Counterpoint: Hyperbaric Oxygen for Diabetic Foot Wounds Is Not Effective

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(See the point by Barnes on pages 188–92)

Background. Diabetic foot ulceration is common, affecting 1.0%–4.1% of diabetic persons per year and up to 25% in a lifetime. Diabetic foot ulcers are multifactorial in origin, and many are slow to heal and/or are complicated by infection, frequently leading to amputation. Hyperbaric oxygen therapy has been suggested for numerous indications, and it is recognized by funding agencies for a smaller number including diabetic foot wounds.

Methods. I reviewed the literature about the history and practice of hyperbaric oxygen therapy and key issues relevant to efficacy, effectiveness, and cost-effectiveness.

Results. Although recognized for reimbursement by Medicare and major insurers, the evidence base for hyperbaric oxygen therapy for diabetic foot care remains weak. A systematic review for the Cochrane Collaboration concluded that hyperbaric oxygen therapy may have value in treating diabetic wounds, but the studies reviewed all had methodological weaknesses, and the positive effect of treatment was not seen in the single reviewed randomized trial to include a sham treatment arm. Hyperbaric oxygen therapy consumes very substantial resources—and has the potential to consume far more—that could be better spent on other aspects of management or prevention of diabetic foot ulceration.

Conclusions. Hyperbaric oxygen therapy should not be offered for diabetic foot wounds until large-scale, adequately blinded, controlled, and powered randomized studies have clearly demonstrated efficacy and cost effectiveness in the healing of ulcers and the prevention of major amputation.

The worldwide epidemic of type 2 diabetes has brought to attention its common complications of foot ulceration, secondary infection, and subsequent major limb amputation [1, 2]. Diabetic foot ulceration is driven predominantly by the effects of peripheral neuropathy on foot biomechanics (foot deformity being associated with high pressures in specific weight-bearing areas) and on protective sensation [3].

Once established, ulceration may extend to deep underlying structures, including bone and joint. Soft-tissue infection, chronic septic arthritis, and chronic osteomyelitis are all frequent events that impair wound healing [4]; so may additional factors, including ischemia (mostly from macrovascular peripheral disease), poorly controlled hyperglycemia, and other possible comorbidities, such as anemia, heart failure, or respiratory disease. Finally, psychological and behavioral factors may play a role, including inappropriate patterns of activity and inactivity [5, 6] or maladaptive health belief models [7].

It is important to recognize the multifactorial etiology of diabetic foot ulceration because of the implications this has for treatment and for the debate over the use of hyperbaric oxygen. Foot ulcers require multidisciplinary management that must always include debridement, off-loading of the high pressure area(s), correction of comorbidities, education about foot care, and advice on (or provision of) protective footwear [3]. Management may need to extend to antibiotic administration and surgical intervention for deep soft-tissue or bone infection [4] and/or to revascularization procedures to treat peripheral ischemia. Finally, other adjunctive therapies can be considered to expedite wound healing; the use of topically applied growth factors [8],...
systemic administration of granulocyte colony-stimulating factor [9], vacuum-assisted closure dressings [10], and, of course, hyperbaric oxygen therapy (HBOT). The debate over the use of HBOT in diabetic foot ulceration is, therefore, not simply a question of whether it has been shown to be efficacious within the confines of clinical trials (although I do not believe it has), but also how it will be used in practice alongside other treatment modalities in a real world with finite health care resources.

Hyperbaric medicine is based on the premise that the delivery of supraphysiological concentrations of oxygen to diseased tissues will result in beneficial physiological changes (see the accompanying article by Barnes [11]). In the case of diabetic foot ulceration, it is believed both that the function of phagocytic cells is improved, assisting in the fight against any infection, and that wound healing is independently aided through effects on cellular processes [11, 12]. Thus, it has been suggested that HBOT is useful for the treatment of infection and for the healing of chronic wounds. These 2 interlinked processes are often elided in diabetic foot medicine, but they are strictly separate processes.

Although the adverse effects of tissue hypoxia are well recognized, the faith that overcorrecting this, to produce hyperoxygenated tissues, will be beneficial has a very limited basis in physiology; it has roots that go directly back to the medical quackery that followed the discovery of oxygen and, separately, the development of hyperbaric technology. Claims for its healing properties have accompanied a market in the inhalation of supplemental oxygen since the early 19th century. This continues to this day, bubbled through aromatic liquids and delivered by nasal cannulae, for recreational use in so-called “oxygen bars” in many major cities [13]. This practice has attracted the attention of both the American Lung Association and the US Food and Drug Administration.

The history of hyperbaric technology predates even that of the discovery and ability to concentrate oxygen itself. Initially, the development of pressurized containers and the pumps needed to generate that pressure were related to the use of diving bells for engineering purposes. By the mid-19th century, there was already comment not only about the use of pressurization as a medical treatment, but also about the need for this to be properly evaluated. The identification of caisson disease, most notably during the construction of the Brooklyn Bridge, highlighted the hazards of hyperbaric conditions and the therapeutic role that pressurization has in treating decompression sickness. Once the technology was developed, however, many different conditions were treated, all on the premise that tissue ischemia could be reversed. Perhaps the most extraordinary example of pressurization (without hyperoxygenation) being used for dubious medical treatment was the so-called “Timken tank,” which was constructed by a Professor of Anesthesitics, Orval Cunningham, in Cleveland, Ohio, in the 1920s. An enthusiast for hyperbaric therapy following theories he had developed in the influenza pandemic of 1918, Cunningham treated many patients with a wide variety of ailments, including a millionaire industrialist who provided funds for the construction of a hyperbaric sphere large enough to accommodate a small hotel. Cunningham’s failure to provide promised experimental evidence of efficacy led to conflict with the medical establishment. Following economic disaster and closure in 1930, the sphere was eventually broken up for scrap during the Second World War, prompting a valedictory editorial from the American Medical Association, “Useless Tank to Become Useful Tanks” [14].

The advocates of hyperbaric medicine have, of course, been careful to dissociate themselves from quackery of this sort. Supplemental oxygen at atmospheric pressure can correct hypoxemia due to lung disease, but the levels of oxygen dissolved in plasma are a fraction of those achieved under hyperbaric conditions, just as inhalation of room air under hyperbaric conditions results in only minor increases in the partial pressure of oxygen. It is the combination of hyperbaric conditions of 2–3 atmospheres pressure and simultaneous inhalation of 100% oxygen that results in high levels of dissolved plasma oxygen, with hemoglobin remaining virtually 100% saturated. To achieve this, the patient must be placed in a chamber capable of containing such pressures; these exist as both monoplace and multiplace chambers, some of which are highly complex spaces, allowing for the accommodation of numerous patients at once or for patients requiring intensive nursing and supervision. Enthusiasm for the provision of hyperbaric oxygen has even stimulated the production of portable monoplace chambers, which have been used by some to promote novel indications for therapy.

So much for the context in which we can view HBOT. What of the evidence for its efficacy in diabetic foot ulceration and for its effectiveness?

A number of case series have suggested benefit in ulcer healing and in the prevention of amputation in diabetic patients [15, 16]. There have also been advocates for the treatment of osteomyelitis with HBOT [17] (another indication with a testable evidence base), and there is some evidence that, for gas gangrene, HBOT may achieve a similar effect, as an adjunct to radical surgery, as antibiotic treatment [18]. Both of these conditions may be relevant to diabetic foot infection. For all these possible indications, however, the key test is what data are available from randomized, controlled trials. This is particularly important because of the great variations in ulcer biology that exist between patients. Variations in ulcer size and depth, in the extent of complicating infection, and in the degree of ischemia all have a potential impact on ulcer healing [19], as does the ulcer care provided and the adherence of the patient to the treatment regimen [20]. So significant is this problem
of interpatient (and, thus, interstudy) comparison that the International Consensus on the Diabetic Foot has produced a novel classification scheme for research purposes, the PEDIS (perfusion, extent, depth, infection severity, and sensation) scheme [21]. Each modality in the scheme can be classified into a value from 1 to a maximum of 4, with the exception of extent, which is the area of the ulcer in square centimeters.

Because the trials in question antedated the PEDIS scheme, we are left relying on the amount of detail provided by the investigators to understand the case mix being treated. We are also highly reliant on the investigators for avoidance of all forms of bias, including unintentional bias in subsequent management decisions, such as amputation. It is obvious that a major risk of bias exists, because patients receiving HBOT could be more motivated (to consider the treatment at all), become more motivated (because of the high levels of support and attention attendant on the treatment), and along with their physicians, then be much less likely to consider amputation as a treatment option.

The available evidence has been carefully reviewed on a number of occasions, including 2 systematic reviews [22, 23] and a third review for the Cochrane Collaboration that is probably most transparent in its methodology [24]. All these reviews concluded that the quality of the studies was poor and that there was little evidence to support a role for HBOT in speeding ulcer healing. The Cochrane review, in particular, pointed out a number of crucial issues that affect interpretation.

First, of 26 studies of the use of HBOT for chronic wounds of all forms, only 5 were considered to be of sufficient methodological quality to merit review. Four of these dealt with diabetic foot wounds. Even among these 4 studies, methodological quality was poor. The authors used the Jadad score, a validated quality score for controlled trials that allocates 1 point for each of randomization, double-blinding, and treatment of withdrawals. Two further points are available for the use of a reliable method for randomization and for use of a placebo control. Two of the studies scored 2 out of 5 [25, 26], 1 scored 4 [27], and 1 scored the maximum of 5 [28]. Table 1 shows the methodological issues, and table 2 shows the outcomes measured in each study. It is evident that in addition to the serious design flaws in some studies, they are also not strictly comparable on the basis of spectrum of ulcers being treated and the outcomes measured.

Interestingly, the 2 studies with the low Jadad scores contributed 100 patients to the analysis; there were only 18 patients included in the highest-quality study [28]. The fourth study, although of acceptable methodological quality, examined only transcutaneous oxygen tension and no clinical end points [27].

There was no significant effect on ulcer healing demonstrated at any time point in any of the studies. However, a beneficial effect on major amputation was seen, with a number-needed-to-treat of 4. This effect was not, however, seen in the study by Abidia et al. [28] (of the highest methodological quality), which included a sham treatment arm (hyperbaric air). Although it could be argued that the sham treatment in fact had activity, this would in effect be an endorsement of normoxic hyperbaric therapy of the kind practiced by some in the 19th and early 20th centuries. The beneficial effect on amputation was contributed especially by the study by Faglia et al. [26], which described 70 patients who were treated unblinded and which did not have a placebo control group. The Cochrane reviewers pointed out their inability to be certain that decisions to amputate were not made in the knowledge of the treatment the patient had received. Furthermore, in the other study that showed clinical benefit [25], patients received only 4 sessions of HBOT in a 2-week period—dramatically less than the standard duration of 30–40 treatments and stretching the bounds of credulity for a likely physiological effect.

The authors concluded that there was insufficient evidence to support the routine use of HBOT in the therapy of diabetic foot ulcers, but that there was a strong case for large randomized, controlled trials with a high level of rigor to establish the true extent of any benefit and whether a particular group exists that would benefit from HBOT. They set down a caveat on the data around major amputation because of the likelihood that, in most studies, any decision to amputate was made in the knowledge of the treatment modality that the patient had received.

This caution, based on a particularly rigorous review of the literature, was not reflected in decisions made by the Center for Medicare and Medicaid Services (CMS) [29]. The CMS determination was based on a technology assessment per-

### Table 1. Methodological features of the 4 studies reviewed by Cochrane Collaboration.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Blinded</th>
<th>Sham treatment arm</th>
<th>Allocation</th>
<th>ITT population</th>
<th>Jadad score</th>
<th>Ulcer grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor et al.</td>
<td>1992</td>
<td>30</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>Wagner 2,3,4</td>
</tr>
<tr>
<td>Faglia et al.</td>
<td>1996</td>
<td>70</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>Wagner 0,1,2</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>2001</td>
<td>29</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
<td>Wagner 0,1,2</td>
</tr>
<tr>
<td>Abidia et al.</td>
<td>2003</td>
<td>18</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>1–10 cm, &gt;6 weeks</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [24]. ITT, intention-to-treat.
formed by the New England Medical Center and other reviews, and despite meticulous noting of numerous methodological flaws and questions in the CMS review, a positive determination was nonetheless made. We cannot know whether the same decision would have made had the negative results from the high-quality (but relatively small) randomized, controlled trial published in 2003 [28] been available to the CMS reviewers.

An additional study, also unavailable to the CMS and the Cochrane group, is that by Kessler et al. [30]. This study randomized 28 of an initial 64 patients with Wagner grade I–III nonischemic ulcers to receive standard ulcer care, with or without HBOT. Exclusions were mainly because of severity of disease and ischemia. The study was neither blinded nor placebo controlled, and so scores 3 points out of the possible 5 on the Jadad score. The investigators found that initial rates of healing were increased immediately after 2 weeks of HBOT, compared with rates for control subjects, but that healing rates subsequently equalized. Overall healing at 4 weeks after end of treatment was not significantly better in the HBOT group, in keeping with the Cochrane findings.

Setting aside the concerns about the lack of robust data demonstrating efficacy, there is also the issue of effectiveness and cost-effectiveness in the real world. The CMS decision states that HBOT can be offered to patients who have diabetic foot ulcers for whom at least 30 days of standard wound care has failed and who have a Wagner grade III lesion or higher (meaning the ulcer must penetrate to tendon, bone, or joint and may be associated with deep abscess, osteomyelitis, gangrene, or septic arthritis). What does this mean for the potential demand for HBOT?

The number of diabetic persons in the United States was estimated to be ~17,700,000 in 2000 [30], although the American Diabetes Association suggests that the number is now 20.8 million (one-third of whom have gone undiagnosed) [31]. Studies suggest a 1.0%–4.1% incidence of foot ulceration among diabetic persons, a prevalence of ulceration of 4%–10%, and a lifetime incidence of 25% [32]. Using the American Diabetes Association estimate, taken together, this suggests there will be between 802,000 and 2,100,000 ulcers undergoing treatment at any time and 210,000–824,000 new ulcers annually in the United States. In a study of a large database of >31,000 individuals treated for foot ulcers by Curative Health Services System, Margolis et al. [33] noted that 25% of ulcers were Wagner grade II or above; at a conservative estimate, 10% of all ulcers will be Wagner grade III or worse, suggesting that 21,000–82,000 will be eligible for HBOT. Treatment generally consists of 30–40 daily sessions, each course of treatment costing ~$12,000 [34]. Total costs for treating all grade III ulcers would be in the range of $252 million to $984 million.

This is assuming that selection of cases for treatment is entirely appropriate, something that, as we shall see, cannot be guaranteed. Considerably higher numbers of cases have major problems in healing. In Margolis and colleagues’ cohort [35], some 45% of cases were unhealed at 20 weeks, and this could be predicted with 69% accuracy using surrogates of wound healing at 4 weeks. The suggestion, therefore, could be that nearly one-half of all ulcers might fulfill the Medicare criteria of failure to progress at 4 weeks (30 days), opening up a much larger group of patients (100–400,000) as potential candidates for treatment, depending on the zeal of the physician and the nuances of classifying the ulcer.

Certainly if HBOT does indeed prevent amputation, with a number-needed-to-treat of 4, this would see the additional average cost (additional to standard ulcer care, and any surgical and antibiotic intervention) per amputation avoided as $48,000, and this might be considered cost-effective. But overall expenditures of this magnitude need to be set against other potential health interventions of far greater proven benefit. For a simple example, with a podiatry consultation costing $60–$100 and a pair of custom shoes costing $250 (David Armstrong, personal communication), $984 million would fund 2 consultations and 2 pairs of custom made pressure-relieving shoes per year for >1 million diabetics. Furthermore, there is evidence that basic care of the diabetic foot is often neglected. In one study of 255 patients admitted to a US teaching hospital with diabetic foot infection, 31% were not evaluated for ischemia, 33% had no foot radiographs obtained, and 60% were not evaluated for protective sensation, and 90% of wounds were not evaluated for involvement of underlying structures [36].
Given the importance of identifying basic prognostic factors such as this when planning treatment, it would seem far more appropriate to concentrate resource on basic preventive and management methods before investing in HBOT.

The view expressed in this article has not been sufficiently widely held to prevent hyperbaric medicine from becoming a thriving industry. In 2000, the Office of the Inspector General of the Department of Health and Human Services reviewed Medicare claims for HBOT for the period of 1995–1998 [34]. The report identified $76 million paid out for 15,687 beneficiaries (a tiny fraction of the possible market in diabetic foot ulcers, with an average cost per patient of over $12,000. The 5% most expensive cases cost $50,000–$325,000 each. Furthermore, charges increased by 52%, beneficiaries by 27%, physician providers by 54%, and hospital outpatient providers by 122%. It was therefore disturbing that the report went on to note that of $49.9 million paid to physicians, it was considered that $14.2 million was paid inappropriately, $4.9 million was paid for treatments considered to be “excessive,” and $11.1 million was paid for appropriate indications but with insufficient evidence of good care.

It is important to understand that, although this report predicted the CMS determination on reimbursement for HBOT (so that, arguably, some of the inappropriateness activity during the studied period may have been subsequently legitimized), this did not stop the Office of Inspector General identifying, in the 2004 Cost Saving Handbook or “Red Book,” more than $19 million in savings to be made by stopping inappropriate payments for HBOT [37].

Meanwhile, ever more extraordinary versions of HBOT are offered, such as topical hyperbaric oxygen therapy. This involves the enclosure of the limb or the ulcer in a container (commonly a plastic bag) that is then filled with oxygen. High pressure cannot be applied, because this would compromise the blood supply to the area. Claims for the effectiveness of this treatment have been made [38, 39], but randomized trials have shown no benefit [40]. Although it is therefore welcome that the Undersea and Hyperbaric Medical Society has specifically rejected topical HBOT as having any basis as a legitimate therapy [41], it is nonetheless a concern that, like any other health care technology, possession of the technology and the faith of doctors and patients in its magical qualities can drive some to offer treatment where there is no supporting evidence base.

The management of diabetic foot ulceration requires coordinated multidisciplinary work for successful outcomes, and significant challenges remain when trying to heal diabetic foot wounds as quickly as possible. The spectre of major limb amputation is ever present, and it is easy to see how HBOT could seem a plausible additional treatment valuable for some patients. A robust review of published data suggests that there are no reliable data on improved rates of healing, and that, although the risk of major amputation may possibly be reduced, this conclusion relies for its validity on the results of flawed, nonblinded, non–placebo-controlled studies. Caution is strongly advised before HBOT becomes widely accepted for diabetic foot ulceration, given the potential for very large numbers of patients to be eligible.

Hyperbaric oxygen is a technology that has been proposed for the treatment of a wide range of indications that now include diabetic foot wounds. It is time that the advocates of this therapy organized large, randomized, placebo-controlled trials to provide definitive answers to the questions: which, if any, patients would benefit from HBOT for a diabetic foot wound, and how great is any measurable benefit? Until such data are forthcoming, hyperbaric oxygen therapy should not be offered for diabetic foot wounds.

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References


