Diabetic Research Directory

Submitted by Dr. Paul Harch, President of the IHMA, to the Center for Medicare and Medicaid Services, November 2, 2001

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.

Paul G. Harch, M.D.

President
International Hyperbaric Medical Association
Clinical Assistant Professor and Director
Hyperbaric Medicine Fellowship
Department of Medicine
Section of Emergency and Hyperbaric Medicine
Louisiana State University School of Medicine
New Orleans, Louisiana

BIBLIOGRAPHY

1. Gottlieb SF. Oxygen under pressure and microorganisms. In: Hyperbaric Oxygen Therapy. Davis JC, Hunt TK, eds. Undersea Medical Society, Inc., Bethesda, MD, 1986. p.79.
2. Hyperbaric Oxygen Therapy Committee Report, 1999. Hampson NB, Chairman and Ed. Undersea and Hyperbaric Medical Society. Kensington, Maryland, 1999. p. 1.
3. Hyperbaric Oxygen Therapy, Its Use and Appropriateness. Office of Inspector General, Department of Health and Human Services. June Gibbs Brown, Inspector General. October 2000. OEI 06-99-00090.
4. Harch PG and Neubauer RA. Hyperbaric Oxygen Therapy in Global Ischemia, Anoxia, and Coma. Chapter 18, Textbook of Hyperbaric Medicine, 3rd Edition. Jain KK, ed. Hogrefe and Huber Publishers, Gottingen, Germany, 1999.

5. Sapico FL, Witte JL, Canawati HN, Montgomerie JZ, Bessman AN. The infected foot of the diabetic patient: quantitative microbiology and analysis of clinical features. Rev Inf Dis, 1984; 6(Suppl 1): S171-177.
6. Millington JT and Norris TW. Effective treatment strategies for diabetic foot wounds. J Fam Pract, November 2000; 49:11(suppl):S40-48.
7. Sapico FL, Canawati HN, Witte JL, Montgomerie JZ, Wagner FW. Quantitative Aerobic and Anaerobic Bacteriology of Infected Diabetic Feet. J Clin Micro 1980; 12: 413-20.
8. Edmonds ME, Blundell MP, Morris ME, Thomas EM, Cotton LT, Watkins PJ. Improved survival of the diabetic foot: the role of the specialised foot clinic. Q J Medicine 1986; 60: 763-771.
9. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990; 13:513-21.
10. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer: The Seattle Diabetic Foot Study. Diabetes Care 1999; 22: 1036-42.
11. Boulton AJ, Kubrusly DB, Bowker JH, Gadia MT, Quinlero L, Becker DM, Skyler JS, Sosenko JM. Impaired vibratory perception and diabetic foot ulceration. Diabetic Med 1986; 3: 335-37.
12. McNeely MJ, Boyko EJ, Ahroni JH, Stensel VL, Reiber GE, Smith DG, Pecoraro RE. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration: How great are the risks? Diabetes Care 1995; 18:216-19.
13. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med 1998; 158: 157-62.
14. Lavery L, Gazewood JD. Assessing the feet of patients with diabetes. J Fam Pract 2000; 49(11): S9-16.
15. Mueller MJ, Minor SD, Diamond JE, Blair VP. Relationship of foot deformity to ulcer location in patients with diabetes mellitus. Phys Ther 1990; 70: 356-62.
16. Molenaar DM, Palumbo PJ, Wilson WR, Ritts RE. Leukocyte chemotaxis in diabetic patients and their nondiabetic first-degree relations. Diabetes 1976; 25: 880-883.
17. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. Am J Surg 1998; 176(Suppl 2A): 5S-10S.
18. Foster DW. Diabetes Mellitus, Chapter 319. In: Harrison's Principles of Internal Medicine, 12th Ed. Wilson, Braunwald, Isselbacher, Petersdorf, Martin, Fauci, Root, eds. McGraw-Hill, Inc, NY, NY, 1991. p.1739-59.
19. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. J Am Coll Cardiol 1996; 27: 567-74.
20. Veves A, Akbari CM, Primavera J, Donaghue VM, Zacharoulis D, Chrzan JS, DeGirolami U, LoGerfo FW, Freeman R. Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease and foot ulceration. Diabetes 1998; 47: 457-63.
21. Schaffer MR, Tantry U, van Wesep RA, Barbul A. Nitric oxide metabolism in wounds. J Surg Res 1997; 71:25-31.
22. Sheffield PJ. Tissue oxygen measurements with respect to soft-tissue wound healing with normobaric and hyperbaric oxygen. Hyperbaric Oxygen Review 1985; 6(1): 18-46.
23. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. Diabetes 1991; 40: 1305-13.
24. Reiber GE, Pecoraro RE, Keopsell TD. Risk factors for amputation in patients with diabetes mellitus: A case control study. Ann Int Med 1992; 117: 97-105.
25. Pecoraro RE. The nonhealing diabetic ulcer-A major cause for limb loss. Prog Clin Biol Res 1991; 365: 27-43.
26. Boykin JV. The nitric oxide connection: Hyperbaric oxygen therapy, becaplermin, and diabetic ulcer management. Adv Skin Wound Care 2000; 13: 169-74.
27. Van Meter K. Systemic hyperbaric oxygen therapy as an aid in resolution of selected chronic problem wounds. In: Chronic Wound Care, Second Edition. Krasner D, Kane D, eds. Wayne, PA, Health Management Publications, Inc., 1997, p 260-75.
28. Knighton D, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z, Banda MJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. Science 1983; 221: 1283-5.

29. Davis JC, Buckley CJ, Barr PO. Compromised soft tissue wounds: correction of wound hypoxia. In: Problem Wounds: The Role of Oxygen. Davis JC, Hunt TK, eds. Elsevier, NY, 1988, p. 143-4.
30. Hohn DC, MacKay RD, Halliday B, Hunt TK. Effect of O2 tension on microbicidal function of leukocytes in wounds and in vitro. Surg Forum 1976; 27: 18-20.
31. Travis J, Salvesen GS. Human plasma proteinase inhibitors. Ann Rev Biochem 1983; 52: 655-709.
32. Lawrence DA, Loskutoff DJ. Inactivation of plasminogen activator inhibitor by oxidants. Biochemistry 1986; 25: 6351-5.
33. Silver IA. Local systemic factors which affect the proliferation of fibroblasts. In: Biology of the Fibroblasts. Kulomen E, ed. Academic Press, New York 1973, p. 507-19.
34. Siddiqui A, Galiano RD, Connors D, Gruskin E, Wu L, Mustoe TA. Differential effects of oxygen on human dermal fibroblasts: acute versus chronic hypoxia. Wound Rep Reg 1996; 4: 211-218.
35. Niinikoski J. The effect of oxygen supply on wound healing and formation of experimental granulation tissue. Acta Physiol Scand 1969; 334: 1-72.
36. Niinikoski J, Heughan C, Chir B, Hunt TK. Oxygen tensions in human wounds. J Surg Res 1972; 12: 77-82.
37. Hunt TK, Twomey P, Zederfeldt B, Dunphy JE. Respiratory gas tensions and pH in healing wounds. Am J Surg 1967; 114: 302-7.
38. Hunt TK, Linsey M, Grislis G, Sonne M, Jawetz E. The effect of differing ambient oxygen tensions on wound infection. Ann Surg 1975; 181: 35-9.
39. Hunt TK. Disorders of repair and their management. In: Fundamentals of Wound Management. Hunt TK, Dunphy JE, eds. Appleton-Century-Crofts, New York, 1979, p.68-168.
40. Hunt TK, Pai MP. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynecol Obstet 1972; 135: 561-7.
41. Prockop DJ, Kivirikko KI, Tuderman L, Guzman NA. The biosynthesis of collagen and its disorders. N Engl J Med 1979; 301: 13-23.
42. La Van FB, Hunt TK. Oxygen and wound healing. Clinc Plast Surg 1990; 17(3): 463-72.
43. Mader JT, Guckian JC, Glass DL, Reiniarz JA. Therapy with hyperbaric oxygen for experimental osteomyelitis due to Staphylococcus aureus in rabbits. J Infectious Diseases 1978; 138: 312-9.
44. Kivisaari J, Niinikoski J. Effects of hyperbaric oxygenation and prolonged hypoxia on the healing of open wounds. Acta Chir Scand 1975; 141: 14-19.
45. Mason J, O'Kaeffet C, Hutchinson A, McIntosh A, Young R, Booth A. A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. II: treatment. Diabet Med 1999; 16: 889-909.
46. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998; 21: 855-9.
47. Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care 1999; 22: 1029-35.
48. Knighton DR, Fiegel VD, Halverson T, Schneider S, Brown T, Wells CL. Oxygen as an antibiotic: the effect of inspired oxygen on bacterial clearance. Arch Surg 1990; 125: 97-100.
49. Chang N, Mathes SJ. Comparison of the effect of bacterial inoculation in musculocutaneous and random-pattern flaps. Plast Reconstr Surg 1982; 70: 1-9.
50. Gottrup F, Firmin R, Hunt TK, Mathes SJ. The dynamic properties of tissue oxygen in healing flaps. Surgery 1984; 95: 527-36.
51. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic: The effect of inspired oxygen on infection. Arch Surg 1984; 119: 199-204.
52. Rabkin JM, Hunt TK. Infection and oxygen. In: Problem Wounds: The role of oxygen. Davis JC, Hunt TK eds. Elsevier, New York 1988, p.1-16.
53. Jonsson K, Hunt TK, Mathes SJ. Oxygen as an isolated variable influences resistance to infection. Ann Surg 1988; 208(6): 783-7.
54. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic: A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance. Arch Surg 1986; 121: 191-5.
55. Mandell GL. Bactericidal activity of aerobic and anaerobic polymorphonuclear neutrophils. Infect Immun 1974; 9: 337-41.

56. Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 1980; 142: 915-22.
57. Mader JT, Adams KR, Sutton TE. Infectious diseases: pathophysiology and mechanisms of hyperbaric oxygen. J Hyperbaric Med 1987; 2: 133-140.
58. Thom SR, Lauermann MW, Hart GB. Intermittent hyperbaric oxygen therapy for reduction of mortality in experimental polymicrobial sepsis. J Infect Dis 1986; 154: 504-10.
59. Thom SR. Hyperbaric oxygen therapy in septicemia. J Hyperbaric Med 1987; 2: 141-46.
60. Robson MC, Stenberg BD, Heggers JP. Wound healing alterations caused by infection. Clin Plast Surg 1990; 17(3): 485-92.
61. Hunt TK. The physiology of wound healing. Ann Emerg Med 1988; 17: 1265-73.
62. Millington JT, Norris TW. Effective treatment strategies for diabetic foot wounds. J Fam Pract 2000; 49(11): S40-8.
63. Wells CH, Goodpasture JE, Horrigan DJ, Hart GB. Tissue gas measurements during hyperbaric oxygen exposure. In: Proceedings of the 6th International Conference on Hyperbaric Medicine. Smith G, ed. Aberdeen University Press 1977, p.118-24.
64. 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.
65. Brummelkamp WH. Considerations on hyperbaric oxygen therapy at three atmospheres absolute for Clostridial infections type welchii. Ann NY Acad Sci 1964; 117: 688-99.
66. McCord JM, Keele B, Fridovich I. An enzyme-based theory of obligate anaerobiosis: the physiological function of superoxide dismutase. Proc Natl Acad Sci USA 1971; 68: 1024-7.
67. McAllister TA, Stark JM, Norman JN, Ross RM. Inhibitory effects of hyperbaric oxygen on bacteria and fungi. Lancet 1963; 2: 1040-2.
68. VanUnnik AJM. Inhibition of toxin production in Clostridium perfringens in vitro by hyperbaric oxygen. Antonie Van Leeuwenhoek 1965;31: 181-6.
69. Verklin RM, Mandell GL. Alteration of effectiveness of antibiotics by anaerobiosis. J Lab Clin Med 1977; 89(1): 65-71.
70. Harrell LJ, Evans JB. Effect of anaerobiosis on antimicrobial susceptibility of staphylococci. Antimicrob Agents Chemother 1977; 11: 1077-8.
71. Keck PE, Gottlieb SF, Conley J. Interaction of increased pressures of oxygen and sulfonamides on the in vitro and in vivo growth of pathogenic bacteria. Undersea Biomed Res 1980; 7: 95-106.
72. Norden CW. Experimental osteomyelitis V. Therapeutic trials with oxacillin and sisomicin alone and in combination. J Infect Dis 1978; 137: 155-160.
73. Tack KJ, Sabath LD. Increased minimum inhibitory concentrations with anaerobiasis for tobramycin, gentamicin, and amikacin, compared to latamoxef, piperacillin, chloramphenicol, and clindamycin. Chemotherapy 1985; 31: 204-10.
74. Adams KR, Mader JT. Aminoglycoside potentiation with adjunctive hyperbaric oxygen therapy in experimental Pseudomonas aeruginosa osteomyelitis. Undersea Biomedical Research 1987; 14(2), Suppl: 37-8.
75. Adams KR, Sutton TE, Mader JT. In vitro potentiation of tobramycin under hyperoxic conditions. Undersea Biomedical Research 1987; 14(2), Suppl: 37.
76. Hehenberger K, Brismar K, Lind F, Kratz G. Dose-dependent hyperbaric oxygen stimulation of human fibroblast proliferation. Wound Rep Regen 1997; 5: 147-50.
77. Winter GD, Perrins DJD. Effects of hyperbaric oxygen treatment on epidermal regeneration. In: Proceedings of the Fourth International Congress on Hyperbaric Medicine. Wada J, Iwa T, eds. The Williams and Wilkins Co., Baltimore, MD, 1970, p.363-8.
78. 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 on Hyperbaric Medicine. Wada J, Iwa T, eds. The Williams and Wilkins Co., Baltimore, MD, 1970, p.388-94.
79. Tompach PC, Lew D, Stoll JL. Cell response to hyperbaric oxygen treatment. Int J Oral Maxillofac Surg 1997; 26: 82-6.
80. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. JADA 1985; 111: 49-55.

81. 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: 1043-9.
82. Wu L, Mustoe TA. Effect of ischemia on growth factor enhancement of incisional wound healing. Surgery 1995; 117: 570-6.
83. Reenstra WR, Dittmer C, Buras JA. Human dermal fibroblasts vary the expression of growth factor receptors in response to in vitro oxygen levels. Undersea Hyper Med 1999; 26 (Suppl): 71.
84. Bonomo SR, Davidson JD, Yu Y, Xia Y, Lin X, Mustoe TA. Hyperbaric oxygen as a signal transducer: upregulation of platelet derived growth factor-beta receptor in the presence of HBO2, and PDGF. Undersea Hyper Med 1998; 25(4): 211-216.
85. Sheikh AY, Gibson JJ, 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: 1293-7.
86. Garret IR, Boyce BF, Oreffo ROC, Bonewald L, Poser J, Mundy GR. Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone in vitro and in vivo. J Clin Invest 1990; 85(3): 632-9.
87. Ueng SW, Lee SS, Lin SS, Wang CR, Liu SJ, Yang HF, Tai CL, Shih CH. Bone healing of tibial lengthening is enhanced by hyperbaric oxygen therapy: a study of bone mineral density and torsional strength on rabbits. J Trauma 1998; 44(4): 676-81.
88. Buras JA, Stahl GL, Svoboda KKH, Reenstra WR. Hyperbaric oxygen downregulates ICAM-1 expression induced by hypoxia and hypoglycemia: the role of NOS. Am J Physiol Cell Physiol 2000; 278: C292-302.
89. Schaffer MR, Tantry U, Gross SS, Wasserkrug HL, Barbul A. Nitric oxide regulates wound healing. J Surg Res 1996; 63(1): 237-40.
90. Bruch-Gerharz D, Ruzicka T, Kolb-Bachofen V. Nitric oxide in human skin: current status and future prospects. J Invest Dermatol 1998; 110: 1-7.
91. Beckman JS. The physiological and pathological chemistry of nitric oxide. In: Nitric Oxide. Lancaster J, ed. Academic Press, New York, NY, 1996, p.1-71.
92. Noiri E, Lee D, Testa J, Quigley J, Colflesh D, Keese CR, Giaever I, Goligorsky MS. Podokinesis in endothelial cell migration: role of nitric oxide. Am J Physiol 1998; 274(1 Pt 1): C236-C244.
93. Lefer AM, Lefer DJ. The role of nitric oxide and cell adhesion molecules on the microcirculation in ischaemia-reperfusion. Cardiovasc Res 1996; 32: 743-51.
94. Shen YH, Wang XL, Wilcken DEL. Nitric oxide induces and inhibits apoptosis through different pathways. FEBS Lett 1998; 433(1-2): 125-31.
95. Papapetropoulos A, Garcia-Cardena G, Madri JA, Sessa WC. Nitric oxide production contributes to the angiogenic properties of vascular endothelial growth factor in human endothelial cells. J Clin Invest 1997; 100: 3131-9.
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 Hyper Med 1988; 3: 127-141.
97. Wattel FE, Mathieu DM, Fossati P, Neviere RR, Coget JM. Hyperbaric oxygen in the treatment of diabetic foot lesions: Search for healing predictive factors. J Hyperbaric Med, 1991; 6(4): 263-7.
98. Oriani G, Michael M, Meazza D, Sacchi C, Ronzio A, Montino O, Sala G, Campagnoli P. Diabetic foot and hyperbaric oxygen therapy: A ten year experience. J Hyperbaric Med, 1992; 7(4): 213-221.
99. Cianci P, Hunt TK. Long term results of aggressive management of diabetic foot ulcers suggest significant cost effectiveness. Wound Repair and Regen 1997; 5: 141-6.
100. 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.
101. Oriani G, Meazza D, Favales F, Pizzi GL, Aldeghi A, Faglia E. Hyperbaric oxygen therapy in diabetic gangrene. J Hyperbaric Med 1990; 5: 171-175.
102. Baroni G, Porro T, Faglia E, Pizzi G, Mastropasqua A,Oriani G, Pedesini G, Favales F. Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care 1987; 10: 81-86.
103. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. J Postgrad Med 1992; 38(3): 112-4.
104. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A. . Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. Diabetes Care 1996; 19: 1338-43.

105. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: A prospective study. Undersea Hyperbaric Med 1997; 24: 175-9.
106. Abidia A, Kuhan G, Laden G, et al. Hyperbaric oxygen therapy for diabetic leg ulcers-a double-blind randomised-controlled trial. Undersea Hyper Med 2001; 28(Suppl): 64.
107. Lin TF, Chen SB, Niu KC. The vascular effects of hyperbaric oxygen therapy in treatment of early diabetic foot. Undersea Hyper Med 2001; 28(Suppl): 67.
108. Cianci P. Review: Adjunctive hyperbaric oxygen therapy in the treatment of the diabetic foot. Wounds 1992; 4(5): 158-66.
109. Mackey WC, McCullough JL, Conlon TP, Shepard AD, Deterling RA, Callow AD, O'Donnell TF. The costs of surgery for limb-threatening ischemia. Surgery 1986; 99: 26-35.
110. Ebskov G, Josephesen P. Incidence of reamputation and death after gangrene of the lower extremity. Prosthet Orthotics Inter 1980; 4: 77-80.
111. Couch NP, David JK, Tilney NL, Crane C. Natural history of the leg amputee. Am J Surg 1977; 133: 469-473.
112. Gibbons GW, Marcaccio EJ Jr, Burgess AM, Pomposelli FB, Freeman DV, Campbell DR, Miller A, LoGerfo FW. Improved quality of diabetic foot care, 1984 vs. 1990. Arch Surg 1993; 128: 576-81.
113. Cianci P. Adjunctive hyperbaric oxygen therapy in the treatment of the diabetic foot. J Am Pod Med Assoc 1994; 84: 448-55.
114. Boulton AJM, Vileikyte L. The diabetic foot: the scope of the problem. J of Fam Pract, 2000; 49(11): S3-S8.
115. Abidia A, Kuhan G, Laden G, Bahia H, Chetter I, McCollum PT. The placebo effect of hyperbaric oxygen therapy-fact or fiction? Undersea Hyper Med 2001; 28(Suppl): 58.
116. Blue Cross and Blue Shield Association. Hyperbaric oxygen therapy for wound healing - Part I. Technical Assessment Center; Assessment Program, August 1999; 14(15).
117. Hyperbaric Oxygen Therapy, April 2000. Medicare Service Advisory Committee application 1018-1020. Draft final assessment report. Manager, Legislative Services, AusInfo, GPO Box 1920, Canberra, ACT 2601.
118. Hunt D, and Gerstein H. Foot ulcers in diabetes. Clinical Evidence 2001; 5: 397-402.
119. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care, 7-8 April, 1999, Boston, MA. Diabetes Care, 1999; 22: 1354-60.
120. Wang C, Lau J. Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds. Agency for Healthcare Research and Quality (Contract # 270-97-0019), New England Medical Center EPC, 2001.
121. Ollendorf DA, Kotsanos JG, Wishner WJ, Friedman M, Cooper T, Bittoni M, Oster G. Potential economic benefits of lower-extremity amputation prevention strategies in diabetes. Diabetes Care 1998; 21(8):1240-5.122 Rith-Najarian SJ, Reiber GE. Prevention of foot problems in persons with diabetes. J Fam Pract 2000; 49(suppl): S30-S39. 123. Lavery L, Gazewood JD. Assessing the feet of patients with diabetes. J Fam Pract 2000; 49(suppl): S9-S16
122. Department of Health and Human Services. Healthy people 2000: national health promotion and disease prevention objectives. Washington, DC: Government Printing Office; 1991: 73-117.
123. Lavery L, Gazewood JD. Assessing the feet of patients with diabetes. J Fam Pract 2000; 49(suppl): S9-S16
124. Department of Health and Human Services. Healthy people 2000: national health promotion and disease prevention objectives. Washington, DC: Government Printing Office; 1991: 73-117

Legal Disclaimer

to be considered Medical Advice. In Full Support of the F.D.A., Hyperbaric Oxygen Therapy is considered Investigational, Experimental, or Off Label.
Please consult with your Treating Medical Physician