stratify outcomes based on hemodynamic data (eg, ABPI >0.5). In a select subgroup of patients, conservative wound care might be sufficient to heal the wound. In some of these patients, wound maintenance will be achieved, maintaining quality of life and ADLs, by reducing the risk of limb loss.[37,39]

If the patient's vasculature is considered nonreconstructable, or if other factors that impede the patient's healing ability cannot be corrected, the wound should be considered a *nonhealable wound*. Such a wound requires moisture reduction with a nonadherent dressing that is able to wick moisture away from the wound bed surface. Bacterial reduction can be attained with povidone-iodine or chlorhexidine. Extreme caution should be taken to prevent

dressing materials from adhering to the wound bed or eschar because this could inadvertently lead to accidental active debridement. Minimal handling is advised with an atraumatic responsibility to the wound bed. Debridement, pressure modalities, and moisture addition are contraindicated.[1]

Dressing selection should be individualized and based on the wound's ability to heal. There is no evidence that the choice of dressing has any influence on the outcome of treatment of patients with arterial ulcers.[40] In a patient where the arterial supply is uncertain and cannot be immediately determined, dressing selection should be based on a nonhealable wound program with moisture reduction and bacterial reduction until further assessments are performed. This program will contain wound deterioration. In arterial ulcers with sufficient arterial inflow to support healing, a nonadherent dressing that will maintain a moist wound-healing environment should be used.[12] Current guidelines suggest selecting cost-effective, appropriate, nonadherent dressings that will minimize the patient's pain and reduce the risk of further complications.

In patients with arterial disease, the skin is often fragile and can be easily injured by tape and adhesive products. Extreme caution should be used. Of the available adhesive products, soft silicones are less likely to cause local trauma during dressing changes. The dressing should be covered with a light bandage because a tight bandage will further impede the blood supply.

Under very close supervision of an experienced team, compression therapy can be beneficial in ulcers of mixed (venous and arterial) etiologies.[41–43] Objective evidence should be obtained that the arterial supply is sufficient before compression is applied. Mosti et al[44] demonstrated in patients with mixed ulceration with an ABPI greater than 0.5 and an absolute ankle pressure of greater than 60 mm Hg, modified compression (inelastic compression of up to 40 mm Hg), does not impede arterial perfusion but may still lead to a normalization of the highly reduced venous pumping function. Treiman et al[45] found that a history of previous deep vein thrombosis was associated with poor outcomes. After bypass surgery, edema is often a significant problem impairing wound healing. Mild compression in this setting is often helpful.[12] Excessive compression should be avoided. The patient should be advised to return to the clinician or to remove compression dressings should pain develop.

If all 5 components of the wound bed preparation paradigm have been corrected (cause, patient-centered concerns, and the 3 components of local wound care: debridement, infection/inflammation control, moisture control) and a healable wound remains stalled, re-evaluation of the current diagnosis and treatment plan is necessary. Evaluate that each component has been adequately addressed before considering active local advanced therapies (edge effect) and adjuvant therapies.[1]

Adjuvant Therapies

Adjuvant therapies may improve healing of the arterial ulcer. However, they do not correct the underlying vascular disease and cannot replace revascularization. Revascularization, as a single intervention, is not always successful or durable; adjuvant therapy may improve outcomes if combined with revascularization.[12] It should be considered with caution and limited to healable wounds. Emphasis should be placed on the importance of using advanced wound-healing modalities as appropriate adjuvant therapies that work synergistically with standard wound care regimens such as provision of adequate vascular supply to the affected area, highly selective debridement, pressure mitigation, and infection control. Without adhering to these important principles, the addition of any adjunctive modality is unlikely to result in improved healing rates.[18,46]

Autografts and allografts can accelerate the closure of wounds after adequate arterial inflow has been restored.[12] Spinal cord stimulation improves limb salvage and rest pain.[32,47] Intermittent pneumatic leg compression has been demonstrated to increase blood flow and may be beneficial in limbs with impaired distal perfusion, either before or after revascularization.[12] Hopf et al[12] recommended that there is insufficient evidence to support the use of biomaterials, ultrasound, electrical stimulation, or topical negative-pressure wound therapy in arterial ulcers.

Vig et al[48] suggested the cautious use of negative-pressure wound therapy in chronic limb ischemia. The group suggested that this should be limited to specialist units and that it should be considered only when all other modalities have failed. Kasai et al[49] also suggested that low-pressure topical negative pressure (−50 mm Hg) could be used with caution under very close supervision of an experienced team. A Wound Healing Association of Southern Africa consensus document recommended that a $TcPo_2$ less than 40 mm Hg be considered a contraindication.[50]

Infection Control

All chronic ulcers are contaminated with bacteria. The patient's resistance to infection depends on the partial pressure of oxygen in the wound.[51,52] Ischemic hypoxia due to peripheral arterial disease increases bacterial proliferation. Devitalized tissue is laden with bacteria. In arterial ulcers with dry gangrene or eschar, debridement should not be performed until arterial inflow has been reestablished.[12] Pre-revascularization debridement should be indicated only in a septic foot where immediate surgery could compromise the patient's life or limb.

The key features of a superficial infection of the wound bed can be recalled by the NERDS mnemonic[1]: **n**onhealing, ↑**e**xudate, **r**ed-friable tissue, **d**ebris, **s**mell. Topical antimicrobial treatment is justified if 3 or more of the NERDS signs are identified. Topical antimicrobial dressings may be beneficial in management of these wounds, decreasing their bacterial load and aiding wound healing.[12]

Topical treatment could include various ionized silver dressings, polyhexamethylene biguanidine, honey products, cadexomer iodine, or methylene blue/gentian violet–based dressings in healable wounds. The use of antimicrobial dressings should be reviewed at weekly intervals and discontinued if critical colonization has been corrected or after 4 weeks.[53] Povidone-iodine or chlorhexidine may be considered for wounds with inadequate blood supply to support healing. Topical antibiotics should be avoided because of the increased risk of bacterial resistance and patient sensitization.[54]

The key features of a systemic infection due to an ulcer can be remembered by the STONEES mnemonic: ↑**s**ize, ↑**t**emperature, **o**s, **n**ew breakdown, ↑**e**xudate, ↑**e**rythema + edema (cellulitis), ↑**s**mell. Systemic antibiotics and topical antimicrobial treatment is justified if 3 or more of the STONEES signs have been identified.

The clinician should be especially vigilant in patients with diabetes and neuroischemic ulcers. These patients often do not exhibit the classic clinical signs of infection because of decreased immune response and impaired sensation. Prolonged outpatient antibiotic therapy may decrease the chance of wound healing and is associated with a significantly decreased chance of limb salvage.[55] Infection will be better prevented and controlled in an environment that is adequately oxygenated.[52]

Perfusion Strategies

Perfusion strategies are aimed at reversing ischemia by either restoring the patency of the arteries, bypassing occluded arteries, or using a combination of these techniques (ie, hybrid procedures). All of these techniques improve the flow of blood to the affected limb and thereby increase tissue perfusion. In patients with arterial ulcers, restoration of blood flow by revascularization will most likely lead to healing.[30] The goal of revascularization is to restore in-line arterial blood flow to the ulcer. This may be manifested by a pulse in the foot, improved ABPI, or improved $TcPo_2$.[56,57]

If a patient has evidence of deteriorating critical limb ischemia, the use of endovascular or surgical perfusion strategies is justified to save the extremity.[58] Vascular surgeons are able to apply both types of interventions to optimize patient outcomes. A selective approach that integrates patient risk, severity of ischemia, arterial anatomy, and conduit availability is advocated. These patients should be cared for by dedicated specialists with advanced training and experience in a well-coordinated interprofessional center.[6,59] The threshold for revascularizing neuroischemic ulcers should be lower (less vascular compromise) than that of purely ischemic ulcers because of the additional factors of microvascular dysfunction causing arteriovenous shunting, capillary ischemia, leakage, and venous pooling.[34]

The choice of endovascular versus open surgical alternatives is often complex. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)[11] offers some guidance by stratifying vascular lesions. So-called ''TASC A'' lesions represent those where endovascular interventions offer good resolution. The ''TASC B'' lesions offer adequate results using endovascular methods; therefore, this approach is the preferred option, unless open revascularization is indicated for other associated lesions in the same anatomical area. The ''TASC C'' lesions have superior long-term outcomes using open revascularization; therefore, endovascular methods are used only in the case of patients with a high operative risk. Finally, ''TASC D'' lesions are where endovascular methods do not yield adequate results, thus excluding them as a primary treatment.

Diagnostic evaluation of patients with critical limb ischemia should provide (*a*) objective confirmation of the diagnosis; (*b*) localization of the responsible lesion(s) with an assessment of relative severity; (*c*) assessment of the hemodynamic requirements for successful revascularization (ie, proximal vs combined revascularization of multilevel disease); and (*d*) assessment of the individual patient's endovascular or operative risk.[60]

The clinician(s) responsible for the revascularization procedure will decide on the appropriate imaging modalities. These tests may include duplex angiography,[61] magnetic resonance angiography,[61–64] contrast tomography angiography,[61,65] or arteriography. Imaging will help to determine the extent of the arterial disease and how to revascularize the affected area. The ability to visualize a potential outflow artery has the potential to increase the limb salvage rate for selected patients. The risk-benefit analysis of these imaging studies should be considered for each individual patient.

The angiosome principle was defined by Ian Taylor in his landmark anatomic study in 1987.[66] The angiosome anatomy, interangiosome connections, and angiosome overlap have since been described extensively by Attinger et al.[67] *Angiosomes* are defined as 3-dimensional blocks of tissue fed by specific arterial and venous sources.[68] Infragenicular revascularization based on the angiosome model seems to provide encouraging wound healing and limb preservation rates for both bypass and endovascular techniques.[67–70] Kabra et al[71] determined that direct revascularization of the ischemic angiosome contributes to improved ulcer healing, but their results did not significantly improve limb salvage rates. Patients should be offered indirect revascularization as this also improves healing albeit at a lower rate than direct revascularization.[71] Ischemic ulcers located in the midfoot and hindfoot were associated with prolonged ulcer healing time.[72]

The risk of intervention should be weighed against the potential likelihood of success (ie, revascularization and ulcer healing after revascularization) given an individual patient's comorbidities.[11,12,39,73] Age is not considered a contraindication to revascularization procedures. A study by Ouriel et al[74] demonstrated statistically significant

benefit in terms of morbidity and mortality, when comparing bypass procedures to amputations in octogenarians. The risk stratification tools (eg, PREVENT III CLI Risk Score) can facilitate accurate risk prediction. This will help inform clinicians and patients of the possible risks associated with a given treatment and thereby inform the decision-making process for all parties involved.[75] This complex risk-benefit analysis should be discussed with the patient in the context of an interprofessional patient conference. This may offer considerable benefit to the patient's understanding of the suggested treatment options. In the words of a *British Medical Journal* editorial, "Good surgeons know how to operate, better ones when to operate, and the best when not to operate."[76]

If an intervention is indicated, and informed consent has been obtained, the procedure should commence as soon as possible because "time is tissue."[34,77] A delay in the diagnosis and management of significant critical limb ischemia may have disastrous complications.

Endovascular Perfusion Strategies

The concept of nonsurgical catheter-based peripheral vascular revascularization was first described by Charles Dotter and further advanced with the development of balloon dilation catheters by Andreas Gruentzig.[11] Despite the fact that endovascular techniques are not superior to surgical techniques with regard to vessel patency, wound healing and limb salvage can still be attained by using endovascular techniques for patients previously considered ineligible for revascularization. Catheter-based revascularization has largely replaced conventional open surgery as the treatment of first choice in selected patients treated for lower-extremity ischemia.[11,13,78]

Despite significant comorbidities, the rates of amputation, procedural morbidity and mortality, along with length of stay have all significantly decreased. Although some of this change could be ascribed to important changes in medical management and wound care, the impact appears to be largely due to the widespread and successful use of endovascular revascularization, earlier intervention, or both. The change has also been driven by the safety of these techniques.[79] Although low patency rates of endovascular procedures have been criticized, the use of endovascular therapies in the management of ischemic wounds provides clinicians with a chance to secure wound healing and limb salvage.[57]

The following endovascular perfusion strategies are commonly used.

Angioplasty. Angioplasty is the least invasive intervention to restore circulation. A percutaneous Seldinger technique is used to insert a cannula into an artery, either proximal or distal to the lesion, under local anesthetic. The common femoral artery is often the point of access or, in selected cases, the brachial artery. A guide wire is placed through the cannula into the artery under fluoroscopic guidance. An arterial sheath is then placed over the guide wire to protect the punctured artery. Intra-arterial contrast is administered to identify lesions within the arterial lumen. These lesions can then be crossed using the guide wire. An angioplasty balloon is inserted over the guide wire, whereupon the diseased section of the artery is dilated by inflation of the balloon. In selected cases, a stent can be placed into the artery to maintain the lumen. The success of the procedure is dependent on the length of the stenosis or occlusion, the quality of inflow proximally, and the quality of run-off distally.

Good long-term outcomes can be attained in the iliac arteries with bare metal stents, but in-stent stenosis may occur. The development of covered stents, with graft material (usually polytetrafluoroethylene) either on one side of the stent metal or enclosing it completely, has demonstrated improved patency rates.[80] Very long occluded segments can also be crossed by means of the subintimal angioplasty technique that tunnels between the tunica intima and tunica media of the artery rather than through the stenosis (Figure 3).[81] The use of drug-eluting balloons shows promise because of the reduced rate of restenosis. Schmidt et al[82] demonstrated that the early restenosis rate of long-segment infrapopliteal disease was significantly lower after treatment with drug-eluting balloons compared with historical data using uncoated balloons.

Potential complications associated with endovascular procedures include hemorrhage, thrombosis, restenosis, and occlusion. Although the patency rates for some of these procedures may only be measured in months, they may allow wounds to heal during that time. It also affords the patient the opportunity to form a more extensive network of collateral vessels. Risk factor modification and optimal medical therapy contribute significantly toward a favorable outcome.

The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) recommends that in situations where outcomes of endovascular revascularization versus open repair/bypass are considered equivocal in terms of short- and long-term symptomatic improvement, endovascular techniques should be used first.[11]

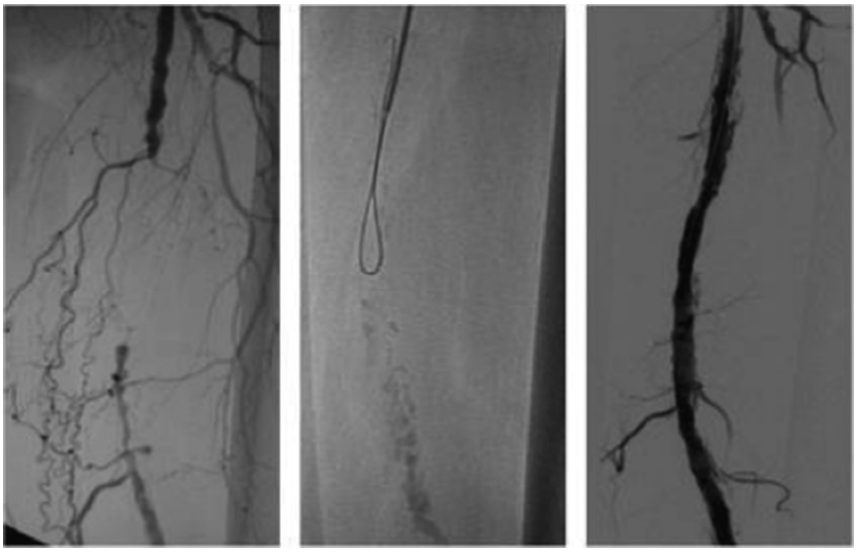
Catheter-Directed Thrombolytic Therapy. Thrombolysis has become increasingly common in emergency, medical, and surgical practice. Within the context of acute thrombotic events involving limb arteries, catheter-directed thrombolysis is used to dissolve thrombus, exposing the underlying stenosis. The stenosis can then be addressed by means of an angioplasty or bypass surgery, if required.

Surgical Perfusion Strategies

The following surgical perfusion strategies are available for selected patients.

Endarterectomy. This is an open surgical procedure, requiring limited access, during which the endothelial lining and subjacent

Figure 3.
PERCUTANEOUS SUBINTIMAL ANGIOPLASTY



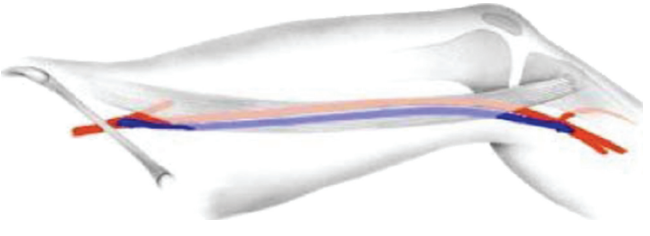
Image/courtesy Dr Gregory R. Weir.

atheromatous lesions are removed from the vessel. It is performed quite frequently for carotid artery stenosis. For ischemia of the lower extremity, femoral artery endarterectomies can be performed in patients with isolated occlusions of that artery. The limited access makes this procedure appropriate for higher risk surgical patients. This procedure can even be performed under local anesthesia.

Arterial Bypass. Extensive vascular pathology sometimes requires the use of vascular bypass procedures. The objective is to create a natural (autogenous vein) or artificial (prosthetic graft) conduit able to bypass the obstruction, restoring inline circulation to the ischemic tissue. The proximal anastomosis is made in a relatively disease-free segment of the artery. The distal anastomosis is done beyond the most distal occlusion. The success of bypass procedure depends on good arterial inflow (ie, proximal arterial circulation), good arterial outflow (ie, distal arterial circulation), and an adequate conduit.

As a rule, the conduit of choice is an autogenous vein. Reversed saphenous vein, when used for a femoropopliteal bypass, has superior patency when compared with prosthetic conduits (ie, polyester or polytetrafluoroethylene)[11,83,84] (Figure 4). This becomes both clinically and statistically significant when the bypass is performed distal to the knee joint. If an autogenous conduit is not available, the use of a prosthetic conduit is justified. Prosthetic conduits are used as a matter of routine in bypass procedures of larger diameter vessels, for example, aorta-bifemoral bypass with a bifurcated prosthesis for aorta-iliac occlusive disease and abdominal aortic aneurysms. The use of prosthetic graft material is associated with a higher risk of sepsis, which carries high morbidity

Figure 4.
FEMOROPOPLITEAL BYPASS WITH REVERSED SAPHENOUS VEIN



Image/courtesy Dr Gregory R. Weir.

and mortality. Notwithstanding these risks, durable salvage can be obtained in 85% to 89% of cases of critical limb ischemia.[11,83,85]

The results of the BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial[83] suggest that patients who are likely to live 2 years are probably better served by a surgical bypass strategy, preferably with vein. Those patients who are unlikely to live 2 years, and possibly those in whom a vein is not available for bypass, are probably better served by a balloon angioplasty strategy because they are unlikely to survive to reap the longer-term benefits of surgery and they may be more likely to have surgical morbidity and mortality. Short-term angioplasties are also significantly less expensive than surgery.

Patients with diabetes and skin ulceration present unique challenges. They typically have extensive pathology of the infrapopliteal arteries. Although some of the lesions can be addressed with balloon angioplasty, a large proportion cannot be managed using endovascular techniques. Femoropedal bypasses have been used with surprisingly good results. Despite the fact that long-term patency rates of these bypasses are low, they still improve overall limb salvage rates. This may be because bypass procedures afford enough time for wounds to heal; they palliate rest pain; and they allow time for new collateral vessels to form. The average patency rates are listed in Table 1.

Oxygenation Strategies

For patients with incomplete arterial obstruction, adequate oxygenation may be achieved by increasing dissolved blood oxygen content using either normobaric (ie, O_2 delivered to the patient at 1 atm) or hyperbaric (ie, O_2 delivered to the patient at 2–3 atm) oxygen therapy.[86,87]

Table 1.
AVERAGE GRAFT RESULTS FOR SURGICAL TREATMENTS[11]

Surgical Treatments	5-y Estimates
Femoropopliteal below-knee prosthetic	<35%
Plantar	41%
Femoropopliteal percutaneous transluminal angioplasty occlusion	42%
Axillounifemoral bypass	51%
Femoropopliteal percutaneous transluminal angioplasty stent	55%
Axillobifemoral percutaneous transluminal angioplasty	71%
Iliac percutaneous transluminal angioplasty	71%
Cross femoral	75%
Aortobifemoral bypass (limb)	91%

Normobaric Oxygen. Oxygen is used daily in surgical theaters and in hospital wards. It is generally underutilized, given the wealth of scientific support confirming its value in wound healing and ability to prevent wound sepsis and dehiscence, particularly following surgery.[52]

Oxygen delivery systems range in terms of the route, volume, and concentration of oxygen they provide. A Venturi mask can offer 24% to 60% oxygen. They deliberately mix the oxygen with air, thereby delivering a high volume of oxygen-enriched air able to keep up with a patient's inspiratory flow rate, without being unduly wasteful of the oxygen supply. For lower concentrations of oxygen, this is the most reliable system. Simple oronasal masks and nasal cannulas are not ideal. Oronasal masks rarely fit properly, and patients frequently dislodge them or have them hanging around their necks or blowing in their ears. Nasal cannulas deliver 24% to 40% oxygen within a tolerable flow rates, but they require nasal breathing. It is not uncommon to see patients snoring through the mouth as the nasal cannula fizzes gently in the background. Tight-fitting nonrebreather masks are the best way to deliver high concentrations of oxygen, that is, 80% to 90%.

Breathing high concentrations of normobaric oxygen can increase plasma-dissolved oxygen by up to 2 mL/dL, which is approximately 40% of the average quantity of oxygen extracted from hemoglobin by body tissues.[87] More important than blood oxygen content is the ability of this increased oxygen concentration in plasma to diffuse further into tissues. This concept is often difficult to convey to medical professionals who consider, quite erroneously, that hemoglobin saturation is a definitive measure of tissue oxygenation.

There are no limits or restrictions on the use of normobaric oxygen at inspired fractions of less than 0.5 (ie, <50%). The continuous delivery of 80% to 100% oxygen should be limited to 24 to 36 hours. Tobacco use results in vasoconstriction, carbon monoxide increase, and ultimately in tissue hypoxia and delayed wound healing. Smoking cessation is therefore of utmost importance.

Hyperbaric Oxygen Therapy. By delivering oxygen to patients at increased ambient pressure, hyperbaric oxygen (HBO) therapy is able to extend the beneficial effects of oxygen supplementation. However, even though HBO therapy can increase dissolved blood oxygen by up to 6 mL/dL (enough to sustain life without blood), it still requires a conduit to transport the oxygen to the affected tissue. There are multiple other physiologic effects that supernormal partial pressures of oxygen exert on the body. Benefits include angiogenesis, fibroblast growth and collagen production, improved osteoclast function, enhanced removal of carbon monoxide from hemoglobin, inhibition of α-toxin production in clostridial myonecrosis, improved leukocyte killing, decreased neutrophil adherence to capillary walls, increased production of superoxide dismutase, and vasoconstriction in normal vessels, all reducing edema. These effects are the physiologic rationale for the use of HBO therapy.[86,88]

The application of HBO therapy has to compete with a number of other medical and surgical therapies that have already established themselves through common practice and modern evidence-based medical processes. To secure more general acceptance and to ensure its appropriate use, HBO has to meet the same standards and should be applied judiciously.[87] At a consensus meeting in Lille, France (December 2004), the evidence supporting the use of HBO therapy was evaluated using modern evidence-based medicine criteria.[89] From a wound care perspective, the accepted indications for HBO treatment were rated (Table 2).

Randomized controlled trials, systematic reviews, and current guidelines for the treatment of arterial ulcers suggest that HBO treatment should be considered as an adjuvant therapy in a patient with nonreconstructable anatomy or whose ulcer is not healing despite revascularization.[12,90–93] 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.[12] Further research should be completed to investigate the benefit of HBO therapy in the treatment of ischemia-reperfusion injury after revascularization in patients with arterial ulcers.

A Cochrane review concluded that HBO treatment significantly reduces the risk of major amputation in patients with diabetic ulcers if performed as part of an interdisciplinary program of wound care.[94] A moderate level of evidence indicates that HBO also promotes healing of calciphylactic and refractory vasculitic ulcers.

A retrospective case series was conducted on a cohort of patients with arterial ulcers of the lower extremity. All patients received HBO as part of an interprofessional treatment program. Healing improved significantly for the group with evidence of better oxygenation of tissue at risk with administration of 100% normobaric oxygen. Where periwound $TcPo_2$ improved by 10 mm Hg, 70% of wounds healed. In contrast, where $TcPo_2$ decreased by 10 mm Hg, only 11% healed.[95] The TASC II document[11] suggests that HBO therapy may be considered in selected patients with ischemic ulcers who have not responded to, or are not candidates for, revascularization.

There is insufficient clinical evidence to justify the use of topical oxygen therapy.[96] The ability of oxygen to penetrate intact skin or the wounded skin is limited. Clinicians should make a clear distinction between topical application of oxygen, systemic normobaric oxygen, and systemic HBO therapy.[12]

Patients with complex ischemic/hypoxic wounds, who either do not have clinically significant arterial disease (ie, they have microvascular disease) or are not candidates for endovascular or surgical perfusion strategies, should be considered for HBO therapy. Transcutaneous oximetry offers an objective method for determining which patients are most likely to benefit from HBO therapy.[97] Patients who have had successful revascularization procedures should also be reconsidered for oxygen therapy if their wounds do not respond adequately following the vascular intervention.

The presence of macrovascular arterial insufficiency per se is not a contraindication to HBO therapy.[12] In the authors' clinical experience, a $TcPo_2$ greater than 40 mm Hg on air or during 100% normobaric oxygen inhalation has been the tipping point for the decision of whether patients with acceptable ABPIs should preferentially receive HBO therapy rather than vascular surgery as the primary intervention. However, to continue HBO therapy, transcutaneous oximetry must confirm that the minimum therapeutic value (ie, >200 mm Hg $TcPo_2$) can be achieved under hyperbaric conditions.[97] This is referred to as a ''hyperbaric challenge.'' If there is no improvement in $TcPo_2$ levels with the patient breathing oxygen and HBO, revascularization should be reconsidered.

In a study by Goldstein et al,[98] HBO therapy recruits stem cells (endothelial progenitor cells) from bone marrow of mice and releases them into the circulation. In the same mouse model, hindlimbs, made ischemic by femoral artery ligation, reperfuse, and ischemic wounds heal. This study concluded that nitric oxide is a key mediator of the HBO effect.[98] Because nitric oxide is an important mediator of epithelialization, wound matrix formation, and neoangiogenesis, it may be that HBO augments many components of healing.

Table 2.
COMMON INDICATIONS FOR THE USE OF HYPERBARIC OXYGEN[89]

Evidence Level	Conditions
I	Anaerobic or mixed bacterial anaerobic infections
	Osteoradionecrosis (mandible)
	Soft tissue radionecrosis
II	Compromised skin graft and musculocutaneous flap
	Diabetic foot lesions
	Ischemic ulcers
	Osteoradionecrosis (other bones)
	Radio-induced lesions of soft tissues
	Refractory chronic osteomyelitis
	Surgery and implant in irradiated tissue (preventive action)
III	Partial-thickness burns >20% of surface area
	Postvascular procedure reperfusion syndrome
	Selected nonhealing wounds secondary to inflammatory processes

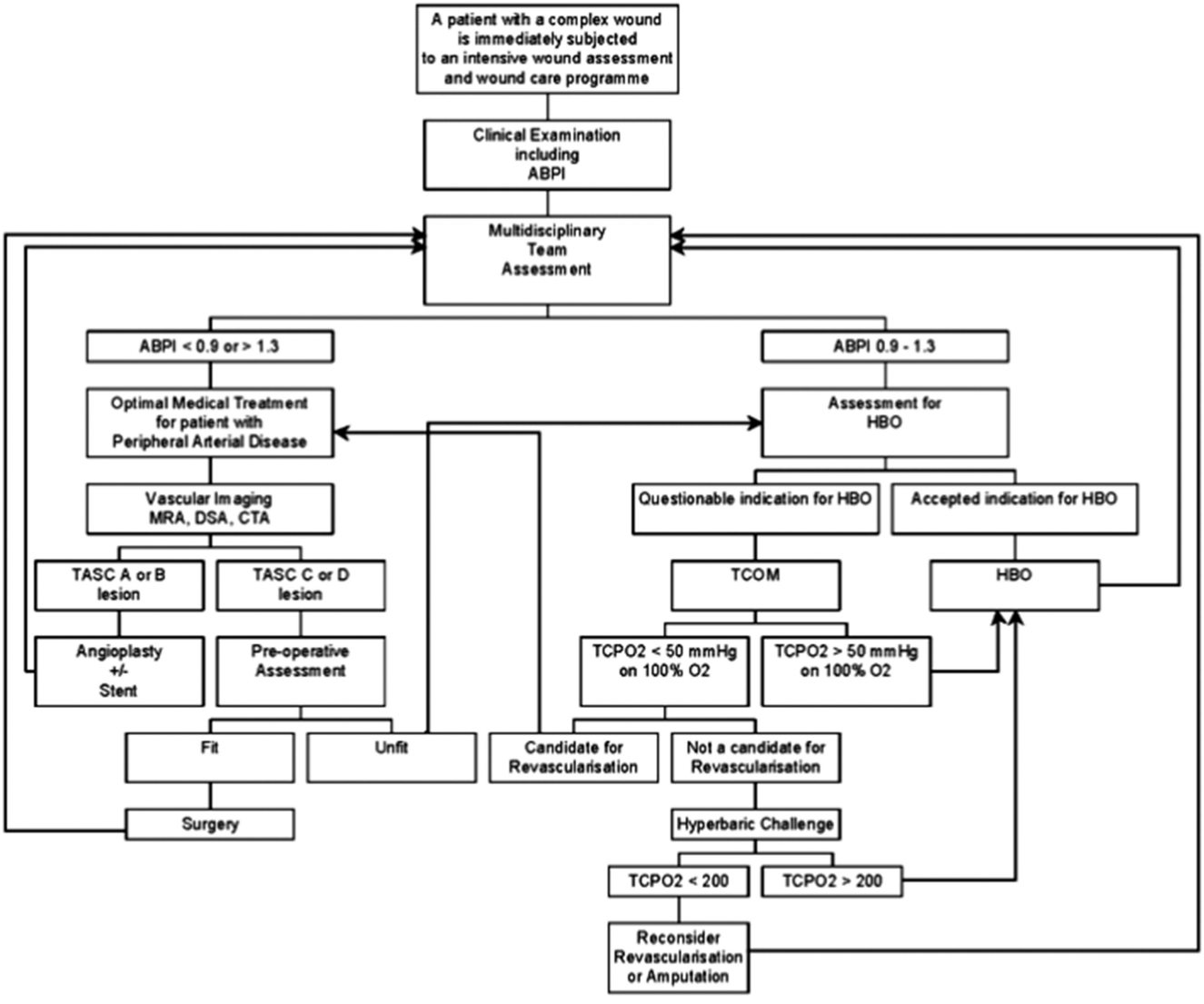
The following flowchart has been used at the authors' vascular and hyperbaric unit (GW). It offers a structured way to evaluate and manage patients with complex wounds (Figure 5).

Patient Education

Teach a patient with an arterial ulcer to do the following[100,101]:

- monitor arterial or graft patency by palpating pulses
- recognize signs and symptoms of graft failure and what to report
- avoid tobacco and nicotine in any form, including secondhand smoke
- begin or maintain a regular exercise program
- manage blood glucose, if diabetes is present
- control hypercholesterolemia
- manage hypertension
- reduce and control weight as part of a low-cholesterol diet
- perform meticulous foot care
- manage ulcer care
- report new ulcers immediately

Figure 5.
FLOWCHART FOR THE MANAGEMENT OF HYPOXIC/ISCHEMIC WOUNDS[99]



Weir GR, Cronje FJ. Ischaemia and hypoxia: the therapeutic options. Wound Heal South Afr 2010;3:11–6. Used with permission from Dr Gregory R. Weir.

Primary Amputation

The decision to amputate and the choice of the level of amputation should be considered carefully.[102] It should weigh the patient's chances of healing, rehabilitation potential, and overall quality of life. For patients with advanced disease and functional impairment, an early amputation and rehabilitation might be more appropriate than a prolonged, expensive, and labor-intensive attempt to salvage a dysfunctional limb. Primary amputation should also be considered in those patients where retaining the limb will directly contribute to an increased risk of mortality or significant decrease in quality of life.[97] Psychological support and rehabilitation are imperative. Orthopedic surgeons, psychologists, orthotists, and rehabilitation physicians are vital members of the interprofessional wound care team. They should be involved early in the overall assessment of the patient, irrespective of the prognosis or the treatment strategies that may be available.

Palliative Treatment

Finally, there are patients who will present with unsalvageable ischemia who also have a negligible chance of survival or quality of life after amputation. The most appropriate, humanitarian decision may then be to opt for effective pain management, palliative wound care, and palliative patient care.[39]

CONCLUSION

The management of an arterial ulcer starts with an accurate diagnosis. Treatment should proceed within an interprofessional team. The development of an appropriate, individualized treatment plan with input from the patient, the patient's circle of care, and an interprofessional wound care team is essential. The primary treatment strategy is revascularization, followed by patient-centered concerns.

Adjuvant therapies should be utilized only in healable wounds when the wound healing process stalls. The patient with a healed arterial ulcer has not been cured from peripheral arterial disease; lifelong clinical surveillance is still required.[101] The strategies described in this article can help to improve the delivery of oxygen and essential nutrients to an ischemic wound. These strategies can also improve the quality of life and prognosis of a patient with peripheral arterial disease through risk factor modification. Despite the fact that clinicians are dealing with a high-risk patient, their endeavors are not futile. The key factor to meeting this challenge is to assemble the best possible interprofessional team.

PRACTICE PEARLS

- Evaluate every patient for signs of arterial disease: dependent rubor, decreased circulation time, and cold extremities along with aggravating factors: smoking, hypertension, elevated cholesterol and, if applicable, poor diabetic control.
- Assess vascular supply in every patient suspected to have arterial disease (pulse, ABPI, segmental duplex Doppler and, in selected patients, angiography).
- Increasing ischemic pain may be an indication for surgical intervention (angioplasty, bypass).
- Ischemic wounds should be treated as maintenance or nonhealable wounds: no active debridement—remove only nonviable slough, bacterial reduction, moisture reduction (consider povidone-iodine or chlorhexidine, topically).
- Consider adjunctive therapies if surgical procedures are not an option (eg, HBO if transcutaneous oxygen is over 20 and oxygen testing demonstrates increase [double in value] in local TCO_2).

REFERENCES

1. Sibbald RG, Goodman L, Woo KY, et al. Special considerations in wound bed preparation 2011: an update©. Adv Skin Wound Care 2011;24:415-36; quiz 437-8.
2. Krasner DL, Rodeheaver GT, Sibbald RG, Woo KY. International Interprofessional Wound Caring (Chapter 1.1). In: Krasner DL, Rodeheaver GT, Sibbald RG, Woo KY, eds. Chronic Wound Care: A Clinical Source Book for Healthcare Professionals. Malvern, PA: HMP Communications; 2012:3-12.
3. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
4. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197-208.
5. Federman DG, Kravetz JD. Peripheral arterial disease: diagnosis, treatment, and systemic implications. Clin Dermatol 2007;25:93-100.
6. Ho V, Wirthlin D, Yun H, Allison J. Physician supply, treatment, and amputation rates for peripheral arterial disease. J Vasc Surg 2005;42:81-7.
7. Schneider SL. In search of realistic optimism. Meaning, knowledge, and warm fuzziness. Am Psychol 2001;56:250-63.
8. Keller VF, Carroll JG. A new model for physician-patient communication. Patient Educ Couns 1994;23:131-40.
9. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the prevention of lower extremity arterial ulcers. Wound Repair Regen 2008;16:175-88.
10. Nunnelee JD. Decision making in prevention and treatment of arterial leg ulcers: use of patho-flow diagramming. J Vasc Nurs 1996;14:72-8.
11. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5-67.
12. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the treatment of arterial insufficiency ulcers. Wound Repair Regen 2006;14:693-710.
13. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47:1239-312.
14. Oral Iloprost in Severe Leg Ischaemia Study Group. Two randomized and placebo-controlled studies of an oral prostacyclin analogue (Iloprost) in severe leg ischemia. Eur J Endovasc Surg 2000;358-62.
15. Ruffolo AJ, Romano M, Ciapponi A. Prostanoids for critical limb ischaemia. Cochrane Database Syst Rev 2010;CD006544.
16. Franz RW, Parks A, Shah KJ, Hankins T, Hartman JF, Wright ML. Use of autologous bone marrow mononuclear cell implantation therapy as a limb salvage procedure in patients with severe peripheral arterial disease. J Vasc Surg 2009;50:1378-90.
17. Wen Y, Meng L, Gao Q. Autologous bone marrow cell therapy for patients with peripheral arterial disease: a meta-analysis of randomized controlled trials. Expert Opin Biol Ther 2011;11:1581-9.

18. Wu SC, Marston W, Armstrong DG. wound care: the role of advanced wound-healing technologies. J Am Podiatr Med Assoc 2010;100:385-94.
19. Ahn C, Mulligan P, Salcido RS. Smoking—the bane of wound healing: biomedical interventions and social influences. Adv Skin Wound Care 2008;21:227-36; quiz 237-8.
20. Gornik HL, Creager MA. Chapter 19—medical treatment of peripheral artery disease. In: Creager MA, Beckman JA, Loscalzo J, eds. Vascular Medicine: A Companion to Braunwald's Heart Disease. 2nd ed. Philadelphia, PA: W. B. Saunders; 2013:242-58.
21. Ameli FM, Stein M, Provan JL, Prosser R. The effect of postoperative smoking on femoropopliteal bypass grafts. Ann Vasc Surg 1989;3:20-5.
22. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand 1987;221:253-60.
23. Wipke-Tevis DD, Williams DA. Effect of oral hydration on skin microcirculation in healthy young and midlife and older adults. Wound Repair Regen 2007;15:174-85.
24. vanAnholt RD, Sobotka L, Meijer EP, et al. Specific nutritional support accelerates pressure ulcer healing and reduces wound care intensity in non-malnourished patients. Nutrition 2010;26:867-72.
25. Wilkinson EA. Oral zinc for arterial and venous leg ulcers. Cochrane Database Syst Rev 2012;8:CD001273.
26. Woo KY, Harding K, Price P, Sibbald G. Minimising wound-related pain at dressing change: evidence-informed practice. Int Wound J 2008;5:144-57.
27. Price P, Fogh K, Glynn C, Krasner DL, Osterbrink J, Sibbald RG. Managing painful chronic wounds: the Wound Pain Management Model. Int Wound J 2007;4(Suppl 1):4-15.
28. World Health Organization. Cancer pain relief. With a guide to opioid availability. 1996. http://whqlibdoc.who.int/publications/9241544821.pdf. Last accessed August 28, 2014.
29. Woo K, Sibbald G, Fogh K, et al. Assessment and management of persistent (chronic) and total wound pain. Int Wound J 2008;5:205-15.
30. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. BMJ 2006;332:347-50.
31. Klomp HM, Spincemaille GH, Steyerberg EW, Habbema JD, van Urk H. Spinal-cord stimulation in critical limb ischaemia: a randomised trial. ESES Study Group. Lancet 1999;353:1040-4.
32. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. Cochrane Database Syst Rev 2005;CD004001.
33. Fife CE, Smart DR, Sheffield PJ, Hopf HW, Hawkins G, Clarke D. Transcutaneous oximetry in clinical practice: consensus statements from an expert panel based on evidence. UHM 2009;36:43-53.
34. Apelqvist JA, Lepantalo MJ. The ulcerated leg: when to revascularize. Diabetes Metab Res Rev 2012;28(Suppl 1):30-5.
35. Nehler MR, Hiatt WR, Taylor LMJ. Is revascularization and limb salvage always the best treatment for critical limb ischemia? J Vasc Surg 2003;37:704-8.
36. Wutschert R, Bounameaux H. Predicting healing of arterial leg ulcers by means of segmental systolic pressure measurements. Vasa 1998;27:224-8.
37. Chiriano J, Bianchi C, Teruya TH, Mills B, Bishop V, Abou-Zamzam AMJ. Management of lower extremity wounds in patients with peripheral arterial disease: a stratified conservative approach. Ann Vasc Surg 2010;24:1110-6.
38. Marston WA, Davies SW, Armstrong B, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg 2006;44:108-4.
39. Campbell WB. Non-intervention and palliative care in vascular patients. Br J Surg 2000;87:1601-2.
40. Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. Cochrane Database Syst Rev 2007:CD001836.
41. Ghauri AS, Nyamekye I, Grabs AJ, Farndon JR, Poskitt KR. The diagnosis and management of mixed arterial/venous leg ulcers in community-based clinics. Eur J Vasc Endovasc Surg 1998;16:350-5.
42. Humphreys ML, Stewart AH, Gohel MS, Taylor M, Whyman MR, Poskitt KR. Management of mixed arterial and venous leg ulcers. Br J Surg 2007;94:1104-7.
43. McLafferty RB, Johnson C. Chapter 21—the venous ulcer and arterial insufficiency. In: Bergan JJ, Shortell CK, eds. Venous Ulcers. San Diego, CA: Academic Press; 2007:299-306.
44. Mosti G, Iabichella ML, Partsch H. Compression therapy in mixed ulcers increases venous output and arterial perfusion. J Vasc Surg 2012;55:122-8.
45. 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.
46. Falanga V. Classifications for wound bed preparation and stimulation of chronic wounds. Wound Repair Regen 2000;8:347-52.
47. Brolmann FE, Ubbink DT, Nelson EA, Munte K, van der Horst CM, Vermeulen H. Evidence-based decisions for local and systemic wound care. Br J Surg 2012;99:1172-83.
48. Vig S, Dowsett C, Berg L, et al. Evidence-based recommendations for the use of negative pressure wound therapy in chronic wounds: steps towards an international consensus. J Tissue Viability 2011;20(Suppl 1):S1-8.
49. Kasai Y, Nemoto H, Kimura N, Ito Y, Sumiya N. Application of low-pressure negative pressure wound therapy to ischaemic wounds. J Plast Reconstr Aesthet Surg 2012;65:395-8.
50. WHASA. Topical negative pressure therapy in wound management—a consensus document (WHASA 2009). Wound Heal South Afr 2009;2:1-3.
51. Hopf HW, 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; discussion 1005.
52. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342:161-7.
53. Leaper D. Appropriate use of silver dressings in wounds: international consensus document. Int Wound J 2012;9:461-4.
54. 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 2012;(Suppl 2):1-19.
55. Majewski W, Cybulski Z, Napierala M, et al. The value of quantitative bacteriological investigations in the monitoring of treatment of ischaemic ulcerations of lower legs. Int Angiol 1995; 14:381.
56. Treiman GS, Oderich GS, Ashrafi A, Schneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. J Vasc Surg 2000; 31:1110-8.
57. Lumsden AB, Davies MG, Peden EK. Medical and endovascular management of critical limb ischemia. J Endovasc Ther 2009;16:II31-62.
58. Graziani L, Piaggesi A. Indications and clinical outcomes for below knee endovascular therapy: review article. Catheter Cardiovasc Interv 2010;75:433-43.
59. Conte MS. Diabetic revascularization: endovascular versus open bypass—do we have the answer? Semin Vasc Surg 2012;25:108-14.
60. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000;31:S1-296.
61. Collins R, Burch J, Cranny G, et al. Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review. BMJ 2007;334:1257.
62. Owen RS, Carpenter JP, Baum RA, Perloff LJ, Cope C. Magnetic resonance imaging of angiographically occult runoff vessels in peripheral arterial occlusive disease. N Engl J Med 1992;326:1577-81.
63. Menke J, Larsen J. Meta-analysis: accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. Ann Intern Med 2010;153:325-34.
64. Eiberg JP, Lundorf E, Thomsen C, Schroeder TV. Peripheral vascular surgery and magnetic resonance arteriography—a review. Eur J Vasc Endovasc Surg 2001;22:396-402.
65. Heijenbrok-Kal MH, Kock MC, Hunink MG. Lower extremity arterial disease: multidetector CT angiography meta-analysis. Radiology 2007;245:433-9.
66. Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg 1987;40:113-41.
67. Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. Plast Reconstr Surg 2006;117(7 Suppl):261S-93S.
68. Alexandrescu V, Soderstrom M, Venermo M. Angiosome theory: fact or fiction? Scand J Surg 2012;101:125-31.
69. Neville RF, Sidawy AN. Surgical bypass: when is it best and do angiosomes play a role? Semin Vasc Surg 2012;25:102-7.
70. Soderstrom M, Alback A, Biancari F, Lappalainen K, Lepantalo M, Venermo M. Angiosome-targeted infrapopliteal endovascular revascularization for treatment of diabetic foot ulcers. J Vasc Surg 2013;57:427-35.
71. Kabra A, Suresh KR, Vivekanand V, Vishnu M, Sumanth R, Nekkanti M. Outcomes of angiosome and non-angiosome targeted revascularization in critical lower limb ischemia. J Vasc Surg 2013;57:44-9.
72. Soderstrom M, Aho PS, Lepantalo M, Alback A. The influence of the characteristics of ischemic tissue lesions on ulcer healing time after infrainguinal bypass for critical leg ischemia. J Vasc Surg 2009;49:932-7.
73. Hinchliffe RJ, Andros G, Apelqvist 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.
74. Ouriel K, Fiore WM, Geary JE. Limb-threatening ischemia in the medically compromised patient: amputation or revascularization? Surgery 1988;104:667-72.
75. Schanzer A. Impact of comorbidities on decision-making in chronic critical limb ischemia. Semin Vasc Surg 2009;22:209-15.
76. Knowing when not to operate. BMJ. 1999;318:7180.
77. Schaper NC, Andros G, Apelqvist J, 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.

78. White CJ. Chapter 20—endovascular treatment of peripheral artery disease. In: Creager MA, Beckman JA, Loscalzo J, eds. Vascular Medicine: A Companion to Braunwald's Heart Disease. 2nd ed. Philadelphia: W. B. Saunders; 2013:259-67.
79. Egorova NN, Guillerme S, Gelijns A, et al. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. J Vasc Surg 2010;51:878-85.
80. Kedora J, Hohmann S, Garrett W, Munschaur C, Theune B, Gable D. Randomized comparison of percutaneous Viabahn stent grafts vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral arterial occlusive disease. J Vasc Surg 2007;45:10-6; discussion 16.
81. Loftus IM, Hayes PD, Bell PR. Subintimal angioplasty in lower limb ischaemia. J Cardiovasc Surg (Torino) 2004;45:217-29.
82. Schmidt A, Piorkowski M, Werner M, et al. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. J Am Coll Cardiol 2011;58:1105-9.
83. Bradbury AW, Adam DJ, Bell J, 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;51:5S-17S.
84. Kreienberg PB, Darling RCr, Chang BB, et al. Early results of a prospective randomized trial of spliced vein versus polytetrafluoroethylene graft with a distal vein cuff for limb-threatening ischemia. J Vasc Surg 2002;35:299-306.
85. Taylor LMJ, Hamre D, Dalman RL, Porter JM. Limb salvage vs amputation for critical ischemia. The role of vascular surgery. Arch Surg 1991;126:1251-7; discussion 1257-8.
86. Hopf HW, Kelly M, Shapshak D. Chapter 11—oxygen and the basic mechanisms of wound healing. In: Neuman TS, Thom SR, eds. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia, PA: W. B. Saunders; 2008:203-28.
87. Mathieu D. Handbook on Hyperbaric Medicine. Dordrecht, Netherlands: Springer; 2006.
88. Grover I, Neuman T. Hyperbaric oxygen therapy. In: Laurent GJ, Shapiro SD, eds. Encyclopedia of Respiratory Medicine. Oxford: Academic Press; 2006:292-6.
89. European Committee for Hyperbaric Medicine. Recommendations of the 7th European Consensus Conference on Hyperbaric Medicine. Eur J Underwater Hyperb Med 2005;6:29-40.
90. Kaur S, Pawar M, Banerjee N, Garg R. Evaluation of the efficacy of hyperbaric oxygen therapy in the management of chronic nonhealing ulcer and role of periwound transcutaneous oximetry as a predictor of wound healing response: a randomized prospective controlled trial. J Anaesthesiol Clin Pharmacol 2012;28:70-5.
91. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 2003;25:513-8.
92. 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.
93. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R 2009;1:471-89.
94. 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.
95. Grolman RE, Wilkerson DK, Taylor J, Allinson P, Zatina MA. Transcutaneous oxygen measurements predict a beneficial response to hyperbaric oxygen therapy in patients with nonhealing wounds and critical limb ischemia. Am Surg 2001;67:1072-9; discussion 1080.
96. Cronje FJ. Oxygen therapy and wound healing—topical oxygen is not hyperbaric oxygen therapy. S Afr Med J 2005;95:840.
97. 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 Repair Regen 2002;10:198-207.
98. Goldstein LJ, Gallagher KA, Bauer SM, et al. Endothelial progenitor cell release into circulation is triggered by hyperoxia-induced increases in bone marrow nitric oxide. Stem Cells 2006;24:2309-18.
99. Weir GR, Cronje FJ. Ischaemia and hypoxia: the therapeutic options. Wound Healing South Africa 2010;3:11-6.
100. Baranoski S, Ayello EA. Wound Care Essentials: Practice Principles, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:624.
101. Sieggreen MY, Kline RA. Arterial insufficiency and ulceration: diagnosis and treatment options. Adv Skin Wound Care 2004;17:242-51; quiz 252-3.
102. Arsenault KA, Al-Otaibi A, Devereaux PJ, Thorlund K, Tittley JG, Whitlock RP. The use of transcutaneous oximetry to predict healing complications of lower limb amputations: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2012;43:329-36.

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