

ENHANCEMENT OF HEALING IN SELECTED PROBLEM WOUNDS

Robert A. Warriner III M.D., FACA, FCCP, CWS
Medical Director
Southeast Texas Center for Wound Care and Hyperbaric Medicine
Conroe Regional Medical Center
Conroe, Texas
Chief Medical Officer
Praxis Clinical Services
Anaheim, California

Harriet W. Hopf, MD
Associate Professor of Anesthesia and Surgery
Associate Director, Wound Healing Laboratory
University of California, San Francisco
San Francisco, California

Rationale

Incidence and prevalence of problem wounds

Problem wounds represent a significant and growing challenge to our healthcare system. The incidence and prevalence of these wounds are increasing in the population resulting in growing utilization of healthcare resources and dollars expended. Venous leg ulcers represent the most common lower extremity wound seen in ambulatory wound care centers with recurrences frequent and outcomes often less than satisfactory. Pressure ulcers are common in patients in long term institutional care settings adding significant increases in cost, disability, and liability. Foot ulcers in patients with diabetes contribute to over half of lower extremity amputations in the United States in a group at risk representing only 3 per cent of the population (1). In response to this challenge specialized programs have emerged designed to identify and manage these patients using a variety of new technology to improve outcomes. Hyperbaric oxygen treatment has been increasingly utilized in an adjunctive role in many of these patients coinciding with optimized patient and local wound care.

Hypoxia in wound healing failure

Normal wound healing proceeds through an orderly sequence of steps involving control of contamination and infection, resolution of inflammation, regeneration of the connective tissue matrix, angiogenesis, and resurfacing. Several of these steps are critically dependent upon adequate perfusion and oxygen availability. The end result of this process is sustained restoration of anatomical continuity and functional integrity. Problem or chronic wounds are wounds that have failed to proceed through this orderly sequence of events and have failed to establish a sustained anatomic and functional result (2). This failure of wound healing is usually the result of one or more local wound or systemic host factors inhibiting the normal tissue response to injury. These factors include persistent infection, malperfusion and hypoxia, cellular failure, and unrelieved pressure or recurrent trauma.

The hypoxic nature of all wounds has been demonstrated (3), and the hypoxia, when pathologically increased, has correlated with impaired wound healing (4) and increased rates of wound infection. Local oxygen tensions in the vicinity of the wound are approximately half the values observed in normal, non-wounded tissue (5,6,7). The rate at which normal wounds heal has been shown to be oxygen dependent. Fibroblast replication, collagen deposition (8), angiogenesis (9,10,11), resistance to infection (12,13), and intracellular leukocyte bacterial killing (14,15) are oxygen sensitive responses essential to normal wound healing. However, if the periwound tissue is normally perfused, steep oxygen gradients from the periphery to the hypoxic wound center support a normal wound healing response. (16,17)

Measurement of wound hypoxia

Transcutaneous oxygen tension (PtcO₂) measurements provide a direct, quantitative assessment of oxygen availability to the periwound skin and an indirect measurement of periwound microcirculatory blood flow. The application of PtcO₂ measurement in the assessment of peripheral vascular disease has been well described by

Scheffler (18) and its application to wound healing problems by Sheffield (19,20). This technology allows objective determination of the presence and degree of local, periwound hypoxia serving as a screening tool to identify patients at risk for failure of primary wound or amputation flap healing. It can also be used during assessment of patients with lower extremity wounds as a screening tool for occult peripheral arterial occlusive disease.

PtcO₂ measurements are made by applying a Clark polarographic electrode on the prepared surface of the skin. A constant voltage is applied to the cathode that reduces oxygen molecules that have diffused from the superficial dermal capillary plexus through the epidermis, stratum corneum, and electrode membrane generating a current that can be measured and converted to a value representing the partial pressure of oxygen in mmHg. The electrode heats the surface of the skin to 43 to 45° C to increase cutaneous blood flow, skin permeability, and oxygen diffusion. The electrode is typically about 0.3mm from the capillary network in normal skin (21). PtcO₂ is non-linear with respect to blood flow exhibiting a hyperbolic response to changes in blood flow that is more pronounced as flow rates decrease (18). PtcO₂ is a more accurate reflection of changes in perfusion than is measurement of ankle brachial index (22).

Although there is some variability in PtcO₂ values obtained based upon the type of electrode and temperature used, in general, values below 25-40 mmHg have been associated with poor healing of wound and amputation flaps with the lower the value the greater the degree of healing impairment. Multiple studies (22-31) have demonstrated that PtcO₂ values are a better predictor of flap healing success or failure following amputation or revascularization procedures than arterial Doppler studies or clinical assessment, particularly in patients with diabetic foot ulcers (32-33). The addition of provocative testing with lower extremity elevation or dependency (34,35) or following occlusion induced ischemia and recovery (36) or with 100% oxygen breathing (37) may increase the sensitivity of the test as a screening tool for detecting occult lower extremity arterial insufficiency.

Breathing 100% oxygen at 1 ATA or under hyperbaric conditions can improve the accuracy of PtcO₂ measurement in predicting successful healing with adjunctive hyperbaric oxygen treatment. The following conclusions were drawn from a study of 1144 diabetic foot ulcer patients who underwent adjunctive hyperbaric oxygen treatment in support of wound healing or limb salvage (38). PtcO₂ measured on air at sea level defines the degree of periwound hypoxia but has almost no value in predicting benefit with subsequent hyperbaric oxygen treatment. These measurements are more useful in predicting who will fail to heal without hyperbaric oxygen treatment. PtcO₂ values below 35 mmHg obtained while breathing 100% oxygen at sea level are associated with a 41% failure rate of subsequent hyperbaric oxygen treatment while values obtained greater than 35 mmHg were associated with a 69% likelihood of a beneficial response. PtcO₂ values measured during hyperbaric oxygen treatment exceeding a cutoff value of 200 mmHg were 74% reliable in predicting wound healing improvement or limb salvage as the result of a therapeutic course of hyperbaric oxygen. This positive predictive value is consistent with those reported by others in both arterial insufficiency and diabetic lower extremity wounds (39-41).

When evaluating problem chronic or acute wounds where local hypoxia is suspected to play a role in wound healing failure, baseline PtcO₂ measurements should be made breathing sea level air to define the presence and degree of periwound hypoxia. Provocative testing with 30 degree elevation of the lower extremities may enhance the sensitivity of testing to identify occult peripheral vascular disease (34,35). If hypoxia is identified, PtcO₂ measurement made while breathing 100% oxygen at sea level or preferably 100% oxygen during hyperbaric oxygen treatment may indicate who is likely to respond successfully to treatment. Testing can also be repeated following lower extremity angioplasty or revascularization to assess the physiological benefit of such interventions.

The laboratory evidence for hypoxia playing a major role in wound healing failure is not in dispute and has been discussed above. Clinical studies identifying the risks of wound or amputation flap healing failure (42) define periwound hypoxia as a primary determinant of future healing failure. In clinical practice, hyperbaric medicine physicians routinely measure transcutaneous PO₂ and use the information obtained to make patient selection and treatment decisions. Unfortunately, however, the clinical trials and case series described below have not used measured periwound hypoxia as a specific patient selection criterion. Unfortunately there is a lack of direct clinical trial data linking periwound hypoxia as a selection criteria for hyperbaric oxygen and demonstrating the contribution of hyperbaric oxygen treatment to improved outcome in these circumstances. Independent evidenced-based reviews of hyperbaric oxygen treatment in problem wounds (43,44) have been unable to define a "hypoxic wound" as a specific wound category. Instead these reviews have endorsed treatment of specific wound types such as diabetic foot ulcers, acute traumatic ischemic injuries, radiation tissue injury, and compromised grafts and flaps among others.

Physiology of hyperbaric oxygenation of wounds

Regardless of the primary etiology of problem wounds, a basic pathway to non-healing is the interplay between tissue hypoperfusion, resulting hypoxia, and infection. A large body of evidence exists which demonstrates that intermittent oxygenation of hypoperfused wound beds, a process only achievable in selected patients by exposing them to hyperbaric oxygen treatment, mitigates many of these impediments and sets into motion a cascade of events that leads to wound healing. Hyperbaric oxygenation is achieved when a patient breathes 100% oxygen at an elevated atmospheric pressure. Physiologically, this produces a directly proportional increase in the plasma volume fraction of transported oxygen that is readily available for cellular metabolism. Arterial PO₂ elevations to 1500 mmHg or greater are achieved with 2 to 2.5 atm abs with soft tissue and muscle PO₂ levels elevated correspondingly. Oxygen diffusion varies in a direct linear relationship to the increased partial pressure of oxygen present in the circulating plasma caused by hyperbaric oxygen therapy. This significant level of hyperoxygenation allows for the reversal of localized tissue hypoxia, which may be secondary to ischemia or to other local factors within the compromised tissue.

In the hypoxic wound, hyperbaric oxygen therapy acutely corrects the pathophysiology related to oxygen deficiency and impaired wound healing. A key factor in hyperbaric oxygen therapy's enhancement of the hypoxic wound environment is its ability to establish adequate oxygen availability within the vascularized connective tissue compartment that surrounds the wound. Proper oxygenation of the vascularized connective tissue compartment is crucial to the efficient initiation of the wound repair process and becomes an important rate-limiting factor for the cellular functions associated with several aspects of wound healing. Neutrophils, fibroblasts, macrophages, and osteoclasts are all dependent upon an environment in which oxygen is not deficient in order to carry out their specific inflammatory or repair functions. Two groups of induced responses occur:

- 1) Improved leukocyte function of bacterial killing (45-46), antibiotic potentiation (48,49), and enhanced collagen synthesis (8) occur during periods of elevated tissue PO₂.

- 2) Suppression of bacterial toxin synthesis (50), blunting of systemic inflammatory responses (51), and prevention of leukocyte activation and adhesion following ischemic reperfusion (52-54) are effects that may persist even after completion of hyperbaric oxygen treatment.

In addition, vascular endothelial growth factor (VEGF) release is stimulated (55) and platelet derived growth factor (PDGF) receptor appearance (56-58) is also induced. The net result of serial hyperbaric oxygen exposures is improved local host immune response, clearance of infection, enhanced tissue growth and angiogenesis (59) with progressive improvement in local tissue oxygenation, and epithelialization of hypoxic wounds.

Diabetic Lower Extremity Wounds, the Prototype Hypoxic Wound

Lower extremity ulcers and amputations are an increasing problem for people with diabetes. Up to 6 per cent of all hospitalizations for diabetics include a lower extremity ulcer as a discharge diagnosis. When present, an ulcer increased hospital length of stay by an average of 59% compared to diabetics admitted without lower extremity ulcers. Finally, once an amputation occurs, nine to 20% of diabetic patients will experience an ipsilateral or contralateral amputation within 12 months and 28-52% within five years (1). The cost of care for a new diabetic foot ulcer has been calculated to be \$27,987 in the two years following diagnosis (60).

The pathophysiology of diabetic foot ulceration, faulty healing, and lower extremity limb loss has been well described (42,61,62). It involves the progressive development of a sensory, motor, and autonomic neuropathy leading to loss of protective sensation, deformity increasing plantar foot pressures, and alternations in autoregulation of dermal blood flow. Diabetics show earlier development and progression of lower extremity peripheral arterial occlusive disease with a predilection for the trifurcation level vessels just distal to the knee. Impaired host immune response to infection and possible cellular dysfunction all contribute to the clinical outcomes described above.

Management, likewise, has been extensively described (63-66) and includes careful attention to identification and management of infection, aggressive surgical debridement, evaluation and correction of vascular insufficiency ambulatory off-loading, and glycemic control (67,68). While a full discussion of these interventions is beyond the scope of this review, they form the basis of effective diabetic foot ulcer management and must be applied consistently if adjunctive interventions are to provide an additive value. Other interventions have recently been advocated including topical application of a recombinant human platelet derived growth factor (PDGF-BB, becaplermin) (69), bioengineered human mono layer fibroblast grafts (70-72) and bi-layer fibroblast and keratinocyte (73,74) grafts, and negative

pressure wound therapy (wound vac) (75,76). Clearly, regardless of the interventions applied, limb salvage rates improve when care is applied in a multidisciplinary setting using comprehensive protocols for care (77).

Local wound hypoxia plays a pivotal role in diabetic wound healing failure and limb loss as evidence by the report by Pecoraro (42) that when periwound PtcO₂ values were below 20 mmHg they were associated with a 39 fold increased risk of primary healing failure. While aggressive distal lower extremity bypass grafting and lower extremity angioplasty have contributed to increased wound healing and limb salvage rates, technical grafting success does not necessarily equate with limb salvage. Hyperbaric oxygen treatment offers an intriguing opportunity to maximize oxygen delivery in the setting of minimal or insufficiently corrected blood flow.

Clinical Experience with Hyperbaric Oxygen Treatment in Diabetic Lower Extremity Wounds

Since 1999 there have been eight published independent evidence-based reviews that have addressed the effectiveness of hyperbaric oxygen treatment in problem, chronic wounds. These reviews have evaluated the results of:

- 1) Four randomized controlled clinical trials of hyperbaric oxygen treatment in diabetic lower extremity wounds (Table 1).
- 2) Two randomized controlled trials in non diabetic leg ulcers or where wound healing was not the outcome indicator (Table 2).
- 3) Two non-randomized controlled trials in diabetic lower extremity wounds (Table 3).
- 4) One prospective case series of hyperbaric oxygen treatment and infra popliteal angioplasty in diabetic lower extremity wounds (Table 4).
- 5) Eight prospective or retrospective uncontrolled case series in diabetic lower extremity wounds (Table 5).

In the controlled trials, 334 patients were included in the hyperbaric oxygen treatment arms and 582 patients in the control arms. In the cases series, 1590 patients were reported. There were additional small retrospective series that were not included in this review.

In general, while specific selection criteria for inclusion for hyperbaric oxygen treatment were not provided, inference from the description of patients included can be made that most were Wagner grade (Table 5) III or greater ulcers since "diabetic gangrene" was frequently mentioned as a descriptor of patients included. Hypoxic transcutaneous PO₂ values were not mentioned as an inclusion criterion for selection for the randomized controlled clinical trials.

The 1999 Blue Cross Blue Shield Technology Assessment (BCBS) (78) and the 2000 Australian Medicare Service Advisory Committee review (MSAC) (79) concluded that there was sufficient evidence to support the use of hyperbaric oxygen therapy in chronic non-healing wounds (BCBS) and diabetic wounds (MSAC). The April 7-8, 1999 Consensus Development Conference on Diabetic Foot Wound Care sponsored by the American Diabetes Association (64) concluded that "it is reasonable...to use this modality to treat severe and limb- or life threatening wounds that have not responded to other treatments, particularly if ischemia that cannot be corrected by vascular procedures is present." The Wound Healing Society Provision Guidelines for Chronic Wound Care, June 21, 1999, Arterial Subcommittee (80) stated that... "in communities where accessible, hyperbaric oxygen treatment should be considered standard of care for wounds that are hypoxic (due to ischemia), and the hypoxia is reversible by hyperbaric oxygenation. The tissue hypoxia, reversibility, and responsiveness to oxygen challenge are measurable by transcutaneous oximetry." The British Journal of Medicine, Clinical Evidence review (81) categorized hyperbaric oxygen treatment as "for diabetic foot ulcer, likely to be beneficial...limited evidence from two small randomized clinical trials suggests that systemic hyperbaric oxygen reduces the risk of foot amputation in people with severe infected foot ulcers. Two small randomized clinical trials have found that, compared with routine care, systemic hyperbaric oxygen reduces the risk of foot amputation in people with severe infected foot ulcers."

In 2001, at the request of the Center for Medicare and Medicaid Services, reviewers from the New England Medical Center under contract with the Agency for Healthcare Research and Quality released a report (43,82) that concluded that "hyperbaric oxygen treatment aids in the healing of chronic non-healing wounds." However, they also stated that "direct evidence on non-diabetic chronic non-healing wounds was not sufficient." It appears that this conclusion was based on the observation that the majority of clinical trials involved diabetic lower extremity wounds.

The randomized controlled clinical trial of hyperbaric oxygen treatment in chronic diabetic lower extremity wounds reported by Doctor, et al (85) involved 30 patients randomized into treatment and control groups. Patients in the hyperbaric oxygen treatment group received only four treatments over a two week period. The treatment group had fewer major amputations (HBO 2/15 vs control 7/15) that was a statistically significant difference ($p < 0.05$). There were also fewer repeat positive cultures in the treatment group ($p, 0.05$).

Faglia, et al (86) reported a randomized controlled clinical trial of hyperbaric oxygen treatment for severe, hospitalized diabetic foot ulcer patients. Seventy consecutively admitted patients were enrolled in the study with 35 completing in the hyperbaric oxygen treatment group and 33 in the control group. All patients underwent a standard evaluation protocol, initial radical surgical debridement, weekly wound cultures with culture specific systemic antibiotic therapy, standardized wound care, and optimized metabolic control. All patients received a vascular evaluation and underwent arteriography if screening ankle-brachial index was < 0.9 or $PtcO_2 < 50$ mmHg and underwent angioplasty or revascularization if indicated. Hyperbaric oxygen treatment was administered daily at 2.4 ATA for 90 minutes after an initial treatment at 2.5 ATA for 90 minutes. The decision to perform a major amputation was performed by a consultant surgeon unaware of the treatment status. The treatment group underwent fewer major amputations (HBO 3/35 [8.6%] including 2 BKA and 1 AKA; control 11/33 [33.3%] including 7 BKA, 4 AKA). This difference was statistically significant ($p = 0.016$). In a multivariate analysis, the authors concluded that hyperbaric oxygen treatment conferred a protective benefit with an odds ratio of 0.084 ($p = 0.033$, 95% CI 0.008-0.821).

Abidia, et al (87) reported a randomized placebo controlled clinical trial that involved 33 patients. Each group received either 30 hyperbaric oxygen treatments for 90 minutes each or 30 sham treatments. At 12 weeks more patients in the hyperbaric oxygen treatment groups were healed (HBO 13/19, 68%; control 4/14, 29%) but no statistical analysis was given.

Kalani, et al. (88) reported a combined randomized and non-randomized controlled clinical trial of hyperbaric oxygen treatment in diabetic foot ulcers involving 38 patients. Seventeen patients received hyperbaric oxygen treatment and 21 were in the control group. The first 14 patients were randomly allocated (7 in each group), but the study was interrupted for two years and the final 24 patients were assigned to treatment or control groups in a non-randomized manner based on the availability of hyperbaric oxygen treatment. All patients underwent a baseline vascular evaluation but none were deemed eligible for revascularization. The treatment group received between 40-60 hyperbaric oxygen treatments at 2.4 ATA for 90 minutes five days per week. At the three year follow up point, more patients in the treatment group were healed (HBO 12/17 [76%]; control 2/17 [12%]) which was not statistically evaluated. Major amputations were also less frequent in the treatment group (2/17 [12%]; control 7/21 [33%]).

In a retrospective multi center case series Fife, et al (38) reported the following outcomes with hyperbaric oxygen treatment in 1144 patients of whom final outcomes could be determined in all but 68 cases. All patients had hypoxic initial $PtcO_2$ values recorded prior to initiation of adjunctive hyperbaric oxygen treatment. Overall, 75.6% of those in whom a Wagner score was available had a positive response to treatment. Table 6. demonstrates the response rate within each Wagner score grouping. These outcomes are superior to other clinical trials or case series reported of similar Wagner score patients. In the becaplermin clinical trials (69) ulcers with significant hypoxia ($PtcO_2$ values less than 30 mmHg) and osteomyelitis (Wagner III) were excluded, and healing rates of only 46.7% were achieved.

In summary, the available evidence supports classifying the use of adjunctive in hyperbaric oxygen treatment for diabetic foot ulcers meets the requirements for AHA Class I definitely recommended based on Level A evidence of positive randomized controlled trials with statistically positive results. In the broader category of hypoxic wounds, based on the absence of trials using measured tissue hypoxia as a patient inclusion criterion, adjunctive hyperbaric oxygen treatment meets the requirements for AHA Class IIb acceptable and useful with fair to good evidence for support based upon limited level clinical trial data but with substantial level B non-randomized retrospective case series where $PtcO_2$ values were reported but not used for inclusion, animal models with very reasonable extrapolations from existing data, and rational conjecture and historical acceptance. Randomized clinical trials should be performed to better define a "hypoxic" wound as a unique wound category and the value of hyperbaric oxygen treatment in this setting.

On August 30, 2002, the Center for Medicare and Medicaid Services announced in CAG-00060N, Coverage Decision Memorandum for Hyperbaric Oxygen Therapy in the Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities (44) and in Transmittal AB-02-183 Program Memorandum for Intermediaries/Carriers its decision

to cover treatment of diabetic wounds of the lower extremities with hyperbaric oxygen effective April 1, 2003, in patients meeting the following criteria:

- (1) Patient has type 1 or 2 diabetes and has a lower extremity wound that is due to diabetes;
- (2) Patient has a wound classified as Wagner grade (Table 5) III or higher (81,82);
- (3) Patient has failed an adequate course of standard wound therapy (defined as 30 days of standard treatment including assessment and correction of vascular abnormalities, optimization of nutritional status and glucose control, debridement, moist wound dressing, off-loading, and treatment of infection).

For treatment to continue, re-evaluations at 30-day intervals must show continued progress to healing.

Other Potentially Hypoxic Wounds

Venous Stasis Ulcers

Compression therapy with multilayer external compression bandaging techniques remains the mainstay of management of venous stasis ulcers of the lower extremity (89,90). Recent evidence suggests that bioengineered tissue grafts (91) used in combination with standard compression bandaging techniques may shorten time to healing. While one prospective, blinded, randomized clinical trial of hyperbaric oxygen treatment in leg ulcers of undefined etiology (92) showed a statistically greater reduction in wound size at six weeks compared to control wounds, hyperbaric oxygen treatment is not indicated in the primary management of venous stasis ulcers of the lower extremities. Hyperbaric oxygen may be required to support skin grafting in patients with concomitant peripheral arterial occlusive disease and hypoxia not corrected by control of edema.

Pressure Ulcers

The management of decubitus ulcers has been well described elsewhere (93) and emphasizes pressure relief, surgical debridement, treatment of infection, nutritional support, and surgical closure for large ulcers. Other interventions such as negative pressure wound therapy (wound vac) may be beneficial. Hyperbaric oxygen treatment is not indicated in routine decubitus ulcer management. It may be necessary for support of skin grafts or flaps showing evidence of ischemic failure, when the ulcer develops in the field of previous radiation treatment for pelvic or perineal malignancies, or when progressive necrotizing soft tissue infection or refractory osteomyelitis is present.

Arterial Insufficiency Ulcers

The primary treatment of refractory ischemic wounds of the lower extremities is improvement in blood flow by angioplasty or surgical revascularization. However, hyperbaric oxygen treatment may be of benefit in those cases where persistent hypoxia remains after attempts at increasing blood flow or when wound failure continues despite maximum revascularization (80). Hyperbaric oxygen treatment may also be required in support of skin grafting in this setting (94).

Hyperbaric Oxygen Treatment Protocols

Treatment protocols vary depending on the severity of the problem and the type of hyperbaric chamber used. In larger multiplace chambers, treatments are delivered at 2.0 to 2.5 ATA for 90 to 120 minutes once or twice daily. In monoplace chambers patients are usually treated at 2.0 ATA. Patients with serious infections may require hospitalization for intravenous antibiotics and better diabetes control. Hyperbaric oxygen treatment in such cases is usually rendered twice daily for 90 minutes. Once stabilized most of these patients can be treated on a once daily basis as outpatients. When infection is controlled, blood flow optimized (wherever possible), other interventions that may hasten tissue growth and wound closure such as negative pressure wound therapy (wound vac), bioengineered tissue grafts, or surgical reconstruction or closure can be used in combination with adjunctive hyperbaric oxygen treatment to hasten recovery. The October 2000 Office of the Inspector General report to the Department of Health and Human Services (95) identified that active physician oversight of hyperbaric oxygen treatment led to improved outcomes.

Utilization Review

Hyperbaric oxygen treatments are performed at 2.0 to 2.5 ATA for 90 to 120 minutes of oxygen breathing. The initial treatment schedule is dictated by the severity of the disease process. In the presence of limb-threatening infection after debridement or incompletely corrected peripheral arterial occlusive disease, patients may require twice daily treatments. Once stabilized, treatment frequency may decrease to once daily. Utilization review is required after the initial 30 days of treatment and at least that frequently thereafter.

Cost Impact

Hyperbaric oxygen therapy as an adjunct to medical and surgical treatment of difficult problem, chronic wounds, particularly diabetic lower extremity wounds, has been shown to be cost effective in limited reviews, especially when compared to major lower extremity amputation (96,97). Preventing a below the knee amputation by salvaging a ray resection or transmetatarsal amputation of the foot or preventing an above the knee amputation by preserving a below the knee amputation represents a satisfactory outcome in these high risk patients. Wounds healed with adjunctive hyperbaric oxygen treatment have also demonstrated excellent durability (98).

Tables

Table 1. Randomized Controlled Trials of HBO in DFU

Author Year, Country	Study Design	N	Condition	PtcO2 Recorded	Results
Doctor (85) 1992, India	RCT	30 (15 HBO, 15 control)	Hospitalized DFU	N	Above ankle amputations: HBO 2/15, Control: 7/15 P<0.05; Minor amputations NS Number of + cultures decreased in HBO group P<0.05
Faglia (86) 1996, Italy	RCT	70 (35 HBO, 33 control)	Severe infected DFU	Y*	Major amputations: HBO 3/35 (8.6%) Control 11/33 (33.3%) P=0.016
Abidia (87) 2001, UK	RCT, placebo Abstract	33 (19 HBO, 14 control)	Diabetic leg ulcers	N	Healing at 12 week follow up point: HBO: 13/19 (68%), Control: 4/14 (29%); No difference in major amputation rates between groups
Kalani (88) 2002, Sweden	RCT + CT	38 (17 HBO, 21 control)	DFU	N	Healing at 3 year follow up point: HBO: 13/17 (76%), Control 10/21 (48%); Amputations: HBO: 2/17 (12%), Control 7/21 (33%)

Table 2. Randomized Controlled Trials of HBO in Non DFU or Where Wound Healing Not the Outcome

Author Year, Country	Study Design	N	Condition	PtcO2 Recorded	Results
Hammarlund (92) 1994, Sweden	RCT, DB, placebo	16 (8 HBO, 8 control)	Non diabetic leg ulcers	N	Mean wound surface area decreased at 6 week endpoint: HBO: 35.7% (+-17%), Control: 2.7% (+-11%) P<0.001
Lin (99) 200, Taiwan	RCT Abstract	29 (17 HBO, 12 control)	DM with Wagner 0,I,II	Y*	Improvement in vascular function: PtcO2 post 30 treatments HBO 57.5 +-20.7 mmHg vs controls 35.8 +-21.2 mmHg P,0.01

Table 3. Prospective Series HBO Combined with Distal Lower Extremity Angioplasty

Author Year, Country	Study Design	N	Condition	PtcO2 Recorded	Results
Hanna (22) 1997, USA	Prospective consecutive uncontrolled series	29 infrapop angioplasty + HBO	DFU with severe PVD	Y*	PtcO2 < 40mmHg associated with poor healing, PtcO2 changes better predictor of ultimate outcomes than ABI, at 6 months 23/29, 79%, had complete healing, 3/29 had failed

					recannalizations with subsequent BKAs, 2/29 had BKAs despite successful recannalization due to persistent severe osteomyelitis, 1/29 expired from AMI with healing wound
--	--	--	--	--	--

Table 4. Controlled Trials of HBO in DFU

Author Year, Country	Study Design	N	Condition	PtcO2 Recorded	Results
Zamboni (100) 1997, USA	CT	10 (5 HBO, 5 control)	DFU	Y*	HBO with standard wound care reduced wound size compared to standard wound care alone P<0.05 At 4-6 months HBO group had higher rate of complete healing (4/5 compared to controls 1/5)
Baroni (101) 1987, Italy	CT	28 (18 HBO, 10 control)	DFU	N	Healing: HBO: 16/18 (89%), Control: 1/10 (10%) P=0.001 Amputations: HBO: 2/18, Control: 4/10

Table 5. Prospective/Retrospective Uncontrolled Series of HBO in DFU

Author Year, Country	Study Design	N	Condition	PtcO2 Recorded	Results
Davis (102) 1987, USA	Retro review	168 HBO	DFU	N	118/168 (70%) patients healed at a level providing for bipedal ambulation, 50/168 (30%) required a BKA or AKA, failures in patients with non bypassable arterial disease at or above ankle
Cianci (96) 1988, USA	Prospective consecutive no controls	39 HBO	Foot ulcers, 49% DFU, 51% other limb threatening, 41% prior bypass	N	Overall limb salvage rate (TMA or less) 35/39, 90%, diabetes and need for revascularization increased risk of failure (only 75% successful if diabetes and revascularization for limb threatening lesion), total hospital charges of \$36,706
Oriani (103) 1990, Italy	Retro comp	80 (62 HBO, 18 control)	DFU	N	"Recovery": HBO: 59/62 (96%), Control: 12/18 (67%); Amputation: HBO: 3/62 (5%), 6/18 (33%) P<0.001
Wattel (104) 1991, France	Retro consec review	59 HBO	DFU	Y*	52/59 (88%) healed without major amputation, 7/59 (12%) required major amputation, significantly higher PtcO2 values achieved during HBO (786 +-258mmHg vs 323 +-214) in success compared to failures
Oriani (105) 1992, Italy	Retro consecutive review uncontrolled	151 HBO (may include patients from 1990 series)	DFU	N	130/151, 86% healed with HBO, 21/15, 14% failed with HBO
Stone (106) 1995, USA	Retro review Abstract	469 (87 HBO, 382 control)	DFU	N	Limb salvage: HBO: 72%, Control: 53% P<0.002
Faglia (107) 1998, Italy	Compare	115 (51 HBO, 64 control)	DFU	Y*	Major amputations: HBO: 7/51, Control: 20/64 P=0.012
Fife (38) 2002, USA	Retro review	1144 HBO	DFU	Y*	Overall 75% of patients improved with HBO, mean 34 treatments; By Wagner score: I: 100% (n=3), II: 83.1% (N=130), III: 77.2% (n=465), IV: 64.5% (n=64.5%), V: 29.7% (n=37)

*PtcO2 values recorded but not utilized as a criterion for inclusion.

Table 5. Wagner Grading System for Diabetic Foot Ulcers

Grade 0:	Intact skin
Grade I:	Superficial without penetration deeper layers
Grade II:	Deeper reaching tendon, bone, or joint capsule
Grade III:	Deeper with abscess, osteomyelitis, or tendonitis extending to those structures
Grade IV:	Gangrene of some portion of the toe, toes, and/or forefoot
Grade V:	Gangrene involving the whole foot or enough of the foot that no local procedures are possible

Table 6. Wagner Score and HBO Outcome, Fife, et al. (38)

Wagner Score	Sample Size	Percent Helped by HBO2
I	3	100.0
II	130	83.1
III	465	77.2
IV	138	64.5
V	37	29.7

References

1. Reiber GE, Boyko EJ, Smith DG. Chapter 18. Lower extremity foot ulcers and amputations in diabetes. In: Diabetes in America, 2nd ed. National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication No. 95-1468, 1995; 409-428.
2. Lazarus GS, Cooper DM, Knighton DR et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Derm 1994;130(4):489-493.
3. Hunt TK, Twomey P, Zederfeldt B, Dunphy JE. Respiratory gas tensions and pH in healing wounds. Am J Surg 1967;114:302-307.
4. Niinikoski J. Effect of oxygen supply on wound healing and formation of experimental granulation tissue. Acta Physiol Scand 1969; 334:1-72.
5. Sheffield, PJ. Tissue oxygen measurements with respect to soft-tissue wound healing with normobaric and hyperbaric oxygen. HBO Rev 1985;6:18-46.
6. Sheffield PJ, Workman WT. Noninvasive tissue oxygen measurements in patients administered normobaric and hyperbaric oxygen by mask. HBO Rev 1985;6:47-62.
7. Sheffield, P. Tissue oxygen tension. In: Davis JC, Hunt TK, eds. Problem Wounds: The Role of Oxygen. New York: Elsevier, 1988:17-51.
8. Hunt TK, Pai MP. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynecol Obstet 1972;135:561-567.
9. Knighton D, Silver I, Hunt TK. Regulation of wound healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. Surgery 1981;90:262-270.
10. Knighton DR, Oredsson S, Banda M, Hunt TK. Regulation of repair: Hypoxic control of macrophage mediated angiogenesis. In: Hunt TK, Heppenstall RB, Pine E, Rovee D, eds. Soft and Hard Tissue Repair. New York: Praeger, 1984:41-49.
11. La Van FB, Hunt TK. Oxygen and wound healing. Clin Plast Surg 1990;17(3):463-472.
12. Robson MC, Stenberg BD, Hegggers JP. Wound healing alterations caused by infection. Clin Plast Surg 1990;17(3):485-492.

13. Grief R, Akca O, et al. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *NEJM* 2000;342(3):61-167.
14. Rabkin J, Hunt TK. Infection and oxygen. In: Davis JC, Hunt TK eds. *Problem Wounds: The Role of Oxygen*. New York: Elsevier, 1988:1-16.
15. Hunt TK. The physiology of wound healing. *Ann Emerg Med* 1988;17:1265-1273.
16. Silver IA. Cellular microenvironment in healing and non-healing wounds. In: Hunt TK, Heppenstall RB, Pines E, Rovee D, eds. *Soft and hard tissue repair*. New York: Praeger, 1984:50-66.
17. Niinikoski J, Hunt TK, Zederfeldt B. Oxygen supply in healing tissue. *Am J Surg* 1972;123:247-252.
18. Scheffler A, Rieger H. Clinical information content of transcutaneous oxymetry (tcpO₂) in peripheral arterial occlusive disease (A review of the methodological and clinical literature with a special reference to critical limb ischemia). *VASA*, Band 1992;21:111-126.
19. Matos LA, Nunez AA. Enhancement of healing in selected problem wounds. In: Kindwall EP, ed. *Hyperbaric Medicine Practice*. Flagstaff AZ: Best Publishing 1994;589-612.
20. Sheffield, PJ. Measuring tissue oxygen tension: A review. *Undersea Hyperbaric Med* 1998;25:179-188.
21. Steenfos HH, Baumbach P. Transcutaneous pO₂ in peripheral vascular disease. *Radiometer Copenhagen TC105*.
22. Hanna GP, Fuise K, Kjellgren O, Feld S, Fife C, Schroth G, Clanton T, Anderson V, Smalling RW. Infrapopliteal transcatheter interventions for limb salvage in diabetic patients: Importance of aggressive interventional approach and role of transcutaneous oximetry. *J Am Coll Cardiol* 1997;30:664-669.
23. Achauer BM, Black KS, Litke DK. Transcutaneous PO₂ in flaps: a new method of survival prediction. *Plastic Reconstruct Surg* 1980;65(6):738-744.
24. Hauser CJ, Klein SR, Mehringer CM, et al. Superiority of transcutaneous oximetry in noninvasive vascular diagnosis in patients with diabetes. *Arch Surg* 1984;119:690-694
25. Christensen KS, Klarke M. Transcutaneous oxygen measurement in peripheral occlusive disease. *J Bone Joint Surg*. 1986;68-B(3):423-426.
26. Malone JM, Anderson GG, Lalka SG, et al. Prospective comparison of noninvasive techniques for amputation level selection. *Amer J Surg* 1987;154:179-184.
27. Wyss CR, Harrington RM, Burgess EM, et al. Transcutaneous oxygen tension as a predictor of success after an amputation. *J Bone Joint Surg* 1988;70-A(2),203-207.
28. Ameli FM, Stein M, Provan JL, et al. Comparison between transcutaneous oximetry and ankle-brachial pressure ratio in predicting runoff and outcome in patients who undergo aortobifemoral bypass. *CJS*, 1989;33(6):428-432
29. Padberg FT, Black TL, Thompson PN, Hobson RW. Transcutaneous oxygen (TcPO₂) estimates probability of healing in the ischemic extremity. *J Surg Res* 1996;60:263-268.
30. Wütschert R, Bounameaux H. Determination of amputation level in ischemic limbs. Reappraisal of the measurement of TcPo₂. *Diabetes Care* 1997;20(8):1315-8.
31. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello P, Barbano A. Change in major rate in a center dedicated to diabetic foot care in the 1980s: prognostic determinants for major amputations. *J Diabetes Complications* 1998;12(2):96-102.

32. Ballard JL, Eke CC, Bunt TJ, Killeen JD. A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems. *J Vasc Surg* 1995;22(4):485-492.
33. Kalani J, Brismar K, Fagrell B, Ostergren J, Jorneskog G. Transcutaneous oxygen tension and toe blood pressure as predictors for outcome of diabetic foot ulcers. *Diabetes Care* 1999;22(1):147-151.
34. Bacharach JM, Rooke TW, Osmundson PJ, Gloviczki P. Predictive value of transcutaneous oxygen pressure and amputation success by use of supine and elevation measurements. *J Vasc Surg* 1992;15:558-563.
35. Hauser CJ, Appel P, Shoemaker WC. Pathophysiologic classification of peripheral vascular disease by positional changes in regional transcutaneous oxygen tension. *Surgery* 1993;95(6):689-693.
36. Kram HB, Appel PL, White RA, Shoemaker WC. Assessment of peripheral vascular disease by postocclusive transcutaneous oxygen recovery time. *J Vasc Surg* 1984;1:628-634.
37. Harward TRS, Volny J, Golbranson F, Bernstein, EF, Fronck A. Oxygen inhalation-induced transcutaneous PO₂ changes as a predictor of amputation level. *J Vasc Surg* 1985;2:220-227.
38. Fife CF, Buyukcakir C, Otto GH, Sheffield PJ, Warriner RA, Love TL, Mader J. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1144 patients. *Wound Rep Reg* 2002;10:198-207.
39. Wattel F, Mathieu D, Coget JM. Prediction of final outcome with transcutaneous oxygen measurements of problem wounds treated with hyperbaric oxygen. *Proceedings, 2nd European Conference on Hyperbaric Medicine, Basel, 1990*;221-223.
40. Wattel FE, Mathieu DM, Fossati P, Nevriere RR, Coget JM. Hyperbaric oxygen in the treatment of diabetic foot lesions search for healing predictive factors. *J Hyperbaric Med* 1991;6(4):263-268.
41. Smith BM, Desvigne LD, Slade JB, Dooley JW, Warren DC. Transcutaneous oxygen measurements predict healing of leg wounds with hyperbaric therapy. *Wound Rep Reg* 1996;4:224-229.
42. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes* 1991;40:1305-1313.
43. Wang C, Lau J. Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds. *Technology Assessment. Agency for Healthcare Research and Quality (AHRQ). November 2, 2001. USA.*
44. CAG-00060N Coverage Decision Memorandum for Hyperbaric Oxygen Therapy in the Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities. *Center for Medicare and Medicaid Services August 30, 2002.*
45. Mandell G. Bacteriicidal activity of aerobic and anaerobic polymorphonuclear neutrophils. *Infect Immun* 1974;9:337-341.
46. Mader JT, Brown GL, Guckian JC, et al. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. *J Infect Dis* 1980;142:915-922.
47. Mader JT, Adams KR, Sulton TE. Infectious diseases: pathophysiology and mechanisms of hyperbaric oxygen. *J Hyperbaric Med* 1987; 2:133-140.
48. Adams KR, Mader JT. Aminoglycoside potentiation with adjunctive hyperbaric oxygen therapy in experimental *Pseudomonas aeruginosa* osteomyelitis. *Undersea Hyperbaric Medical Society Annual Scientific Meeting, 1987*;Abstract 70.

49. Adams KR, Sutton TE, Mader JT. *In vitro* potentiation of tobramycin under hyperoxic conditions. Undersea Hyperbaric Medical Society Annual Scientific Meeting, 1987;Abstract 69.
50. VanUnnik AJM. Inhibition of toxin production in *Clostridium perfringens in vitro* by hyperbaric oxygen. *Antonie Van Leeuwenhoek* 1965;31:181-186.
51. Luongo C, Imperatore F, Cuzzocrea S, Filippelli A, Scafuro MA, Mangoni G, Portolano F, Rossi F. Effects of hyperbaric oxygen exposure on a zymosan-induced shock model. *Crit Care Med* 1998;26:1972-1976.
52. Zamboni WA, Roth AC, Russell RC, et al. The effect of acute hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. *J Reconstr Microsurg* 1989;5:343-347.
53. Zamboni WA, et al. Morphologic analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effects of hyperbaric oxygen. *Plast Reconstr Surg* 1993;91 1110-1123.
54. Thom SR. Functional inhibition of leukocyte B₂ integrins by hyperbaric oxygen in carbon monoxide-mediated brain injury in rats. *Toxicol Appl Pharmacol* 1993;123:248-256.
55. Sheikh AY, Gibson JL, Rollins MD, Hopf HW, Hussain Z, Hunt TK. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg* 2000;135:1293-1297.
56. Zhao LL, Davidson JD, Wee SC, Roth SI, Mustoe TA. Effect of hyperbaric oxygen and growth factors on rabbit ear ischemic ulcers. *Arch Surg* 1994;129:1043-1049.
57. Siddiqui A, Davidson JD, Mustoe TA. Ischemic tissue oxygen capacitance after hyperbaric oxygen therapy: A new physiologic concept. *Plast Reconstr Surg* 1997 99:148-155
58. Bonomo SR, Davidson JD, Yu Y, Yja Y, Lin, Mustoe TA. Hyperbaric oxygen as a signal transducer: upregulation of platelet derived growth factor-beta receptor in the presence of HBO, and PDGF. *Undersea Hyper Med* 1998;25(4)211-216.
59. Ketchum SA III, Thomas AN, Hall AD. Angiographic studies of the effects of hyperbaric oxygen on burn wound revascularization, In: *Proceedings of the Fourth International Congress in Hyperbaric Medicine* (J Wada, T Iwa, eds), Williams and Wilkins, Baltimore, 1969 388-394.
60. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, Wagner EW. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 1999;22:382-387.
61. Reiber GE, Pecoraro RE, Keopesell TD. Risk factors for amputation in patients with diabetes mellitus. *Ann Int Med* 1992;117:97-105.
62. Reiber GE, Vileikyte L, Boyko EJ, Aguilu M, Smith DG, Lavery LA, Boulton AJM. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999;22:157-162.
63. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. Current concepts. *NEJM* 1994;331(13):854-860.
64. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care. *Diabetes Care* 1999;22(8):1354-1360.
65. Mason J, O'Keeffe C, McIntosh A, Hutchinson A, Booth A, Young RJ. A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. II: treatment. *Diabet Med* 1999;16:889-909.
66. Han P, Ezquerro R. Diabetic foot wound care algorithms. *J Am Podiatr Med Assoc* 2002;92(6):336-349.

67. Gibbons GW, Marcaccio EJ Jr, Burgess AM, Pomposelli FB Jr, Freeman DV, Campbell DR, Miller A, LoGerfo FW. Improved quality of diabetic foot care, 1984 vs. 1990. *Arch Surg* 1993;128:576-581.
68. Akbari CM, Pomposelli FB, Gibbons GW, Campbell DR, Pulling MC, Mydlarz D, LoGerfo FW. Lower extremity revascularization in diabetes late observations. *Arch Surg* 2000;125:452-456.
69. Smiell JM, Wieman J, Steed DL, Perry BH, Sampson AR, Schwab BH. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Rep Reg* 1999;7:335-346.
70. Gentzkow GD, Iwasaki SD, Herson KS, Mengel M, Prendergast JJ, Ricotta JJ, Steed DP, Lipkin S. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 1996;19(4):350-354.
71. Gentzkow GD, Jensen JL, Pollak RA, Kroeker RO, Lerner JM, Lerner M, Iwasaki SD. Improved healing of diabetic foot ulcers after grafting with a living human dermal replacement. *Wounds* 1999;11(3):77-84.
72. Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. *J Foot & Ankle Surg* 2002;41(5):291-299.
73. Pham HT, Rosenblum BI, Lyons TE, Giurini JM, Chrzan JS, Habershaw GM, Veves A. Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective, randomized, clinical trial. *Wounds* 1999;11(4):79-86.
74. Veves A, Falanga V, Armstrong DG, Saboinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: A prospective randomized multicenter clinical trial. *Diabetes Care* 2001;24:290-295.
75. McCallon SK, et al. Vacuum-assisted closure vs saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy/Wound Management*, 2000;46(8):28-34.
76. Armstrong DG, et al. Outcomes of subatmospheric pressure dressing therapy on wounds of the diabetic foot. *Ostomy/Wound Management*. 2002;48:64-68.
77. Knighton DR, Fylling CP, Fiegel VD, Cerra F. Amputation prevention in an independently reviewed at-risk diabetic population using a comprehensive wound care protocol. *Am J Surg* 1990;160:466-472.
78. Hyperbaric Oxygen Therapy for Wound Healing – Part I. Blue Cross Blue Shield Association TEC, Technology Assessment, August 1999. USA.
79. Hyperbaric Oxygen Therapy. Australian Medicare Service Advisory Committee (MSAC). Technology Assessment. April 2000. Canberra, Australia.
80. Hopf H, West J. Arterial subcommittee: Should hyperbaric oxygen therapy be utilized in the control arm of clinical research studies of arterial (ischemic) wounds? Provisional Guidelines for Chronic Wound Care: Arterial, Diabetic, Pressure and Venous. WOCN/WHS June 21, 1999.
81. Care of diabetic foot ulcer. *British J Med Clinical Evidence* Issue 5 and subsequent, June 2001.
82. Wang C, Schwaitzberg S, Berliner E, Zarine DA, Lau J. Hyperbaric oxygen for treating wounds. A systematic review of the literature. *Arch Surg* 2003;138:272-279.
83. Wagner FW. The dysvascular foot: A system for diagnosis and treatment. *Foot & Ankle* 1981;2(2):64-122.
84. Smith RG. Validation of Wagner's classification: a literature review. *Ostomy/Wound Management* 2003;49(1):54-62.

85. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Medicine* 1992;38(3):112-114.
86. Faglia E, et al. Adjunctive systemic hyperbaric oxygen therapy in the treatment of diabetic foot ulcer. A randomized study. *Diabetes Care* 1996;19:1338-1343.
87. Abidia A, Kuhan G, Laden G, et al. Hyperbaric Oxygen therapy for diabetic leg ulcers – a double blind randomized controlled trial. *Undersea Hyperbaric Med* 2001;28(Suppl):64 (abstract)
88. Kalani M, Jorneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers long-term follow-up. *J Diabetes and Its Complications* 2002;16:153-158.
89. Goldman MP, Fronck A. Consensus paper on venous leg ulcer. *J Dermatol Surg Oncol* 1992;18:592-602.
90. Moffatt CJ, O'Hare L. Venous leg ulceration: Treatment by high compression bandaging. *Ostomy/Wound Management* 1995;41(4):16-25.
91. Falanga V, Margolis D, Alvarez O, Auletta M, Maggiasimo F, Altman M, Jensen J, Sabolinski M, Hardin-Young J. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. *Arch Dermatol* 1998;293-300.
92. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: A randomized double blind study. *Plast Reconstr Surg* 1994;93:829-834.
93. Treatment of pressure ulcers. Clinical Practice Guideline Number 15. U.S. Dept of Health and Human Services, Agency for Health Care Policy and Research Publication No. 95-0652, December 1994.
94. Davis JC, Buckley CJ, Barr PO. Compromised soft tissue wounds: Correction of wound hypoxia. In: Davis JC, Hunt TK, eds. *Problem Wounds: The Role of Oxygen*. New York: Elsevier. 1988:143-152.
95. Hyperbaric oxygen therapy: Its use and appropriateness OEI-06-09-00090. Dept of Health and Human Services, Office of the Inspector General, 2000.
96. Cianci P, Petrone G, Drager S, Lueders H, Lee H, Shapiro R. Salvage of the problem wound and potential amputation with wound care and adjunctive hyperbaric oxygen therapy: An economic analysis. *J Hyperbaric Med* 1988;3(3):127-141.
97. Cianci P, Petrone G, Green B. Adjunctive hyperbaric oxygen in the salvage of the diabetic foot. *Undersea Biomed Res* 1991;18(Suppl):108.
98. Cianci P, Hunt TK. Long term results of aggressive management of diabetic foot ulcers suggest significant cost effectiveness. *Wound Rep Regen* 1997;5:141-146.
99. Lin TF, Chen SB, Niu KC. The vascular effects of hyperbaric oxygen therapy in treatment of early diabetic foot. *Undersea Hyperbaric Med* 2001;28(Suppl):67 (abstract)
100. Zamboni W, Wong H, Stephenson L, et al. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *Undersea Hyperbaric Med* 1997;24(3):175-179.
101. Baroni G, Porro T, Faglia E, et al. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* 1987;10(1):81-86.
102. Davis JC. The use of adjuvant hyperbaric oxygen in the treatment of the diabetic foot. *Clin Pod Med Surg* 1987; 4(2):429-437.

103. Oriani G, Meazza D, Favales F, et al. Hyperbaric oxygen therapy in diabetic gangrene. *J Hyperbaric Med* 1990;5(3):171-175.
104. Wattel FE, Mathieu DM, et al. Hyperbaric oxygen in the treatment of diabetic foot lesions: Search for healing predictive factors. *J Hyperbaric Med* 1991;6(4):263-268.
105. Oriani G, Michael M, Meazza D, et al. Diabetic foot and hyperbaric oxygen therapy: A ten-year experience. *J Hyperbaric Med* 1992;7(4):213-221
106. Stone JA, Scott RG, Brill LR, Levine BD. The role of hyperbaric oxygen therapy in the treatment of the diabetic foot. *Diabetes*, 1995;44(Suppl 1): 71A.
107. Faglia E.. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognosis determinants for major amputation. *J Diabetes Comp* 1998;2:96-102.