

**Diabetes Wound Care Submission to the Federal Government
Submitted by Dr. Paul Harch, President of the IHMA, to the Center for
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**ARGUMENT FOR MEDICARE/MEDICAID COVERAGE OF HYPERBARIC OXYGEN
THERAPY**

TREATMENT OF DIABETIC FOOT WOUNDS

Hyperbaric oxygen therapy (HBOT) was first defined as a drug in 1977 by Gottlieb (1). Unfortunately, this critical definition has been long forgotten and substitute definitions have mis-characterized HBOT as a therapy for "certain recalcitrant, expensive, or otherwise hopeless medical problems." (2) This mischaracterization has resulted in a confusing collection of different lists e.g., CMS, UHMS Accepted Indications, and international lists (3), of seemingly unrelated reimbursable diagnoses (chronic refractory osteomyelitis, air embolism, cyanide poisoning, compromised flaps and grafts, carbon monoxide poisoning, acute stroke, etc) supported by widely varying amounts of basic science and clinical evidence. In 1999, the drug definition of HBOT was refined and restated as the use of greater than atmospheric pressure oxygen as a drug to treat basic pathophysiologic processes and their diseases (4). With that definition the above lists could now be understood as cohesive sets of diagnoses connected by HBOT effects on the acute and/or chronic underlying pathophysiology common to the diseases. Furthermore, the definition suggested and argued for the application of HBOT to additional diseases that shared this pathophysiology. The 1999 drug definition of HBOT will be used in this paper to argue for HBOT effectiveness in the treatment of infected diabetic foot wounds, and hence, CMS reimbursement for the same. The argument will be constructed by identifying the underlying pathophysiology in diabetic foot wounds, presenting the evidence for the beneficial effects of HBOT on this pathophysiology, demonstrating a similar benefit in patients with diabetic foot wounds, and then showing the risk/benefit and cost/effectiveness evidence for HBOT in diabetic foot wounds. This argument will lead to the conclusion that CMS coverage of HBOT should be extended to diabetic foot wounds.

Diabetic foot wounds are complex microcosms of multiple pathophysiologic processes. The wounds are predominantly characterized by polymicrobial infection (5,6,7,8), peripheral neuropathy (9,10,11,12), structural deformity (10,13,14,15), altered immune function or increased susceptibility to infection (16,17,18), decreased wound nitric oxide (NO) production (19,20,21), and often hypoxia/ischemia (22,23,24,25). Decreased NO production, infection, and hypoxia are the most important for inhibition of wound healing. Decreased NO production is responsible for impaired cutaneous vasodilation, decreased neurogenic vascular response, diabetic neuropathy, and endothelial cell dysfunction that inhibit the processes necessary for granulation tissue formation (26). Hypoxia, on the other hand, is both necessary for and inhibitory of wound healing (27). Hypoxia is responsible for initiating wound healing through regulation of macrophage angiogenesis factor (28), but impairs the cellular repair processes, which are oxygen dependent (29). These repair processes are: leukocyte bacterial killing of aerobes and anaerobes (30), white blood cell proteolysis of necrotic tissue (31), thrombolysis of wound and periwound capillary microthrombi (32), fibroblast proliferation (33), collagen synthesis (34,35,36,37,38,39,40,41), granulation tissue formation (33,40), angiogenesis (42), osteoclastic and osteoblastic bone repair (43), and

epithelialization (44). In addition, hypoxia alters the rate at which wounds heal (34,35,36,37,39,40,41). When hypoxia is combined with infection wound healing is maximally decreased and results in the main cause of amputation in diabetic foot wounds (24,45,46,47).

Hypoxia and infection are also very closely related; hypoxia impairs leukocyte bacterial killing (48,30), lowers tissue resistance to infection (36,38,49,50,51,52,53), alters the local response to infection (38,39,51,54,55,56,57,58,59), and facilitates growth of anaerobic and microaerophilic organisms that further compromise the wound (60,61). Bacterial growth also competes with normal cells for oxygen and nutrients (62) and generates toxic byproducts. In summary, the combination of hypoxia, infection, and decreased NO are characteristic of diabetic foot wounds and responsible for decreased healing and increased amputation rates. Therefore, correction of these wound factors should be the primary goal of therapy. If these factors can be reversed improved healing and decreased major amputations should be the result.

The question is whether HBOT can impact these factors and lead to improved clinical results. A review of the animal and human literature shows that HBOT has positive drug-like effects on the pathophysiology identified in and actual components of diabetic foot wounds. HBOT increases tissue oxygen levels that remain elevated for up to 4-6 hours after treatment (63,64). This correction of hypoxia directly reverses many, if not all, of the above processes resulting from hypoxia and initiates the wound-healing process. HBOT increases PO₂ in the region of infected tissue (65), controls infection (56), improves leukocyte bacterial killing (51,54,56,57,58,59) has direct toxic effects on anaerobic bacteria (66,67), suppresses exotoxin production (68), and is synergistic with antibiotics (69,70,71,72,73,74,75). HBOT increases fibroblast replication and collagen synthesis in tissue (35,40) and fibroblast proliferation in fibroblasts derived from chronic diabetic wounds (76), epithelialization (77), ischemic tissue oxygen capacitance (64), angiogenesis (78,79,80), granulation tissue (81), platelet derived growth factor receptor mRNA (82), PDGF receptor protein levels alone (83) or in combination with PDGF (84), wound healing synergy with PDGF (81), vascular endothelial growth factor in wounds (85), osteoclastic and osteoblastic activity (86,87), and increases endothelial nitric oxide synthase (88) and NO production (26).

NO is important in wound repair (21,89,90) through its enhancement of cellular immunomodulation and bacterial cytotoxicity (91), regulation of vasodilatation (90), stimulation of cellular migration (92), collagen deposition and cross-linking (89), inhibition of platelet aggregation (91) and white blood cell/endothelial adhesions (93), modulation of endothelial proliferation and apoptosis (94), and promotion of angiogenesis (95).

In essence, HBOT has positive effects on the great majority of the pathological processes identified in diabetic wounds and promotes wound repair and healing through a variety of mechanisms, many of which are mediated by signal induction (drug-like) effects on DNA and nitric oxide.

With the plethora of basic science data it is no surprise that the HBOT animal data has been validated in the human diabetic foot wound literature. Beginning with Davis in 1987, five uncontrolled studies have documented the success of HBOT added to a multidisciplinary approach to treat mostly resistant non-healing diabetic foot wounds

(96,97,98,99). Limb salvage and/or healing rates were 70%, 90%, 88%, 86%, and 85%, respectively. In the 1997 Cianci study (99) the results were shown to be durable: of 28 contacted patients of the 35 who achieved limb salvage, 27 (96%) were still healed at late follow up. These substantial HBOT-induced limb salvage and healing rates in uncontrolled studies have been confirmed in controlled trials.

In a large retrospective controlled trial Stone (100) compared diabetic foot wound patients with low transcutaneous oxygen measurements who received topical growth factors to similar patients who received both growth factors and HBOT. The HBOT group had larger wounds, more wounds/patient, and a 65% increase in the number of patients initially recommended for amputation, yet a greater eventual limb salvage rate, 72 vs. 53%.

In another retrospective controlled study Oriani (101) showed a statistically significant reduction in major amputations, 4.8% (HBOT) vs. 33% (controls); the control group's amputation rate was nearly identical to the amputation rate in similar patients treated five years earlier before the use of adjunctive HBOT. These results confirmed the findings of this same group in a prospective controlled study reported three years earlier (102) which achieved a statistically significant improvement in healing, 88 vs. 10%, and reduction in below knee amputation, 13 vs. 40%, in HBOT patients compared to controls.

Prospective controlled trials have underscored the Baroni findings (102). Doctor (103) reported a statistically significant quicker control of infection (one of the major risk factors for amputation identified above) and reduction in major amputation, 13% vs. 46%, in HBOT patients. Faglia (104) duplicated the Doctor data with major amputation rates of 9% in HBOT vs. 33% in control patients. Zamboni (105) recorded an 80% healing rate in HBOT patients vs. 20% in controls. These findings were recently reproduced by Abidia (106) in a randomized prospective double-blinded study of non-healing ischemic diabetic leg ulcers. At 12 weeks healing with complete epithelialization was achieved in 68% of the HBOT treated ulcers vs. 29% of the control ulcers. The median reduction in wound area was 96% in the HBOT group and 41% in the controls ($p=.043$). While there was no difference in major amputation the HBOT group reported significant improvement in vitality ($p=.01$), mental health ($p=.05$), and general health ($p=.008$) as assessed by the quality of life SF-36 Health Survey.

Lastly, Lin (107) reported improved hemoglobin A1C, transcutaneous oxygen measurements, and laser-Doppler perfusion scanning, all $p<.01$, in the HBOT treated group of a randomized prospective controlled trial of early diabetic foot ulcers. While the data points to improved healing, resolution of hypoxia, and prevention of major amputations in diabetic foot wound patients who undergo HBOT, cost-effectiveness and risk-benefit are important considerations.

Risks are easily addressed; HBOT is a minimal risk medical treatment where the most common problems are middle ear and sinus barotrauma and reversible hyperoxic myopia (108). All other risks are extremely rare, a surprising finding given the generally complicated medical patients treated with this modality.

Costs have been explored by Cianci and Petrone (96), Mackey (109), and Cianci (99) and strongly suggested to be lower with HBOT. These costs should be even less after the 2000-2001 CMS reduction in HBOT reimbursement. In those wounds treated with

HBOT reduction in costs would also come from avoidance of prosthesis and rehabilitation charges [estimated to be \$40-50,000-(108)], stump revision, and reamputation. Ipsilateral, often higher, amputation occurs in 22% of cases and after five years 50% will have undergone a bilateral amputation (110,111).

Amputation causes mortality and expensive morbidity, 4% and 14%, respectively, in one study (112). Considering the durability of HBOT-induced healing, up to 55 months (99), savings would result from prevention of stump revisions and reamputation (102,112) and their associated morbidity and mortality costs.

Indirect cost savings are also important. Since only 40-50% of elderly amputees alive after four years will have been successfully rehabilitated (110,111) amputation often commits the patient to a wheelchair life. This is accompanied by multiple problems, including depression and loss of self-esteem, which are difficult to quantify. Costs "resulting from loss of function, life, and the skills contributed by these patients to society are generally neglected" and "may well be as high as 50% of the total costs of the disease." (114). Beyond costs diabetic foot ulcers have a marked effect on quality of life. In the Abidia study (115) above HBOT resulted in improved quality of life measures and a reduction of depression. The impact of such improvements are difficult to measure, but likely are significant and contribute to the reduction in indirect costs associated with diabetic foot ulcers and amputation. The weight of the above data has now prompted recommendation of HBOT in diabetic foot wounds by various groups.

In 1999, the Blue Cross/Blue Shield Tech Assessment Report for Kaiser Permanente (116) supported HBOT for adequately perfused wounds of the lower extremity in combination with standard wound care. These wounds included diabetic foot wounds. Similarly, the Australian Hyperbaric Oxygen Therapy April 2000 Draft Final Assessment Report (117) found evidence of HBOT effectiveness in diabetic wounds and that it could be cost-effective if rehabilitation costs are included. Given other considerations "HBOT might have a cost effectiveness ratio of many times those calculated above." Clinical Evidence 5 of the British Medical Journal Publishing Group came to the conclusion that "two small RCTs suggest that systemic hyperbaric oxygen reduces the risk of foot amputation in people with severe infected foot ulcers."(118)

In addition, the American Diabetes Association's 1999 Consensus Development Conference on Diabetic Foot Wound Care recommends HBOT 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 (119)." Lastly, and most importantly, a recent Rapid Response Report (126) by the Evidence-based Practice Center of the New England Medical Center endorsed HBOT in the treatment of diabetic foot wounds. This report was funded by a grant from the Agency for Healthcare Research and Quality (AHRQ) to review the literature on CMS HBOT indications. They summarized all of the recent TEC assessments, e.g. Blue Cross/Blue Shield, Australian MSAC, etc., and HBOT literature and found that the scientific evidence supported the use of HBOT in the treatment of diabetic foot wounds.

The implications of their findings cannot be overemphasized; the findings are consistent with, and powerfully recapitulate, all of the above evidence and arguments for HBOT in diabetic foot wounds. Because of the above noted morbidity,

mortality, direct and indirect costs of diabetic foot wounds and amputations studies have recommended multiple strategies to reduce lower extremity amputations (45,62,122,123,124).

The Department of Health and Human Services' Healthy People 2000 report targeted a 40% reduction in amputations in 1991 (124). This goal has not been achieved (114). Since 50-70% of amputations in the United States are in diabetic patients (99) any strategy that could reduce amputations in diabetics, especially major amputations, could have a dramatic impact on health and costs. That therapy is HBOT.

As argued above HBOT treats the underlying pathophysiology of diabetic foot wounds, effectively treats diabetic foot wounds in uncontrolled and controlled clinical trials, reduces costs, improves health and outcomes, prevents major amputations, and satisfies the directives and goals of the Department of Health and Human Services of the United States Government. Its use is increasingly endorsed by institutions, including insurance companies, governments, and scientific groups and thus has come in concert with the past thirty years' practice habits and knowledge of hyperbaric physicians.

Interestingly, the major source of "inappropriate use" of HBOT noted in the OIG's October 2000 Report on Hyperbaric Oxygen Therapy was in the physician miscoding of diabetic foot wounds as other covered diagnoses "to align treatment practices with their own medical judgements (3)." Both treatment practices and medical judgement are supported by the overwhelming data presented in this report.

In short, HBOT saves limbs and possibly lives in patients with diabetic foot wounds. It appears that it is time to recognize this body of data, reduce healthcare costs, and improve health and outcomes by endorsing HBOT in the treatment of diabetic foot wounds. This can be achieved by extending CMS coverage to this diagnosis.

Thank you.

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