A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers

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ABSTRACT

BACKGROUND: The role of hyperbaric oxygen (HBO_2) for the treatment of diabetic foot ulcers (DFUs) has been examined in the medical literature for decades. There are more systematic reviews of the HBO_2 / DFU literature than there have been randomized controlled trials (RCTs), but none of these reviews has resulted in a clinical practice guideline (CPG) that clinicians, patients and policy-makers can use to guide decision-making in everyday practice.

METHODS: The Undersea and Hyperbaric Medical Society (UHMS), following the methodology of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, undertook this systematic review of the HBO_2 literature in order to rate the quality of evidence and generate practice recommendations for the treatment of DFUs. We selected four clinical questions for review regarding the role of HBO_2 in the treatment of DFUs and analyzed the literature using patient populations based on Wagner wound classification and age of the wound (i.e., acute post-operative wound vs. non-healing wound of 30 or more days). Major amputation and incomplete healing were selected as critical outcomes of interest.

RESULTS: This analysis showed that HBO_2 is beneficial in preventing amputation and promoting complete healing in patients with Wagner Grade 3 or greater DFUs who have just undergone surgical debridement of the foot as well as in patients with Wagner Grade 3 or greater DFUs that have shown no significant improvement after 30 or more days of treatment. In patients with Wagner Grade 2 or lower DFUs, there was inadequate evidence to justify the use of HBO_2 as an adjunctive treatment.

CONCLUSIONS: Clinicians, patients, and policy-makers should engage in shared decision-making and consider HBO_2 as an adjunctive treatment of DFUs that fit the criteria outlined in this guideline. The current body of evidence provides a moderate level of evidence supporting the use of HBO_2 for DFUs. Future research should be directed at improving methods for patient selection, testing various treatment protocols and improving our confidence in the existing estimates.

EXECUTIVE SUMMARY: Recommendations for the use of hyperbaric oxygen therapy in diabetic foot ulcers

RECOMMENDATION 1: In patients with Wagner Grade 2 or lower diabetic foot ulcers, we suggest against using hyperbaric oxygen therapy (very low-level evidence in support of HBO_2, conditional recommendation).

RECOMMENDATION 2: In patients with Wagner Grade 3 or higher diabetic foot ulcers that have not shown significant improvement after 30 days of treatment, we suggest adding hyperbaric oxygen therapy to the standard of care to reduce the risk of major amputation and incomplete healing (moderate-level evidence, conditional recommendation).

RECOMMENDATION 3: In patients with Wagner Grade 3 or higher diabetic foot ulcers who have just had a surgical debridement of an infected foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; incision and drainage [I&D] of deep space abscess; or necrotizing soft tissue infection), we suggest adding acute post-operative hyperbaric oxygen therapy to the standard of care to reduce the risk of major amputation and incomplete healing (moderate-level evidence, conditional recommendation).

INTRODUCTION

The Centers for Disease Control (CDC) estimates that approximately 25.8 million people, or roughly 8.3% of the U.S. population, are affected by diabetes [1]. More than 60% of non-traumatic amputations in the United States occur in people with diabetes, and a foot ulcer precedes 85% of lower-limb amputations in patients with diabetes. Contralateral leg amputation follows for 56% of patients within three to five years, and the five-year mortality rate for diabetic patients who have had a single-leg amputation is 60% [2]. This figure is higher than the overall five-year mortality rate of breast cancer (10%), bladder cancer (19%), colorectal cancer (33%), and all cancers combined (32%) [3].

Examination of the literature provides nine randomized controlled trials (RCTs) [4-12], over 20 observational (OBS) studies [13-36], and nearly a dozen review articles [37-48]. These studies are hampered by small sample sizes, inconsistent treatment protocols, and less-than-rigorous methodology, leading to continuous debate about the role of hyperbaric oxygen (HBO_2) for the treatment of DFUs. What is not debated is that HBO_2 should be considered an adjunctive treatment and cannot take the place of surgical removal of devitalized tissue and high-quality wound management.

The use of comprehensive foot care programs that included early screening and evaluation of problems, foot care education, preventive therapy and referral to specialists has been shown to reduce amputation rates by 49%-85% [49]. After reviewing the literature, it is obvious that "standard wound care" is highly variable. The International Working Group on the Diabetic Foot (IWGDF) guidelines for the best practice treatment of DFUs includes four tenets: treatment of underlying infection; revascularization if appropriate and feasible; offloading to minimize trauma to the ulcer site; and management of the wound bed to promote healing [46]. Failure to address these tenets obviates any discussion about the utility of HBO_2 for DFUs.

One difficulty in analyzing the existing body of literature lies in the heterogeneity of the patient populations being studied, the interventions being used and the outcomes being compared. Wound classification is not standardized, comorbidities are not screened consistently, and subgroups of patient acuity are not consistently reported. Modern use of the Wagner classification system (Table 1) grades wounds on observations such as deformity, depth, infection, gangrene and location [51]. The University of Texas classification system (Table 1) combines the presence or absence of infection plus perfusion in a vertical scale and the depth of the wound on a horizontal scale to generate a 16-choice matrix [52]. The Infectious Disease Society of America (IDSA) bases its classification system (Table 1) on the severity of diabetic foot infections and has shown an increased trend for more frequent and higher levels of amputation with the seriousness of infection [53]. It is difficult to find a single classification system that addresses all of the relevant comorbidities contributing to the pathology of a diabetic foot ulcer, but the IWGDF attempted to do this by developing a classification system (Table 1) for research purposes based on five key categories: perfusion; extent/size; depth/tissue loss; infection; and sensation (PEDIS) [54,55].

Strauss described a similar system (Table 1) but adds an assessment of the wound base using a 0 to 10 scoring system to make logical decisions between limb salvage or major amputation [56]. A recent guideline by the Society for Vascular Surgery (Table 1) published similar risk stratification based on three major factors that impact amputation risk and clinical management – wound, ischemia and foot infection (WIfI) – to generate a matrix of 32 permutations of wound categories that generally have worse outcomes as one moves down and to the right [57].

Despite consensus between foot and ankle surgeons and hyperbaric physicians that the Wagner grade is archaic and inadequate, most of the historical and contemporary studies and most reimbursement determinations with regard to the use of HBO_2 for DFUs are based on the Wagner DFU wound appearances.

METHODS

The Institute of Medicine published eight standards for the development of reliable Clinical Practice Guidelines [58]. These standards include conducting a systematic review, appropriate management of existing conflicts of interest, transparent guideline development process and clearly articulated recommendations derived and

Table 1. Features of wound grading systems

GRADING CLASSIFICATION	GRADE TIER	GRADING SYSTEM
Classic Wagner Grading System	6 grades based on anatomy and presence of infection	Grade 0 no open lesion, may have healed lesions Grade 1 superficial ulcer without penetration to deeper layers Grade 2 deeper ulcer, reaching tendon, bone, or joint capsule Grade 3 deeper tissues are involved, and there is abscess, osteomyelitis, or tendonitis Grade 4 there is gangrene of some part of the toe, toes, and/or forefoot Grade 5 gangrene involves the whole foot or enough of the foot that no local procedures are possible and BKA is indicated
University of Texas Health Science Center at San Antonio	4 stages based on absence or presence of ischemia and infection	Stage A no infection Stage B infection Stage C ischemia Stage D infection and ischemia
	4 grades based on extent and depth of wound	Grade 0 epithelialized wound Grade 1 superficial wound Grade 2 wound penetrating tendon or capsule Grade 3 wound penetrating bone or joint
IDSA (Infectious Disease Society of America)	4 grades 4 IDSA levels of based on severity of severity of infection	Grade 1 infection with at least two of following criteria: localized swelling, erythema, pain, warmth, purulent discharge; PEDIS 1; IDSA infection severity: uninfected Grade 2 local infection involving only skin and subcutaneous tissue with erythema >0.5 cm and < 2 cm around ulcer; PEDIS 2; IDSA infection severity: mild Grade 3 local infection with erythema > 2 cm or involving structures deeper to skin and subcutaneous tissue with no signs of systemic inflammation; PEDIS 3: IDSA infection severity: moderate Grade 4 local infection with systemic inflammation response signs (SIRS) with two or more of the following criteria: temp > 38 degrees or < 36 degrees, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg, white blood count (WBC) > 12,000 or < 4000 cells/microliter or > 10% immature band forms; PEDIS 4: IDSA infection severity: severe

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rated in a standardized fashion. The review and the guideline should be developed by a multidisciplinary group of content and methodological experts (Guideline Development Group), followed by external assessment of recommendations, and frequent regular updates.

The Undersea and Hyperbaric Medical Society has sought to adhere to these standards by using the following protocol:

Oversight Committee

The Oversight Committee consists of a representative from the UHMS Board of Directors, the UHMS Oxygen Therapy Committee, the UHMS Quality, Utilization, Authorization and Reimbursement Committee, the UHMS Publications Committee, the UHMS International Membership and a member of the GRADE Working Group. The Oversight Committee is tasked with the development of a series of clinical practice guidelines (CPGs) for the appropriate use of HBO_2. The Oversight Committee invites potential members of the CPG review committee based on individual areas of expertise, which may or may not include HBO_2. The Oversight Committee reviews curriculum vitae of potential members and evaluates each candidate for potential conflicts of interest using responses to a questionnaire detailing the potential reviewers' financial interests involving the HBO_2 indication in question. Any reviewer who is deemed to have an unacceptable conflict of interest is not included on the review committee. In addition, the Oversight Committee also serves in the internal review process of manuscripts for publication resulting from the systematic reviews.

Table 1. Features of wound grading systems *(continued from previous page)*

GRADING CLASSIFICATION	GRADE TIER	GRADING SYSTEM
International Working Group on the Diabetic Foot	Five categories, scored based on different criteria	**Perfusion** Grade 1 no signs/symptoms of PAD Grade 2 symptoms or signs of PAD, but not of critical limb ischemia (CLI) Grade 3 critical limb ischemia as defined by systolic ankle blood pressure <50 mm Hg or systolic toe blood pressure <30 mm Hg or $TcPO_2$ < 30 mm Hg.
		Extent/size No scoring system was provided. Recommendations were that wounds should be measured after debridement and that the frequency distribution of the size of the ulcers should be reported in each study as quartiles.
		Depth/tissue loss Grade 1 superficial full-thickness ulcer, not penetrating any structure deeper than the dermis. Grade 2 deep ulcer, penetrating below the dermis to subcutaneous structures, involving fascia, muscle or tendon Grade 3 all subsequent layers of the foot involved, including bone and/or joint (exposed bone, probing to bone)
		Infection Grade 1 no symptoms or signs of infection Grade 2 infection involving the skin and the subcutaneous tissue only (without involvement of deeper tissues and without systemic signs) Grade 3 erythema >2 cm plus one of the items described above (swelling, tenderness, warmth, discharge) or infection involving structures deeper than skin and subcutaneous tissues such as abscess, osteomyelitis, septic arthritis, fasciitis. No systemic inflammatory response signs, as described below Grade 4 any foot infection with the following signs of a systemic inflammatory response syndrome. This response is manifested by two or more of the following conditions: temperature >38°C or <36°C; heart rate >90 beats/minute; respiratory rate >20 breaths/minute; $PaCO_2$ <32-mm Hg; white blood cell count >12.000 or<4.000/cu mm; 10% immature (band) forms.
		Sensation Grade 1 no loss of protective sensation on the affected foot detected, defined as the presence of sensory modalities described below. Grade 2 loss of protective sensation on the affected foot is defined as the absence of perception of one of the following tests in the affected foot: • Absent pressure sensation, determined with a 10-g monofilament, on two out of three sites on the plantar side of the foot, as described in the International Consensus on the Diabetic Foot. • Absent vibration sensation, (determined with a 128-Hz tuning fork) or vibration threshold >25 V (using semi-quantitative techniques), both tested on the hallux.

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Review Committee

CPG review committee members were oriented to the review process and GRADE methodology using slide presentations, reading lists and webcasts. Review committee members were then asked to participate in the multistep process outlined below.

GRADE methodology

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework is based on the clear separation between quality of evidence and strength of recommendations, an explicit evaluation of the importance of outcomes or alternative management strategies, explicit and comprehensive criteria for downgrading and upgrading the quality of evidence rating, a transparent system of moving from evidence to recommendations, explicit acknowledgment of values and preferences of patients and clear, pragmatic interpretation of strong versus conditional recommendations for clinicians, patients, and policy-makers (Table 2) [59-73]. This methodology has been adopted

Table 1. Features of wound grading systems *(continued from previous page)*

GRADING CLASSIFICATION	GRADE TIER	GRADING SYSTEM
Strauss Wound Score	Five assessments, each graded 0 – 2 points (half points used for mixed or intermediate findings)	**Appearance** (wound base) 2 points for red 1 point for white (biofilm-fibrous membrane)/yellow (exudate) 0 points for black (necrotic, wet gangrene or fluctuant eschar)
	Healthy wound 7.5 – 10 points	**Size** 2 points for less than the surface area of patient's thumbprint 1 point for thumbprint to fist-size 0 points for larger than fist size
	Problem wound 3.5 – 7 points	**Depth** (including maximum depth of probe) 2 points for skin coverage and 1.5 points for subcutaneous tissue 1 point for muscle and/or tendon 0 points for bone and/or joint
	Futile wound 0 – 3 points	**Bioburden** 2 points for colonized 1 point for cellulitis, maceration, and/or deep infection (bone, joint, bursa, or cicatrix) 0 points for septic (unstable blood sugars, leukocytosis, positive blood cultures, fever, chills)
		Perfusion (use secondary findings of color, temperature & capillary refill if exam obscured by edema, scar, hidebound skin and/or previous surgery) 2 points for palpable pulses 1 point for biphasic or triphasic dopplerable pulses (cool, pale or dusky, capillary refill 2-5 secs) 0 points for monophasic or imperceptible pulses (cold, black/cyanotic/purplish, capillary refill >5 secs)
Society for Vascular Surgery Wound Ischemia Foot Infection (WIfI) System	4 grades for each of three criteria of wound, ischemia and foot infection (WIfI)	**Wound** Grade 0 no ulcer or gangrene Grade 1 shallow ulcer; no gangrene Grade 2 deeper ulcer with exposed joint or tendon; gangrene limited to digits Grade 3 deep ulcer involving forefoot, midfoot, heel; extensive gangrene involving forefoot, midfoot, or heel
		Ischemia Grade 0 ABI ≥ 0.80; arterial systemic pressure >100 mm Hg; and/or $TcPO_2$ ≥ 60 mm Hg Grade 1 ABI 0.6-0.79; arterial systemic pressure 70-100 mm Hg; and/or $TcPO_2$ 40-59 mm Hg Grade 2 ABI 0.4-0.59; arterial systemic pressure 50-70 mm Hg; and/or $TcPO_2$ 30-39 mm Hg Grade 3 ABI ≤ 0.39; arterial systemic pressure 50-70 mm Hg; and/or $TcPO_2$ <30 mm Hg
		Infection Grade 0 uninfected: no signs or symptoms Grade 1 local infection: erythema > 0.5 cm and ≤ 2 cm with pain, warmth, purulent discharge (mild) Grade 2 local infection with > 2 cm erythema; involves deeper structures (moderate) Grade 3 local infection with signs of SIRS (refer to IDSA definition) (severe)

by over 70 organizations including the Cochrane Collaboration, the World Health Organization (WHO), the Centers for Disease Control (CDC), and the Agency for Healthcare Research and Quality (AHRQ).

Formulation of questions and selection of outcomes

The first task of the Review Committee is to create a list of clinically relevant questions to be answered in the guideline. These questions are created using the Patient, Intervention, Comparison and Outcomes (PICO) format. This allows for the creation of a clearly defined patient population, an intervention to be compared with an alternative treatment, and a set of clinical outcomes rated on a nine-point scale defining that outcome as critical, important, or not important.

Table 2. Steps of the GRADE review methodology

- **Formulate question (PICO format)**
- **Select outcomes of importance**
- **Rate importance of outcomes (1-9)**
- **Literature review**
  - create evidence profile of outcomes across studies
  - summary of findings and estimate of effect for each outcome
- **Rate quality of evidence for each outcome using criteria in Table 3**
  - rate overall quality of evidence across outcomes based on the lowest quality of critical outcomes
- **Formulate recommendations**
  - for or against
  - strong or conditional
    - taking into account quality of evidence, balance of harms vs. benefits, and the values and preferences of patients and clinicians
    - recommendations may also take into account resource use (cost)

The term "standard wound care" is meant to represent the optimal management of surgical debridement, mechanical offloading, infection control, revascularization and metabolic control. Pre-HBO_2 treatment of Wagner Grade 3 and 4 DFUs is assumed to include surgical excision of all devitalized tissues. These four questions were formulated by the Review Committee:

1. For a patient with a diabetic foot ulcer, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?
2. For a patient with a Wagner Grade 2 or lower DFU that has not shown significant improvement after 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?
3. For a patient with a Wagner Grade 3 or higher DFU that has not shown significant improvement after 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?
4. For a patient with a Wagner Grade 3 or higher DFU who has just had a surgical debridement of the foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; I&D of deep space abscess; or necrotizing soft tissue infection), is acute postoperative HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

Table 3. Outcomes of interest

- **Critical outcomes**
  - major amputation
  - incomplete healing at one year
- **Important outcomes**
  - resolution of infection
  - quality of life (SF36)
  - minor amputation

Outcomes of interest

The outcomes of interest selected by the Review Committee are listed in Table 3. Each member of the Review Committee rated outcomes for clinical importance using a nine-point scale. A consensus on critical outcomes was then obtained via group discussions.

Search strategy

We identified published systematic reviews of HBO_2 for DFU [37-47] and cross-referenced them to identify RCTs and OBSs of interest (Table 4). Observational studies (OBSs) included any non-randomized comparative studies using either historical or contemporary control groups. We decided to include OBSs because the number of available RCTs was small and was unlikely to answer all our questions about the various types of patients included in the scope of this guideline. We then performed a subsequent librarian-assisted search of the Medline, Embase and Cochrane databases to identify if there were any RCTs that were not included in the published systematic reviews. Search dates included articles published up through April 2015. Medical Subject Headings (MeSH) terms were used. The keywords "leg ulcers," "diabetes" and "hyperbaric oxygenation' were used, along with their synonyms. A detailed search strategy is included in Appendix A.

Trial selection

Titles and abstracts from the search results were independently reviewed by two panelists (E.H. and E.W.) to select potentially relevant articles. The inclusion criteria were RCTs comparing patients with diabetic foot ulcers with a control group. We eliminated studies if they did not include the populations as defined by the PICO questions, if they did not include the outcomes of interest, or if they did not include a comparison group.

Table 4. Systematic reviews of HBO_2 as adjunctive treatment for DFU

Systematic review	Databases used	RCT	Non-RCT
Wunderlich et al. **2000**	Medline	Doctor Faglia	Baroni Oriani Wattel Zamboni
Wang 2003	Medline	Doctor Faglia	Baroni Faglia Oriani Wattel Zamboni
Roeckl-Wiedmann et. al. **2005**	Medline, Embase, Cochrane Library, DORCTHIM	Abidia Doctor Faglia Kessler Lin	none
Goldman 2009	Ovid Medline	Abidia Doctor Faglia Kessler	Baroni Faglia Fife Kalani Oriani Zamboni
Kranke, et al. **2012**	Central, Ebsco Ovid Medline Ovid Embase CINAHL	Abidia Doctor Duzgun Faglia Kessler Lin Löndahl	none
Bishop and Mudge 2012	PubMed CINAHL	Abidia Duzgun Faglia Kessler Löndahl	Baroni Cianci Faglia Fife Kalani Lyon Ong Oriani Oubre Zamboni Zgonis
Game, et al. **2012**	Medline Embase	Duzgun Löndahl	Chen
Liu, et al. **2013**	Medline Embase Cochrane Library	Abidia Doctor Duzgun Faglia Kessler Löndahl	Baroni Kalani Oriani Zamboni
Löndahl 2013	Not given	Abidia Doctor Duzgun Faglia Kessler Löndahl	Baroni Chen Kalani Kaya Lyon Margolis Oriani Wattel Zamboni
Murad 2013	Medline Embase Cochrane Library Scopus	Abidia Doctor Duzgun Faglia Kessler Löndahl	none
O'Reilly, et al. **2014**	Medline Embase CINAHL PubMed Biosis Cochrane Library	Abidia Doctor Duzgun Faglia Kessler Löndahl	Baroni Faglia Kalani Lyon Oriani Zamboni
Stoekenbroeck et al. **2014**	Medline Embase Cochrane Library	Abidia Doctor Duzgun Faglia Kessler Löndahl Ma	none

Data extraction

Two panelists (E.H. and E.W.) independently extracted the data using predetermined criteria and presented the summary of evidence to the remainder of the panel to reach consensus. We attempted to contact authors of studies to obtain original trial data if we could not identify clear patient groups, but we did not receive any replies to our inquiries.

Statistical techniques

Meta-analysis of relevant RCTs and observational studies was carried out using the Revman software package (Review Manager, version 5.2). A description of statistical terms is provided in Table 5. We pooled outcome data using the number of events and sample size of the control and experimental groups reported in published manuscripts. The results were depicted in a forest plot showing the individual effect sizes as well as the weighted pooled summary effect size with con-

TABLE 5. Summary of statistical techniques in forest plots [1]

Statistical/ parameter technique	Definition/Purpose	Application in GRADE methodology
Forest plot	A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result.	Used to evaluate for GRADE criteria including imprecision inconsistency and large effect size
Odds ratio	The ratio of the odds of an event in one group to the odds of an event in another group. In studies of treatment effect, the odds in the treatment group are usually divided by the odds in the control group. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome. When the risk is small, odds ratios are very similar to risk ratios.	Used for dichotomous data.
Risk ratio	The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome.	Used for dichotomous data.
Confidence intervals	A measure of the uncertainty around the main finding of a statistical analysis. Estimates of unknown quantities, such as the odds ratio comparing an experimental intervention with a control, are usually presented as a point estimate and a 95% confidence interval. This means that if someone were to keep repeating a study in other samples from the same population, 95% of the confidence intervals from those studies would contain the true value of the unknown quantity.	Wide confidence intervals suggest imprecision; non-overlapping confidence intervals suggest inconsistency (heterogeneity)
Tests of heterogeneity: I^2	A measure used to quantify heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity.	I^2 statistic used to determine level of inconsistency across studies (i.e., degree of heterogeneity)
Random effects model	A statistical model in which both within-study sampling error (variance) and between- studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.	Used in meta-analysis when there is variation in effect size
Fixed effects model	A model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance.	Used in meta-analysis when there is similarity in effect size
Peto method/ odds ratio analysis	A way of combining odds ratios that has become widely used in meta-analysis. It is a fixed-effects model.	Peto odds ratio effect size used in meta-analysis with experimental or control groups with low or zero number of events

[1] Definitions of statistical terms provided are taken from the *Glossary of Terms in the Cochrane Collaboration* (Version 4.2.5, Cochrane Collaboration, 2006). (https://www.cochrane.org/sites/default/files/uploads/glossary.pdf)

Table 6. Factors that affect the rating of the quality of evidence

- **RATE DOWN**
  - **risk of bias**
    - lack of blinding
    - stopping early for benefit
    - no allocation concealment
    - patients lost to follow-up
    - no intention to treat analysis
  - **inconsistency**
  - **indirectness**
  - **imprecision**
  - **publication bias**
- **RATE UP**
  - **large magnitude of effect**
  - **evidence of dose-response effect**
  - **all plausible confounders would increase confidence in the magnitude of effect**

Table 7. Levels of evidence

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate of effect.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate of effect.
Very low	Any estimate of effect is very uncertain.

fidence intervals. We calculated the I^2 as a measure of heterogeneity. The I^2 statistic represents the proportion of variability that is attributable to heterogeneity rather than chance or random error. The higher the I^2 statistic is, the greater the degree of heterogeneity. When heterogeneity was judged to be substantial, we rated down the quality of evidence. There is no specific I^2 cutoff point above which the evidence is rated down for heterogeneity. An arbitrary cutoff of 50% is often used, but this is paired with a judgment of whether the majority of studies support a specific action and whether the observed heterogeneity is clinically meaningful (i.e., a very high I^2 may not be important if the difference in effect size is not clinically important across studies).

We presented results using risk ratios (i.e., relative risk) for binary outcomes and mean differences for continuous outcomes. Peto odds ratio was used when events were rare (small or zero events). Considering the heterogeneity of available studies, we decided *a priori* to use the random effects model for meta-analysis. The random effects model takes into account the variation in effect size between studies. In cases where there was only one study to analyze, we calculated a simple odds ratio and confidence interval.

Rate quality of evidence for each outcome

The committee constructed summary of evidence tables and assessed the risk of bias of the studies. Whenever possible, we used intention-to-treat analysis (even if the original manuscripts did not report it in this manner) by using a worst-case scenario assuming healing in the control group and failure to heal in the study group. This data matrix allowed reviewers to extract evidence profiles for each of the five outcomes from the entire body of literature. Randomized controlled trials and observational studies were both analyzed, and the body of literature (RCT vs. OBS) with the highest level of evidence was used for decision-making. If there was equivalent level of evidence and the magnitude of effect was similar, the RCT and OBS studies were analyzed together. If there was equivalent level of evidence but the magnitude of effect was dissimilar, only the RCT studies were used.

The committee applied the relevant factors outlined in the GRADE methodology to rate the quality of evidence up (more reliable) or down (less reliable) (Table 6), and assigned a final rating for each outcome for each PICO question. In many analyses, the effect size was large or very large (i.e., two to five times reduction in relative effect). We opted to rate up only one level (as opposed to two for very large effect). It is also reasonable to not rate up in the presence of factors that lead to rating down. This decision is explicit in the tables that describe our judgments and process. This semi-quantitative "score" corresponds to an overall quality of evidence rating using the four-tiered GRADE quality levels (very low; low; moderate; and high) (Table 7).

Formulating recommendations

A final rating of the quality of evidence (across all outcomes) was given based on the critical outcome with the lowest level of evidence. The Review Committee then formulated recommendations for each PICO question. This step required assigning a level of strength

Table 8. Strength of recommendations and implications for the general population, healthcare workers and policy-makers

STRONG

Population
Most people in this situation would want the recommended course of action, and only a small proportion would not.

Healthcare workers
Most people should receive the recommended course of action.

Policy-makers
The recommendation can be adapted as a policy in most situations.

CONDITIONAL

Population
The majority of people in this situation would want the recommended course of action, but many would not.

Healthcare workers
Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision-making.

Policy-makers
There is a need for substantial debate and involvement of stakeholders.

for each recommendation using the two-tiered GRADE levels (conditional or strong) (see Table 8). The final recommendations were agreed upon by consensus.

External review

The UHMS Oversight Committee reviewed the document before undergoing additional review by content experts. Content experts included specialists who treat DFUs but who do not provide HBO_2. Once the review committee addressed any concerns, the document was posted for public comment. After the review committee addressed any public comments, the manuscript was submitted for publication. All public comments and committee responses are posted on the UHMS website (*www.uhms.org/cpg*).

Patient engagement

Two groups of patients with DFU were invited to participate in the formulation of this guideline. Both patients who had received HBO_2 and patients who had not received HBO_2 were included. The first group was recruited from a wound and hyperbaric medicine clinic to answer an online survey rating the outcomes selected by the Review Committee using a nine-point scale. This was an IRB-approved approach. The second group was recruited from a wound and hyperbaric medicine clinic to attend a face-to-face meeting with members of the Review Committee using video conferencing technology. The CPG development process and recommendations were presented to the patients. The Review Committee solicited patient perspective on multiple issues ranging from their fears and concerns at their initial consultation to their view of the successes and failures of their treatment course. The values, opinions and perspectives of these patients are reported below.

RESULTS

Patient survey results

An IRB-approved survey was offered to all diabetic patients of one of the authors' hospital system. Six patients completed the online survey. No patients had any financial relationship with a hyperbaric chamber manufacturer or hyperbaric operations. Three patients had a DFU and three did not. By chance, all three patients with a DFU had received HBO_2 or were scheduled to receive HBO_2. One patient had an incomplete course of HBO_2 based on a clinical decision regarding the wound progress. No patients had any portion of their foot amputated. When rating the outcomes of interest for importance, three of the three patients who answered this question rated all of the outcomes nine of nine (of critical importance).

Evidence review

The review committee used published systematic reviews to identify nine randomized controlled trials and 21 observational studies for initial review. The subsequent formal review included 655 references but did not identify any additional RCTs that were not previously identified from the systematic reviews. Studies were eliminated from consideration if they did not report data on the outcomes of interest or did not include patients in the specific study populations (Table 9).

Five of the RCTs (Doctor 1992, Faglia 1996, Abidia 2003, Duzgun 2008, and Löndahl 2010) were included for this analysis (Table 10). Of note, the Doctor study did not report the number of patients in each

Table 9. Outcomes reported by study

		OUTCOME REPORTED					COMMENTS
type	study	major amputation	incomplete healing (1 yr)	minor amputation	persistent infection	no change in quality of life	
RANDOMIZED CONTROLLED TRIALS	Doctor 1992						included
	Faglia 1996						included
	Lin 2001						excluded: abstract only without any outcomes of interest
	Abidia 2003						included: data on quality of life were not able to be included
	Kessler 2003						excluded: reported only for short-term outcomes (< 6 weeks)
	Duzgun 2008						included
	Löndahl 2010						included: data on quality of life were able to be included
	Kaur 2012						excluded: did not include populations of interest and did not include outcomes of interest
	Ma 2013						excluded: did not include outcomes of interest
OBSERVATIONAL TRIALS	Hart 1979						excluded: did not include outcomes of interest
	Davis 1987						excluded: did not include outcomes of interest
	Baroni 1987 Oriani 1990						included: these studies may have had overlapping patients, so the last dataset for 1990 was used for analysis
	Oriani 1992						excluded: did not include non-HBO_2 comparison grp
	Wattel 1991						excluded: did not include non-HBO_2 comparison grp
	Cianci 1994						excluded: did not include any outcomes of interest
	Zamboni 1997						included
	Faglia 1998						excluded: did not include non-HBO_2 comparison grp
	Kalani 2001						included
	Grollman 2001						excluded: did not include any outcomes of interest
	Fife 2002						excluded: did not include non-HBO_2 comparison grp
	Strauss 2002						excluded: did not include non-HBO_2 comparison grp
	Niinikoski 2003						excluded: did not include any outcomes of interest
	Fife 2007						excluded: did not include any outcomes of interest
	Oubre 2007						excluded: did not include non-HBO_2 comparison grp
	Ong 2008						excluded: did not include non-HBO_2 comparison grp
	Lyon 2008						excluded: did not include any outcomes of interest
	Kaya 2009						excluded: did not include non-HBO_2 comparison grp
	Chen 2010						excluded: did not include any outcomes of interest
	Margolis 2013						included
	Tongson 2013						excluded: did not include any outcomes of interest
	Bishop 2013						excluded: did not include non-HBO_2 comparison grp

Table 10. Summary of evidence table (included randomized controlled trials)

Study	Treatment groups HBO_2 protocol	Results		Outcomes – HBO_2 group vs. Standard care group*				Comment
Doctor 1992	15 HBO_2 vs. 15 SC 3 atm abs x 45 min, 4 treatments over 2 weeks	**Sub-groups**	**Major amputation**	**Incomplete healing**	**Minor amputation**	**Persistent infection**	**No change in quality of life**	Patients were all inpatients. HBO_2 protocol is not a standard treatment protocol.
		All	2/15 vs. 7/15	1/11 vs. 3/11				
		Wagner 2						
		Wagner 3	2/15 vs. 7/15		4/15 vs. 2/15	3/19 vs. 12/16		
		Wagner 4						
Faglia 1996	36 HBO_2 vs. 34 SC 2.2-2.5 atm abs x 90 min, 5-7 days/week	**Sub-groups**	**Major amputation**	**Incomplete healing**	**Minor amputation**	**Persistent infection**	**No change in quality of life**	Patients were all inpatients. Wagner subgroup analysis did not use intention-to-treat analysis, resulting in discrepancy in the denominator.
		All	3/36 vs. 11/34		21/35 vs. 12/33	9/35 vs. 16/33		
		Wagner 2	0/4 vs. 0/5					
		Wagner 3	1/4 vs. 0/8					
		Wagner 4	2/22 vs. 11/20					
Abidia 2003	9 HBO_2 vs. 9 HBAir (sham) 2.4 atm abs daily x 90 min, 5 days/week vs. 30 sham	**Sub-groups**	**Major amputation**	**Incomplete healing**	**Minor amputation**	**Persistent infection**	**No change in quality of life**	Double-blinded trial with use of sham hyperbaric air treatments.
		All	1/9 vs. 1/9	4/9 vs. 9/9	1/9 vs. 0/9			
		Wagner 2	1/9 vs. 1/9	4/9 vs. 9/9	1/9 vs. 0/9			
		Wagner 3						
		Wagner 4						
Duzgun 2008	50 HBO_2 vs. 50 SC 2.2-2.5 atm abs x 90 min, 5-7 days/wk	**Sub-groups**	**Major amputation**	**Incomplete healing**	**Minor amputation**	**Persistent infection**	**No change in quality of life**	Randomized trial of HBO_2 or SC, but no sham treatments or blinding of investigators.
		All	0/50 vs. 17/50	19/50 vs. 50/50	4/50 vs. 24/50			
		Wagner 2	0/6 vs. 0/12	6/6 vs. 12/12	0/6 vs. 4/12			
		Wagner 3	0/19 vs. 0/18	6/19 vs. 18/18	1/19 vs. 17/18			
		Wagner 4	0/25 vs. 17/20	7/25 vs. 20/20	3/12 vs. 3/18			
Löndahl 2010	49 HBO_2 vs. 45 HBAir (sham) 2.2-2.5 atm abs x 90 min, 5-7 days/wk	**Sub-groups**	**Major amputation**	**Incomplete healing**	**Minor amputation**	**Persistent infection**	**No change in quality of life**	Double-blinded trial with use of sham hyperbaric air treatments.
		All	3/49 vs. 1/44	24/49 vs. 33/45	4/49 vs. 4/45		26/49 vs. 35/45	
		Wagner 2						
		Wagner 3						
		Wagner 4						

* Whenever possible, intention-to-treat analysis was used if denominator of each group could be extrapolated from the manuscript.

Table 11. Risk of bias table

	Doctor 1992	Faglia 1996	Abidia 2003	Duzgun 2008	Löndahl 2010
no stopping early for benefit					
strict allocation concealment					
none lost to follow-up					
blinded study					
intention-to-treat analysis					
RISK of BIAS	MOD	MOD	MOD	MOD	LOW

study arm [5]. For the purposes of this analysis, we assumed an equal distribution in each group. The remaining studies were excluded because they did not report data on the preselected outcomes. Risk of bias was evaluated for the remaining RCTs using five criteria (Table 11). An indeterminate score was assigned if a study did not explicitly state whether it did or did not adhere to one of the criteria.

Table 12. Summary of evidence table (included observational studies)

		Outcomes (HBO_2 group vs. Standard group)					
study	**treatment groups HBO_2 protocol**	**major amputation**	**incomplete healing**	**minor amputation**	**persistent infection**	**no change in quality of life**	**comment**
Oriani 1990	2.8/2.5 atm abs x 90 min multiplace	3/62 vs. 6/19					Surgical staff performing debridements were blinded to treatment group; all patients were admitted for duration of study; inpatients only
Zamboni 1997	2.0 atm abs x 120 min	0/5 vs. 0/5		0/5 vs. 0/5			All wounds > 6 months old; only 5 patients in each group
Kalani 2001	2.5 atm abs x 90 min	2/17 vs. 7/21	4/17 vs 11/21				Followed patients out to 3 years; all Wagner <2 as none had deep space infection or gangrene
Margolis 2013	2.0 or 2.4 atm abs x 90 min	26/793 vs. 70/5466		27/793 vs. 45/5466			Healing was reported at Week 16

Two of the observational studies (Baroni 1987 and Oriani 1990) may have had overlapping datasets, so only the larger data set (Oriani 1990) was evaluated. Five of the observational studies (Oriani 1990, Zamboni 1997, Faglia 1998, Kalani 2001 and Margolis 2013) were included for this analysis (Table 12). The remaining studies were excluded because they either did not report data on the preselected outcomes or failed to provide a comparison group.

GRADE analysis was applied to the body of literature of both RCTs and OBSs, and the higher quality body of evidence was used to derive the recommendations (analysis of the observational studies is provided in the Supplemental Data section). The rationale as to why certain studies were included or excluded, as well as the justification for the GRADE scores that were used to arrive at the final GRADE level of evidence assignments is discussed below.

QUESTION 1

For a patient with a diabetic foot ulcer, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

RESPONSE

There were five randomized controlled trials (Doctor 1992, Faglia 1996, Abidia 2003, Duzgun 2008, and Löndahl 2010) and four observational studies (Oriani 1990, Zamboni 1997, Kalani 2001, and Margolis 2013) reviewed for this question. After comparing the final GRADE levels of evidence for both of the critical outcomes, the RCTs provided a higher quality of evidence and were used for decision-making (Supplemental Figures 1 and 2).

This patient population represented the most heterogeneity of all the groups, as it involved patients with diabetic foot ulcers of widely varying severity.

Critical Outcome:

Major amputation (Figure 1)

Five RCTs (Doctor 1992, Faglia 1996, Abidia 2003, Duzgun 2008, and Löndahl 2010) reported data on major amputation. One study (Faglia 1996) reported that one patient from each study arm was lost to follow-up. Their analysis did not include either of these patients, so was not by intention to treat (ITT). We were able to perform ITT analysis by assuming a worst-case scenario (i.e., assuming healing in the control group and failure to heal in the study group). In one study (Faglia 1996), the investigators were unblinded, but the surgeon who made the clinical decision to amputate or not was blinded. For this reason, this study received an indeterminate score for the risk of bias category for blinding. The heterogeneity in the major amputation rate between the Löndahl 2010 study and the remaining RCTs could be the result of stricter exclusion criteria in that study [10].

Forest plots using random effect risk ratio as well as Peto odds ratio were compared. The overall estimate of effect favoring HBO_2 was not significantly different (Supplemental Figure 1).

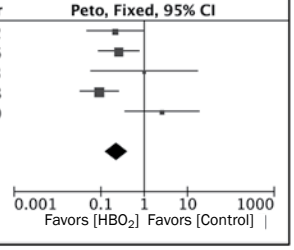
The final rating of the quality of evidence was *moderate*. Of note, there was a large magnitude of effect for this outcome (Figure 1).

Figure 1. **Forest plots and GRADE analysis for Question 1: For a patient with a diabetic foot ulcer, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?**

1a. Major Amputation

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Doctor 1992	2	15	7	15	16.7%	0.22 [0.05, 1.00]	1992
Faglia 1996	4	36	12	34	32.1%	0.26 [0.09, 0.78]	1996
Abidia 2003	1	9	1	9	4.8%	1.00 [0.06, 17.41]	2003
Duzgun 2008	0	50	17	50	36.5%	0.09 [0.03, 0.26]	2008
Londahl 2010	3	49	1	45	9.9%	2.58 [0.35, 18.94]	2010
Total (95% CI)		**159**		**153**	**100.0%**	**0.23 [0.12, 0.43]**	
Total events	10		38				

Heterogeneity: $Chi^2 = 9.70$, df = 4 (P = 0.05); $I^2 = 59\%$
Test for overall effect: Z = 4.58 (P < 0.00001)

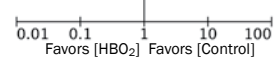


All DFU (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 4/5 studies, patients lost to follow-up in 2/5 studies, unblinded study in 2/5 studies and unclear blinding in 1/5 studies, lack of intention to treat analysis in 1/5 studies and unclear intention to treat analysis in 2/5 studies.
	Inconsistency	-1	The point estimates from the studies varied, the confidence intervals do not overlap to some extent and the I^2 is >50%
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision as Estimate of Effect had narrow Confidence Intervals. Peto analysis showed tighter confidence interval, but Random Effects Risk Ratio analysis was also deemed acceptable.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

1b. Incomplete Healing

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Abidia 2003	4	9	9	9	23.4%	0.47 [0.24, 0.95]	2003
Duzgun 2008	17	50	50	50	37.2%	0.35 [0.24, 0.51]	2008
Londahl 2010	24	49	33	45	39.4%	0.67 [0.48, 0.93]	2010
Total (95% CI)		**108**		**104**	**100.0%**	**0.48 [0.30, 0.77]**	
Total events	45		92				

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 3.07 (P = 0.002)



All DFU (Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 2/3 studies, patients lost to follow-up in 1/3 studies, no blinding in 1/3 studies, and unclear intention to treat analysis in 1/3 studies.
	Inconsistency	-1	The data for Incomplete Healing shows some inconsistency as the I^2 was >50%, resulting in rating down 1 point
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

Critical Outcome: Incomplete healing at one year (Figure 1)

All RCTs reported the proportion of ulcers healed at various time points, but only three (Abidia 2003, Duzgun 2008, and Löndahl 2010) reported healing at one year.

All studies reported results as the rate of complete healing. However the review committee felt that for the sake of consistency, the data should be reported as the risk of adverse outcomes (i.e., risk of incomplete healing or wound persistence). This analysis did result in differences in the estimate of effect, but ultimately had no difference in the overall quality of evidence (Supplemental Figures 2 and 3).

The final rating of the quality of evidence was *moderate*. Again, there was a large magnitude of effect present (Figure 1).

Outcome: Minor amputation
(Supplemental Figure 4)
Five RCTs reported data on minor amputation, defined as amputation distal to the ankle (Doctor 1992, Faglia 1996, Abidia 2003, Duzgun 2008, and Löndahl 2010). Forest plots using both random effects risk ratio and Peto odds ratio were constructed. The use of Peto OR resulted in a slightly more significant estimate of effect (0.96 vs. 0.72) and narrower confidence intervals. Neither the risk ratio nor odds ratio estimate of effect for minor amputation was statistically significant.

The final quality of evidence for this outcome was *very low.*

Outcome: Persistent infection
(Supplemental Figure 5)
Two RCTs (Doctor 1992, Faglia 1996) addressed the outcome of persistent infection. Both of these studies used wound cultures as a surrogate marker for infection instead of the IDSA criteria for clinical infection. This feature of these studies resulted in downgrading the quality of evidence for indirectness.

The final quality of evidence for this outcome was *very low*.

Outcome: Quality of life
Two studies (Abidia 2003, Löndahl 2010) addressed the outcome of quality of life, but data were not available to conduct a meta-analysis.

QUESTION 2

For a patient with a Wagner Grade 2 diabetic foot ulcer that has not shown significant improvement after 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

RESPONSE
There were three randomized controlled (Faglia 1996, Abidia 2003, and Duzgun 2008) and one observational study (Kalani 2001) that were reviewed for this question. While it did not specify that it included only patients with Wagner Grade 2 or lower DFUs, the Kalani study reported that none of the patients in that study had a deep infection or gangrene. Additional studies included patients with Wagner Grade 2 or lower DFUs (Löndahl 2010, Margolis 2013) but the data were not reported in such a way that it could be analyzed. The quality of evidence of both study designs was equal, but the effect sizes were not similar; thus, they were not combined and only the RCTs were included (Supplemental Figures 6 and 7).

Critical Outcome: Major Amputation (Figure 2)
Three RCTs (Faglia 1996, Abidia 2003, and Duzgun 2008) reported rates of major amputation. Two of the studies (Faglia 1996 and Duzgun 2008) had zero incidences of major amputation, and the remaining study (Abidia 2003) had equal number of amputations in each group. There was no evidence that HBO_2 had any effect on major amputation in this population.

Results were similar using a risk ratio or Peto odds ratio (Supplemental Figure 8).

The final GRADE quality of evidence for this outcome was *very low*.

Critical Outcome: Incomplete healing (Figure 2)
Only one RCT reported this outcome (Duzgun 2008). It may be noted that although the estimate of effect was very large, there was a wide confidence interval and no blinding of the study participants, leading to concerns about increased risk of bias. If this outcome was presented as complete healing (instead of the reciprocal, incomplete healing), the results are the same (Supplemental Figure 8).

The final GRADE quality of evidence for this outcome was *very low*.

Outcome: Minor amputation
(Supplemental Figure 9)
One RCT (Duzgun 2008) reported the outcome of minor amputation. A simple odds ratio was used for analysis.

The final GRADE quality of evidence for this outcome was *low*.

Outcome: Persistent infection
There were no RCTs or OBS studies that reported this outcome.

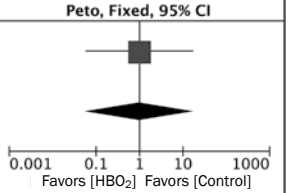
Outcome: Quality of life
There were no RCTs or OBS studies that reported this outcome.

Figure 2. **Forest plots and GRADE analysis for Question 2: For a patient with a Wagner Grade ≤ 2 diabetic foot ulcer that has not healed in 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?**

2a. Major Amputation

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Faglia 1996	0	4	0	5		Not estimable	1996
Abidia 2003	1	9	1	9	100.0%	1.00 [0.06, 17.41]	2003
Duzgun 2008	0	6	0	12		Not estimable	2008
Total (95% CI)		**19**		**26**	**100.0%**	**1.00 [0.06, 17.41]**	
Total events	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Wagner ≤2 (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	2/3 had unclear allocation concealment, 1/3 had unclear patients lost to follow-up, 1/3 studies was unblinded, and 1/3 had unclear intention-to-treat analysis and 1/3 had no intention-to-treat analysis
	Inconsistency	0	There was no evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-2	Wide confidence intervals in a single study with small number of events
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No evidence of large magnitude of effect
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

2b. Incomplete Healing

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	0	6	6	0.003 (0.001 - 0.175) Favors HBO_2
	Control	12	0	12	
	Total	12	6		

Wagner ≤2 (Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Study was not blinded
	Inconsistency	0	There was no evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-2	Wide confidence intervals in a single study with small number of events
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect however we did not rate up due to the small number of events and unblinded nature of the study.
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

QUESTION 3

For a patient with a Wagner Grade 3 or higher diabetic foot ulcer that has not shown significant improvement after 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

RESPONSE

There was one randomized controlled trial (Duzgun 2008) and two observational studies (Zamboni 1997 and Kalani 2001) that were reviewed for this question. After comparing the quality of evidence, data from RCTs were used for the analysis (Supplemental Figures 10-12).

Critical Outcome: Major amputation (Figure 3)

While additional RCTs (Löndahl 2010 and Faglia 1996) included patients with these criteria, the data were not reported in such a way that they could be analyzed. As a result, only one RCT was analyzed. This RCT had the largest number of subjects and had zero major amputations in the HBO_2 group. There is some concern about risk of bias, as this single study was unblinded. The remaining criteria for risk for bias were low, leading to an intermediate risk of bias.

The final quality of evidence for this outcome was *moderate*.

Critical Outcome: Incomplete healing (Figure 3)

The same RCT (Duzgun 2008) was also analyzed for the outcome incomplete healing. This study showed that no patients in the standard wound care group had complete healing at one year. The analysis for wound healing had similar odds ratios when reported as complete healing (Supplemental Figures 11 and 12).

The final quality of evidence for this outcome was *moderate*.

Figure 3. GRADE analysis for Question 3: For a patient with a Wagner Grade ≥ 3 diabetic foot ulcer that has not healed in 30 days of treatment, is HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

3a. **Major Amputation**

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	0	44	44	0.014 (0.0008 - 0.241) Favors HBO_2
	Control	17	21	38	
	Total	17	65		

Wagner ≥3 and ≥30 Days (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	Study was not blinded
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	0	Borderline imprecision due to small number of events
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect; however we did not rate up since study is unblinded
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

3b. Incomplete Healing

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	13	31	44	0.006 (0.0003 - 0.098) Favors HBO_2
	Control	38	0	38	
	Total	51	31		

Wagner ≥3 and ≥30 Days (Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Study was not blinded
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	0	Confidence interval boundaries are adequate for decision making
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect; however, since the study is unblinded, we did not rate up
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

Outcome: Minor amputation
There were no RCTs or OBS studies that reported this outcome.

Outcome: Persistent infection
There were no RCTs or OBS studies that reported this outcome.

Outcome: Quality of life
There were no RCTs or OBS studies that reported this outcome.

QUESTION 4

For a patient with a Wagner Grade 3 or higher diabetic foot ulcer who has just had a surgical debridement of the foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; I&D of deep space abscess; or necrotizing soft tissue infection), is acute post-operative HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?

RESPONSE
There were two randomized controlled trials (Doctor 1992 and Faglia 1996) and one observational study (Oriani 1990) that were reviewed for this question. The effect sizes of the two study designs were similar; thus, they were combined (Figure 4).

Critical Outcome: Major amputation (Figure 4)
In all three of the studies analyzed, patients were treated as inpatients with lengthy hospital stays. This in and of itself did not lead to a high level of indirectness, as the advantages of extended inpatient care were for enforced offloading, glycemic control, aggressive surgical debridement, and infection control – all of which are tenets of optimal wound care. All of these studies included HBO_2 as part of an aggressive surgical algorithm, where patients would be treated with HBO_2 soon after surgery, as opposed to having a delay of 30 days. One of the studies (Doctor 1992), however, had an atypical treatment protocol using only four 45-minute treatments at 3 atmospheres absolute (atm abs) in a two-week span. As a result, there may

Figure 4. **Forest plot and GRADE analysis for Question 4: For a patient with a Wagner Grade ≥ 3 diabetic foot ulcer who has just had a surgical debridement of the foot (e.g., partial toe or foot amputation, incision and drainage of deep space abscess, progressive necrotizing soft tissue infection), is acute post-operative HBO_2 with standard wound care more effective than standard wound care alone for the outcomes of interest?**

4a. Major Amputation: Observational Studies

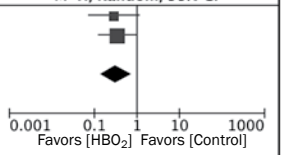
	Study Group	Event	Non-Event	Total	Odds Ratio
Oriani 1990	HBO_2	3	59	62	0.11 (0.24 - 0.50) Favors HBO_2
	Control	6	13	19	
	Total	9	72		

All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-1	Very small number of events
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect but very small number of events; therefore, we did not rate up
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

4b. Major Amputation: Randomized Controlled Trials

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Doctor 1992	2	15	7	15	35.8%	0.29 [0.07, 1.16]	1992
Faglia 1996	4	36	11	34	64.2%	0.34 [0.12, 0.98]	1996
Total (95% CI)		**51**		**49**	**100.0%**	**0.32 [0.14, 0.74]**	
Total events	6		18				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$
Test for overall effect: Z = 2.66 (P = 0.008)

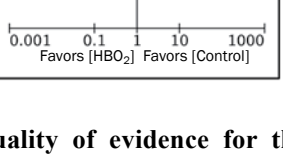


Wagner ≥3 and Surgical DFU (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	1/2 studies unblinded and 1/2 had single blinding, 2/2 had unclear allocation concealment, 1/2 had unclear patients lost to follow-up, 1/2 had unclear intention-to-treat analysis and 1/2 had no intention-to-treat analysis
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	We did not rate down although there is some evidence of indirectness as all patients in this study were inpatients, and 1/2 studies had a non-standard treatment protocol
	Imprecision	0	No evidence of imprecision; narrow confidence intervals with I^2 of 0%
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect however the number of events is small, therefore we did not rate up
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

4c. Major Amputation: Randomized Controlled Trials and Observational Studies Combined

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Oriani 1990	3	62	6	18	29.8%	0.15 [0.04, 0.52]	1990
Doctor 1992	2	15	7	15	25.1%	0.29 [0.07, 1.16]	1992
Faglia 1996	4	36	11	34	45.1%	0.34 [0.12, 0.98]	1996
Total (95% CI)		**113**		**67**	**100.0%**	**0.25 [0.13, 0.51]**	
Total events	9		24				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 2 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 3.84 (P = 0.0001)



be an element of indirectness, as the treatment profile in this study is not the one used in current practice.

When a meta-analysis of a combination of RCTs and OBSs was conducted, the effect size was slightly larger (lower relative risk) favoring HBO_2 over standard wound care. This effect size was statistically significant and the I^2 was 0%, indicating homogeneity of the results.

The final quality of evidence for this outcome was *moderate*.

Critical Outcome: Incomplete healing

There were no RCTs or OBS studies that reported this outcome.

Outcome: Minor amputation
(Supplemental Figure 13)
Only two RCTs (Doctor 1992 and Faglia 1996) reported data on minor amputation rate in this patient population.

It is important to note that there were other studies that included patients with Wagner Grade 3 or higher, but these patients were not stratified in the study, so subgroup analysis was not possible. The outcome of minor amputation was actually more common in the HBO_2 group. This result is consistent with what is found in clinical practice, as patients in this group may often undergo minor amputation instead of major amputation.

The final quality of evidence for this outcome was *low*.

Outcome: Persistent infection
There were no RCTs or OBS studies that reported this outcome.

Outcome: Quality of life
There were no RCTs or OBS studies that reported this outcome.

FROM EVIDENCE TO RECOMMENDATIONS
This guideline starts with the assumption that practitioners have aggressively addressed revascularization of the ischemic foot, debrided devitalized tissue, managed deformities by offloading the neuropathic foot, and utilized anti-infective therapies either before or concurrently with adjunctive hyperbaric oxygen therapy.

We have summarized how each RCT addressed these four tenets in their study protocol (Table 13). Previously published clinical practice guidelines have outlined the necessity of these interventions as part of the best practices treatment of diabetic foot ulcers [50,74-77], and readers are referred to these guidelines for further clarification of this issue.

For patients with diabetic foot ulcers, we were able to find moderate level evidence that hyperbaric oxygen therapy reduced major amputations and promoted complete healing. We considered studies that included patients with the broadest definition of DFU, including Wagner Grade 2 through Wagner Grade 4 ulcers. These studies included inpatient and outpatient HBO_2 treatment groups, which resulted in the increased heterogeneity of both patient populations and interventions. With regard to other outcomes of interest, there was a very low quality of evidence that HBO_2 reduced infection, reduced minor amputation, or improved quality of life. We opted to not provide an overarching recommendation based on Question 1 due to the heterogeneity of included population and attempt to better stratify patients (questions 2-4) to develop more implementable recommendations. Nevertheless, the quality of evidence derived from Question 1 was supportive of subsequent recommendations.

The Review Committee's next step was to try to standardize patient populations by using variations of the PICO question. Experts disagree on the best method of classifying diabetic foot ulcers and infections, as there are inherent strengths and weaknesses to these various systems [78]. The review committee felt that the Wagner scale was an inadequate tool by which patients should be stratified, so we attempted to stratify patients using different clinical grading systems in order to create stronger recommendations (Table 14). This attempt to reclassify patients using other systems was impossible based on the limited information reported in the source documents. As a result, we were left with only the Wagner classification system for review. Recent publications have shown that there is an incomplete understanding of the Wagner scale, even by experienced hyperbaric practitioners [79]. First, there is a failure to recognize that a Wagner Grade 3 DFU includes either deep space abscess or tendonitis and not solely osteomyelitis, and the hyperbaric oxygen community (with CMS endorsement) has utilized Wagner's original DFU classification system differently than originally proposed. Assigning a Wagner Grade to a foot ulcer is an incomplete utilization of Wagner's classification system, as Wagner intended the Grade to be incorporated into a decision-making algorithm. Aggressive surgical management for the Wagner Grade 3 or greater DFU is recommended by Wagner's algorithm as opposed to conservative medical management (Figure 5). We recommend that if one is to use the Wagner classification system, one should follow the management algorithms of the Wagner system while supplementing with HBO_2 if indicated [51].

Current clinical practice among many practitioners is to risk-stratify patients using periwound transcutaneous oximetry measurements ($P_{tc}O_2$) [25,80]. Data from multiple studies showed that for patients who had a

Table 13. Four tenets of pre-hyperbaric diabetic ulcer foot care

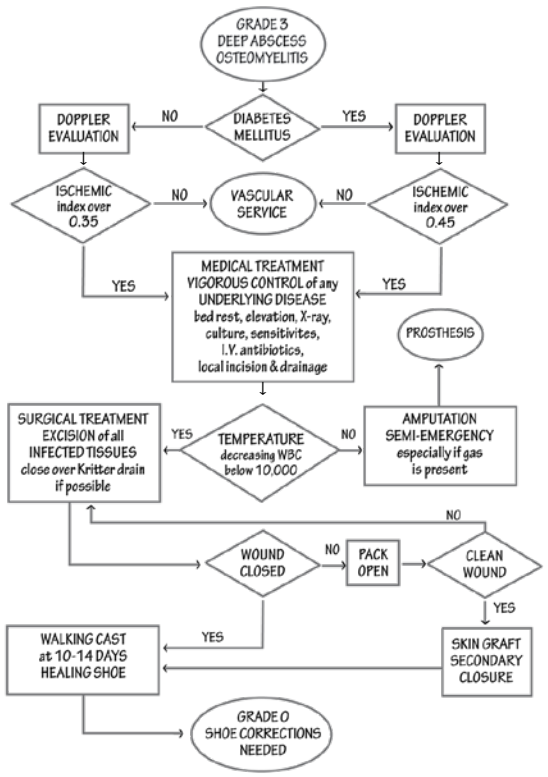
STUDY	VASCULAR	OFFLOADING	INFECTION	DEBRIDEMENT	COMMENT
Doctor 1992	**Unknown:** There was no documentation of revascularization attempts; vascular assessment was limited to normal or absence of distal pulses.	**Unknown:** There was no mention of any standard offloading; however, all patients were admitted for the duration of their treatment.	**Good:** "Antibiotics were administered along with metronidazole for 3 days. Antibiotics commonly used were cephalosporins and aminoglycosides and were changed according to sensitivity patterns."	**Good:** "All patients received regular surgical treatment consisting of incision and drainage of abscesses and debridement of the wound."	All patients were admitted, so glucose control and offloading were better able to be enforced. Antibiotic coverage and debridement were addressed.
Faglia 1996	**Excellent:** "In the subjects with ABI < 0.0 and/or $TcPO_2$ < 5- mm HG, a therapy with prostacyclin was established and arteriography by intra-arterial digital subtraction technique was performed if there were no contraindications (creatinine > 221 µmol/l, or paraproteinemia). In these subjects the opportunity and possibility of carrying out a percutaneous transluminal angioplasty (PTA) or a bypass graft (BPG) was assesses. The presence of focal stenosis involving > 50% of vessel lumen was considered an indication of PTA. The stenosis completely occluding the lumen or with length > 10 cm was respectively considered as an impossibility or a contraindication for PTA. When there was an impossibility of performing PTA, the angiogram was evaluated by vascular surgeons to carry out a BPG. Based on angiographic criteria bypasses were performed when a patent vessel in continuity with the foot was present."	**Excellent:** "During hospitalization, all patients were provided with orthopedic devices to remove mechanical stress and pressure at the site of the ulcer, while maintaining ambulation. The orthoesis was made up of an alkaform insole molded in a plastic cast and an extra-deep special shoe with a rigid sole (Buratto, Italy) allowing the insertion of a bandaged foot."	**Excellent:** "On admission to the hospital, all patients – after collecting a specimen of the ulcer for culture examination – were given empirical broad-spectrum antibiotic therapy, subsequently modified if necessary, according to susceptibility testing results. The antibiotic therapy was continued during the hospital stay until the culture exam, repeated each week, was negative. After discontinuation of the antibiotic therapy, reculturing to assess the cure was performed every two days a total of three times."	**Excellent:** "In all subjects an aggressive and radical debridement was performed by a consultant surgeon. After surgical curettage, the wound was cleaned with uncolored topical antimicrobial agents and wadded with occlusive dressing. Dressing with debridement if necessary was carried out no less than twice a day when necrosis or exudate was present, daily when the ulcer was clean, and every two days during the granulation period."	All patients were admitted, so glucose control and offloading were better able to be enforced. The investigators aggressively managed peripheral arterial disease and addressed all four tenets of DFU care even before the IWGDF came out with its recommendations.
Abidia 2003	**Moderate:** "All patients underwent diagnostic angiography as part of their diagnostic assessment. Vascular intervention was by clinician choice. Vascular surgeons are generally aggressive toward distal revascularization. Any patient for whom vascular surgery, angioplasty or thrombolysis was planned was excluded. Occlusive arterial disease was confirmed by an ankle brachial pressure index < 0.8 (or great toe brachial index pressure index < 0.9 if calf vessels were incompressible)."	**Moderate:** "Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained."	**Moderate:** "Antibiotic therapy was given if there were clinical signs of infection."	**Moderate:** "Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained."	Any patient for whom revascularization was planned was excluded, so this patient population represented those who has exhausted their vascular options. Standard care was stated to address offloading, infection control and aggressive debridement, but no specifics were given.
Duzgun 2008	**Poor:** "We did not distinguish between foot ulcers that were primarily attributable to ischemia vs. those attributable to both peripheral ischemia and prolonged pressure that went undetected due to neuropathy."	**Poor:** "We did not distinguish between foot ulcers that were primarily attributable to ischemia vs. those attributable to both peripheral ischemia and prolonged pressure that went undetected due to neuropathy."	**Good:** "Infection controls were carried out by clinical follow-up, and by performing culture-antibiograms of surgically obtained specimens to determine appropriate antibiotic therapy."	**Moderate:** "ST [standard therapy] entailed daily wound care, including dressing changes and local debridement at bedside or in the operating room, as well as amputations when indicated."	Did not describe vascular status or offloading status of study participants.
Löndahl 2010	**Good:** "All patients were assessed by a vascular surgeon at the time of inclusion, and only patients with adequate distal perfusion or non-reconstructable peripheral vascular disease were included in the study. Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, debridement, offloading and metabolic control according to high international stds."	**Good:** Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, debridement, offloading and metabolic control according to high international standards.	**Good:** Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, debridement, offloading and metabolic control according to high international standards.	**Good:** "Study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetes foot clinic, which included treatment of infection, revascularization, debridement, offloading and metabolic control according to high international standards."	All four tenets of good DFU care were followed, although there were not details as to how they were accomplished.

Table 14. RCT subgroups by wound classification systems

study	treatment groups / HBO_2 protocol	group	POPULATION BY GRADING SYSTEM						comment
			Wagner	Univ./Texas	IWGDF	IDSA	Strauss	WIfI	
Doctor 1992	15 HBO_2 vs. 15 SC 3 atm abs x 45 min, 4 treatments over	**HBO_2**	II: 0 III: 15 IV: 15	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	Documentation of infection was solely by positive or negative wound culture, so we were unable to use the UT, IDSA or WIfI scales. Vascular
	2 weeks	**No HBO_2**	II: 0 III: 15 IV: 15	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	assessment was limited to presence or absence of "normal" pulses, which was inadequate to stratify on the UT, IWGDF, Strauss or WIFI scales.
Faglia 1996	36 HBO_2 vs. 34 SC 2.2-2.5 atm abs x 90 min 5-7 days/wk	**HBO_2**	II:4 III: 4 IV: 22	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	Documentation of infection was solely by positive or negative wound culture, so we were unable to use the UT, IDSA or WIfI scales. ABI and $TcPO_2$
		No HBO_2	II: 5 III: 8 IV: 20	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	were measured, but no breakdown within each group was given for the UT, IWGDF, Strauss or WIfI scales.
Abidia 2003	9 HBO_2 vs. 9 HBAir (sham) 2.4 atm abs daily	**HBO_2**	II: 9 III: 0 IV: 0	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	There was no documentation of infection severity in either group, so we could not use the UT, IDSA, Strauss, or WIfI scales. All patients had ABI <0.8
	x 90 min 5 days/wk vs. 30 Sham	**No HBO_2**	II: 9 III: 0 IV: 0	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	or TBI <0.7, but there was no further breakdown so we could not stratify using UT, IWGDF, Strauss or WIfI scales.
Duzgun 2008	50 HBO_2 vs. 50 SC 2.2-2.5 atm abs x 90 min	**HBO_2**	II: 6 III: 19 IV: 25	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	There was no documentation of infection severity in either group, so we could not use the UT, IDSA, Strauss, or WIfI scales.
	5-7 days/wk	**No HBO_2**	II: 12 III: 18 IV: 20	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	
Löndahl 2010	49 HBO_2 vs. 45 HBAir (Sham) 2.2-2.5 atm abs	**HBO_2**	unable to stratify [1]	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	Did not break down Wagner grades, There was no documentation of infection severity in either group, so we could not use the UT, IDSA,
	x 90 min 5-7 days/wkstratify [1]	**No HBO_2**	unable to to stratify [1]	unable to stratify [2]	unable to stratify [2]	unable to stratify [3]	unable to stratify [4]	unable to stratify [2]	Strauss, or WIfI scales.

[1] no breakdown by Wagner grade; [2] no breakdown by perfusion or infection; [3] no breakdown by infection; [4] no breakdown by appearance, size, depth, infection or perfusion

Figure 5. Wagner's Grade 3 DFU algorithm



Algorithm for Grade 3 foot – deep abscess or osteomyelitis.
Used with permission from Wagner FW Jr. The Dysvascular Foot: A System for Diagnosis and Treatment. Foot and Ankle 2(2):64-122, 1981.

DFU, $P_{tc}O_2$ > 200 mm Hg under hyperbaric conditions predicted whether the wound would heal with 75% to 80% accuracy when hyperbaric oxygen was used as an adjunct to wound management [19,25]. Unfortunately, we were not able to find any publications that provided comparative outcome data stratified on this variable, and $P_{tc}O_2$ stratification is not included in these CPGs.

RECOMMENDATION 1

In patients with Wagner Grade 2 or lower diabetic foot ulcers <u>we suggest against</u> using hyperbaric oxygen therapy *(very low, conditional)*

Six of the RCTs included patients with Wagner Grade 2 DFUs, but we were able to extract data from only three of these studies for analysis. These three studies showed no evidence that HBO_2 reduced major amputation or increased complete healing of DFUs in this population. The quality of evidence for these studies was very low, and we did not feel that adjunctive HBO_2 had any regular role in the treatment of DFUs. This conclusion mirrors clinical practice for the majority of hyperbaric physicians; however, a recent retrospective review of a national wound management database showed that over 50% of patients who received HBO_2 had a Wagner Grade 2 DFU [22]. This is an alarming statistic, as it would seem to indicate an unsubstantiated use of HBO_2 and highlight the concern that some have had regarding the potential overuse of HBO_2 [81]. The Review Committee did feel that there might be selected clinical situations where patients with a previous DFU of greater severity presenting with a subsequent Wagner Grade 2 DFU may be candidates for HBO_2, but this would be the exception rather than the rule.

RECOMMENDATION 2

In patients with Wagner Grade 3 or higher diabetic foot ulcers that have not healed after 30 days of treatment <u>we suggest adding</u> hyperbaric oxygen therapy to the standard of care with regard to preventing major amputation and promoting complete healing *(moderate, conditional).*

The biggest discrepancy between the classic Wagner scale and the modern utilization of Wagner's grading system is defining which patients meet the Wagner Grade 3 criteria [79]. The source of this confusion is unclear, but the Wagner Grade 3 cutoff is one that has been utilized in algorithms of hyperbaric physicians because of United States reimbursement guidelines. Although four of the RCTs included patients with Wagner Grade 3 or higher DFU, we were able to exclude only Wagner Grade 2 or lower DFU from one of these RCTs, leading to an analysis of a single RCT for this patient population. Based on this analysis, we did find moderate-quality evidence that HBO_2 reduced major amputation rates and increased complete healing. We also noted a decrease in the rate of minor amputations, although this was not one of the critical outcomes upon which we based this recommendation. The potential for overuse of HBO_2 is of concern, as patients may receive a prolonged course of therapy before ultimately getting an amputation [22]. One of the greatest clinical challenges is identifying patients who have confounding factors such as uncontrolled deformities, deep infections, wound ischemia/hypoxia or combinations of these that need to be managed to achieve satisfactory out-

comes. Hyperbaric oxygen is an intervention that addresses wound hypoxia. For this reason, the wound characteristics with confounding factors must be documented before making decisions about HBO_2.

RECOMMENDATION 3

In patients with Wagner Grade 3 or higher diabetic foot ulcers who have just had a surgical debridement of the foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; I&D of deep space abscess; or necrotizing soft tissue infection), we suggest adding acute postoperative hyperbaric oxygen therapy to the standard of care with regard to preventing major amputation and promoting complete healing *(moderate, conditional).*

The review of the DFU literature revealed a historical shift in the treatment of DFUs from a primarily surgical, inpatient-based approach to a less surgical outpatient-based approach. Treatment paradigms seemed to follow an arbitrarily mandated delay in initiation of HBO_2 based on reimbursement-related issues such as insurance coverage. While this CPG is intended to avoid reimbursement-driven recommendations, it is possible that financially motivated practice patterns may have influenced the evidence-based practice of hyperbaric medicine. Analysis of patients who were treated using the classic Wagner DFU treatment algorithm shows that aggressive surgical intervention, revascularization, metabolic control, infection control and initiation of HBO_2 soon after I&D, debridement or amputation of a limb with Wagner Grade 3 or higher DFU had superior results with regard to reducing major amputation rates and increased wound healing [7]. Conversely, there was an increase in the minor amputation rate, but this trend was recognized as an acceptable alternative to major amputation rather than as a negative result.

While HBO_2 has many antimicrobial properties (i.e., enhancing leukocyte-killing activity, direct bacteriostatic effect on anaerobic organisms) [82], a common misconception in the community is that the primary role of HBO_2 is intended to help resolve the diabetic foot infection. This impression is illustrated by comments from physicians that a patient does not require HBO_2 after amputation of an infected toe "because the infected bone is gone." In such situations the rationale for hyperbaric oxygen changes to salvaging limbs by preserving flaps threatened by reduced perfusion, healing of the residual ischemic wound, or a combination of the two. This misconception is the result of the requirement by many insurance companies that patients fit into a pigeonhole of being diagnosed with a Wagner Grade 3 DFU in order to receive HBO_2, with the defining characteristic of a Wagner 3 DFU as the presence of osteomyelitis (although the classic Wagner classification would also include abscess and tendonitis). A deeper understanding of the original Faglia study shows that infection is only the instigating event for immediate surgical intervention of the dysvascular foot, and the actual benefit of HBO_2 is to allow the wound to heal and avoid major amputation by providing oxygenation of ischemic tissue.

This recommendation is in direct contrast to what is commonly practiced, namely the utilization of HBO_2 in an outpatient setting for DFUs that have not shown significant healing after 30 days. The reason for this may be economically driven, as reimbursement policies may have unfortunately abrogated clinic decision-making. The lack of acute, inpatient HBO_2 for Wagner Grade 3 or higher DFUs may also be the reason that more recent trials have shown an increase in wound healing but no improvement in major amputation rate. This factor may also be the reason that the Margolis study did not show the effectiveness of HBO_2 [22], although numerous studies have demonstrated superior efficacy compared to standard of care.

Adverse events

We considered benefits and harms when developing recommendations. The analysis of the RCTs for occurrence of adverse events yielded few meaningful results as the overall incidence of adverse events was very low, and the sample size of these studies was too low to be useful. The RCTs included in this analysis predominantly reported adverse events only related to HBO_2, although there were several studies that reported non-HBO_2-related side effects. In general, large retrospective studies are more useful for identifying serious adverse events related to HBO_2. National registries like the U.S. Wound Care Registry as well as proprietary databases from for-profit management companies also allow for reporting of adverse events related to HBO_2 from a larger sample of patients treated with HBO_2.

There are obviously some adverse events that are solely related to HBO_2 and would not be seen in patients treated with alternative therapies (i.e., baro-

trauma, central nervous system oxygen toxicity, hyperoxic myopia). Data from one management company revealed 463,293 monoplace hyperbaric chamber treatments of 17,267 patients from 2009-2010. In 2009, there were 916 adverse events reported for 207,479 treatments in 7,781 patients (adverse event rate of 0.44%), and in 2010 there were 954 adverse events reported for 255,814 treatments in 9.296 patients (adverse event rate of 0.37%). In order of decreasing rate of occurrence were ear pain (20 per 10,000 treatments), confinement anxiety (eight per 10,000), hypoglycemic events (five per 10,000), shortness of breath (two per 10,000), seizures (two per 10,000), sinus pain (one per 10,000), and chest pain (one per 10,000). Overall, the risk of adverse events from HBO_2 can be considered to be very low and self-limited when they do occur [83].

Cost-effectiveness

Few studies have been published regarding the cost-effectiveness of HBO_2 in the treatment of DFUs. Cianci reported in a cohort study of 41 patients that the estimated cost (in 1991 dollars) of below-knee amputation (US$40,000) plus rehabilitation (US$30,000) was greater than the cost of HBO_2 to salvage a limb (US$31,265) [16]. Bennett reported 2003-2004 Australian data that the average cost for wound care and HBO_2 was AUS$14,928 for each amputation prevented, and that HBO_2 might decrease the overall cost of health care when the costs of amputation and rehabilitation were considered [85]. Chuck used 2008 Canadian data on DFU prevalence and HBO_2 efficacy data to create a computer model that estimated the 12-year cost for patients receiving HBO_2 was CND$40,695, compared with CND$49,786 for standard care alone. This study concluded that adjunctive HBO_2 for DFU was cost-effective when compared to standard care [86]. Only a single RCT prospectively addressed the cost-effectiveness of the use of HBO_2 in the treatment of DFUs (Abidia 2003). This study evaluated the cost of ulcer dressings per visit per patient for one year in both the treatment and control groups and found an average savings of UK£2,960 per patient treated with HBO_2. This analysis took into account the additional costs of HBO_2 and treatment of any associated complications. The Review Committee was unable to obtain the raw data for this study to include it in our GRADE analysis.

Due to recent trends in insurance coverage and reimbursement policies, the cost-effectiveness of HBO_2 is likely to become an important factor in any discussions focusing on the use of HBO_2 in clinical practice. Cost-effectiveness studies are often conducted using decision modeling and simulations (e.g., Markov, Monte Carlo) due to the complex economic variables and uncertainty involved. Thus, it is somewhat challenging to interpret the significance of cost-effectiveness data using these existing studies.

Patient perspective

Two patients (one who received HBO_2 and one who was eligible for – but did not receive – HBO_2) were invited to attend a CPG Committee Meeting to give their perspective on several aspects of the process. Neither patient had a financial interest in any hyperbaric chamber manufacturer or operations. The patients were given a brief overview of the scope and nature of the purpose and methodology of this CPG. The patients were given the opportunity to describe their impressions of the outcomes of interest and rank-order them without knowing what reviewers had chosen. The patients were in agreement that major amputation rate and healing percentage at the one-year mark ranked high in their lists, but they also felt that mortality, quality of life, healing durability and time to heal were also important outcomes. Once revealed, they concurred with the committee's rank order of the outcomes and the reasons some outcomes of interest were not deemed as critical as others. Specifically, they understood that a minor amputation could be an acceptable outcome when done to prevent a more serious proximal limb amputation and that a healed wound at the one-year mark was a surrogate measure for healing durability. These opinions are in contrast to the online survey results (rating all outcomes as critical), which highlight the importance of having a conversation between patient and provider.

The patients' comments about the components of standard care indicated that while it was easily understood why each component was important, it could be very difficult to carry out in practice. Overall, they agreed that the CPG would be an important tool for clinicians and patients, but stressed that the greatest need was information about their treatment options presented in language that was understandable to the patient. While patients would in most cases defer to the recommendations of the medical professionals,

their comfort level in the treatment choice was influenced greatly by the amount of information provided to them at the time of the decision. They understood that the CPG was designed to provide busy clinicians a summary of the data in a way that could be passed along to patients. This perspective reinforces the concept that shared decision-making between the patient and provider is an essential part of any CPG.

Differences from other technology reviews and potential for bias

The UHMS advocates for the responsible, evidence-based use of hyperbaric oxygen therapy. As experts in the field, we possess the experience to analyze the hyperbaric literature with clinical perspective. Non-hyperbaric physicians are included in the review committee to provide even more objectivity in the analysis. The results of this review, utilizing the same source material, differs from similar reviews conducted by Cochrane and the Canadian Program for Assessment of Technology in Health (PATH) because of differences in purpose and judgment. The Cochrane review is a summary of the evidence that does not seek to make clinical recommendations. The PATH review based their inferences on statistical significance (p-values), whereas we considered how precise the estimates were to support a particular decision. The GRADE methodology, and the transparency that is employed in this extensive statistical analysis, allows others to make their own judgments and compare them with the conclusions of this review committee.

Technical Comments

RECOMMENDATION 1

> **In patients with Wagner Grade 2 or lower diabetic foot ulcers we suggest against adding hyperbaric oxygen therapy to the standard of care with regard to preventing major amputation and promoting complete healing *(very low, conditional).***

Patients with Wagner Grade 2 or lower DFU should receive optimal wound care, but HBO_2 should not typically be part of the treatment plan. There may be cases where a patient has previously required HBO_2 for a Wagner Grade 3 or higher DFU and is now presenting with another ulcer. In rare cases, it may be advisable to incorporate HBO_2 before the ulcer progresses, but this should be the exception and not the rule. As in all other cases, this will be in combination with addressing mechanical offloading, optimizing revascularization, elimination of infection, debriding devitalized tissue, and improving metabolic control.

RECOMMENDATION 2

> **In patients with Wagner Grade 3 or higher diabetic foot ulcers who have not shown significant improvement after 30 or more days, we suggest adding hyperbaric oxygen therapy to the standard of care with regard to preventing major amputation and promoting complete healing *(moderate, conditional).***

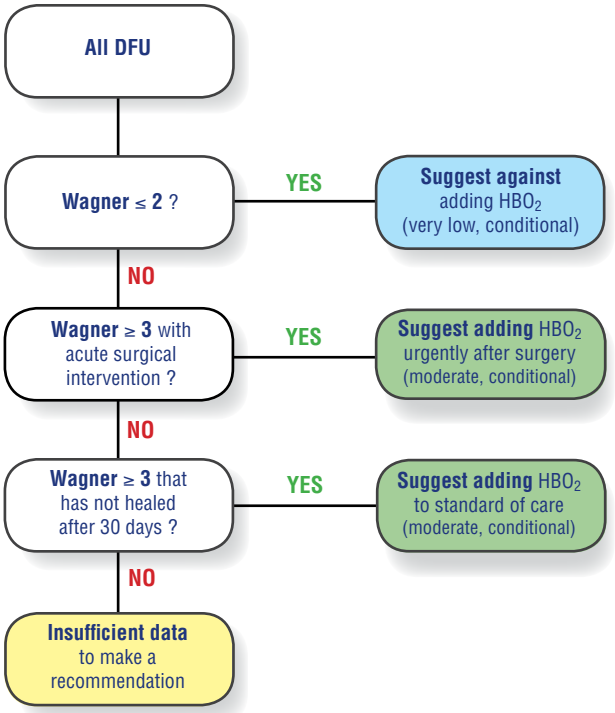
Patients who have not shown significant improvement after 30 days of optimal wound care should receive adjunctive HBO_2. Treatment pressure of 2.0-2.4 atm abs is recommended for 90-120 minutes. A course of 30 sessions is recommended but is dependent on ensuring that other barriers to healing (i.e., infection, vascular status, removal of devitalized tissue, etc.) have been adequately addressed. Additional HBO_2 can be considered if there has been improvement in the wound, but concerns about the above factors have not been resolved completely. It should be explained to patients that HBO_2 is only a part of the treatment plan and will not necessarily be used until the DFU is completely healed. Patients who receive HBO_2 should have continued offloading, optimization of revascularization, elimination of infection, debridement of devitalized tissue, and excellent diabetes management.

RECOMMENDATION 3

> **In patients with Wagner Grade 3 or higher diabetic foot ulcers that require immediate surgery, we suggest adding inpatient post-operative hyperbaric oxygen therapy to the standard of care with regard to preventing major amputation and promoting complete healing *(moderate, conditional).***

Patients who require surgery for a Wagner Grade 3 or higher DFU should receive HBO_2 within 24 hours of the time of surgery. Treatment pressure of 2.0-2.4 atm abs is recommended for 90-120 minutes. A course of 30 sessions is recommended, but is subject to the goals being sought, such as survival of a flap (seven or less days of treatments, angiogenesis (two weeks

Figure 6. Algorithm for the use of HBO_2



of treatments), or refractory osteomyelitis (30 to 40 treatments). Additional HBO_2 can be considered if there has been improvement in the wound, but concerns about the above factors have not been resolved. It should be explained to patients that HBO_2 is only a part of the treatment plan and would not necessarily be used until the DFU was completely healed. Patients who receive HBO_2 should have continued offloading, optimization of revascularization, elimination of infection, debridement of devitalized tissue, and excellent diabetes management.

CONCLUSIONS

The use of HBO_2 for DFU is founded on the assumption that practitioners have aggressively addressed revascularization of the ischemic foot, debridement of devitalized tissue, offloading of the neuropathic foot lesion, and appropriate anti-infective therapies before utilizing adjunctive HBO_2. Hyperbaric oxygen should be included as part of a comprehensive diabetic foot ulcer program. The level of evidence is of moderate quality, and the Review Committee felt that taking patient values and preferences into account justified conditional recommendations to add HBO_2 to the standard of wound care management of diabetic foot ulcers. Proper selection of patients should pair these guidelines with clinical acumen to identify patients who will heal without HBO_2 and exclude patients who will not heal even after receiving HBO_2.

An algorithm that incorporates all of the recommendations is provided in Figure 6.

Research recommendations

This analysis of the HBO_2 / DFU body of literature indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate of effect. This echoes numerous systematic reviews that call for "more studies." Other than the Cochrane Review, those reviews lacked specific recommendations to guide future research. We provide some specific recommendations here.

Methodology

Future studies need to be scientifically rigorous and well-designed. GRADE penalizes RCTs that have high risk of bias. Future studies should be designed with strict allocation concealment, blinding of study groups, and intention-to-treat analysis. Data reporting should follow the Consolidated Standards of Reporting Trials (CONSORT) so that outcome data can be more easily interpreted.

Study populations

In order to better establish the efficacy of HBO_2 for the various populations of patients with DFUs, future studies must include discrete subgroups of patients upon which treatment groups are stratified. While imperfect, the Wagner classification is the most widely used. If alternative wound classification systems are to be accepted as criteria for utilizing HBO_2, future studies will need to be randomized on these new wound classifications.

Treatment standards

Both hyperbaric treatment standards and "standard wound care" need to be better defined. A standard treatment pressure, length, frequency and duration should be chosen for future studies. Hyperbaric air (sham) therapy should be standardized so that all studies can be properly blinded. Standard wound care needs to be clearly defined for future studies and should include optimization of vascular status, offloading of the neuropathic foot, diabetes control, aggressive sur-

gical debridement, and infection control. Adherence to standard wound care should also be reported, as the patient contributors to this CPG have indicated that it is difficult to follow recommendations all of the time.

Outcomes of interest

Critical outcomes of major amputation and incomplete healing should be reported for all future studies. Additional data on minor amputation rate, quality of life, and persistence of infection should be reported so that more evidence can be collected about these outcomes. Cost-effectiveness studies are needed to provide more concrete analysis rather than through extrapolations based on limited data from surrogate markers of healthcare costs.

Treatment of infection

As noted above under Recommendation 3, a common misconception in the community is that the primary role of HBO_2 is intended to help resolve the diabetic foot infection. Surprisingly there is little to no direct evidence to support the role of HBO_2 in the treatment of infection. The studies that did include infected patients did not stratify the severity of the infection by any one of the recognized systems (i.e., IDSA or PEDIS). Some used surrogate markers [5,7] such as changes in culture results as opposed to more widely accepted clinical endpoints such as the presence or absence of clinical signs and symptoms of infection. Before a recommendation can be made in the effectiveness of HBO_2 specifically for the treatment of diabetic foot infection, we believe that a well-designed trial, utilizing widely recognized evidenced-based diagnostic criteria and endpoints, is needed.

Proposed studies

Recommendation 3 identifies that there is a population of DFU patients who should receive acute post-operative HBO_2 without waiting 30 days from the time of diagnosis. A study that would confirm this could be designed to randomize all patients who have

- an incision and debridement (Group A)
- amputation at level of the metatarsal-phalangeal joint (Group B)
- amputation at the metatarsal level (Group C)

to either HBO_2 or to HBAir (sham) therapy. Outcomes of major amputation and incomplete healing would be recorded for all patients using intention-to-treat analysis. Additional outcomes of cost-effectiveness, quality of life, persistence of infection and minor amputation would be recorded as well.

Patient selection based on tissue oxygenation ($P_{tc}O_2$) stratification has been proposed to allow more judicious use of HBO_2. This has not been evaluated prospectively, but a study that would allow for this to be tested would be to take patients with a Wagner Grade 3 or higher DFU and stratify them based on baseline sea-level air $P_{tc}O_2$ greater than 40 mm Hg (Group I) or 40 mm Hg or less (Group 2). Group 2 could be then stratified on whether a single in-chamber $P_{tc}O_2$ at 2.0 atm abs rises over 200 mm Hg (Group 2a) or fails to rise over 200 mm Hg (Group 2b). Each group would then be randomized to HBO_2 or HBAir (sham) therapy. Outcomes of major amputation and incomplete healing would be recorded for all patients using intention-to-treat analysis. Additional outcomes of cost effectiveness, quality of life, persistence of infection and minor amputation would be recorded as well. ■

Contributors to this Clinical Practice Guideline

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Practice background: Pathology

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Conflict of interest: Less than 25% of Dr. Worth's clinical practice income involves HBO_2 as an adjunctive therapy for managing DFU.

■

Appendix A: Detailed search strategy

PubMed 4/30/15 Total: 377

(Diabetic Foot[Mesh] OR Foot Ulcer[Mesh] OR Leg Ulcer[Mesh] OR ((diabetes[tiab] OR diabetic[tiab]) AND (foot[tiab] OR feet[tiab] OR ulcer*[tiab] OR wound*[tiab])) OR (foot[tiab] AND ulcer*[tiab]) OR (feet [tiab] AND ulcer*[tiab]) OR plantar ulcer*[tiab] OR leg ulcer*[tiab] OR ulcus cruris[tiab] OR crural ulcer*[tiab]) AND (Hyperbaric Oxygenation[Mesh] OR (hyperbaric[tiab] AND oxygen*[tiab]) OR HBO[tiab] OR HBOT[tiab] OR (oxygen* [tiab] AND (high pressure[tiab] OR high tension[tiab])) OR hyperbaric chamber*[tiab]) NOT case report

Embase 4/30/15 Total: 200

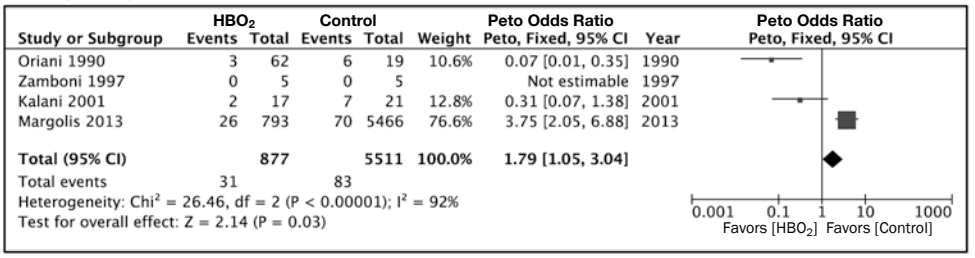
('leg ulcer'/exp OR 'foot ulcer'/exp OR 'diabetic foot'/exp OR 'diabetic feet':ti,ab OR (diabetes NEAR/3 ulcer*):ti,ab OR (diabetic NEAR/3 ulcer*):ti,ab OR (diabetic NEAR/3 wound*):ti,ab OR (diabetes NEAR/3 wound*):ti,ab OR (leg* NEAR/3 ulcer*):ti,ab OR (foot NEAR/3 ulcer*):ti,ab OR (ulcer* NEAR/3 feet):ti,ab OR (plantar* NEAR/3 ulcer*):ti,ab OR 'ulcus cruris':ti,ab OR 'crural ulcer':ti,ab OR 'crural ulcers':ti,ab OR (diabetic NEAR/3 foot):ti,ab OR (diabetic NEAR/3 feet):ti,ab) AND ('hyperbaric oxygen'/exp OR (hyperbaric NEAR/1 oxygen*):ti,ab OR hbo:ti,ab OR hbot:ti,ab OR 'hyperbaric chamber':ti,ab OR 'hyperbaric chambers':ti,ab OR (oxygen* and ('high pressure' OR 'high tension')):ti,ab) NOT 'case report'/exp AND [embase]/lim NOT [medline]/lim

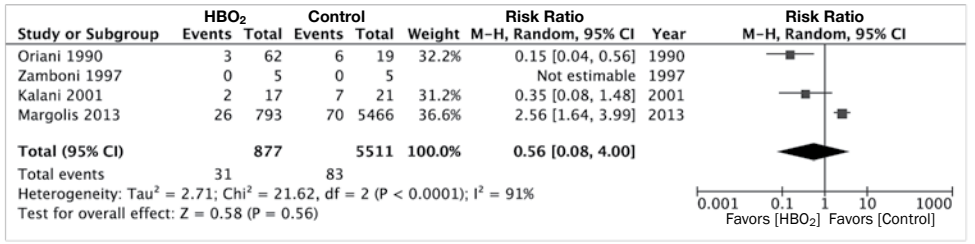
Cochrane 4/30/15

	SEARCH TERMS	
#1	[mh "diabetic foot"] or [mh "foot ulcer"] or [mh "leg ulcer"]	1228
#2	(diabet*:ti,ab,kw and (foot:ti,ab,kw or feet:ti,ab,kw or ulcer*:ti,ab,kw or wound*:ti,ab,kw)) or "plantar ulcer*":ti,ab,kw or "ulcus cruris":ti,ab,kw or "crural ulcer":ti,ab,kw	1884
#3	#1 AND #2	2546
#4	[mh "hyperbaric oxygenation"]	379
#5	(hyperbaric:ti,ab,kw and oxygen*:ti,ab,kw) or hbo:ti,ab,kw or hbot:ti,ab, kw or oxygen*:ti,ab,kw or "high pressure":ti,ab,kw or "high tension":ti,ab,kw or "hyperbaric chamber*":ti,ab,kw	28857
#6	#4 or #5	28857
#7	#3 and #6	150

Supplemental Figure 1. Alternate forest plots and GRADE analysis for Question 1: Comparison of observational studies vs. randomized controlled trials

1a. Major Amputation: Observational Studies



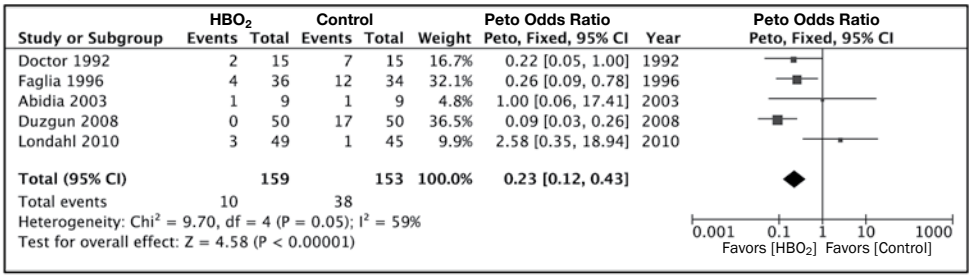


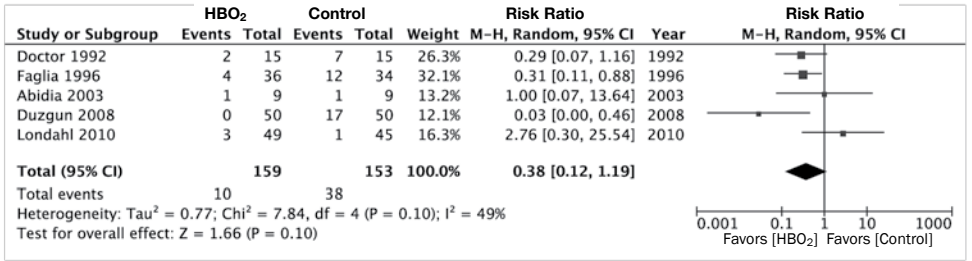
All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	-2	The point estimates from the studies varied, the confidence intervals do not overlap to some extent and the I^2 is >50%
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision as Estimate of Effect had narrow Confidence Intervals. Peto analysis showed tighter confidence interval, but Random Effects Risk Ratio analysis was also deemed acceptable.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

continued >

Supplemental Figure 1. Alternate forest plots and GRADE analysis for Question 1: Comparison of observational studies vs. randomized controlled trials

1b. Major Amputation: Randomized Controlled Trials





All DFU (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 4/5 studies, patients lost to follow-up in 2/5 studies, unblinded study in 1/5 studies and unclear blinding in 2/5 studies, lack of intention to treat analysis in 1/5 studies and unclear intention to treat analysis in 2/5 studies.
	Inconsistency	-1	The point estimates from the studies varied, the confidence intervals do not overlap to some extent and the I square is >50%
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision as Estimate of Effect had narrow Confidence Intervals. Peto analysis showed tighter confidence interval, but Random Effects Risk Ratio analysis was also deemed acceptable.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

Supplemental Figure 2. Alternate forest plots and GRADE analysis for Question 1: Comparison of observational studies vs. randomized controlled trials

2a. Incomplete Healing: Observational Studies

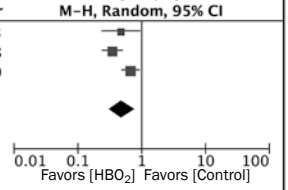
	Study Group	Event	Non-Event	Total	Odds Ratio
Kalani 2001	HBO_2	4	13	17	0.28 (0.068 – 1.15) Favors HBO_2
	Control	11	10	21	
	Total	15	23		

All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	There was no inconsistency because there is only one study
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision as Estimate of Effect had narrow Confidence Intervals. Peto analysis showed tighter confidence interval, but Random Effects Risk Ratio analysis was also deemed acceptable.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**2**	**Low Level of Evidence**

2b. Incomplete Healing: Randomized Controlled Trials

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Abidia 2003	4	9	9	9	23.4%	0.47 [0.24, 0.95]	2003
Duzgun 2008	17	50	50	50	37.2%	0.35 [0.24, 0.51]	2008
Londahl 2010	24	49	33	45	39.4%	0.67 [0.48, 0.93]	2010
Total (95% CI)		**108**		**104**	**100.0%**	**0.48 [0.30, 0.77]**	
Total events	45		92				

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 3.07 (P = 0.002)



All DFU (Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 2/3 studies, patients lost to follow-up in 1/3 studies, unclear blinding in 1/3 studies, and unclear intention to treat analysis in 1/3 studies.
	Inconsistency	-1	The data for Incomplete Healing shows some inconsistency as the I^2 was >50%, resulting in rating down 1 point
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

Supplemental Figure 3. Alternate forest plots and GRADE analysis for Question 1: Comparison of observational studies vs. randomized controlled trials

3a. Complete Healing: Observational Studies

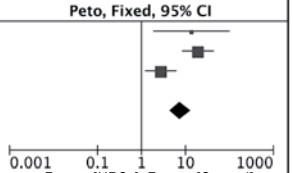
	Study Group	Event	Non-Event	Total	Odds Ratio
Kalani 2001	HBO_2	13	4	17	3.58 (0.87 – 14.65) Favors HBO_2
	Control	10	11	21	
	Total	23	15		

All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	There was no inconsistency because there is only one study
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision as Estimate of Effect had narrow Confidence Intervals. Peto analysis showed tighter confidence interval, but Random Effects Risk Ratio analysis was also deemed acceptable.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**2**	**Low Level of Evidence**

3b. Complete Healing: Randomized Controlled Trials

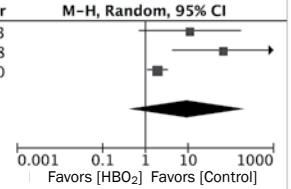
Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Abidia 2003	5	9	0	9	7.8%	13.67 [1.84, 101.50]	2003
Duzgun 2008	33	50	0	50	45.8%	19.21 [8.38, 44.02]	2008
Londahl 2010	25	49	12	45	46.4%	2.74 [1.20, 6.26]	2010
Total (95% CI)		**108**		**104**	**100.0%**	**7.58 [4.33, 13.29]**	
Total events	63		12				

Heterogeneity: $Chi^2 = 11.00$, df = 2 (P = 0.004); $I^2 = 82\%$
Test for overall effect: Z = 7.08 (P < 0.00001)



Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Abidia 2003	5	9	0	9	30.3%	11.00 [0.70, 173.66]	2003
Duzgun 2008	33	50	0	50	30.2%	67.00 [4.22, 1064.23]	2008
Londahl 2010	25	49	12	45	39.5%	1.91 [1.10, 3.34]	2010
Total (95% CI)		**108**		**104**	**100.0%**	**9.53 [0.44, 207.76]**	
Total events	63		12				

Heterogeneity: $Tau^2 = 6.19$; $Chi^2 = 13.75$, df = 2 (P = 0.001); $I^2 = 85\%$
Test for overall effect: Z = 1.43 (P = 0.15)



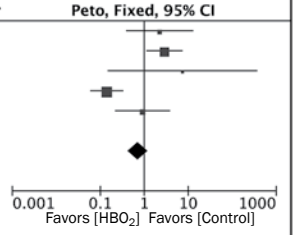
All DFU (Outcome: Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 2/3 studies, patients lost to follow-up in 1/3 studies, unclear blinding in 1/3 studies, and unclear intention to treat analysis in 1/3 studies.
	Inconsistency	-1	The data for Complete Healing shows some inconsistency as the I^2 was >50%, resulting in rating down 1 point
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

Supplemental Figure 4. **Forest plots and GRADE analysis for Question 1: Non-critical outcome of minor amputation**

Minor Amputation: Randomized Controlled Trials

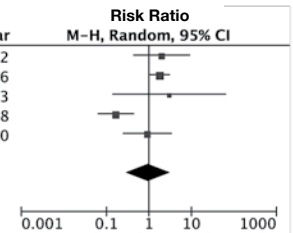
Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Doctor 1992	4	15	2	15	9.8%	2.24 [0.39, 13.00]	1992
Faglia 1996	21	35	11	33	33.8%	2.87 [1.12, 7.39]	1996
Abidia 2003	1	9	0	9	2.0%	7.39 [0.15, 372.38]	2003
Duzgun 2008	4	50	24	50	40.0%	0.14 [0.06, 0.33]	2008
Londahl 2010	4	49	4	45	14.5%	0.91 [0.22, 3.86]	2010
Total (95% CI)		**158**		**152**	**100.0%**	**0.72 [0.42, 1.25]**	
Total events	34		41				

Heterogeneity: $Chi^2 = 24.89$, df = 4 ($P < 0.0001$); $I^2 = 84\%$
Test for overall effect: $Z = 1.16$ ($P = 0.25$)



Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Doctor 1992	4	15	2	15	19.2%	2.00 [0.43, 9.32]	1992
Faglia 1996	21	35	11	33	26.5%	1.80 [1.04, 3.13]	1996
Abidia 2003	1	9	0	9	9.9%	3.00 [0.14, 65.16]	2003
Duzgun 2008	4	50	24	50	23.6%	0.17 [0.06, 0.45]	2008
Londahl 2010	4	49	4	45	20.9%	0.92 [0.24, 3.46]	2010
Total (95% CI)		**158**		**152**	**100.0%**	**0.96 [0.29, 3.18]**	
Total events	34		41				

Heterogeneity: $Tau^2 = 1.34$; $Chi^2 = 20.10$, df = 4 ($P = 0.0005$); $I^2 = 80\%$
Test for overall effect: $Z = 0.07$ ($P = 0.94$)



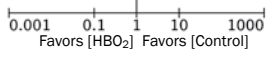
All DFU (Outcome: Minor Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 4/5 studies, patients lost to follow-up in 2/5 studies, unblinded study in 1/5 studies and unclear blinding in 2/5 studies, lack of intention to treat analysis in 1/5 studies and unclear intention to treat analysis in 2/5 studies.
	Inconsistency	-1	Not all confidence intervals overlap in forest plot; I^2 >50%
	Indirectness	0	No evidence of Indirectness
	Imprecision	-1	Wide confidence intervals including substantial benefit and harm.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

Supplemental Figure 5. **Forest plots and GRADE analysis for Question 1: Non-critical outcome of persistent infection**

Persistent Infection – Randomized Controlled Trials

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Doctor 1992	3	19	12	16	39.3%	0.21 [0.07, 0.62]	1992
Faglia 1996	9	35	16	33	60.7%	0.53 [0.27, 1.03]	1996
Total (95% CI)		**54**		**49**	**100.0%**	**0.37 [0.15, 0.90]**	
Total events	12		28				

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 2.09$, df = 1 ($P = 0.15$); $I^2 = 52\%$
Test for overall effect: $Z = 2.19$ ($P = 0.03$)



All DFU (Outcome: Resolution of Infection)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear methodology for allocation concealment in 2/2 studies, patients lost to follow-up in 1/2 studies, unblinded study in 1/2 studies and unclear blinding in 1/2 studies, lack of intention to treat analysis in 1/2 studies and unclear intention to treat analysis in 1/2 studies.
	Inconsistency	-1	There is no overlap in the confidence intervals seen in forest plot and an I^2 > 50%
	Indirectness	-1	Surrogate markers of infection (Wound Cultures) used rather than IDSA diagnostic criteria
	Imprecision	-1	Wide confidence intervals that include substantial benefit and harm
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

Supplemental Figure 6. Alternate forest plots and GRADE analysis for Question 2: Comparison of observational studies vs. randomized controlled trials

6a. Major Amputation: Observational Studies

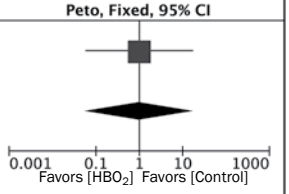
	Study Group	Event	Non-Event	Total	Odds Ratio
Kalani 2001	HBO_2	2	15	17	0.27 (0.047 – 1.51) Favors HBO_2
	Control	7	14	21	
	Total	9	29		

All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	There was no inconsistency because there is only one study
	Indirectness	0	No evidence of indirectness
	Imprecision	-1	Wide confidence intervals
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Low Level of Evidence**

6b. Major Amputation: Randomized Controlled Trials

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Faglia 1996	0	4	0	5		Not estimable	1996
Abidia 2003	1	9	1	9	100.0%	1.00 [0.06, 17.41]	2003
Duzgun 2008	0	6	0	12		Not estimable	2008
Total (95% CI)		**19**		**26**	**100.0%**	**1.00 [0.06, 17.41]**	
Total events	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

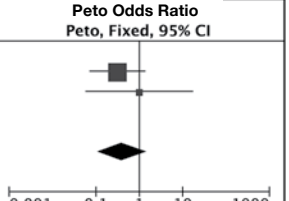


Wagner ≤2 (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	2/3 had unclear allocation concealment, 1/3 had unclear patients lost to follow-up, 1/3 studies was unblinded, and 1/3 had unclear intention-to-treat analysis and 1/3 had no intention-to-treat analysis
	Inconsistency	0	There was no evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-2	Wide confidence intervals in a single study with small number of events
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No evidence of large magnitude of effect
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

6c. Major Amputation: Observational Studies and Randomized Controlled Trials

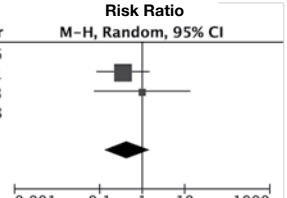
Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Faglia 1996	0	4	0	5		Not estimable	1996
Kalani 2001	2	17	7	21	78.8%	0.31 [0.07, 1.38]	2001
Abidia 2003	1	9	1	9	21.2%	1.00 [0.06, 17.41]	2003
Duzgun 2008	0	6	0	12		Not estimable	2008
Total (95% CI)		**36**		**47**	**100.0%**	**0.40 [0.11, 1.49]**	
Total events	3		8				

Heterogeneity: $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 1.36 (P = 0.17)



Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Faglia 1996	0	4	0	5		Not estimable	1996
Kalani 2001	2	17	7	21	76.8%	0.35 [0.08, 1.48]	2001
Abidia 2003	1	9	1	9	23.2%	1.00 [0.07, 13.64]	2003
Duzgun 2008	0	6	0	12		Not estimable	2008
Total (95% CI)		**36**		**47**	**100.0%**	**0.45 [0.13, 1.58]**	
Total events	3		8				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.47$, df = 1 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 1.25 (P = 0.21)



Supplemental Figure 7. Alternate forest plots and GRADE analysis for Question 2: Comparison of observational studies vs. randomized controlled trials

7a. Incomplete Healing: Observational Studies

	Study Group	Event	Non-Event	Total	Odds Ratio
Kalani 2001	HBO_2	4	13	17	0.28 (0.068 – 1.15) Favors HBO_2
	Control	11	10	21	
	Total	15	23		

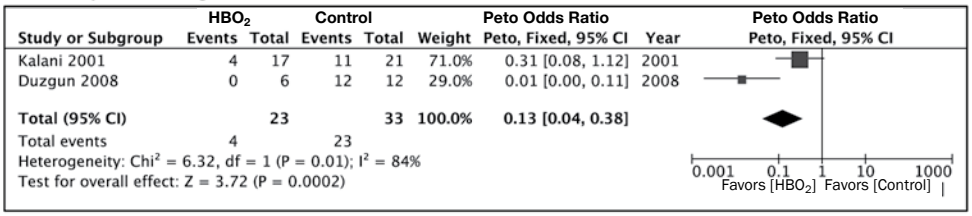
All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	There was no inconsistency because there is only one study
	Indirectness	0	No evidence of indirectness
	Imprecision	-1	Wide confidence interval
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Low Level of Evidence**

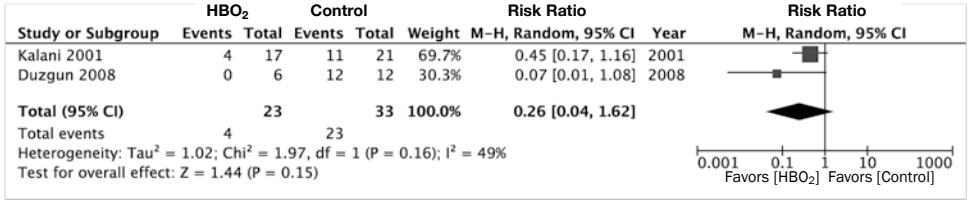
7b. Incomplete Healing: Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	0	6	6	0.003 (0.001 - 0.175) Favors HBO_2
	Control	12	0	12	
	Total	12	6		

Wagner ≤2 (Major Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	2/3 had unclear allocation concealment, 1/3 had unclear patients lost to follow-up, 1/3 studies was unblinded, and 1/3 had unclear intention-to-treat analysis and 1/3 had no intention-to-treat analysis
	Inconsistency	0	There was no evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-2	Wide confidence intervals in a single study with small number of events
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No evidence of large magnitude of effect
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

7c. Incomplete Healing: Observational Studies and Randomized Controlled Trials



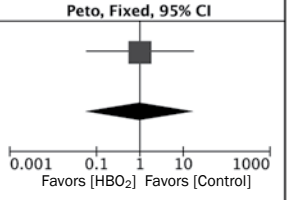


Supplemental Figure 8. Alternate forest plots for Question 2

8a. Major Amputation - Randomized Controlled Trials

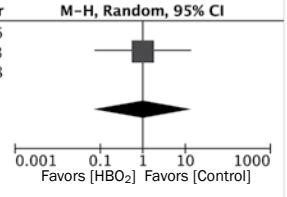
Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Faglia 1996	0	4	0	5		Not estimable	1996
Abidia 2003	1	9	1	9	100.0%	1.00 [0.06, 17.41]	2003
Duzgun 2008	0	6	0	12		Not estimable	2008
Total (95% CI)		**19**		**26**	**100.0%**	**1.00 [0.06, 17.41]**	
Total events	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Faglia 1996	0	4	0	5		Not estimable	1996
Abidia 2003	1	9	1	9	100.0%	1.00 [0.07, 13.64]	2003
Duzgun 2008	0	6	0	12		Not estimable	2008
Total (95% CI)		**19**		**26**	**100.0%**	**1.00 [0.07, 13.64]**	
Total events	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



8b. Incomplete Healing – Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	0	6	6	0.003 (0.001 - 0.175) Favors HBO_2
	Control	12	0	12	
	Total	12	6		

8c. Complete Healing – Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	6	0	6	325 (5.76 – 18338.95) Favors HBO_2
	Control	0	12	12	
	Total	6	12		

Supplemental Figure 9. Additional GRADE analysis for Question 2: Non-critical outcome of minor amputation

Minor Amputation - Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	0	6	6	0.15 (0.0066 – 3.21) Favors HBO_2
	Control	4	8	12	
	Total	4	12		

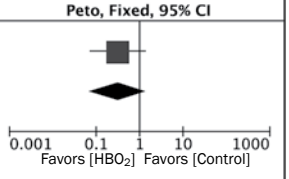
Wagner ≤2 (Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Study not blinded
	Inconsistency	0	Not all confidence intervals overlap in forest plot
	Indirectness	0	No evidence of indirectness
	Imprecision	-2	Wide confidence intervals in this single study
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**2**	**Low Level of Evidence**

Supplemental Figure 10. **Alternate forest plots and GRADE analysis for Question 3: Comparison of observational studies vs. randomized controlled trials**

10a. Major Amputation: Observational Studies

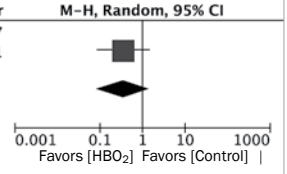
Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Zamboni 1997	0	5	0	5		Not estimable	1997
Kalani 2001	2	17	7	21	100.0%	0.31 [0.07, 1.38]	2001
Total (95% CI)		**22**		**26**	**100.0%**	**0.31 [0.07, 1.38]**	
Total events	2		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.12)



Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Zamboni 1997	0	5	0	5		Not estimable	1997
Kalani 2001	2	17	7	21	100.0%	0.35 [0.08, 1.48]	2001
Total (95% CI)		**22**		**26**	**100.0%**	**0.35 [0.08, 1.48]**	
Total events	2		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)



	Starting Score	2	Rationale
All DFU (Outcome: Major Amputation)	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-1	Wide confidence intervals
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

10b. Major Amputation - Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	0	44	44	0.014 (0.0008 – 0.24) Favors HBO_2
	Control	17	21	38	
	Total	17	65		

	Starting Score	4	Rationale
Wagner ≥3 and ≥30 Days (Major Amputation)	Risk of Bias	-1	Study had unclear blinding
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	-1	Wide confidence intervals
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**3**	**Moderate Level of Evidence**

Supplemental Figure 11. Alternate forest plots and GRADE analysis for Question 3: Comparison of observational studies vs. randomized controlled trials

11a. Incomplete Healing – Observational Studies

	Study Group	Event	Non-Event	Total	Odds Ratio
Kalani 2001	HBO_2	4	13	17	0.279 (0.068 – 1.146) Favors HBO_2
	Control	11	10	21	
	Total	15	23		

All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	There was no inconsistency because there is only one study
	Indirectness	0	No evidence of indirectness
	Imprecision	-1	Confidence intervals are wide
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No evidence of a large magnitude of effect
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**≤1**	**Very Low Level of Evidence**

11b. Incomplete Healing – Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	13	31	44	0.006 (0.0003 - 0.098) Favors HBO_2
	Control	38	0	38	
	Total	51	31		

Wagner ≥3 and ≥30 Days (Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Study had unclear blinding
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**4**	**High Level of Evidence**

Supplemental Figure 12. **Alternate GRADE analysis for Question 3: Comparison of observational studies vs. randomized controlled trials**

12a. Complete Healing: Observational Studies

	Study Group	Event	Non-Event	Total	Odds Ratio
Kalani 2001	HBO_2	13	4	17	3.58 (0.87 – 14.65) Favors HBO_2
	Control	10	11	21	
	Total	23	15		

All DFU (Outcome: Major Amputation)	Starting Score	2	Rationale
	Risk of Bias	0	No Risk of Bias because of OBS studies
	Inconsistency	0	There was no inconsistency because there is only one study
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision as Estimate of Effect had narrow Confidence Intervals. Peto analysis showed tighter confidence interval, but Random Effects Risk Ratio analysis was also deemed acceptable.
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No significant effect using either Random Effects RR or Peto OR
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**2**	**Low Level of Evidence**

12b. Complete Healing: Randomized Controlled Trials

	Study Group	Event	Non-Event	Total	Odds Ratio
Duzgun 2008	HBO_2	31	13	44	179.66 (10.27 – 3142.69) Favors HBO_2
	Control	0	38	38	
	Total	31	51		

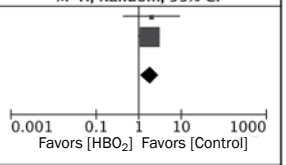
All DFU (Outcome: Incomplete Healing)	Starting Score	4	Rationale
	Risk of Bias	-1	Rated down because of unclear blinding
	Inconsistency	0	No evidence of inconsistency
	Indirectness	0	No evidence of indirectness
	Imprecision	0	No evidence of imprecision
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	+1	Large magnitude of effect (direct evidence, relative risk [RR] = 2-5 or RR = 0.5-0.2 with no plausible confounders); Very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals)
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening confidence of the magnitude of effect
	Final Score	**4**	**High Level of Evidence**

Supplemental Figure 13. **Forest plots and GRADE analysis for Question 4: Non-critical outcome of minor amputation**

Minor Amputation – Randomized Controlled Trials

Study or Subgroup	HBO_2 Events	HBO_2 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Doctor 1992	4	15	2	15	11.4%	2.00 [0.43, 9.32]	1992
Faglia 1996	21	35	11	33	88.6%	1.80 [1.04, 3.13]	1996
Total (95% CI)		**50**		**48**	**100.0%**	**1.82 [1.08, 3.07]**	
Total events	25		13				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0\%$
Test for overall effect: Z = 2.26 (P = 0.02)



Wagner ≥3 and Surgical DFU (Minor Amputation)	Starting Score	4	Rationale
	Risk of Bias	-1	1/2 studies unblinded and 1/2 had single blinding, 2/2 had unclear allocation concealment, 1/2 had unclear patients lost to follow-up, 1/2 had unclear intention-to-treat analysis and 1/2 had no intention-to-treat analysis
	Inconsistency	0	Not all confidence intervals overlap in forest plot
	Indirectness	-1	Some evidence of indirectness as all patients in this study were inpatients, and 1/2 studies had a non-standard treatment protocol
	Imprecision	0	No significant evidence of imprecision
	Publication Bias	0	Could not be assessed with a small number of studies
	Large Magnitude of Effect	0	No evidence of large magnitude of effect
	Dose Response Relationship	0	No evidence of dose response relationship
	Confounders Strengthen Effect	0	No evidence of confounders strengthening magnitude of effect
	Final Score	**2**	**Low Level of Evidence**

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