Hyperbaric Oxygen Therapy for Wound Healing and Limb Salvage: A Systematic Review

Robert J. Goldman, MD

This article is a systematic review evaluating published clinical evidence of the efficacy of hyperbaric oxygen therapy (HBOT) for wound healing and limb salvage. The data source is the Ovid/Medline database for key word "Hyperbaric Oxygenation" with search limits (human studies, 1978-2008). Results were combined by Boolean AND with 1 of the 3 following searches: (a) wound healing (10 permutations); (b) compromised flap or graft (3); and (c) osteomyelitis (1). The author evaluated 620 citations, of which 64 reported original observational studies and randomized controlled trials (RCTs) on HBOT and healing outcomes. All citations with 5 subjects were selected for full text review (44 articles) and evaluated according to GRADE criteria for high, medium, low, or very low level of evidence. A Cochrane review identified 1 additional study with a low level of evidence. This systematic review discusses and tabulates every article of high or moderate level of evidence. For patients with diabetic foot ulcers (DFU) complicated by surgical infection, HBOT reduces chance of amputation (odds ratio [OR] 0.242, 95% CI: 0.137-0.428) (7 studies) and improves chance of healing (OR 9.992, 95% CI: 3.972-25.132) (6 studies). Positive efficacy corresponds to HBOT-induced hyperoxygenation of at-risk tissue (7 studies) as measured by transcutaneous oximetry. HBOT is associated with remission of about 85% of cases of refractory lower extremity osteomyelitis, but an RCT is lacking to clarify extent of effect. There is a high level of evidence that HBOT reduces risk of amputation in the DFU population by promoting partial and full healing of problem wounds. There is a moderate level of evidence that HBOT promotes healing of arterial ulcers, calciphylactic and refractory vasculitic ulcers, as well as refractory osteomyelitis. There is a low to moderate level of evidence that HBOT promotes successful "take" of compromised flaps and grafts.

INTRODUCTION

Wound care practice is traditionally an important role for physiatrists [1]. The practice continues today in treatment of pressure ulcers of patients with spinal cord injury. Physiatrists can also participate in wound care of potential amputees with "tissue at risk" because with improved wound healing techniques limb salvage is increasingly an option for this patient population [2].

Outpatient wound centers currently number 1000 (compared with about 100 15 years ago) and a sizable number of these are for-profit wound management organizations. Such outpatient settings offer new opportunities to physiatrists to focus on wound care. In addition, teaching and research opportunities for such wound care specialists have recently expanded. A notable example is the Physical Medicine and Rehabilitation Department at East Carolina University, which launched the first academic-based physiatry-directed wound center in 2007 [3].

Because many of these wound care centers also offer hyperbaric oxygen therapy (HBOT), an increasing number of physical medicine and rehabilitation physicians are becoming certified in or practice HBOT. HBOT (unlike wound care) is an American Board of Medical Specialties recognized subspecialty, offered by the Board of Preventive Medicine. Physiatrists in HBOT practice, with 2 years of part-time experience, may sit for the Undersea and Hyperbaric Medicine Board Examination until 2010. After 2010, an HBOT Fellowship will be required [4].

HBOT is defined as compression of the whole body with at least 1.4 atmospheres absolute pressure (ATA) of pure oxygen [5]. Since the 19th century, HBOT has been

R.J.G. Wound Care and Rehab Medicine, LLC, P.O. Box 18870, Philadelphia, PA 19119. Address correspondence to: R.G.; e-mail: robert.goldman@verizon.net
Disclosure: 9A

Disclosure Key can be found on the Table of Contents and at www.pmrjournal.org

Submitted for publication August 30, 2008; accepted March 8, 2009

Table 1. *Partial list of applications of hyperbaric oxygen therapy sanctioned by the Undersea and Hyperbaric Medicine Society (9)*

Type of Therapy	Discipline, Focus	Specific Application
Urgent, primary therapy	Diving medicine	Decompression sickness: Arterial gas embolism (AGE)
Urgent, adjunctive	Emergency room and critical care	Carbon monoxide poisoning.
		Crush injury/compartment syndrome
		Gas gangrene
		Retinal artery occlusion
Non-urgent, adjunctive	Late effects of radiation	Osteoradionecrosis (ORN) prophylaxis
		Declared ORN
		Radionecrosis head and neck
		Radionecrosis elsewhere (including radiation cystitis)
	Chronic wound and limb salvage	Diabetes mellitus foot ulcer, Wagner III, IV, V
		Hypoxic wound
		Refractory osteomyelitis
		Compromised skin graft or flap

employed successfully to resolve decompression sickness [6]. Studies showing the beneficial effect of HBOT on gas gangrene and on carbon monoxide poisoning were published in 1961 and 1962, respectively. After encouraging initial reports during the 1960's, there was an upsurge in number of chambers for use as operating rooms for cardiopulmonary surgery. After the advent of cardiopulmonary bypass, however, HBOT fell out of favor for this use. A number of anecdotal reports of HBOT without sound rationale led to calls for better regulation during the 1970s [7].

In 1977, the first major textbook of HBOT was published [8]. Since then, the field has achieved full professional status in terms of regulation, staffing, training, certification, and peer review [7]. The Undersea and Hyperbaric Medicine Society, the professional society for HBOT, displays on its website [9] a list of emergent and nonemergent indications for which there is reasonable evidence (Table 1).

An HBOT session is commonly referred to as a "compression." Compression at 2.0 ATA is equivalent to 10 m (33 ft) of seawater. There are compression tables developed by the US Navy that delineate depth and time of compression employed, depending on the condition being treated, from 5 ATA (arterial gas embolism) to 2 ATA (wound healing). Typical compression times range from 90 min (wound healing) to 5 hours or longer (for decompression sickness).

HBOT may be delivered to patients in monoplace or multiplace chambers. Monoplace chambers have space for 1 patient, usually supine, with 100% oxygen to the entire chamber. The attendant is outside the chamber. Multiplace chambers have accommodations for 2 or more patients (typically 5-10). Also, there is an inside tender (ie, trained attendant) and an outside attendant. Within the chamber, compressed air is provided at depth with 100% oxygen via well-secured hoods over the head and neck [10].

Either monoplace or multiplace chambers may be used for critical care. Critical care in the multiplace chamber involves the inside tender functioning in a role similar to an intensive care unit nurse at the bedside. With special equipment in experienced hands, the monoplace chambers may also be used to safely manage critically ill patients [11]. Between cases, physicians and staff provide around-the-clock coverage.

In contrast, many outpatient wound care and HBOT centers restrict their practices to nonemergent applications, operating monoplace chambers during business hours. Nonemergent conditions include wound care, limb salvage, and late effects of radiation, with the latter condition being appropriate for outpatient management. Thus HBOT is used extensively for adjunctive treatment of radionecrosis of soft tissue and bone post radiation therapy for various types of cancer (Table 1). The efficacy of HBOT for treating late effects of radiation is the subject of an excellent Cochrane Database review [12]. In addition, physiatrists should be aware of the neurorehabilitation applications of HBOT. McDonagh [13] has recently reviewed the literature on HBOT and traumatic brain injury; however, the findings reported are controversial. Other major outpatient applications fall under the wound healing umbrella.

Having defined HBOT and outlined its specific applications in the practice of physiatry, the remainder of this article will systematically review the evidence for use of HBOT for chronic wound healing and limb salvage. The citations reviewed are evaluated according to strength of evidence for specific types of wounds treated and the level of success for limb salvage. Such a comprehensive review should assist those who teach and practice physiatry to understand this emerging subspecialty of HBOT.

METHODS

The author endeavored to systematically review and prioritize by level of evidence every citation on the Ovid Medline Databases (Wolters Kluwer Health) relevant to chronic wounds, limb salvage, and hyperbaric oxygenation. Citations with the key word "Hyperbaric Oxygenation" were identified (8794 entries). To this general search, the following limits were applied: Human studies and years 1978-2008 inclusive. The result was combined by Boolean AND with various key word combinations over 3 separate searches: Search A: wound healing and limb salvage; search B: flaps and grafts; and search C: osteomyelitis. (See Figure 1 for further elaboration of the search process and search terms).

For inclusion, citations must have described original human research with wound healing, tissue salvage, or limb

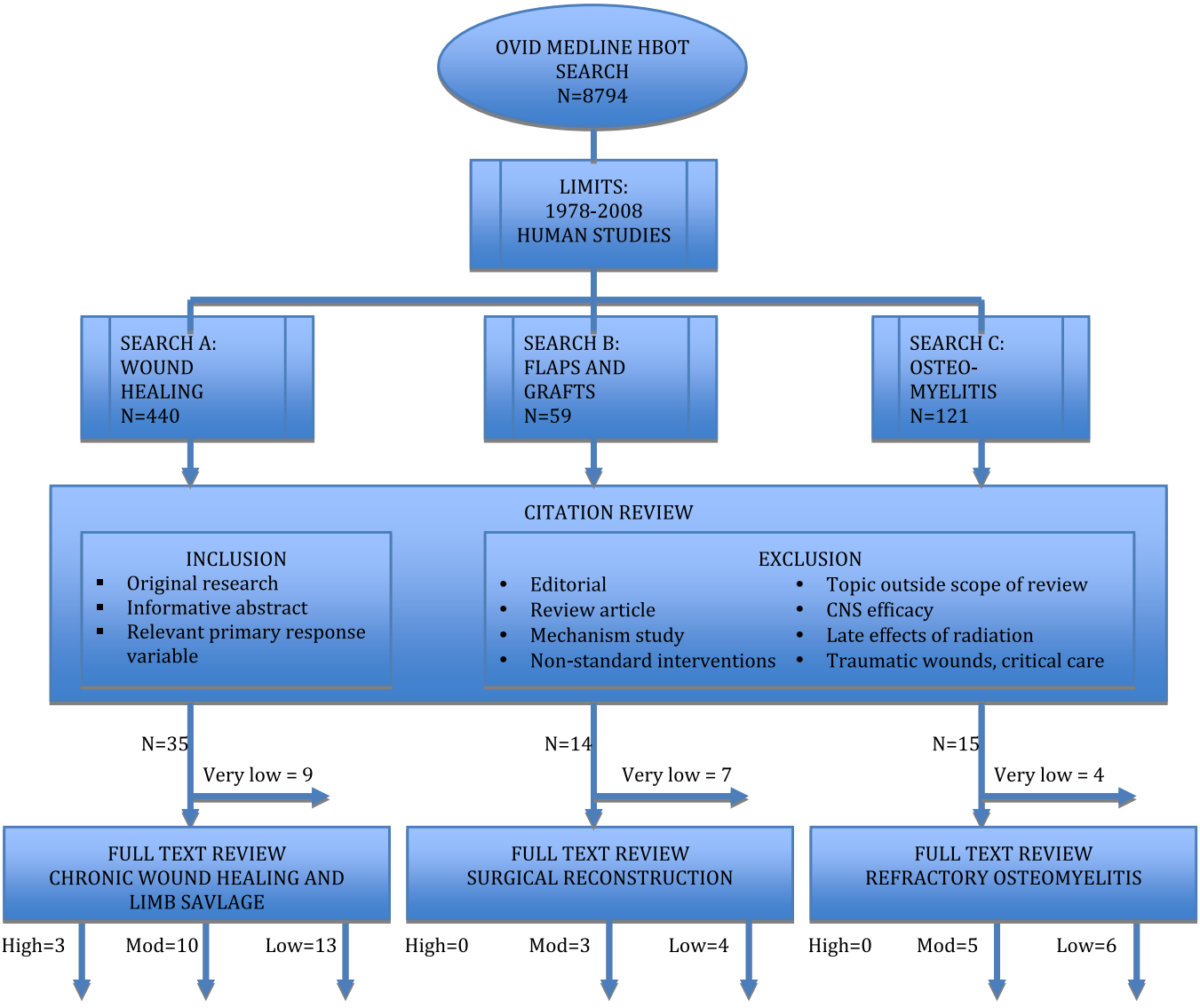

Figure 1. Flow chart of systematic review. Search A uses the following combination of key words relevant to chronic wound healing (suggested by a Cochrane review on the same subject [15]): "Wound healing"; "Wounds and injuries"; "Skin ulcer"; "Foot ulcer"; "Ulcer"; "Pressure ulcer"; "Varicose ulcer"; "Leg ulcer"; "Venous ulcer" (a text phrase); "Diabetic foot". Search B pertains to compromised flap or graft and utilized the following key words: "Surgical Flaps"; "Reconstructive Surgical Procedures"; "Compromised flap" (a text phrase). Search C combines HBOT with the key word "osteomyelitis".

salvage as the primary outcome variable. Excluded were articles that addressed: HBOT and central nervous system efficacy (reviewed elsewhere [13]); late effects of radiation; and acute wounds associated with multiple trauma and critical care, including necrotizing fasciitis and crush injury. Almost all citations had abstracts that provided substantive information on the following: study design; subcategory (eg, diabetic foot ulcer); primary outcome variable; and number of patients.

All 3 searches followed a similar process. For instance, Search A captured and displayed 440 citations in Ovid format. Inspection of these citations revealed 101 especially relevant citations that were downloaded and saved in an Excel spreadsheet. Once downloaded, a further filtering process excluded citations for the following reasons: duplicated an included citation (1); described a plan for a future study (1); were editorials or review articles (11); had irrelevant endpoints (9); focused on mechanism (2); employed non-standard interventions (3); were more relevant to searches on surgical reconstruction or osteomyelitis (12); discussed topic outside the scope of this review (23); or had no abstract (4). In the final analysis, Search A identified 35 citations pertaining HBOT, wound healing, and limb salvage.

Then, citations were assigned a preliminary strength of evidence rating according to criteria of the GRADE working group, published in 2004 in the British Medical Journal [14] (Table 2). GRADE strength of evidence criteria are suitable for research studies that do not necessarily reach the level of

Table 2. *Criteria for assigning grade of evidence: Results of the GRADE working group, published by the British Medical Journal (14)*

Strength of Evidence Ratings "Grade"	Decrease Grade if	Increase Grade if
• Randomized trial: high • Observational study (time series, case-control studies, cohort studies): low • Any other evidence (case series, case studies): very low	• Serious (-1) or very serious (-2) limitations to study quality • Important inconsistency (-1) • Some (-1) or major (-2) uncertainty about directness • Imprecise or sparse data (-1) • High probability of reporting bias (-1)	• Strong evidence of association: significant relative risk (2; <.05) from 2 or more observational studies, with no plausible confounders (+1) • Very strong evidence of association: significant relative risk (<.02, 5) based on direct evidence with no major threats to validity (+2) • Evidence of dose-response gradient (+1)

Study quality refers to detailed study methods and execution. Consistency refers to similarity of estimates across studies. Directness is the extent to which the patients, treatments, and outcomes are similar to those of interest. Sparse data lead to wide confidence intervals.

prospective randomized controlled trials (RCTs). This is appropriate, as most studies related to HBOT are not of a "high" level of evidence, yet have a degree of merit.

Applying GRADE criteria, studies of "high" strength of evidence refer to prospective RCTs with or without blinding, with case series warranting "low" strength of evidence [14]. A moderate level of evidence refers to those case series or cohort studies of a high quality that report strong or very strong strength of association that are consistent with other studies, or that demonstrate a dose-response gradient. Last, articles of very low strength of evidence describe retrospective uncontrolled trials, typically with fewer than 5 subjects (an arbitrary number assigned by the author).

A preliminary survey separated citations of very low level of evidence from the others (n = 9). The remainder (n = 26) underwent full text review, and a final determination of level of evidence. (One article in this group was not available in English full text and was nevertheless included because of its high apparent quality). Of the 35 citations within this category, 3 demonstrated high strength of evidence, 10 moderate, and 13 low.

The author completed a similar process for searches B and C.

As a quality measure and to ensure capture of relevant citations, those gleaned from Ovid Medline were informally compared with bibliographies of a relevant Cochrane review on HBOT and wound healing [15], identifying 1 additional citation relevant to Search A. Bibliographies of full-text articles reviewed were additionally scanned for relevant citations, and none identified.

In the Results section of this article, all articles with high or moderate level of evidence gleaned from this search are discussed and tabulated. Those with a low level of evidence are discussed only if the findings have special significance.

At the conclusion of the full text review, the author derived a final determination of level of evidence for each subcategory based on a synthesis of reviews of individual articles of that subcategory according to GRADE benchmarks [14]:

- High strength of evidence: further evidence very unlikely to change our impression of confidence of an effect.
- Moderate strength of evidence: Further evidence is likely to change our estimate of confidence of an effect and may change the estimate.
- Low strength of evidence: Further research is very likely to change our confidence in an effect and is likely to change the estimate.

RESULTS

This section includes full text reviews of original human research pertaining to the following 3 topics (and Ovid/Medline searches; Figure 1): chronic wound healing and limb salvage (search A); surgical reconstruction (search B); and refractory osteomyelitis (search C).

Chronic Wound Healing and Limb Salvage

After full citation analysis, Search A uncovered the following subcategories (number of citations): wounds (in general) (4), diabetic foot ulcers (13), hypoxic wounds (2), stasis wounds of the leg (1), and miscellaneous types (15). Miscellaneous types included ulcers from atrophy blanch, calciphylaxis, scleroderma, thalassemia, hydroxyurea, vasculitis, and pyoderma gangrenosum. Positive efficacy was reported for 33 citations, equivocal for 1, and negative efficacy for 1 (of low strength of evidence, discussed in the following section). All told, there were 4057 patients for whom data were reported in these 35 citations. Twenty-six articles reached a threshold level of quality and were reviewed in full text. These separated into the following subcategories: diabetic foot ulcers (DFU); arterial ulcers; leg ulcers; calciphylaxis; and refractory vasculitis. Two studies of equivocal or negative results are also discussed in detail.

Diabetic Foot Ulcers. The risk for limb loss is greater for more complex lesions that require surgical intervention and hence have a higher Wagner grade (Table 3). Thirteen articles on DFU revealed high (3), moderate (5), and low (5) strength of evidence. For these articles, the key outcome variables were healing and limb salvage (Table 4).

Table 3. *Definition of key wound types and grades (2)*

Leg ulcer	Most are venous stasis ulcers (85%) and are associated with edema. Edema is important in causation of most additional types of leg ulcers including congestive heart failure, lymphedema, or immobility. The standard of care is toe to knee compression. Leg ulcers typically occur in the presence of adequate arterial flow (71).
Arterial wound	There is not consensus on definition of an "arterial" wound. Proposals include wounds associated with: (1) Macrovessel disease (eg, arterial brachial index <.08; arterial occlusion by angiogram). (2) Microvessel disease (eg, periwound or distal segment TCOM <40 mm Hg; others have suggested TCOM <20 mm Hg (74)). (3) Positive surgical history, including history of minor or major dysvascular amputations, lower extremity angioplasty, or bypass. The standard of care for arterial wounds is revascularization.
Neuropathic wounds	These usually occur on the plantar foot and are associated with peripheral neuropathy (75). Most cases in the developed world are due to diabetics. However, a variety of toxic neuropathies (eg, alcoholic) and infections (Hansen disease) and congenital types (eg, hereditary motor sensory neuropathy type I) cause a similar presentation. Outpatient standard of care is off loading and debridement of callus.
Diabetic foot ulcer (DFU)	Diabetic wounds seen in the outpatient world fall into two basic categories: diabetic neuropathic and diabetic ischemic. Of diabetics whose wounds lead to amputation, 50% primarily have diabetic neuropathy, 20% primarily from poor circulation and 30% with mixed poor circulation and neuropathy (ie, mixed disease) (28).
Wagner grade	This scale provides a framework for surgical decision making for diabetic foot ulcers (76,77). There are 5 categories: I) superficial ulcer; II) deep ulcer to tendon, capsule, or bone; III) deep ulcer with abscess, osteomyelitis, or septic arthritis; IV) gangrene of toe, toes, forefoot, or heel; V) generalized gangrene, entire foot. Patients with Wagner I and II wounds are usually treated as outpatients; those with Wagner III, VI, and V wounds present for hospital admission for surgical debridement, parenteral antibiotics, revascularization, or amputation.
Transcutaneous oximetry (TCOM)	"Blood gas" through the skin, measured by noninvasive Clarke electrode placed on the skin (72). Room air periwound TCOM 40 mm Hg is normal (good prognosis for healing) and TCOM <20 mm Hg has guarded prognosis for healing (73). Definition of oxygen challenge is breathing 100% by face mask (normobaric oxygen). Oxygen challenge is alternately defined as breathing 100% Oxygen at 2-2.4 atmospheres absolute pressure (ATA) within a hyperbaric oxygen chamber. Either method of oxygen challenge increases TCOM around tissue at risk, and has been advocated as prognostic indicator of successful hyperbaric oxygen therapy (21). Normobaric O_2 = 760 mm Hg; hyperbaric O_2 at 2.4 ATA = 1824 mm Hg.

Faglia [16] conducted a prospective RCT without blinding: 70 consecutively hospitalized Wagner II-IV patients were considered, with 68 actually enrolled. After randomization (random number table), 35 underwent HBOT and 33 did not. Most patients had significant arterial disease, distal ischemia, and peripheral neuropathy. Patients received standard local wound care, including off-weighting devices and careful diabetes control [17]. A surgeon unaware of treatment decided whether or not to perform an amputation.

There was a significantly lower major amputation rate in the HBOT group [16]: 3 subjects (8.6%) had a major amputation compared with 11 (31%) in the control group (P = .0016). For Wagner IV subjects, 2 (9%) had major amputation in the HBOT group and 11 (55%) in the non-HBOT group (P = .002). Consistently, skin microcirculation transcutaneous oxygen measurement (TCOM) for the HBOT cohort (discharge vs admission) increased 14 ± 11 mm Hg, but increased only slightly in the non-HBOT group 5 ± 5 mm Hg (P = .004). As an RCT, this study provides high strength of evidence that HBOT is an effective adjunct to surgical management in treating "surgical" diabetic foot ulcers, thus reducing the risk of amputation. Note that patients in this study were hospitalized for an average of 46 days, a longer period than is usual in the United States for this diagnosis.

The previous RCT was conducted between 1993 and 1995. Before this study, Faglia [17] and colleagues had noted a progressive decrease in amputation rate over the previous 15 years: 1979-1981, 40.5%; 1986-1989, 33.3%; and 1990-1993, 23.5%. The authors attributed this improvement in amputation rate to the implementation of an interdisciplinary model of diabetic wound management.

For this last period of 1990-1993, HBOT was employed on about half of 115 patients. They were assigned nonrandomly to the non-HBOT group either because of their refusal or by their preference. The HBOT and non-HBOT cohorts were statistically equivalent in terms of metabolic, neuropathic, and vascular parameters, but the HBOT group was older: 61.4 ± 9.7 vs 65.1 ± 9.8 years (P < .05), respectively. All were admitted for Wagner Grade II-IV (60% Wagner IV). Most had significant arterial disease and sensorimotor neuropathy. HBOT was effective: in the HBOT group, major amputations were performed on 7 (12.9%) compared with 20 (32.1%) in the non-HBOT group (P = .012). Because this is a well-described cohort study with a strong likelihood of benefit consistent with other observational studies, this Faglia citation warrants a moderate level of evidence.

Abidia [18] conducted a prospective, double-blind RCT of 16 patients with DFU that were not infected but had reached the fascia, tendon, or joint capsule (Wagner II , n = 15; Wagner I, n = 1). Data were analyzed on an "intent to treat" basis. These wounds had been present for 6-9 months and ranged from 1 to 10 cm^2 in area. These patients had mild

Table 4. *Efficacy of hyperbaric oxygen therapy (HBOT) in treatment of diabetic foot ulcers (DFU)*

Study (Year)	n	Design	Evidence	Setting	Patients	Vascular Status, *Oxygen Challenge (TCOM)*
Faglia (1996) (16)	68	Randomized, controlled (unblinded) HBOT = 35; control = 33	High	Milan, Italy, University Hospital	Age = 63 ± 9 48M, 20F HA1C = 8.9 (admit) HA1C = 6.9 (D/C)	1) ABI average 0.64/0.65 (HBOT vs control) 2) revascularization procedures: 13/13) 3) *Ambient foot dorsum TCOM 23/21*
Abidia (2003) (18)	18	Randomized, controlled, blinded. HBOT = 9; control = 9	High	University Hospital, UK	Age = 71 ± 9 9M, 9F HA1C <8.5	1) Arterial disease present: ABI <.8, 3 minor and 2 major amputations. *Ambient TCOM >40.*
Kessler (2003) (19)	27	Randomized, controlled HBOT = 14; control = 13	High	University Hospital, Strasbourg, France	Age = 64 ± 10 19M, 8F HA1C = 8.8	HBOT group: *Ambient peri-wound TCOM 21 ± 12,* *HBO TCOM 454.2 ± 128.1 mm Hg (P < .001).*
Faglia (1998) (17)	115	Retrospective cohort HBOT = 51 non-HBOT = 64	Moderate	Milan, Italy, University Hospital	Age = 63 ± 9 81M, 34F HA1C = 8.8 (admit) HA1C = 7.1 (D/C)	1) ABI average 0.64 ± 0.25 2) *Ambient foot dorsum TCOM 28 ± 13*
Fife (2002) (20)	641	Retrospective case series	Moderate	5 HBOT facilities, Texas and California	Average age = 64	*HBO TCOM 0-800 mm Hg.* *HBO TCOM 200-800 mm Hg positive response.* *HBO TCOM <100, negative response.*
Doctor (1990) (23)	30	Prospective, controlled, randomized HBOT = 15 control = 15	Moderate	University Hospital, Mumbai, India	Age = 57 (range, 40-70) HAiC NR	Absent pedal pulses: 18%
Kalani (2002) (24)	38	Prospective cohort HBOT = 17; non-HBOT = 21	Moderate	Karolinskia Hospital, Sweden	Age = 60 ± 13 HA1C = 7	*Ambient TCOM = 25 mm Hg* *HBOT group:* *Normobaric TCOM = 198 ± 135 mm Hg* *Non-HBOT group:* *Normobaric TCOM = 185 ± 88 mm Hg*
Zamboni (1997) (25)	10	Prospective cohort	Moderate	US plastic surgery department	Age = 60 ± 3.5 8M, 2F HA1C NR	*Ambient TCOM:* *HBOT = 12, non-HBOT = 35 mm Hg* *Normobaric TCOM:* *HBOT = 71 mm Hg* *non-HBOT = 80 mm Hg* *HBO TCOM:* *HBOT = 563 mm Hg*
Baroni (1987) (26)	28	Prospective cohort	Low	Milan, Italy, University Hospital	Age 17M, 11F HA1C = 8.8 (admit) HA1C = 6.9 (D/C)	NR
Oriani (1990) (53)	80	Retrospective cohort	Low	Milan, Italy, University Hospital	HBOT	NR

Abbreviations: n, total number of patients; M = male; F = female; "Evidence", level of evidence by GRADE criteria [14]; AE = adverse events; HA1C = hemoglobin A1C; ATA = atmospheres absolute; NR = not recorded.

Wagner score (I through V) and transcutaneous oximetry (TCOM) are defined in Table 3.

peripheral arterial disease (arterial brachial index <0.8) and were not candidates for revascularization. All patients underwent a comprehensive program of wound care. Six weeks after the last HBOT session, 5 (62%) of ulcers healed for the HBOT group, and the median area reduction was 100% with the control group 52% ($P < .026$). At 1 year, the number healed for the HBOT group was 5 (62%); the control group was 0% ($P = .027$). There was no difference in major amputations between groups (n = 1 in each group), after a 1-year observation. This study rates a high strength of evidence.

Kesser [19] conducted a prospective RCT of 27 patients with Wagner I-III diabetic foot ulcers. Wounds averaged 2.5

Neuropathy	Wagner Score	Dose	Efficacy: Amputation Efficacy: Healing	*P* Value	AE
97%	II-IV	2.2-2.4 ATA for 90 min, 38 ± 8 sessions	Amputation: HBOT: (9%); control: 11 (33%)	.002	NR
Present	I-II	2.4 ATA, 90 min, 30 sessions. Control hyperbaric air	Healing 6 weeks post-HBOT: 1) Area reduction: HBOT group = 100%; control group = 54% complete healing at 1 year post-HBOT: 2) HBOT group = 5/8 healed; control group = 0/5 healed	1) .026 2) .027	NR
NR	I-III	2.5 ATA, 90 min, 20 sessions (2/day)	Healing 1) Day 15: 41% vs 27% area decrease (HBOT vs control) 2) Day 30: 48% vs 41% area decrease (NS)	<.01	Ear barotrauma (n = 1)
82%	II-IV	2.5 ATA, 90 min, 33 ± 11 sessions	Amputation: HBOT: 7 (14%); non-HBOT 20 (31%)	.012	NR
NR	II-V	2.0 or 2.4 ATA, average 27 treatments.	Healing: Wagner II HBOT "helped" 84%; Wagner III helped 77 %; Wagner IV helped 64%; Wagner V helped 28%. ("helped" = partial granulation to complete healing)	<.001	NR
18%	III-IV	3.0 ATA, 45 min, 4 sessions over 2 weeks	Amputation: HBOT: 2 (13%); Control: 7 (47%)	<.05	NR
NR	I-II	2.5 ATA 90 min 40-60 sessions	Amputation: HBOT: 2 (12%); non-HBOT 7 (33%) Healing (closure): HBOT 13 (76%); non-HBOT 10 (48%)	NS	Cataract (n = 1); ear pain resolved with decongestant (n = 1)
NR	III-IV	2.0 ATA 120 minutes, 30 sessions.	Healing (area reduction). At the completion of each of the 7-wk treatment periods, a significantly greater reduction in wound surface area was noted in the HBO_2 vs the control group	<.05	NR
NR	II-IV	2.5-2.8 ATA. 90 min 34 ± 21 sessions	Amputation HBOT: 2 (11%); non-HBOT 4 (40%) Healing (closure): HBOT 16 (89%); non-HBOT 1 (10%)	<.001	NR
95%	IV	2.5-2.8 ATA 72 ± 29 sessions	Amputation HBOT: 3 (5%): non-HBOT 6 (33%)	<.001	NR

cm^2 for both groups. At the end of 2 weeks of twice-daily HBOT, HBOT wounds were significantly smaller than the controls. However, within an additional 2 weeks, control wounds "caught up" in terms of area reduction. At 4 weeks, the final recorded point of observation, 2 wounds in the HBOT group had healed and 0 in the control group. It should be noted that the observation period of 4 weeks is short relative to the 12-16 weeks expected for healing to occur. However, the good initial response of the HBOT group was consistent with excellent response to oxygen challenge on initial HBOT evaluation (Table 4). In design and execution as an RCT, this study rates a high strength of evidence rating.

Table 5. *Efficacy of hyperbaric oxygen therapy (HBOT) in treatment of wounds other than diabetic foot ulcers*

Category	Study (Year)	n	Design	Evidence	Setting	Patient (mean)
Arterial ulcers	Grolman (2001) (29)	36	Retrospective cohort	Moderate	Baltimore Hospital	Age = 69 ± 2 21M, 15F
Stasis ulcers	Hammarlund (1994) (30)	16	Randomized, controlled, blinded. HBOT = 8 non-HBOT = 8	High	Sweden	Age = 67 9M, 7F
Calciphylaxis	Basile (2002) (34)	11	Case series	Moderate	Italy	Age = 56 ± 7 5M, 6F
Intractable vasculitic ulcers	Efrati (2007) (36)	35	Case series	Moderate	Israel	Age 53 ± 18 8M, 27F
Reconstruction (without graft or flap)	Reedy (1994) (41)	30	Prospective cohort, (n = 8); historical control	Moderate	Temple, TX, University Hospital	Age 61 ± 20, Historical control: Age = 71
Compromised graft or flap	Mathieu (1993) (44)	15	Case series	Low	Lille France, University Hospital	Age = 42 12M, 13F

For abbreviations see Table 4 footnote.

Fife [20,21] and colleagues conducted a multicenter retrospective case series that included 641 patients. (They started with a data set of 1006 patients, excluding incomplete records. Patients with renal failure and those treated with autologous platelet growth factor were also excluded. These groups had different healing rates than the core data set and were excluded in order not to confound it.) For these 641 patients comprising the core data set, a "positive healing response" was defined as partial granulation, complete granulation, or healing. Healing outcomes correlated significantly with 3 patient characteristics: Wagner grade, TCOM response to oxygen challenge, and smoking history. First, Wagner Grade predicted positive healing response with a very high significance ($P < .001$). Second, with respect to oxygen challenge, outcomes correlated significantly with in-chamber TCOM. Patients with an in-chamber TCOM <100 mm Hg had a 14% likelihood of benefit, whereas those with an in-chamber TCOM>200 mm Hg had an 84% chance of benefit. The accuracy of these predictors was 75% [20]. Third, with respect to smoking history, patients with a greater than 40 pack per year history had a significantly less favorable outcome than patients with less than 40 pack per year history, or those who never smoked [22]. Of those wounds that were partially granulated or better at the end of HBOT, 87% went on to heal. In this same group, only 3.4% went on to amputation. Because of the several plausible dose-response gradients extracted from this large data set, this study rates a moderate strength of evidence.

Doctor [23], in a prospective RCT trial set in Mumbai, India, reported significantly fewer amputations in an HBOT-treated group. From the descriptions, patients primarily meet the criteria of Wagner III or IV (according to wound descriptions; Wagner grade is not explicitly stated). Patients enrolled (n = 30) had diabetes with foot ulcers. Wounds were very chronic, averaging at least 10 years in each group. Distal pulses were present in 82%; neuropathy was present in 18%. Patients underwent inpatient surgical debridement. Surgeons (not stated if blinded to HBOT group) amputated limbs for "spreading" infection, out-of-control diabetes, or gangrene. There were 7 major amputations in the control group, and 2 in the HBOT group ($P < .05$). Although an RCT, concerns with this study include unusual HBOT dosing schedule and incomplete disclosure of study details (including nondisclosure of n per group, subject attrition, and randomization details). These quality concerns lower strength of evidence to moderate.

Kalani [24] conducted a prospective cohort study, initiated as an RCT. However, the HBOT chamber was not available after the 14th subject enrolled. Overall, 38 patients enrolled with DFU of Wagner I and II present for more than 2 months. Patients had TCOM <40 mm Hg, which increased to 100 mm Hg on inhalation of 100% O_2. They were not

Vascular status, *Oxygen challenge (TCOM)*	Dose	Efficacy: Healing	*P* Value	AE
1) *ΔTCOM>10 mm Hg: Ambient TCOM 16 ± 2.5 mm Hg. Normobaric O_2 TCOM = 76 mm Hg. (P < .05).* 2) *ΔTCOM<10 mm Hg: Ambient TCOM 5.8 ± 1.9 mm Hg. Normobaric O_2 TCOM = 6.5 ± 2 mm Hg*	2.4-2.5 ATA, 90 min, average 29 sessions	Healing ΔTCOM>10 mm Hg: 19 (70%) of wounds healed ΔTCOM <10 mm Hg: 1 (11%) of wounds healed	<.01	AE rate 28%. Anxiety n = 1, myopia n = 1; middle ear barotrauma n = 5 myringotomy n = 4; CHF n = 2; seizure n = 1
1) subjects nonarterial, not diabetic, smokers excluded 2) wounds open 1 year. 3) compression provided	2.5 ATA, 90 min	Healing 1) 4 weeks: % of initial area ↓78% vs 96% (HBOT vs control) 2) 6 weeks: % of initial area ↓64% vs 97%	1) < 0.5 2) <.001	NR
NR	2.5 ATA, 90 min, 40 (20-108) sessions	Healing: 8 (73%) Amputation: 1 (9%) (dropouts = 2)	NA	None observed
1) *Ambient TCOM: 23 ± 18 mm Hg* 2) *Normobaric TCOM: 104 ± 89 mm Hg* 3) *HBO TCOM: 443 ± 223 mm Hg*	2.0 ATA, 90 min, 20 sessions	Healing: 28 patients (80%) healed, 4 (11.4%) partial healing and 3 (8.6%) did not improve	NA	None observed
NR	2.0 ATA, 90-120 min, average 9 daily sessions	Healing: HBOT: 1 (16%) had breakdown. Non-HBOT: 6 (77%) had breakdown	0.35	Anxiety n = 1. Ear pain no barotrauma n = 1
Successful flaps: *HBO TCOM: 378 ± 385 mm Hg* *Failed flaps:* *HBO TCOM: 12 ± 12 mm Hg*	2.5 ATA, 1 week	HBO TCOM>50 mm Hg 7 (100%) successful flaps HBO TCOM <50 mm Hg 0 (0%) successful flaps = 0	<.01	None observed

candidates for vascular surgery. Patients were followed by a comprehensive wound program. HBOT appeared effective, even after follow-up of 3 years: 13 (76%) in the HBOT group had healed vs 10 (48%) in the conventional group. (This is despite the observation that at enrollment, the HBOT group wound area averaged 10.7 cm^2 as opposed to the non-HBOT group = 4.49 cm^2; $P = .03$). HBOT showed a positive trend toward efficacy: after 3 years of observation, 2 patients had major amputations (12%) for the HBOT group; this contrasted to 7 (33%) for the non-HBOT group (not significant). For both groups combined, the rate of limb salvage was positively related to the ability to respond to oxygen challenge. The periwound TCOM increase to normobaric O_2 was almost twice as high for the limb salvage group than the limb loss group: 234 ± 110 vs 142 ± 65 mm Hg (P = .03). This study provides full disclosure of relevant information. Results are not statistically significant but there is strong strength of association. Amputation percentages are quite similar to a previous RCT and other observational studies, serving to reproduce their findings [16]. The study was originally set up as an RCT. For these reasons, this study rates a moderate strength of evidence.

Zamboni [25] conducted a prospective cohort study of patients with DFU comparing a group (5 patients) receiving HBOT to a conventional group (5 patients) that refused or was not appropriate for HBOT. The majority of patients in each group had osteomyelitis (Wagner III). An additional confounder was ischemia, with the HBOT group more ischemic on average than the non-HBOT group (12 mm Hg vs 35 mm Hg, respectively). Both cohorts had good response to oxygen challenge. Consistently, HBOT was effective with wounds 40%-60% smaller in the HBOT group as compared with the non-HBOT group for each of the 7 weeks after discontinuation of HBOT (for each week, $P < .05$). After HBOT, patients were followed for an additional 4-6 months. During this time, 4 of 5 patients in the HBOT group spontaneously healed their wounds; the remaining wound had a successful flap procedure. In contrast, for the non-HBOT group all wounds remained open and none healed ($P = .057$). Although there are minor quality concerns concerning lack of disclosure of osteomyelitis treatment, there is also strong evidence of association of HBOT with healing, consistent with a positive oxygen dose-response gradient. Therefore, on balance, this study rates a moderate level of evidence.

Baroni [26] conducted a prospective cohort study comparing patients with diabetes and gangrenous foot ulcers or "perforating ulcers" (interpreted to be Wagner II-IV). Twenty-eight patients were considered for HBOT: 10 refused or were not appropriate and became the "control" cohort. HBOT was effective: 16 (89%) of subjects in the HBOT group healed their wounds. In contrast, for the non-HBOT group, only 1 healed ($P < .001$). Additionally, 4 wounds worsened,

Table 6. *Efficacy of hyperbaric oxygen therapy (HBOT) in treatment of refractory osteomyelitis*

Study (Year)	n	Design	Evidence	Setting	Age (Mean) Sex	Location *(Ceiby Mader)*	Patient Characteristics Pre-HBOT *Post-HBOT*
Davis (1986) (47)	38	Case series with time comparison	Moderate	University Hospital, Texas	Age = 40 24M, 14F	Tibia, fibula *CM: NR*	1) OM present average 8.9 years (range, 6 months to 50 years). 2) All had draining wounds at onset. 3) *Follow-up 34 months (range, 24-59 months)*
Morrey (1979) (48)	40	Case series with time comparison	Moderate	Brooks AFB	Age = 38 31M, 9F	42 bones, lower extremity (femur or below) (38) *CM: NR*	1) OM duration 30 months (6 months-23 years) 2) 3.1 previous surgeries (range. 1-7) for 33 patients, 7 reporting "numerous". 3) *Follow-up 23 months (12-53 months)*
Chen (2004) (49)	13	Case series with time comparison	Moderate	Taiwan	Age = 40 12M, 1F	Femur *CM: III or IV*	2) *Follow-up period, 22 months (12-42)*
Chen (1998) (50)	15	Case series with time comparison	Moderate	Taiwan	Age = 41 12M, 3F	Tibia *CM: III or IV*	1) OM present 19.4 months (range, 6-84 months) 2) *Follow up average 17 months*
Esterhai (1987) (51)	28	Prospective Cohort (HBOT = 14; non-HBOT = 14)	Moderate	Philadelphia, PA University Hospital	Age = 40 19M, 9F	Tibia (18) femur (6) calcaneus (3). *CM recorded, not disclosed*	1) OM present 70 months (range, 8-628 months). 2) Included patients with pain, sepsis, bone destruction, foul drainage. 3) *Follow- up was on average 41 months. (range, 11 to 71 months)*

For abbreviations see Table 4 footnote.

Also, note the Cierny-Mader (CM) system of staging osteomyelitis [68]. For this system, there are 4 anatomic classifications: type I through IV. For type I or medullary osteomyelitis, the primary lesion is within the medullary canal or marrow region. For type II or superficial osteomyelitis, the soft-tissue envelope is compromised and compromises cortical bone. For type III or localized osteomyelitis, there is full thickness cortical sequestration that has both superficial and medullary osteomyelitis components. For type IV or diffuse osteomyelitis, there is through-and-through disease of the hard and soft tissue.

eventually leading to major amputations, in contrast to 2 major amputations in the HBOT group. Despite the positive effect, wounds healed faster than would be expected if there were an arterial component, and there was incomplete disclosure of arterial disease [27]. Additionally, investigators relegated patients that refused HBOT and hence potentially nonadherent to other treatments to a control group, potentially biasing the outcome in favor of HBOT. Because of these quality concerns, this cohort study rates low strength of evidence.

Oriani (1990) conducted a cohort study of limb salvage of 62 patients treated with HBOT, relative to a non-HBOT cohort of 18 subjects that refused or were not appropriate for HBOT. Subjects had gangrene (ie, Wagner IV). For the HBOT group, there were 3 amputations (4%). In contrast, for the non-HBOT group, there were 6 amputations (33%) ($P < .0001$). This was a significant reduction in risk of amputation (OR = 0.102, 95% CI 0.22-0.49). Despite strong strength of association of HBOT with limb salvage, this study might have overestimated risk reduction: there are concerns about the comparability of the groups and incomplete disclosure of data. Therefore, this study was rated as low strength of evidence.

Arterial Ulcers. Patients with arterial ulcers have some combination of macrovessel and microvessel disease, ischemia or history of revascularization (Table 3). This systematic review identified only 1 article that specifically addresses the effectiveness of HBOT to treat patients with arterial ulcers. (Note that there is significant overlap between diabetes and peripheral arterial disease. In 1 large series, about half of patients with DFU-related amputation have significant peripheral arterial disease [28]).

Grolman [29] conducted a retrospective case series including 36 consecutive patents seen at their wound center with apparent arterial disease and ischemic lower extremity ulcers (ie, periwound TCOM <20 mm Hg on room air). Sixty-seven percent of patients had diabetes, and 33% did not. Twenty-five percent of these patients had end-stage renal disease (58% had significant coronary artery disease). There were 28 leg and foot ulcers, 18 digit amputation sites, and 1 transfemoral and 1 transmetatarsal amputation site. Twenty had previous bypass grafts. At the time of inclusion into this study, none were bypass candidates. All patients received HBOT as detailed in Table 5.

After receiving treatment, data were analyzed retrospectively. Post hoc, healing improved significantly for the group

Dose	Surgical Management	Efficacy	"Cure" HBOT	AE
2.4 ATA for 90 min (mean 45 sessions for successful treatment)	Debridement (foreign bodies, sinus tracts, and sclerotic and dead bone). Reconstruction: secondary intention (20), autologous bone grafting (14), rotational muscle flaps (4)	"Cure" 34 of 38 (89%) *Recurrences: 0*	89%	Myringotomy n = 3, visual acuity changes n = 2
2.4 ATA for 90 min	Debridement 64% sequestrectomy 30% and saucerization (12%) Reconstruction: Autogenous bone grafting (7, 18%) soft-tissue reconstruction (7, 18%).	"Cure" = 34 (85%); *Recurrences = 6 (15%), 4 resolved with surgery + HBOT*	85%	None reported
2.5 ATA, 2 h	Surgical debridement. Reconstruction: Cancellous bone grafting (11). Also, for 11 patients with type IV OM: plating (2), nailing (2), external fixation (7).	"Cure" = 12 (92)% *Recurrence = 0*	92%	None reported
2.5 ATA, 2 hours, average 26 sessions (6-43)	Patients received surgery, not further described	"Cure" = 13 (87%) *Recurrence = 0*	87%	Anxiety n = 1
2.0 ATA, 2-h duration, ("at least 20" compressions)	Multiple debridements on 22 of 28 patients; 2 debridements in 15, 3 in 3 and 4 in 4. Bone grafting was required in 5 patients	"Cure" = 24 healed (86%) 11 (78%) HBOT group 13 (93%) non-HBOT group. *Recurrences (not retreated)* *2 (14%) HBOT group* *1 (7%) non-HBOT* *Not recorded = 1*	57%	None reported

with evidence of better oxygenation of tissue at risk with administration of 100% oxygen at sea level. Where peri-wound ΔTCOM>10 mm Hg, 19 (70%) of wounds healed. In contrast, where ΔTCOM<10 mm Hg ($P < .01$), only 1 wound (11%) healed. This is a cohort study without apparent deficiencies, buttressed by a positive oxygen dose-response gradient. Therefore, the level of evidence is moderate.

Leg Ulcers (Stasis Ulcers). Hammarlund [30] conducted a prospective, double-blind RCT. Patients with nonischemic, nondiabetic leg ulcers (assumed to be stasis ulcers) that were open for longer than 1 year were included. There was significantly greater wound area reduction for the HBOT group at week 4 (74% of baseline HBOT vs 96% for control; $P < .05$) and week 6 (64% vs 98%; $P < .001$). By week 18 in the HBOT group, 2 wounds were healed, and none in the control group. This study rates a high level of evidence (even noting that compression dressings are not standardized). Effect of HBOT is clinically significant: well-perfused leg wounds open for longer than 1 year have a guarded prognosis, even with optimum conservative care (Table 5).

Calciphylaxis. Calciphylaxis presents on the skin as aggressive expanding gangrene, 75% of the time in the setting of end stage renal disease. Elevated calcium phosphate product is specific for the condition [31]. Elevated parathyroid hormone has been implicated in pathogenesis. By an unclear mechanism, calcium is deposited in the tunica media of peripheral arteries [32]. There is no standard care; treatment usually involves increasing frequency of dialysis, use of phosphate binders and when parathyroid hormone is high, parathyroidectomy [33]. However, parathyroidectomy does not improve a dismal 46% 1-year survival rate in 1 recent case review of 64 patients from the Mayo Clinic (relative to 88% 1-year survival for dialysis controls, $P < .001$). There was no difference in survival for patients with distal vs proximal lesions. One-year survival improved to 62% for patients who had surgical debridement of cutaneous gangrene [31].

Basile [34] conducted a retrospective case series of patients with calciphylaxis who underwent HBOT. They included 11 patients with end-stage renal disease (dialysis was 163 $\pm$ 84 months) treated for calciphylaxis in the period between 1996 and 2002. All had distal lesions. Diagnosis of calciphylaxis was by biopsy (4) and clinical grounds (7). Three had hyperparathyroidism, with 2 having had previous parathyroidectomies. In addition to local wound care, including aggressive surgical debridement, patients received

HBOT. Two patients dropped out before they completed 10 sessions (for reasons unrelated to HBOT; 1 died). Notably, 8 of the remaining 9 completely healed, although the ninth eventually required amputation. This patient had biopsy-proven disease, along with 3 others that healed, yielding an unexpected result of 75% healing for those with a tissue diagnosis. Further, all 9 patients survived to 1-year follow up, with no recurrence of skin lesions. The results of this study are remarkable in light of the usually poor prognosis for both limb preservation and survival [31,35]. Because of the strong association of HBOT healing, this study rates a moderate strength of evidence (Table 5).

Intractable Vasculitic Ulcers. Efrati [36] reports a case series on leg ulcers from histologically proven vasculitis, without improvement despite at least 3 months of immunosuppressive medication. The primary outcome variable is complete healing and partial healing (ie, granulation is over a tendon or deeper structures and there is resolution of infection). At the start of HBOT, about 70% of the wounds extended to tendon or joint capsule, with duration of 12 ± 27 months. HBOT was effective in resolving these lesions: after the last session, 28 patients (80%) healed completely, 4 (11.4%) healed partially, and 3 (8.6%) did not heal at all. Patients decreased their prednisone dose by a mean of 60% ($P = .002$). Note that there is a high strength of association. Assuming an optimistic healing rate of 40% for vasculitic wounds that are by definition intractable, HBOT speculatively improves chance of healing by a factor of 2. This case series rates a moderate strength of evidence rating.

Wound Care: Reports of Negative Effectiveness. There are 2 studies of equivocal or negative efficacy. The equivocal study was a retrospective case series on partial foot amputation (35 patients studied), of which 70% healed and 30% did not [37]. The group which failed to heal had lower TCOM than the group that did; however, the number of HBOT sessions was equivalent. No conclusions about effectiveness could be drawn from this study. Another study reported negative results [38]. This is a case series of 54 patients with diabetic, arterial, and postsurgical ulcers. Of these, 43 (80%) demonstrated no improvement and no patients completely healed. (There is no comparison cohort). Besides negative efficacy, 40 of 63 patients had adverse events: 17 patients had myringotomy tubes placed for barotrauma, 1 patient had an oxygen seizure, and 4 had cardiac arrhythmias in-chamber, with 1 resulting in death. The high rate of serious adverse events is grossly inconsistent with large descriptive studies [39] and suggests deficiencies in training and expertise. (In fact, this facility was closed down before the article was published). Certainly related to the lack of efficacy, there is no mention in this article about a wound care program, which is a prerequisite for adjunctive HBOT. As case series with quality concerns, both of these studies rate with low or very low level of evidence.

Surgical Reconstruction

In addition to the above subcategories of wounds, this review will also include those citations reporting effectiveness of HBOT as an adjunct to surgical care for wounds or soft-tissue defects: surgical reconstruction of wounds (without flaps or grafts) and compromised flaps or grafts.

Surgical Reconstruction (Without Flaps or Grafts). Results of the first Ovid/Medline citation search (search A) found 2 articles that fit this subcategory both of moderate level of evidence: (1) postoperative breakdown of the surgical site after radical vulvectomy and (2) a cohort study on microsurgical nerve reconstruction. For the latter of these, Zhao et al [40] studied success of microsurgical reconstruction of peripheral nerve with or without adjunctive HBOT. In addition to reconstruction, 54 patients (65 nerves) underwent HBOT and 60 did not. Results supported HBOT: "excellent" and "good" results were obtained in 89.2% of reconstructions with HBOT, and 73.2% for the non-HBOT group ($P < .05$). Full text was not available in English.

Reedy [41] reported HBOT reduced wound dehiscence after radical vulvectomy for patients with squamous or Bartholin gland cancer. The surgeons compared results with HBOT with results observed before HBOT was available. HBOT was effective for the cohort undergoing radical vulvectomy with lymph node dissection; for the HBOT group, 1 (17%) had breakdown and infection. For the group without HBOT, 7 (78%) had breakdown ($P < .01$) and 4 had infection. As an observational cohort study with strong association of HBOT to healing, this study achieves a moderate level of evidence.

Compromised Flap or Graft. Both search A and B identified citations pertaining to compromised flaps or grafts. These studies propose HBOT for "rescue" of a flap or graft that exhibits edema, stasis, or cyanosis. Additionally, HBOT is used for prophylaxis when it is anticipated that the blood supply might not be adequate to insure graft viability [42]. There are 4 case series (cumulatively n = 63 patients), 1 rated moderate and 3 low strength of evidence. There are also 6 case studies of very low strength of evidence. All report positive results.

Saber [43] conducted a case series with time comparison (ie, time series) of 35 patients with intractable, chronic, large ulcers that were of venous, arterial, or diabetic type: mean ulcer duration was 2.8 years, size 73 cm^2. All received 10 daily preoperative HBOT treatments at 2.0 ATA and 120 min, deep excision and split-thickness skin grafting and 10 postoperative HBOT treatments. At 18 months follow-up, 18 (50%) of skin grafts showed complete take, 15 (42%) partial take, and 3 (8.3%) no take. Failure was apparent 3 weeks postoperatively. It is suggested that HBOT improved wound bed vascular status. "Pretreatment TCOM" was 26 mm Hg, and "posttreatment" TCOM, 66 mm Hg. The particulars of TCOM measurement are unclear, and conservative wound care is not delineated. Still, this is an excellent result for a challenging population with an otherwise mediocre healing prognosis, and as such rates a moderate level of evidence.

Mathieu [44] conducted a prospective case series of 15 patients with compromised pedicle musculocutaneous flaps. In an effort to prognosticate success, TCOM electrodes were placed on the flap during the first treatment. Patients then received HBOT for 10 days. Success, defined as 90% "take," occurred for 7 flaps, with failure for 8. In response to hyperbaric oxygen challenge, all flaps healed on TCOM>50 mm Hg, and failed on TCOM <50 mm Hg ($P < .01$). There is no specific mention of HBOT parameters or number of treatments, although the article implies they received HBOT over 10 days. Because of lack of disclosure, the level of evidence is deemed low.

Composite grafts contain multiple structures, such as cartilage, subcutaneous fat, and skin [42]. Gonnering [45] reports on a case series with 6 subjects who underwent periorbital reconstructions using composite grafts. These grafts were larger than normal composite grafts (eg, 2 by 0.7 cm); all survived. Friedman [46] used HBOT for 6 patients undergoing nasal reconstruction with composite grafts for either cleft nasal defects or cancer reconstruction. All grafts showed complete take except for 1 that did not get HBOT; the procedure was repeated with use of HBOT with success. Both studies are small case series and hence are of low level of evidence.

Refractory Osteomyelitis

The third Ovid/Medline search (search C) identified 121 citations (hyperbaric oxygenation AND osteomyelitis) examined by the author. Of these, 15 citations listed original observational studies; 14 reported positive findings, and 1 study, equivocal findings. Included citations defined healing as an endpoint: resolution of recalcitrant osteomyelitis from a combination of surgical care, antibiotics, and adjunctive hyperbaric oxygen. Including data reported in all 15 abstracts, the median remission rate (defined most consistently as resolution of drainage) was 89% of patients (range, 37-100%) for follow-up as long as 63 months, for 309 patients reported over 15 studies. Within this distribution, the "cure" rate tended to be lower for mandibular osteomyelitis (4 articles, median 66%) than other sites (femur, tibia, pelvis, humerus; median "cure rate" 89.5%).

On full review, 5 studies rated "moderate" strength of evidence, 6 "low," and 4 "very low." The 5 studies of moderate strength of evidence are reviewed in Table 6.

Davis [47] reported a retrospective time series. Pre-HBOT, nonhematogenous osteomyelitis had to be present for greater than 6 months, and the patient had to fail at least 1 surgical procedure designed to eliminate the infection. All patients had actively draining wounds at onset. Twenty had previous open fracture, including 4 with open fractures sustained in wartime. In no case did osteomyelitis arise from a chronic wound. Surgery plus antibiotics (directed to culture sensitivities from bone biopsies) was standard of care. Successful outcome was defined as complete healing and absence of drainage, cellulitis, or pain. This result was achieved by 34 patients (89%). Post-HBOT, there were no recurrences. Assuming admitted patients were "nonresponders" to conventional treatment, there is strong strength of association. With no obvious flaws in quality, the strength of evidence is moderate.

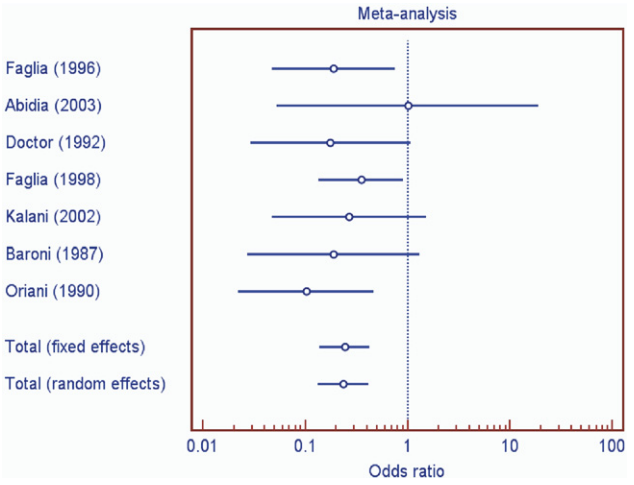

Figure 2. Meta-analysis of cited studies indicates odds of amputation are lower as a result of hyperbaric oxygen therapy (HBOT) plus standard care, compared to standard care alone. (Left of vertical line favors HBOT.) Odds are derived for studies where limb salvage is an outcome variable and there is a contemporaneous non-HBOT comparison group. The graph is generated by the MedCalc statistical package, which displays results of different studies and the overall effect with 95% confidence interval (CI) on a forest plot with a logarithmic x-axis. To calculate odds ratios, MedCalc employs the Mantel-Haenszel technique (69). This "stratified" technique avoids the tendency of logistic odds ratio to overestimate common effects (70). Mantel-Haenszel calculates fixed effects, which assumes all studies come from a common population. If this is not true a random effects statistic is more appropriate. The random effects statistic usually provides a more conservative estimate of overall effect and CI (69). Random effects odds ratios and CIs are reported in this article.

Morrey [48] also reported a retrospective time series of 40 patients. To be included, patients must have had infection for at least 6 months before HBOT and have had at least 1 surgical procedure but had had recurrence, and had more than 1 year of follow-up post-HBOT. All received surgery plus antibiotics directed to results of bone biopsy as the standard of care. Standard of care plus adjunctive HBOT was effective: for the 40 records analyzed, during the follow-up period averaging 23 months, 34 (85%) remained clinically free of disease. There were 6 recurrences (15%) that occurred on average 4.3 months after termination of HBOT. Of these, 5 resolved again after combined surgery and HBOT. This is a well-defined time series without significant flaws, raising the level of evidence to "moderate."

Chin-En Chen [49] conducted a retrospective time series of 13 cases with refractory osteomyelitis of the femur; for inclusion, disease had to be of at least 6 months' duration, as well as failed aggressive surgical debridement and antibiotics. Once included, patients received surgery plus antibiotics

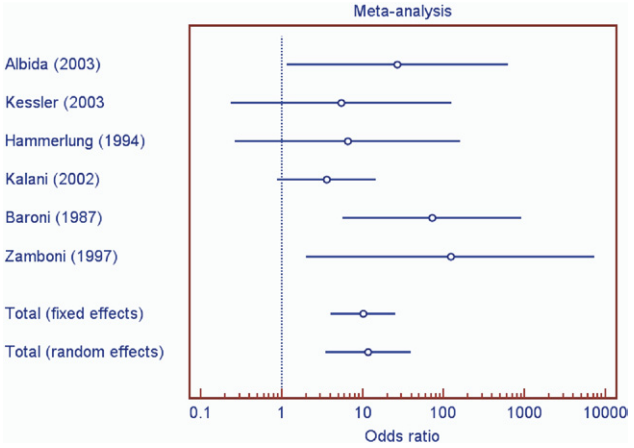

Figure 3. Meta-analysis of cited studies indicates odds of healing are improved as a result of hyperbaric oxygen therapy (HBOT) plus standard care, compared with standard care alone. (Right of vertical line favors HBOT.) The 6 studies reported here each have (1) a contemporaneous comparison group (whether or not randomized) and (2) describe wounds as healed/not healed (if there is more than 1 determination, the final observation is employed). The graph is generated by the MedCalc statistical package, which displays results of different studies and the overall effect with 95% confidence interval (CI) on a forest plot with a logarithmic x-axis. To calculate odds ratios, MedCalc employs the Mantel-Haenszel technique (69). For further elaboration, see Figure 2.

directed to the results of bone cultures and HBOT. With this treatment regimen, 12 (92%) showed complete wound healing with no recurrence over 22 months (average follow-up period). This is a time series of moderate level of evidence.

Chao-Yu Chen [50] conducted a prospective case series of refractory tibial osteomyelitis. Patients included had 1 infection for at least 6 months, recurrence after 3 surgical procedures, and previous treatment with parenteral antibiotics. Once admitted for treatment, patients had multidisciplinary treatment including surgical and infectious disease management. Thirteen (87%) patients healed "uneventfully." No recurrences were apparent after an average of 17 months of follow-up. As a time series, this rates a moderate level of evidence.

Esterhai [51] reports a prospective cohort study. The author allocated patients to 1 cohort or the other based on matching Ceiby-Mader score [52] without randomization. Included were patients with pain, systemic sepsis, aggressive bone and soft-tissue destruction, and foul-smelling drainage, "not simply presence of infection." Aggressive surgery plus antibiotics was the standard of care. In addition, half the patients included also received HBOT. Eradication of osteomyelitis occurred in 11 (79%) in the HBOT group, and 13 (93%) in the non-HBOT group. There were 3 recurrences, 2 in the HBOT group and 1 in the non-HBOT group noted over a follow-up period averaging 41 months. Note that the overall treatment success for the HBOT group was 57%. However, the median "cure" rate for all other trials was 87-92%. Outcomes were not in agreement, and possible sources of the discrepancy are discussed in the following section.

DISCUSSION

This systematic review reveals many studies linking HBOT to wound healing and limb salvage. This section integrates results into a broader discussion of efficacy, mechanism, cost, and safety of HBOT.

Efficacy and Meta-analyses

There are 4 prospective RCTs for HBOT, for which the primary endpoint is wound healing and/or limb salvage. Only RCTs were analyzed by a recent Cochrane review of HBOT and wound healing [15]. With such limited data and resultant analysis that did not attempt to delineate amputation vs healing as separate entities, their endorsement had to remain limited as well. Because this current systematic review allowed the inclusion of studies with moderate strength of evidence according to GRADE criteria [14], the resultant findings may be illuminating. Such inclusion clarifies the previously held belief that HBOT promotes limb salvage for diabetic patients with foot ulcers complicated by deep soft-tissue infection or gangrene.

This conclusion arises from a meta-analysis of RCTs and observational studies described in the Results section of this article (Figure 2). Over all of the studies surveyed, the statistical odds for major amputation decrease where HBOT is employed (odds ratio 0.236, 95% CI: 0.133-0.418). Three prospective RCTs [16,18,23], 1 prospective cohort study [24] and 3 retrospective cohort studies [17,26,53] make up these findings. Together, they demonstrate a strong and consistent level of association pointing to a 3-fold reduction in risk of major amputation where HBOT is included as part of a comprehensive program of care. Further, the effect appears durable: HBOT may reduce the chance of amputation for patients with "stable" Wagner II ulcers 3 years after treatment [24].

One potential confounding point was noted during this review. Fifty-seven percent of the 291 patients reported in the above studies received treatment at hospitals with co-authors in common. Since these trials were not blinded, any potentially resultant bias introduced would impact this estimation of amputation risk [54]. A blinded multicenter RCT of HBOT for limb salvage is now under way [55].

Beyond reducing amputation risk, there is a positive association between HBOT and healing itself. This is brought out by a meta-analysis (Figure 3) of 6 studies where extractable data determine the odds of healing; 3 RCTs with high strength of evidence, 2 with moderate, and 1 with low. On the basis of these studies, it is apparent that odds of healing are better with than without HBOT (OR 11.64, 95% CI: 3.457-39.196). If the 1 study of low strength of evidence (Baroni et al [26]) is excluded, the odds of healing are still better (OR 6.484, 95% CI: 2.2-19.033).

Expanding the filter to include studies of moderate level of evidence highlights patient groups for which HBOT is relatively effective: a) nonsmokers [22]; and b) positive responders to oxygen challenge, measured by periwound TCOM. TCOM increase to hyperbaric oxygen challenge of 200 mm Hg prognosticates treatment success [21]. Six other studies presented in this systematic review (1 RCT, 5 moderate, 1 low level observational study) each observe TCOM increase to oxygen challenge to be positively associated with healing; no studies report the opposite. Therefore, there is strong justification to propose that any future RCT investigating the effectiveness of HBOT for wound healing include only subjects that respond well to oxygen challenge.

Oxygen challenge response is an important factor in selecting patients with arterial ulcers for HBOT, based on the work of Grolman et al [29] (Table 5). Grolman determined that there are 2 separate patient populations based on ability to oxygenate tissue at risk, as measured with periwound TCOM, while breathing 100% oxygen. However, there are no RCTs specifically on effectiveness of HBOT on healing of arterial ulcers and limb salvage. One challenge is to reach consensus on the definition of an arterial ulcer (Table 3).

At this time, strength of evidence for flap failure is low based on expert opinion as well as animal studies and case series with "low" level of evidence. Because these wounds are complex and surgeries are specific, it is difficult to draw general conclusions.

In terms of recalcitrant osteomyelitis, the results are controversial (Table 6). There are no RCTs on which to determine strength of association. In the absence of RCT, one infers an effect from time series or cohort studies, but the data conflict: as analyzed, there are 4 time series of moderate quality, all of which determine that osteomyelitis refractory to standard care (and hence unlikely to resolve spontaneously), resolves in 85-92% of patients (n = 108, 4 studies). On the other hand, Esterhai [51] asserts that aggressive surgical intervention achieves a similar remission rate (85%, n = 14), with the "cure" rate for standard care plus HBOT comparing unfavorably (60%, n = 14). Careful analysis reveals 6 differences between the 4 time studies and the cohort study of Esterhai et al. The latter study had the following potential confounders: (1) sampling error (small sample size); (2) fewer HBOT sessions; (3) 1 year longer follow-up than the other studies [56]; (4) more severe disease at onset; (5) more aggressive surgical technique; and (6) treatment at 2.0 ATA (instead of 2.4 ATA).

The Undersea and Hyperbaric Medicine Society recommends that HBOT be employed at 2.0 to 2.5 ATA [5] for refractory osteomyelitis. By this recommendation, the Society takes the reasonable position that within this range of dose efficacy is equivalent. However, the question of oxygen dose-response remains open. A study directly comparing 1.0, 2.0, and 2.4 ATA "head to head" would be beneficial.

It would additionally be beneficial to study the effectiveness of HBOT to treat osteomyelitis that complicates chronic wounds on elderly patients. Instead, the literature focuses on relatively young patients (mean age about 40) primarily with osteomyelitis arising from complex fracture or trauma. These complex fractures develop into "full-thickness" cortical and medullary osteomyelitis. When osteomyelitis develops from wounds, it is typically to cortical bone only. The question remains open if a coordinated program of care including HBOT eradicates refractory osteomyelitis for wound patients.

Mechanism

The stages of normal wound healing include inflammation, provisional matrix formation, collagen synthesis, epithelialization, neoangiogenesis, and finally wound closure. Chronic wounds appear "stuck" in the inflammatory phase [57]. Inflammation becomes overwhelming for Wagner III, IV, and V DFU, wherein inflammation itself promotes hypoxia and gangrene in tissue at risk. For these very complex wounds, preclinical studies have elucidated a mechanism whereby HBOT controls infection, reduces inflammation, enhances perfusion, and promotes wound repair, all of which are important for healing and limb salvage.

HBOT may promote the efficiency of leukocytes to kill pathogens by phagocytosis. Phagocytosis requires large quantities of oxygen to form reactive species such as free radicals within phagosomes to inactivate pathogens. This mechanism is blunted in a hypoxic environment in infected tissue or bone. In a rabbit experimental model of osteomyelitis, *Staphylococcus aureus* inoculum decreases after exposure to hyperoxia (150 mm Hg) [58]. This suggests HBOT helps the host to overcome infection within hypoxic soft tissue and bone.

HBOT also has anti-inflammatory properties. When ischemic tissue is reperfused (for instance, after reattachment of a flap or graft) inflammatory cells paradoxically "attack" the previously ischemic tissue, leading to what is known as ischemia-reperfusion injury. Reperfusion injury involves leukocyte margination and extravasation from capillaries, a process mediated by endothelial cell expression of intercellular adhesion molecule 1. Intercellular adhesion molecule 1 expression is tightly controlled by endothelial cell-derived nitric oxide in inverse fashion; nitric oxide concentration increases in the presence of HBOT. This is because HBOT upregulates endothelial derived nitric oxide synthetase [59], which increases local nitric oxide concentration and hence reduces intercellular adhesion molecule 1 expression. By a similar mechanism of effect, HBOT is thought to reduce leukocyte margination as part of a general inflammatory response, protecting endothelium, reducing its porosity and hence reducing interstitial edema.

Protection against reperfusion injury is a rationale for use of HBOT adjunctively for reconstructive surgery with flaps or grafts. Preclinical studies offer additional evidence. In a rabbit composite ear graft model, graft survival increased significantly from 26% to 81% after exposure to twice-daily HBOT for 5 days [60].

In the early wound repair phase, fibroblasts repopulate and proliferate within the wound bed. There is evidence that HBOT facilitates this process. Fibroblasts proliferation in-

creases in a dose-dependent manner between 1.0 and 2.5 ATA. This occurs for both normal and diabetic skin fibroblasts [58].

Fibroblasts participate in wound repair by synthesis of collagen. Procollagen is formed in a hypoxic environment. However, maturation of collagen requires oxygen. HBOT promotes polymerization and cross-linking of collagen in a dose dependent manner. This process involves proline hydroxylation. Proline hydroxylase uses oxygen as a substrate and is maximally active at 225 mm Hg and higher [58].

HBOT also promotes neoangiogenesis within the wound bed. In a rat model, HBOT applied at 2.1 ATA twice per day for 7 days significantly increases vascular endothelial growth factor within wounds. Vascular endothelial growth factor is a well known mediator of neovascularization [61]. In an in vivo mouse model and in an experimental wound, HBOT directly promotes neoangiogenesis in a dose-dependent manner, which peaks at 2.5 ATA. The authors postulate that the cyclic nature of HBOT facilitates the process since neovascularization requires collagen to form microvessel tubes, procollagen forming during periods of hypoxia, and collagen export and maturation occurring during hyperoxic periods [62].

Recent evidence suggests that HBOT recruits stem cells known as endothelial progenitor cells from bone marrow of mice and releases them into the circulation. In the same mouse model, hind limbs made ischemic by femoral artery ligation reperfuse and ischemic wounds heal. Both reperfusion and stem cell mobilization are blocked by an inhibitor of nitric oxide synthetase, indicating that nitric oxide is a key mediator of the HBOT effect [63]. Because nitric oxide is an important mediator of epithelialization, wound matrix formation, and neoangiogenesis [57], it may be that HBOT augments many components of healing.

Payment Challenges

In spite of its efficacy in wound healing and limb salvage, HBOT is expensive; the cost of a single HBOT session is $1000, combining the Medicare part A and part B component. Obviously, over 30-45 treatments, the cost is additive and may approach $50,000. Because of this, insurance companies consider cost-effectiveness in approval for HBOT. For instance, Medicare has approved HBOT for treating diabetic foot ulcers Wagner Grades III, IV, and V, because the cost of limb loss both in human and financial terms is arguably more for amputation than for a course of HBOT. On the other hand, although HBOT has a moderate strength of evidence to heal very chronic stasis leg ulcers, insurance does not cover this condition, because less expensive treatments are likely available. Very rare but likely devastating conditions, such as calciphylaxis, are not typically covered, even though there is moderate evidence of benefit. Nevertheless, given the grim prognosis of this condition, HBOT should be considered as compassionate use.

One other important issue in the United States is outpatient versus inpatient management of DFU. Inpatient payment (Medicare A) is derived from lump-sum payments (diagnostic related groups) to hospitals and skilled care facilities from which all clinical services are paid. Clearly, there is a positive inducement, given the cost of HBOT, to wait until after discharge to make an HBOT referral. However, after the patient is appropriate for discharge, by definition the infection has stabilized and the wound is no longer Wagner III (hence not appropriate for HBOT by Medicare rules). This is paradoxical and requires clarification. Furthermore, there are no studies of outpatient HBOT and limb salvage. Studies to date are primarily European, involving patients in long-term (ie, 30 days) acute hospital settings, which is currently not the standard of care in the United States.

Safety

Experience has shown that adverse events of HBOT, in accredited facilities with well-trained personnel are usually minor and tolerable [39,64-67]. Serious adverse events are rare because of the relative safety of the technique and appropriate prescreening. In terms of screening, there are 6 types of adverse effects to keep in mind: cardiovascular effects; oxygen toxicity (central nervous system, pulmonary, ocular); barotrauma (middle ear, inner ear, sinus, dental, pulmonary); hypoglycemia; and confinement anxiety. A complete overview is beyond the scope of this article and is available elsewhere [64,65].

Oxygen is a peripheral vasoconstrictor and HBOT may increase cardiac afterload. Patients with relatively normal left ventricular function compensate well. However, it has been postulated that an ejection fraction $<40\%$ predisposes a patient to acute congestive heart failure (CHF), although the exact ejection fraction leading to increased risk has not been established. Weaver et al [66] reported incidence of acute CHF as 1 per 300 patients. Of 3 patients for which acute CHF was reported, there was 1 fatality for an incidence of 1:1024 patients. This fatality was of a patient with subcritical aortic stenosis (36 mm Hg gradient, 0.6 cm^2 orifice) and a previous acute CHF episode in-chamber [66].

Oxygen toxicity is mediated by oxygen free radicals, and is a function of oxygen partial pressure and duration of continuous exposure. Seizures are the hallmark of central nervous system oxygen toxicity. Oxygen seizures are relatively rare, and incidence is consistent between population studies. Of 2 reports, the incidence is roughly 1 per 200 patients, or 0.5% [39,67].

Conditions that lower central nervous system toxicity seizure threshold include: febrile illness; inadequately managed seizure disorder or hyperthyroidism; concomitant treatment with steroids, acetazolamide, penicillin, imipenem; poor sleep; or elevated blood alcohol [67]. Potential oxygen toxicity is mitigated by so-called "air breaks," where the patient alternates between breathing hyperbaric O_2 for 20-30 min and hyperbaric air for 5-10 min. "Air breaks" are required at 2.4 ATA, but not at 2.0 ATA.

There are also pulmonary manifestations of oxygen toxicity, including pulmonary fibrosis and progressive decrease in

vital capacity. Population studies surveyed do not report this adverse effect in usual HBOT practice [64]. At baseline, potential HBOT candidates receive chest radiographs, which are reviewed for evidence of scarring, air trapping, or fibrosis. Additionally, patients with underlying pulmonary disease receive pulmonary function testing. If pulmonary function testing reveals forced expiratory volume in the first second, forced vital capacity, or vital capacity less than 70% predicted the patient may not be a candidate for HBOT [67].

Ocular effects are generally mild and limited to progressive myopia (from temporary effects of hyperbaric oxygen on the lens), which almost always completely resolves in 6 weeks. HBOT can also cause cataracts to mature more quickly. There is no risk of new cataract formation in usual practice [64].

Barotrauma results from pressure differential and compression or expansion of a gas within a closed volume. The most ominous type of barotrauma is tension pneumothorax, which potentially could occur because of expansion of trapped hyperbaric air in the pleural space during decompression. Fortunately, tension pneumothorax is extremely rare. It was not observed by authors of numerous population series. These series comprised 9000 patients over 180,000 treatments [39,66,67].

The most common type of barotrauma involves the middle ear and distraction of the tympanic membrane during compression. In most cases, ear barotrauma is preventable through education and demonstration of maneuvers to equilibrate ear pressure. Plafki [67] observed an incidence of barotrauma of 1 in 6 patients, for a series of 782 patients treated for various conditions in a multiplace chamber. The average age of this sample was 45 years. For patients 60 years, the incidence of barotrauma was higher ($P < .05$).

Manifestations of middle ear barotrauma range in severity from mild tympanic membrane erythema to frank rupture. Fortunately, most barotrauma is mild, self-limited, and reversible. As a symptom of barotrauma, neurologically intact patients will invariably report ear discomfort. If barotrauma continues during successive treatments, elective myringotomy is an option. The incidence of elective myringotomy is 1 in 60 patients in 1 series [67].

Another issue for diabetic patients is management of blood sugar. For a monoplace facility, blood sugar may be monitored before and after the compression. For unclear reasons, a fall of blood glucose of 50 mg/dL is not uncommon during HBOT. Fortunately, management is straightforward: the HBOT session may be planned after eating, with sliding scale insulin reduced or eliminated. A good rule of thumb is that patients should not undergo compression in a monoplace chamber with a blood sugar level lower than 150 mg/dL.

Claustrophobia when it occurs is usually mild. It may be treated by reassurance, education, distraction, and if necessary, anxiolytics. Fewer than 1 of 70 patients cannot complete a course of HBOT because of confinement anxiety [39].

The above data refer to observations for large numbers of patients from major centers logged between 1970 and 2000 for all HBOT indications [39,66]. The mean age for 1 such study is 45 years [67]. Regarding the subset of older patients with nonhealing arterial wounds, the incidence of adverse events is likely higher than those observed in large population series published to date. Consider the experience of Grolman et al [29]. Their sample including 36 patients 69 ± 2 years of age (mean, SD), all with peripheral artery disease. Twenty-one patients had "significant" coronary artery disease, 9 had end-stage renal disease, and 7 were active smokers. Ejection fraction was not disclosed. There was a relatively high incidence of 28% having adverse events the most serious being exacerbation of CHF (n = 2), seizure (n = 1), and middle ear barotrauma requiring myringotomy tubes (n = 4). Although the numbers are too small to draw conclusions, it is clear that risk versus benefit must be carefully considered for at-risk populations.

CONCLUSIONS

- There is a high level of evidence that HBOT decreases risk of amputation for patients with DFU complicated by surgical infection if they receive HBOT as part of an interdisciplinary program of wound care. However, a multicenter, blinded RCT to clarify effect size would certainly strengthen this conclusion.
- There is a high level of evidence that HBOT promotes partial and complete healing of problem wounds.
- The cost-effectiveness of HBOT needs to be considered, especially for venous leg ulcers, for which less expensive, alternate strategies are likely available.
- There is a moderate level of evidence that HBOT promotes healing of arterial ulcers as part of an interdisciplinary program. Consensus on a definition of "arterial ulcer" is an essential step in advancing the evidence base.
- Calciphylactic and refractory vasculitic ulcers are unusual and particularly catastrophic. There is a moderate level of evidence that HBOT promotes wound healing. Further observational work will help clarify effect.
- There is a low to moderate level of evidence, technique-specific, that HBOT promotes uncomplicated healing after ablative or reconstructive surgery, and promotes salvage of compromised flaps or grafts.
- There is a moderate level of evidence that HBOT, in combination with a comprehensive program of surgery and antibiotics, promotes remission of refractory osteomyelitis. RCTs are necessary to confirm and establish effect size. Additionally, RCT or high quality observational cohort trials are needed on patients who present initially with DFU or pressure ulcers.
- There is a high level of evidence that transcutaneous oximetry prognosticates success of HBOT.
- HBOT is reasonably safe when applied under the supervision of experienced practitioners after careful patient screening and selection.

REFERENCES

1. Kosiak M. Etiology and pathology of ischemic ulcers. Arch Phys Med Rehab 1959;40:62-69.
2. Goldman RJ, Popescu A, Thomas C, et al. Prevention and management of chronic wounds. In: Braddom R, editor. Physical Medicine & Rehabilitation. Philadelphia, PA: Saunders Elsevier; 2007, p. 685-708.
3. Physical Medicine and Rehabilitation, The Brody School of Medicine at East Carolina University 2008; Available at www.ecu.edu/rehab/. Accessed Nov 28, 2008.
4. American Board of Preventive Medicine. Undersea & hyperbaric medicine 2008; Available at: www.abprevmed.org/uhm.cfm. Accessed Nov 28, 2008.
5. Feldmeier J. Hyperbaric oxygen 2003: indications and results: the Hyperbaric Oxygen Committee Report 2003;Flagstaff, AZ: Undersea and Hyperbaric Medicine Society.
6. Elliott D, Kindwall EP. Decompression sickness. In: Kindwall EP, Wheelan H, eds. Hyperbaric medicine practice, 2nd ed, revised. Flagstaff, AZ: Best Publishing Company; 2004, p. 433-488.
7. Kindwall EP. A history of hyperbaric medicine. In: Kindwall EP, Wheelan H, eds. Hyperbaric medicine practice, 2nd ed, revised. Flagstaff, AZ: Best Publishing Company; 2004, p. 1-20.
8. Davis JC, Hunt TK. Hyperbaric oxygen therapy. Bethesda, MD: Undersea and Hyperbaric Medicine Society; 1977.
9. Undersea and Hyperbaric Medicine Society 2008. Available at www.uhms.org. Accessed Nov 29, 2008.
10. Kindwall EP. The monoplace chamber. In: Kindwall EP, Wheelan H, eds. Hyperbaric medicine practice, 2nd ed, revised. Flagstaff, AZ: Best Publishing Company; 2004, p. 127-142.
11. Hart GB. The monoplace chamber. In: Kindwall EP, Wheelan H, eds. Hyperbaric medicine practice, 2nd ed, revised. Flagstaff, AZ: Best Publishing Company; 2004, p. 99-124.
12. Bennett MH, Feldmeier J, Hampson N, et al., Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database System Rev 2005:3.
13. McDonagh M, Helfand M, Carson S, et al. Hyperbaric oxygen therapy for traumatic brain injury: a systematic review of the evidence [see comment]. Arch Phys Med Rehab 2004;85:1198-1204.
14. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. Br Med J 2004;328:19.
15. Kranke P, Bennett M, Roeckl-Wiedmann I, et al. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database System Rev 2004:2.
16. Faglia E, Favales F, Aldeghi A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study [see comment]. Diabetes Care 1996;19:1338-1343.
17. Faglia E, Favales F, Aldeghi A, et al. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. J Diabetes Complications 1998;12:96-102.
18. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial [see comment]. Eur J Vasc Endovasc Surg 2003;25:513-518.
19. Kessler L, Bilbault P, Ortega F, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care 2003;26:2378-2382.
20. Fife CE, Buyukcakir C, Otto GH, et al. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. Wound Repair Regen 2002;10(4):198-207.
21. Fife CE, Buyukcakir C, Otto G, et al. Factors influencing the outcome of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy. Wound Repair Regen 2007;15(3):322-331.
22. Otto GH, Buyukcakir C, Fife CE. Effects of smoking on cost and duration of hyperbaric oxygen therapy for diabetic patients with nonhealing wounds. Undersea Hyperbaric Med 2000;27(2):83-89.
23. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. J Postgrad Med 1992;38(3):112-114.
24. Kalani M, Jorneskog G, Naderi N, et al. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. J Diabetes Complications 2002;16(2):153-158.
25. Zamboni WA, Wong HP, Stephenson LL, et al. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyperbaric Med 1997;24(3):175-179.
26. Baroni G, Porro T, Faglia E, et al., Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care 1987;10(1):81-86.
27. Goldman R, Brewley B, Golden M. Electrotherapy re-oxygenates inframalleolar ischemic wounds on diabetic patients - a case series. Adv Skin Wound Care 2002;15(May/June):112-120.
28. Margolis D. Foot ulcers and amputations in CRIC (FACRIC). Philadelphia; 2005, p. 116-151.
29. Grolman RE, Wilkerson DK, Taylor J, et al., Transcutaneous oxygen measurements predict a beneficial response to hyperbaric oxygen therapy in patients with nonhealing wounds and critical limb ischemia. Am Surg 2001;67(11):1072-1079.
30. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plast Reconstruct Surg 1994;93(4):829-833.
31. Weenig RH, Sewell LD, Davis MD, et al. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 2007;56(4):569-579.
32. Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. J Am Acad Dermatol 2008;58(3):458-471.
33. Hruska K. Renal osteodystrophy. In: Goldman L, Ausiello D, editors. Cecil textbook of medicine. Philadelphia, PA: Saunders Elsevier; 2008, p. 931-936.
34. Basile C, Montanaro A, Masi M, et al. Hyperbaric oxygen therapy for calcific uremic arteriolopathy: a case series. Jf Nephrol 2002;15(6):676-680.
35. Mureebe L, Moy M, Balfour E, et al. Calciphylaxis: a poor prognostic indicator for limb salvage. J Vasc Surg 2001;33(6):1275-1279.
36. Efrati S, Bergan J, Fishlev G, et al. Hyperbaric oxygen therapy for nonhealing vasculitic ulcers. Clin Exp Dermatol 2007;32(1):12-17.
37. Zgonis T, Garbalosa JC, Burns P, et al. A retrospective study of patients with diabetes mellitus after partial foot amputation and hyperbaric oxygen treatment [see comment]. J Foot Ankle Surg 2005;44(4):276-280.
38. Ciaravino ME, Friedell ML, Kammerlocher TC. Is hyperbaric oxygen a useful adjunct in the management of problem lower extremity wounds? Ann Vasc Surg 1996;10(6):558-562.
39. Sheffield P, Sheffield J. Complication rates for hyperbaric oxygen therapy patients and their attendants: a 22 year analysis. Proceedings of the Fourteenth International Congress on Hyperbaric Medicine, F. Cramer and P. Sheffield, editors. San Francisco: Best Publishing Company; 2003, p. 312-318.
40. Zhao DW. [Therapeutic effect of hyperbaric oxygen on recovery of surgically repaired peripheral nerve injury]. Chung Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 1991;29(2):118-120.
41. Reedy MB, Capen CV, Baker DP, et al. Hyperbaric oxygen therapy following radical vulvectomy: an adjunctive therapy to improve wound healing. Gynecol Oncol 1994;53(1):13-16.
42. Friedman HI, Fitzmaurice M, Lefaivre JF, et al. An evidence-based appraisal of the use of hyperbaric oxygen on flaps and grafts. [Erratum: Plast Reconstr Surg. 2006 Aug;118(2):62e Note: Friedman, H I F [corrected to Friedman, HI]]. Plast Reconstr Surg 2006;117(7 Suppl).
43. Saber AA, Yahya KZ, Rao A, et al., A new approach in the management of chronic nonhealing leg ulcers. J Invest Surg 2005;18(6):321-323.
44. Mathieu D, Neviere R, Pellerin P, et al. Pedicle musculocutaneous flap transplantation: prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. Plast Reconstr Surg 1993;91(2):329-334.
45. Gonnering RS, Kindwall EP, Goldmann RW. Adjunct hyperbaric oxygen therapy in periorbital reconstruction. Arch Ophthalmol 1986;104(3):439-443.

46. Friedman HI, Stonerock C, Brill A. Composite earlobe grafts to reconstruct the lateral nasal ala and sill. Ann Plast Surg 2003;50(3):275-281.

47. Davis JC, Heckman JD, DeLee JC, et al. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Jt Surg Am 1986;68(8):1210-1217.

48. Morrey BF, Dunn JM, Heimbach RD, et al. Hyperbaric oxygen and chronic osteomyelitis. Clin Orthop Related Res 1979;144:121-127.

49. Chen CE, Ko JY, Fu TH, et al. Results of chronic osteomyelitis of the femur treated with hyperbaric oxygen: a preliminary report. Chang Gung Med J 2004;27(2):91-97.

50. Chen CY, Lee SS, Chan YS, et al. Chronic refractory tibia osteomyelitis treated with adjuvant hyperbaric oxygen: a preliminary report. Changgeng Yi Xue Za Zhi 1998;21(2):165-171.

51. Esterhai JL, Jr., Pisarello J, Brighton CT, et al. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis. J Trauma Inj Infect Crit Care 1987;27(7):763-768.

52. Mader JT, Hicks CA, Calhoun J. Bacterial osteomyelitis. Adjunctive hyperbaric oxygen therapy. Ortho Rev 1989;18(5):581-585.

53. Oriani G, Meazza D, Favales F, et al. Hyperbaric oxygen therapy in diabetic gangrene. J Hyperbaric Med 1990;5(3):171-175.

54. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective [comment]. Clin Infect Dis 2006;43(2):193-198.

55. Londahl M, Katzman P, Nilsson A, et al. A prospective study: hyperbaric oxygen therapy in diabetics with chronic foot ulcers. J Wound Care 2006;15(10):457-459.

56. Maynor ML, Moon RE, Camporesi EM, et al. Chronic osteomyelitis of the tibia: treatment with hyperbaric oxygen and autogenous microsurgical muscle transplantation. J South Ortho Assoc 1998;7(1):43-57.

57. Goldman R. Update on growth factors and wound healing: past, present and future. Adv Skin Wound Care 2004;17(1):24-35.

58. Cianci P. Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy? Wound Repair Regen 2004; 12(1):2-10.

59. Buras JA, Stahl GL, Svoboda KK, et al. Hyperbaric oxygen downregulates ICAM-1 expression induced by hypoxia and hypoglycemia: the role of NOS. Am J Physiol Cell Physiol 2000;278(2):C292-C302.

60. Lewis D, Goldztein H, Deschler D. Use of hyperbaric oxygen to enhance auricular composite graft survival in the rabbit model. Arch Facial Plast Surg 2006;8(5):310-313.

61. Sheikh AY, Gibson JJ, Rollins MD, et al. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. Arch Surg 2000; 135(11):1293-1297.

62. Hopf HW, Gibson JJ, Angeles AP, et al. Hyperoxia and angiogenesis. Wound Repair Regen 2005;13(6):558-564.

63. Goldstein LJ, Gallagher KA, Bauer SM, et al. Endothelial progenitor cell release into circulation is triggered by hyperoxia-induced increases in bone marrow nitric oxide. Stem Cells 2006;24(10):2309-2318.

64. Clark J, Whelan HT. Oxygen toxicity, In: Kindwall EP, Whelan HT, editors. Hyperbaric medicine practice, 2nd ed. Flagstaff, AZ: Best Publishing Company; 2004: p. 69-82.

65. Kindwall EP. Contraindications and side effects to hyperbaric oxygen treatment. In: Kindwall EP, Whelan HT, editors. Hyperbaric medicine practice, 2nd ed. Flagstaff, AZ: Best Publishing Company; 2004: p. 83-97.

66. Weaver LK, Churchill S. Pulmonary edema associated with hyperbaric oxygen therapy. Chest 2001;120(4):1407-1409.

67. Plafki C, Peters P, Almeling M, et al. Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 2000;71(2):119-124.

68. Cierny G, 3rd, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Clin Orthop Relat Res 2003;414:7-24.

69. MedCalc Statistical Software: Meta-analysis: odds ratio. 2009, http://www.medcalc.be/manual/meta-oddsratio.php. Accessed Jan 1, 2009.

70. McNutt LA, Wu C, Xue X, et al. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003;157(10):940-943.

71. Falanga V. Venous ulceration. Dermatol Surg Oncol 1993;19:764-771.

72. Sheffield P. Measuring tissue oxygen tension: a review. Undersea Hyperbaric Med 1998;25:179-187.

73. Padberg F, Back T, Thompson P, et al. Transcutaneous oxygen (TcPO2) estimates probability of healing in the ischemic extremity. J Surg Res 1996;60:365-369.

74. Goldman R, Brewley B, Zhou L, et al. Electrotherapy reverses inframalleolar ischemia: a retrospective, observational study. Adv Skin Wound Care 2003;16(3):79-89.

75. Caputo G, Cavanagh P, Ulbrecht J, et al. Assessment and management of foot disease in patients with diabetes. N Engl J Med 1994;331(13): 854-860.

76. Kominsky S. Outpatient management of pedal complications. In: Kominsky S, editor. Medical and Surgical management of the diabetic foot. St Louis, MO: Mosby Year Book; 1994, p. 223-247.

77. Wagner F. The Dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981;2(2):64-122.