The effect of hyperbaric oxygen in the enhancement of healing in selected problem wounds

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ABSTRACT / RATIONALE

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 more than half of lower-extremity amputations in the United States in a group at risk, representing only 3 percent of the population [1]. In response to this challenge, specialized programs have emerged designed to identify and manage these patients, using standardized protocols and a variety of new technologies to improve outcomes. Hyperbaric oxygen treatment (HBO₂T) has been increasingly utilized in an adjunctive role in the care of many of these patients, coinciding with optimized patient and local wound care.

HYPOXIA AND WOUND HEALING FAILURE

Although the underlying physiology and basic science support the contention that hyperbaric oxygen therapy (HBO₂T) is likely to be useful in a variety of problem wounds, the best evidence exists for treatment of ischemic, infected (Wagner Grade III or worse) diabetic foot ulcers. This review will therefore focus on these areas, along with suggesting appropriate areas for further research. As more studies are completed in other types of wounds, for example in ischemic, non-diabetic foot ulcers, the recommendations in this review will be updated.

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 [3].

The hypoxic nature of all wounds has been demonstrated [4], and the hypoxia, when pathologically increased, correlates with impaired wound healing [5] and increased rates of wound infection [6]. Local oxygen tensions in the vicinity of the wound are approximately half the values observed in normal, non-wounded tissue [7,8,9]. The rate at which normal wounds heal has been shown to be oxygen-dependent. Fibroblast replication, collagen deposition [10], angiogenesis [11, 12,13,14], resistance to infection [15,16,17] and intra-cellular leukocyte bacterial killing [18,19] 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 [20,21].

Peripheral arterial occlusive disease (PAOD) is common and progressive. It often results in critical limb ischemia, non-healing ulcers and amputation. PAOD is a common co-morbidity that frequently complicates the management of both venous leg ulcers and diabetic foot ulcers [95].

MEASUREMENT OF WOUND HYPOXIA

Transcutaneous oxygen tension (PtcO$_2$) 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 PtcO$_2$ measurement in the assessment of peripheral vascular disease has been well described by Scheffler [22] and its application to wound healing problems by Sheffield [23]). 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.

PtcO$_2$ 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 0.3 mm from the capillary network in normal skin [24]. PtcO$_2$ 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. PtcO$_2$ is a more accurate reflection of changes in perfusion than is measurement of ankle brachial index [25].

Although several tests intended to identify significant wound hypoxia and / or ischemia have been used, including ankle brachial index, skin perfusion pressure and laser Doppler flow, transcutaneous oximetry (PtcO$_2$ or transcutaneous oxygen measurements/TCOM) is generally accepted as most useful [26] for predicting failure to heal a wound without intervention, failure to heal a planned amputation and failure to respond to HBO$_2$T, as well as evaluating the success of revascularization.

There is some variability in PtcO$_2$ 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 [27,28,29,30,31,32,33,34, 35] have demonstrated that PtcO$_2$ 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 [36,37]. The addition of provocative testing with lower extremity elevation or dependency [38,39], or following occlusion-induced ischemia and recovery [40] or with 100% oxygen breathing [41] may increase the sensitivity of the test as a screening tool for detecting occult lower extremity arterial insufficiency.

The laboratory evidence for hypoxia playing a major role in wound healing failure is not in dispute. Clinical studies identifying the risks of wound or amputation flap healing failure define periwound hypoxia as a primary determinant of future healing failure. Pecoraro [42] reported that when periwound PtcO$_2$ values were below 20 mmHg they were associated with a 39-fold increased risk of primary healing failure. In clinical practice, hyperbaric medicine physicians routinely measure transcutaneous PO$_2$ 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.

Identifying wounds most likely to benefit is paramount for cost-effective application of HBO$_2$T. Patients with wounds that fall within a category defined as potentially appropriate for adjunctive HBO$_2$T should be evaluated for likelihood of benefit. Hypoxia (*i.e.*, wound PO$_2$ < 40 mmHg) generally best defines wounds appropriate for HBO$_2$T – or rather, lack of hypoxia (*i.e.*, wound PO$_2$ >40-50 mmHg) defines wounds potentially not appropriate for HBO$_2$T. Breathing 100% oxygen at 1 atmosphere absolute or under hyperbaric conditions can improve the accuracy of PtcO$_2$ measurement in predicting successful healing with adjunctive hyperbaric oxygen treatment. The following conclusions were drawn from a study of 1,144 diabetic foot ulcer patients who underwent adjunctive hyperbaric oxygen treatment in support of wound healing or limb salvage [43]. PtcO$_2$ 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. $PtcO_2$ 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.

$PtcO_2$ 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. [44,45,46]. Lack of an increase in $PtcO_2$ to >100 mmHg appears to be an appropriate cut-off for predicting failure to heal, at least in ischemic diabetic foot ulcers. This requirement for achieving supraphysiologic wound oxygen concentration lends support to the argument that restoration of wound normoxia is not the primary mechanism of action of HBO_2T in healing hypoxic wounds. The failure rate for <100 mmHg is not 100%, however, so that it is not unreasonable to give a trial of HBO_2T (10-15 treatments) to such patients for whom the alternative is amputation.

It is notable that $PtcO_2$ is a better predictor of failure than success. 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 and ultimately to increase wound blood flow via neovascularization in the setting of minimal or insufficiently corrected blood flow.

This underlines the central role of oxygen in wound healing. That is, there is a level of oxygen below which a wound does not have the capacity to heal. Wounds with a PO_2 higher than that level, however, are not guaranteed to heal, because there are a variety of non-oxygen related impediments to healing that may prevent the normal progression of repair in the presence of adequate tissue oxygen.

Unfortunately there is a lack of prospective clinical trial data linking periwound hypoxia as a selection criterion 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 [47,48] 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 achievable only 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 [49]. 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. Availability of substrate for oxygen-dependent enzymatic reactions critical to repair and resistance to infection is even more important than normalization of metabolic rate. Furthermore, oxidants appear to be among the most important signals that control the healing process, and this may be another mechanism for the benefits of HBO_2T in hypoxic wounds. Arterial PO_2 elevations to 1500 mmHg or greater are achieved with 2 to 2.5 atm abs, with soft tissue and muscle PO_2 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 (e.g., edema and inflammation).

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. Improved leukocyte function of bacterial killing [50,51,52] and antibiotic potentiation [53,54] have been demonstrated. Suppression of the synthesis of many bacterial toxins [55] occurs when tissue PO_2 values are sufficiently elevated during treatment. Blunting of systemic inflammatory responses [56] and prevention of leukocyte activation and adhesion following ischemic reperfusion [57,58,59] are effects that may persist even after completion of hyperbaric oxygen treatment.

Stimulation of tissue growth supporting wound healing has also been demonstrated by a variety of mechanisms:

1. Vascular endothelial growth factor (VEGF) release is stimulated(60) and platelet derived growth factor (PDGF) receptor appearance [61,62,63] is also induced.

2. Boykin [64] has recently demonstrated persistent increases in nitric oxide in wound fluid in diabetic ulcers associated with increased granulation tissue formation and wound closure when patients are exposed to 20 hyperbaric oxygen treatments at 2.0 atm abs for 90 minutes,

3. Thom [65] has shown that stem/progenitor cell release from bone marrow through a nitric oxide-dependent mechanism occurs in patients receiving hyperbaric oxygen treatment for soft-tissue and osteoradionecrosis. The population of CD34 cells in peripheral circulation doubled in response to single HBO_2 treatment (2 atm abs, 120 minutes). Over the course of 20 treatments, circulating CD34 cells increased eightfold, total WBC count unchanged.

The net result of serial hyperbaric oxygen exposures is improved local host immune response, clearance of infection, enhanced tissue growth and angiogenesis, leading to progressive improvement in local tissue oxygenation and healing of hypoxic wounds.

PATIENT SELECTION CRITERIA
Diabetic lower extremity wounds

Lower extremity ulcers and amputations are an increasing problem for people with diabetes. Up to 6 per cent of all hospitalizations for person with diabetes 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 with-

out lower extremity ulcers. Finally, once an amputation occurs, 9 to 20% of diabetic patients will experience an ipsilateral or contralateral amputation within 12 months and 28-52% within five years [66]. The cost of care for a new diabetic foot ulcer has been calculated to be $27,987 in the two years following diagnosis [67].

The pathophysiology of diabetic foot ulceration, faulty healing and lower extremity limb loss has been well described [68]. 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.

Cellular dysfunction also plays a role in impaired healing, with associated decreases in nitric oxygen synthesis [69] and growth factor and growth factor receptor expression. Impaired host immune response to infection and possible cellular dysfunction all contribute to the clinical outcomes described above.

Management, likewise, has been extensively described [70,71] 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. 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) [72], bioengineered human mono layer fibroblast grafts [73,74,75] and bilayer fibroblast and keratinocyte [76,77] grafts, and negative pressure wound therapy [78,79]. Regardless of the interventions applied, limb salvage rates improve when care is applied in a multidisciplinary setting using comprehensive protocols for care.

Since 1999 there have been 10 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 five randomized controlled clinical trials, two controlled clinical trials, six retrospective case series, and one comparative case series, as described in Table 1 *(facing page)*.

TABLE 1 – *Trials of HBO$_2$T in diabetic foot ulcers (DFU)*

Author, Year Country	Study design	N	Condition	Results
Doctor[87] 1992 India	RCT	30 (15 HBO$_2$, 15 control)	Hospitalized DFU	Above-ankle amputations: HBO$_2$ 2/15, Control 7/15 $p<0.05$; Minor amputations NS; Number of + cultures decreased in HBO$_2$ group $p<0.05$
Faglia[88] 1996 Italy	RCT	70 (35 HBO$_2$, 33 control, 2 lost to follow-up)	Severe, infected, ischemic DFU	Major amputations: HBO$_2$ 3/35 (8.6%) Control 11/33 (33.3%) $p=0.016$
Abidia[89] 2003 UK	RCT, double-blind sham	18 (8 HBO$_2$, 8 control; 2 lost to follow-up)	Ischemic DFU, 1-10 mm diameter	Healing at 12-week follow-up point; HBO$_2$ 5/8, Control 1/8
Kalani[90] 2002 Sweden	RCT + CT	38 (17 HBO$_2$, 21 control)	DFU	Healing at 3-year follow-up point: HBO$_2$ 13/17 (76%), Control 10/21 (48%); Amputations: HBO$_2$ 2/17 (12%), Control 7/21 (33%)
Kessler[105] 2003	RCT	28	Wagner 1-3 DFU	HBO$_2$: wounds smaller at 2 and 4 weeks, more healed at 2 weeks
Zamboni[106] 1997 USA	CT	10 (5 HBO$_2$, 5 control)	DFU	HBO$_2$ with standard wound care reduced wound size compared to standard wound care alone $p<0.05$ At 4-6 months HBO$_2$ group had higher rate of complete healing (4/5 compared to controls 1/5)
Baroni[107] 1987 Italy	CT	28 (18 HBO$_2$, 10 control)	DFU	Healing: HBO$_2$ 16/18 (89%), Control 1/10 (10%) $p=0.001$ Amputations: HBO$_2$ 2/18, Control 4/10
Davis[108] 1987 USA	Retro review	168 HBO$_2$	DFU	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
Oriani[109] 1990 Italy	Retro comp	80 (62 HBO$_2$, 18 control)	DFU	"Recovery": HBO$_2$ 59/62 (96%), Control 12/18 (67%); Amputation: HBO$_2$ 3/62 (5%), 6/18 (33%) $p<0.001$
Wattel[110] 1991 France	Retro consec review	59 HBO$_2$	DFU	52/59 (88%) healed without major amputation; 7/59 (12%) required major amputation; Significantly higher PtcO$_2$ values achieved during HBO$_2$ (786 +-258mmHg *vs.* 323 +-214) in success compared to failures
Oriani[111] 1992 Italy	Retro consec review uncontrolled	151 HBO$_2$ (may include patients from from 1990 series)	DFU	130/151, 86% healed with HBO$_2$, 21/15, 14% failed with HBO$_2$
Stone[112] 1995 USA	Retro review abstract	469 (87 HBO$_2$, 382 control)	DFU	Limb salvage: HBO$_2$ 72%, Control 53% $p<0.002$
Faglia[113] 1998 Italy	Compare	115 (51 HBO$_2$, 64 control)	DFU	Major amputations: HBO$_2$ 7/51, Control 20/64 $p=0.012$
Fife[91] 2007 USA	Retro review	1144 HBO$_2$	DFU	Overall 75% of patients improved with HBO$_2$, 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)

TABLE 2 – *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

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 III or greater (Table 2, *above*) ulcers since "diabetic gangrene" was frequently mentioned as a descriptor of patients included. Hypoxic transcutaneous PO$_2$ 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) [80] and the 2000 Australian Medicare Service Advisory Committee review (MSAC) [81] 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 [82] 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 [83] 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."

In 2001, a British Journal of Medicine Clinical Evidence review [84] 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 [85] 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.

A 2004 Cochrane review [86] of randomized controlled clinical trials of hyperbaric oxygen treatment in chronic wounds concluded that "in people with foot ulcers due to diabetes, HBO$_2$T significantly reduced the risk of major amputation and may improve the chance of healing at 1 year. The application of HBO$_2$T to these patients may be justified where HBO$_2$T facilities are available, however economic evaluations should be undertaken."

The randomized controlled clinical trial of hyperbaric oxygen treatment in chronic diabetic lower extremity wounds reported by Doctor *et al.* [87] 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$_2$ 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. [88] 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 atm abs for 90 minutes after an initial treatment at 2.5 atm abs 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$_2$ 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.* [89] 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$_2$ 13/19, 68%; control 4/14, 29%), but no statistical analysis was given.

Kalani *et al.* [90] 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 (seven 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 atm abs for 90 minutes five days per week. At the three year follow-up point, more patients in the treatment group were healed (HBO$_2$ 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 multicenter case series Fife et al. [91] reported the following outcomes with hyperbaric oxygen treatment in 1,144 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.

While the accumulated evidence suggests that all hypoxic diabetic lower extremity wounds could benefit from HBO$_2$T, the majority of clinical trials of HBO$_2$T in this setting have included wounds on the basis of severity and level of tissue involvement. In this setting, the Center for Medicare and Medicaid Services announced on August 30, 2002, in CAG-00060N, Coverage Decision Memorandum for Hyperbaric Oxygen Therapy in the Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities 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 III [92] or higher;

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 in healing.

Arterial insufficiency ulcers

The primary treatment of refractory ischemic wounds of the lower extremities is improvement in blood flow by angioplasty or surgical revascularization. While the majority of clinical trials and large reported case series have addressed hyperbaric oxygen treatment in diabetic foot ulcers, in most of these studies periwound hypoxia as determined by transcutaneous oxygen measurement was noted in patients in the trials but was not used as an entry criteria for the trial or case series. Nonetheless, 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. A recent publication by Zhang et al. [93] has elucidated some aspects of the

mechanisms by which HBO$_2$T impacts ischemic wound healing in a validated ischemic wound model demonstrating reduction in expression of HIF-1α and other inflammatory mediators with attenuation of cell apoptosis.

Venous stasis ulcers

Compression therapy with multilayer external compression bandaging techniques remains the mainstay of management of venous stasis ulcers of the lower extremity [94]. Recent evidence suggests that bioengineered tissue grafts used in combination with standard compression bandaging techniques may shorten time to healing [95]. While one prospective, blinded, randomized clinical trial of hyperbaric oxygen treatment in leg ulcers of undefined etiology [96] 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 [97] 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 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.

CLINICAL MANAGEMENT - 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 atm abs for 90 to 120 minutes once or twice daily. In monoplace chambers patients are usually treated at 2.0 atm abs. 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, 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 [98] identified that active physician oversight of hyperbaric oxygen treatment led to improved outcomes.

EVIDENCE-BASED REVIEW

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.

The Wound Healing Society clinical practice guideline for diabetic foot ulcer care published in 2006 [99]in Guideline #7.3.1 states: " . . .hyperbaric oxygen therapy may be of benefit in reducing the amputation rate in patients with ischemic diabetic foot ulcers (Level I)."

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.

The Wound Healing Society clinical practice guideline for arterial insufficiency ulcers published in 2006 [100] in Guideline #6.B.1a states: "In patients with non-reconstructable anatomy or whose ulcer is not healing despite revascularization, hyperbaric oxygen therapy (HBO$_2$T) should be considered as an adjuvant therapy. Selection criteria include ulcers that are hypoxic (due to ischemia) and the hypoxia is reversible by hyperbaric oxygenation" and gives hyperbaric oxygen a level of evidence determination of IIIB. Guideline #6.B.1b states "HBO$_{[2]}$T should be investigated in the treatment of ischemia-reperfusion injury after revascularization

in patients with arterial ulcers." This was based on the likelihood that such treatment would be effective, based on studies in other patient populations (*e.g.*, compromised flaps). No level of evidence was assigned because of the lack of studies in this area.

UTILIZATION REVIEW

Hyperbaric oxygen treatments are performed at 2.0 to 2.5 atm abs 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.

Because $PtcO_2$ at pressure (2-2.5 atm abs) may be most predictive of response to HBO_2T, it is reasonable to treat a patient who will have uncertain benefit once in order to make the measurement. If the values obtained suggest a lack of efficacy, but no alternative to amputation exists, it is appropriate to treat a patient 10-15 times in order to determine whether he/she will respond. By two to three weeks into treatment, one should begin to see the effects of neovascularization. Lack of response corroborates the $PtcO_2$ findings and should discourage further HBO_2T.

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 with durability of healing well established [101,102]. 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. Guo *et al.* [103] in an economic model of the application of HBO_2T in diabetic foot ulcer healing based upon the outcome generated in controlled clinical trials determined that HBO_2T produced long-term cost benefits of treatment in diabetic limb salvage. In a 1,000-wound cohort model, 155 cases of major lower extremity amputation would be averted, with approximately 50.2, 265.3 and 608.7 quality-adjusted life-years/QALYs are gained in years 1, 5 and 12 respectively due to use of HBO_2T. In this 2003 publication the incremental cost per additional QALY gained $27,310, $5,166, and $2,255 at the 1-, 5- and 12-year periods, making HBO_2T more cost-effective based on long-term perspective. One observation of the authors was that the relatively broad variations in cost effectiveness ratios across different scenarios of applications of HBO2T point out the need for proper clinical practice guidelines.

The Canadian Agency for Drugs and Technologies in Health [104] has also reviewed HBO_2T in diabetic foot ulcer care and has concluded that HBO_2T is more effective than standard care alone, reduces major lower extremity amputations from 32 percent to 11 percent in those receiving HBO_2T, and decreases the proportion of unhealed wounds, with an acceptable 12-year cost to outcome compared to standard care.

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