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) 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/DFU literature than randomized controlled trials (RCTs). Clinicians, patients, and policy makers have need of a rigorous analysis of the literature in order to generate clear, practical, and accessible Clinical Practice Guidelines (CPGs).

Methods

The Undersea and Hyperbaric Medical Society (UHMS) undertook a systematic review of the HBO literature in order to generate CPGs for the treatment of DFUs. We utilized the methodology developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group to rate the quality of evidence and generate practice recommendations. We selected four clinical questions for review regarding the role of HBO 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 is beneficial in preventing amputation and promoting complete healing in patients with Wagner Grade 3 or greater DFUs who have undergone surgical debridement of the foot as well as in patients with Wagner Grade 3 or greater DFUs that have not healed after 30 or greater days of treatment. In patients with Wagner Grade 2 or lower DFUs, there was inadequate evidence to justify the use of HBO as an adjunctive treatment.

Conclusions

Clinicians, patients, and policy makers should engage in shared decision-making and consider HBO as an adjunct treatment of DFUs that fit the criteria outlined in this guideline. Future research should be directed at raising the quality of the evidence through improved study methodology, better reporting of outcomes, and better stratification of enrolled patients based on known prognostic risk factors.

Introduction

The CDC estimates that approximately 25.8 million people, or roughly 8.3% of the US population, are affected by diabetes.[1] More than 60% of non-traumatic amputations 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 3-5 years, and the 5-year mortality rate for diabetic patients who have had a single-leg amputation is 60%.[2] This figure is higher than the overall 5-year mortality rate of breast cancer (10%), bladder cancer (19%), colorectal cancer (33%), and all cancers combined (32%).[3] Diabetic foot ulcers pose an important public health problem due to their incidences, morbidity, and costs to manage.

The role of HBO for the treatment of DFUs continues to be debated. Examination of the literature provides 9 randomized controlled trials (RCTs),[4-12] over 20 observational (OBS) studies,[13-34] and nearly a dozen review articles.[35-45] These studies show that HBO increases wound healing, decreases amputation rates, increases healthcare related quality of life, and improves outcomes of DFUs, but general acceptance of these results are hampered by small sample sizes, inconsistent treatment protocols, and less than rigorous methodology.

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 45-85%.[1] The biggest caveat to using HBO is that it is an adjunctive treatment and cannot take the place of high quality wound management. 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 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, co-morbidities are not consistently screened, and sub-groups of patient acuity are not consistently reported. The Wagner classification system first addresses perfusion then grades the wound on single markedly different observations such as deformity, depth, infection, gangrene and location.[47] The University of Texas classification system 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.[48] The Infectious Disease Society of America (IDSA) bases its classification system 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.[49] It is difficult to find a single classification system that
addresses all of the relevant co-morbidities contributing to the pathology of a diabetic foot ulcer. The IWGDF developed a classification system for research purposes based on five key categories: Perfusion, Extent/Size, Depth/Tissue loss, Infection and Sensation (PEDIS).[50, 51] Strauss described a similar system but adds an assessment of the wound base and an easy to derive, intuitively obvious 0 to 10 scoring system to make logical decisions between limb salvage or major amputation.[52] A recent guideline by the Society for Vascular Surgery published similar risk stratification based on three major factors that impact amputation risk and clinical management: Wound, Ischemia, and foot Infection (WIFI).[53]

With regard to the use of HBO2 treatments for DFUs, most of the contemporary studies and most reimbursement determinations are based on the Wagner DFU wound appearances. A Wagner Grade is assigned from the appearance of the wound at a single observation. Wagner’s Grade 3 DFU has been interpreted by the hyperbaric medicine community (with CMS concurrence) to include deep DFUs that have not improved over a 30 day period with standard wound management. This interpretation differs from Wagner’s deep abscess/osteomyelitis description of the Grade 3 DFU, which requires acute interventions.[47]

**Executive Summary: Recommendations for the use of hyperbaric oxygen therapy in diabetic foot ulcers**

**Recommendation One:** In patients with Wagner Grade 2 or lower diabetic foot ulcers, we suggest against using Hyperbaric Oxygen Therapy (very low level evidence, conditional recommendation).

**Recommendation Two:** In patients with Wagner Grade 3 or higher diabetic foot ulcers that have not healed for 30 days, we suggest adding Hyperbaric Oxygen Therapy to the Standard of Care to reduce the risk of major amputation and incomplete healing (low level evidence, conditional recommendation).

**Recommendation Three:** 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; I&D of deep space abscess; or necrotizing soft tissue infection), we suggest adding 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).

**Methods**

The Institute of Medicine published eight standards for the development of reliable Clinical Practice Guidelines.[54] These standards include conducting a systematic review, appropriate management of existing conflicts of interest, transparent guideline development process, and clearly articulated recommendations derived and 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 UHMS 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 oversees the development of a series of Clinical Practice Guidelines (CPGs) for the appropriate use of HBO2 and chooses members of each CPG review committee and evaluates each member for potential conflicts of interest. In addition, the Oversight Committee also serves in the internal review process of manuscripts for publication resulting from the systematic reviews.

**Review Committee**

The UHMS CPG Oversight Committee invited members of the DFU CPG review committee based on individual areas of expertise. Curriculum vitae and Conflict of Interest questionnaires were reviewed before final approval. Selected individuals 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 multi-step 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 acknowledgement of values and preferences of patients, and clear, pragmatic interpretation of strong versus conditional recommendations for clinicians, patients, and policy makers (Table 1).[55-69] This methodology has been adopted 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. The term “standard wound care” is meant...
to represent the optimal management of surgical debridement, mechanical offloading, infection control, revascularization, and metabolic control.

The following four questions were formulated by the Review Committee:

1. For a patient with a Diabetic Foot Ulcer, is HBO₂ 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 healed after 30 days of treatment, is HBO₂ 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 healed after 30 days of treatment, is HBO₂ 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 post-operative HBO₂ with Standard Wound Care more effective than Standard Wound Care alone for the outcomes of interest?

Outcomes of Interest
The outcomes of interest selected by the Review Committee are listed in Table 2. 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.

Literature Review
We identified published systematic reviews of HBO₂ for DFU[35-45] and cross-referenced them to identify RCTs and OBs of interest (Table 3). A supplemental literature search using Pubmed (MEDLINE), EMBASE, and COCHRANE databases was performed to identify any additional studies that were not included in the published systematic reviews. All members of the DFU CPG Review Committee reviewed these studies. 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.

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 4. 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 confidence intervals. We calculated the I² as a measure of heterogeneity. The I² statistic represents the proportion of variance that is attributable to heterogeneity. The higher the I² statistic is, the greater the degree of heterogeneity. The degree of heterogeneity can be used to determine the level of inconsistency across studies.

Effect sizes for dichotomous data are usually expressed as risk ratios, and effect sizes for continuous data are expressed as mean differences. When the true effect sizes among studies are not expected to be similar, a random effects model is used for analysis. The random effects model takes into account the variation in effects sizes between studies. When the number of events in any group (i.e., control or experimental) is very low or zero or the effect sizes are very similar in the experimental and control groups, a Peto odds ratio is used.

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. If there was equivalent level of evidence and the magnitude of effect was similar, the RCT and OBS studies were analyzed together. If the magnitude of effect was dissimilar, 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 5), and assigned a final rating for each outcome for each PICO question. 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) (see Table 6). A low level of evidence suggests that 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.

Formulating recommendations
A final rating of the quality of evidence (across all outcomes) was given based on the critical outcome with the lowest level. The Review Committee then formulated recommendations for each PICO question. This step required assigning a level of strength for each recommendation using the two-tiered GRADE levels (conditional or strong) (see Table 7). The final recommendations were agreed upon by consensus.

External Review
The UHMS Oversight Committee reviewed the document before undergoing additional review by content experts. 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.

Patient Involvement
Two sets of patients with DFU were invited to participate in the formulation of this guideline. Both patients who had received HBO, and patients who had not received HBO, 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 9-point scale. This was an IRB approved study. The second group was recruited from a wound and hyperbaric medicine clinic to attend a live meeting with a conference call with members of the Review Committee. 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
Six patients with diabetes completed the online survey. Three patients had a diabetic foot ulcer and three did not. No patients had any financial relationship with a hyperbaric chamber manufacturer or hyperbaric operations. Three patients had received HBO, or were scheduled to receive HBO. One patient had an incomplete course of HBO 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, 3 of the 3 patients who answered this question rated all of the outcomes 9 of 9 (of critical importance).

Evidence Review
The review committee identified 9 randomized controlled trials and 21 observational studies for review (Table 8).

Five (5) of the RCTs (Doctor 1992, Faglia 1996, Abidia 2003, Duzgun 2008, and Löndahl 2010) were included from this analysis (Table 9). Of note, the Doctor study did not report the number of patients in each 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 pre-selected outcomes. Risk of bias was evaluated for the remaining RCTs using five criteria (Table 10). An indeterminate score was assigned if a study did not explicitly state whether it did or did not adhere to one of the criteria.

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. [5] of the observational studies (Oriani 1990, Zamboni 1997, Faglia 1998, Kalani 2001, and Margolis 2013) were included (Table 11). The remaining studies were excluded because they either did not report data on the pre-selected 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 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 (Table 12) is discussed below. Peto Odds Ratio analysis was used when the number of events was zero.

Question One: For a patient with a Diabetic Foot Ulcer, is HBO, with Standard Wound Care alone more effective than Standard Wound Care alone for the outcomes of interest?

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 RCT groups had a higher score and were used for these analyses (Supplemental Figures 1 and 2).

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

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 (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 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.

Forest plots using Random Effect Risk Ratio as well as Peto Odds Ratio were compared. The overall estimate of effect favoring HBO 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).
Outcome: Incomplete Healing at 1 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 1 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 (5) 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 Two: For a patient with a Wagner Grade 2 or lower Diabetic Foot Ulcer that has not healed after 30 days of treatment, is HBO₂ with Standard Wound Care more effective than Standard Wound Care alone for the outcomes of interest?

There were three randomized controlled trials (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 only included 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).

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 HBO₂ 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.

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 Low.

Outcome: Minor Amputation (Supplemental Figure 9)
One RCT (Duzgun 2008) reported the outcome of Minor Amputation. Due to the low number of events in this single study, a Peto Odds ratio was used although the results were similar using Risk Ratio.

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.

**Question Three:** For a patient with a Wagner Grade 3 or higher Diabetic Foot Ulcer that has not healed after 30 days of treatment, is HBO, with Standard Wound Care more effective than Standard Wound Care alone for the outcomes of interest?

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).

**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 (0) major amputations in the HBO 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.

**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 1 year. The forest plots for wound healing had a similar estimate of effect when reported as Complete Healing (Supplemental Figures 11 and 12).

The final quality of evidence for this outcome was High, but given the fact that there was only a single study and the study was unblinded, the review committee reduced this score to Moderate.

**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 Four:** 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, with Standard Wound Care more effective than Standard Wound Care alone for the outcomes of interest?

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

**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 as part of an aggressive surgical algorithm, where patients would be treated with HBO, soon after surgery, as opposed to waiting for recovery. All three studies used HBO for the analysis of a combination of RCTs and OBSs was conducted, the effect size was even smaller, favoring HBO over Standard Wound Care. This effect size was statistically significant and the $$I^2$$ was 0%, indicating homogeneity of the data. This case exemplifies the point that the combination of RCTs and OBSs in a meta-analysis may make the effect size more precise due to the greater number of events. However, this strategy should only be performed when there is no significant discrepancy between effect sizes of the RCTs and OBSs and when the quality of evidence is similar between these two bodies of evidence.

The final quality of evidence for this outcome was Moderate.

**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 HBO₂ 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.

Discussion
This guideline starts with the assumption that practitioners have aggressively addressed re-vascularization 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. Previously published clinical practice guidelines have outlined the necessity of these interventions as part of the best practices treatment of diabetic foot ulcers,[46, 70-73] 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 HBO₂ 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 HBO₂ reduced infection, reduced minor amputation, or improved quality of life.

The Review Committee’s next step was to try and standardize patient populations by using variations of the PICO question. We attempted to stratify patients using a clinical grading system in order to create stronger recommendations. Experts disagree on the best method of classifying diabetic foot ulcers and infections, as there are inherent strengths and weaknesses to these various systems.[74] The Review Committee was limited in its attempt to filter the existing literature using any grading system other than the Wagner scale, as this was the most established system in the hyperbaric community. Recent publications have shown that there is an incomplete understanding of the Wagner scale even by experienced hyperbaric practitioners.[75] There is a failure to recognize that a Wagner 3 DFU includes deep space abscess or tendinitis, and the hyperbaric oxygen community (with CMS endorsement) has interpreted Wagner’s original DFU classification system differently than originally proposed. Aggressive surgical management for the Wagner Grade 3 or greater DFU is recommended by Wagner’s algorithm as opposed to conservative medical management. We provide the original Wagner scale for reference in Table 10 and recommend that if one is to use the Wagner classification system, one should follow the management algorithms of the Wagner system while supplementing with HBO₂ if indicated.[47]

Current clinical practice is to risk-stratify patients using peri-wound transcutaneous oximetry measurements (TCOM).[25, 76] Data from multiple studies showed that for patients who had a DFU, TCOM > 200 mmHg under hyperbaric conditions predicted whether the wound would heal with 75-80% 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.

Recommendation One: In patients with Wagner Grade 2 or lower Diabetic Foot Ulcers, we suggest against using Hyperbaric Oxygen Therapy (very low, conditional).

Six of the RCTs included patients with Wagner 2 DFUs, but we were only able to extract data from three of these studies for analysis. These three studies showed no evidence that HBO₂ 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 adding adjunctive HBO₂ 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 HBO₂ had a Wagner 2 DFU.[22] This is an alarming statistic, as it would seem to indicate an unsubstantiated use of HBO₂, and highlight the concern that some have had regarding the potential overuse of HBO₂.[77] 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 2 DFU may be candidates for HBO₂, but this would be the exception rather than the rule.

Recommendation Two: In patients with Wagner Grade 3 or higher Diabetic Foot Ulcers that have not healed after 30 days of treatment, we suggest adding 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 3 criteria.[75] The source of this confusion is unclear, but the Wagner 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 only able to exclude 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 HBO2 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 HBO2 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 outcomes. 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 HBO2.

**Recommendation Three:** 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 post-operative 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 HBO2 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 classification system shows that aggressive surgical intervention, revascularization, metabolic control, infection control and initiation of HBO2 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 HBO2 has many antimicrobial properties (i.e., enhancing leukocyte killing activity, direct bacteriostatic effect on anaerobic organisms),[78] a common misconception in the community is that the primary role of HBO2 is intended to help resolve the diabetic foot infection. This impression is illustrated by comments from physicians that a patient does not require HBO2 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 pincushion of being diagnosed with a Wagner 3 DFU in order to receive HBO2 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 dysfunctional foot, and the actual benefit of HBO2 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 HBO2 in an outpatient setting for DFUs that have not healed after 30 days. The reason for this is economically driven, as reimbursement policies have unfortunately abrogated clinic decision-making. The lack of acute, inpatient HBO2 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 HBO2 although numerous studies have demonstrated superior efficacy compared to standard of care.

**Adverse Events**

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 HBO2, although there were several studies that reported non-HBO2 related side effects. In general, large retrospective studies are more useful for identifying serious adverse events related to HBO2. National registries like the US Wound Care Registry as well as proprietary databases from for-profit management companies also allow for reporting of adverse events related to HBO2 from a larger sample of patients treated with HBO2.

There are obviously some adverse events that are solely related to barotrauma that would not be seen in patients treated with alternative therapies (i.e., barotrauma, 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 (8 per 10,000), hypoglycemic events (5 per 10,000), shortness of breath (2 per 10,000), seizures (2 per 10,000), sinus pain (1 per 10,000), and chest pain (1 per 10,000). Overall, the risk of adverse events from HBO2 can be considered to be very infrequent and self-limited when they do occur.

**Cost Effectiveness**

Few studies have been published regarding the cost effectiveness of HBO2 in the treatment of DFUs. Cianci reported in a cohort [33] study of 41 patients that the estimated cost (in 1991 dollars) of below-knee amputation ($40,000) plus rehabilitation ($30,000) was greater than the cost of HBO2 to salvage a limb ($31,265).[79] Chuck used 2008 Canadian data on DFU prevalence and HBO2
efficacy data to create a computer model that estimated the 12-year cost for patients receiving HBOT was CND$40,695 compared with CND$49,786 for standard care alone. This study concluded that adjunctive HBO₂ for DFU was cost-effective when compared to standard care.[80] Only a single RCT prospectively addressed the cost-effectiveness of the use of HBO₂ 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 £2,960 per patient treated with HBO₂. This analysis took into account the additional costs of HBO₂ 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 HBO₂ is likely to become an important factor in any discussions focusing on the use of HBO₂ 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 HBO₂ and one who was eligible for – but did not receive – HBO₂) 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 1-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 they 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.

**Technical Comments**

**Recommendation One:** 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 HBO₂ should not typically be part of the treatment plan. There may be cases where a patient has previously required HBO₂ for a Wagner Grade 3 or higher DFU and is now presenting with another ulcer. In these cases, it may be advisable to incorporate HBO₂ before the ulcer progresses. 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 Two:** In patients with Wagner Grade 3 or higher diabetic foot ulcers who have not healed 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 (low, conditional).

Patients who have failed to heal after 30 days of optimal wound care should receive HBO₂. Treatment depth of 2.0 – 2.4 ATA 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 (7 or less days of treatments, angiogenesis with 2 weeks of treatments, or refractory osteomyelitis with 30 to 40 treatments). Additional HBO₂ 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 HBO₂ is only a part of the treatment plan and would not necessarily be used until the DFU was completely healed. Patients who receive HBO₂ should have continued offloading, optimizing of revascularization, elimination of infection, debridement of devitalized tissue, and excellent diabetes management.

**Recommendation Three:** 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 HBO₂ within 24 hours of the time of surgery. Treatment depth of 2.0 – 2.4 ATA 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 (7 or less days of treatments, angiogenesis with 2 weeks of treatments, or refractory
osteomyelitis with 30 to 40 treatments. Additional HBO2 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 HBO2 is only a part of the treatment plan and would not necessarily be used until the DFU was completely healed. Patients who receive HBO2 should have continued offloading, optimization of revascularization, elimination of infection, debridement of devitalized tissue, and excellent diabetes management.

Conclusions
It is worth repeating that this guideline 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 hyperbaric oxygen therapy. Hyperbaric oxygen should be included as part of a comprehensive diabetic foot ulcer program. Although the level of evidence is of moderate quality, the Review Committee felt that taking patient values and preferences into account justified conditional recommendations to add HBO2 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 HBO2 and patients who will not heal even after receiving HBO2.

An algorithm that incorporates all of the recommendations is provided in Figure 5.

Research Recommendations
This analysis of the HBO2/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.” What those analyses lacked, however, were specific recommendations to guide future research. We provide those 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 allocations 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 HBO2 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, 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 depth, 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 surgical 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 health care costs.

Treatment of Infection
As noted above under Recommendation Three, a common misconception in the community is that the primary role of HBO2 is intended to help resolve the diabetic foot infection. Surprisingly there is little to no direct evidence to support the role of HBO2 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 HBO2 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 Three identifies that there may be a population of DFU patients who should receive acute post-operative HBO2 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 HBO2 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 (TCOM) stratification has been proposed to allow more judicious use of HBO₂. 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 TCOM greater than 40 mmHg (Group I) or 40 mmHg or less (Group 2). Group 2 could then be stratified on whether a single in-chamber TCOM at 2.0 atm abs rises over 200 mmHg (Group 2a) or fails to rise over 200 mmHg (Group 2b). Each group would then be randomized to HBO₂ 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.

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